NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Midostaurin for untreated acute myeloid leukaemia

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Midostaurin for untreated acute myeloid leukaemia [ID894]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Midostaurin for untreated acute myeloid leukaemia

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

1

Abbreviation	In full
AE	Adverse effect
AML	Acute myeloid leukaemia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence intervals
CR	Complete remission
DFS	Disease-free survival
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EQ-5D	EuroQol five dimensions questionnaire
ERG	Evidence review group
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
KM	Kaplan-Meier
NMA	Network meta-analysis
OS	Overall survival
QALY	Quality-adjusted life year
SCT	Stem cell transplantation
SOC	Standard of care
SMR	Standardised mortality ratio
RDI	Relative dose intensity
TTO	Time trade off

2

Key issues – clinical effectiveness

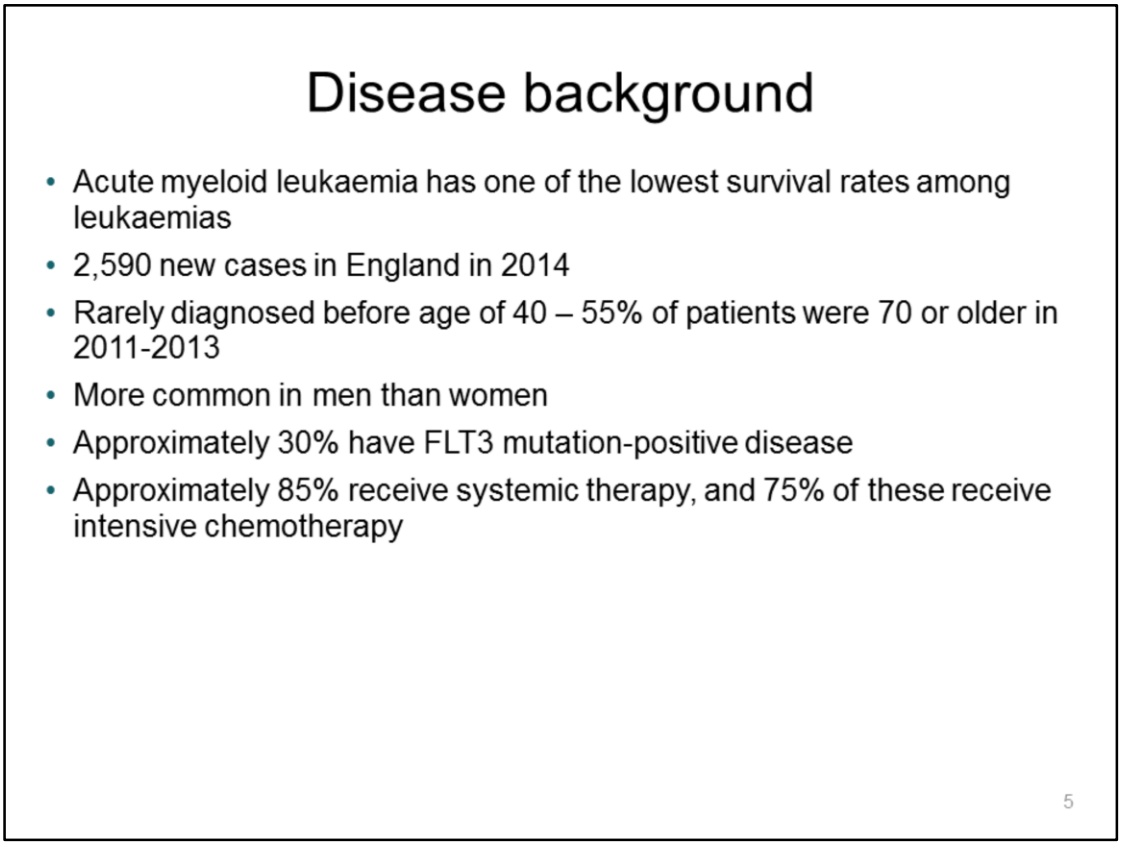
- Is the treatment schedule used in RATIFY representative of clinical practice in the NHS?
- Is the population in the trial relevant to clinical practice in the NHS?
- Will midostaurin be used for older patients (over 60/over 70)?
- Is midostaurin clinically effective?
- Are the adverse effects of midostaurin acceptable compared with standard of care?
- Is there uncertainty in the results because subsequent therapies were not recorded in the trial (including subsequent chemotherapy and stem cell transplant data)?
- Does the company's phase II trial provide evidence that midostaurin is effective across different age groups?

3

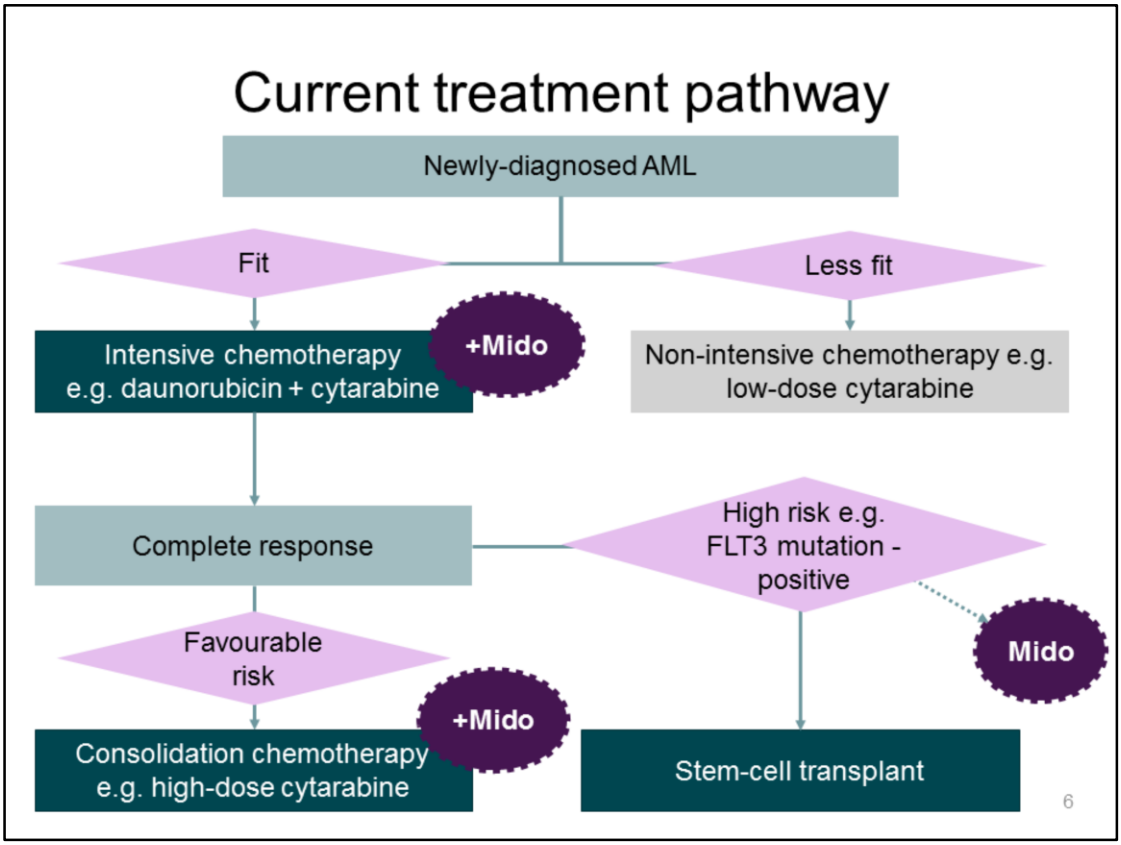
Key issues – cost effectiveness

- Is the model structure appropriate for decision-making?
- Should response to subsequent therapy (including stem cell transplant) be incorporated into the model?
- What long-term routine care costs should be included in the CR-1L (complete remission after first-line treatment discontinuation) and stem cell transplant recovery health states?
- What increase in mortality risk should be assumed after the cure point for patients with AML compared to the general population?
- Should utility values be adjusted for age?
- Should disutilities for adverse effects of stem cell transplant be included?
- What is the most plausible cure point?
- Is it appropriate to extrapolate the cost-effectiveness results to an older population?
- Are the end-of-life criteria met?
- Is midostaurin an innovative treatment?

4



Source: company submission section 3.4, Cancer Research UK



Source: company submission section 3.3, figure 3

To note:

- Treatment should be initiated ideally within 5 days of diagnosis
- 3+7 or 3+10 regimen may be used for induction chemotherapy
- In general, people receive 4-6 cycles of induction-consolidation therapy
- In most people who achieve complete remission after induction chemotherapy, disease will recur within 3 years

Related NICE guidance

TA399

Azacitidine is not recommended, within its marketing authorisation, for treating acute myeloid leukaemia with more than 30% bone marrow blasts in people of 65 years or older who are not eligible for haematopoietic stem cell transplant.

TA218

Azacitidine is recommended as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have acute myeloid leukaemia with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification, and if the manufacturer provides azacitidine with the discount agreed as part of the patient access scheme.

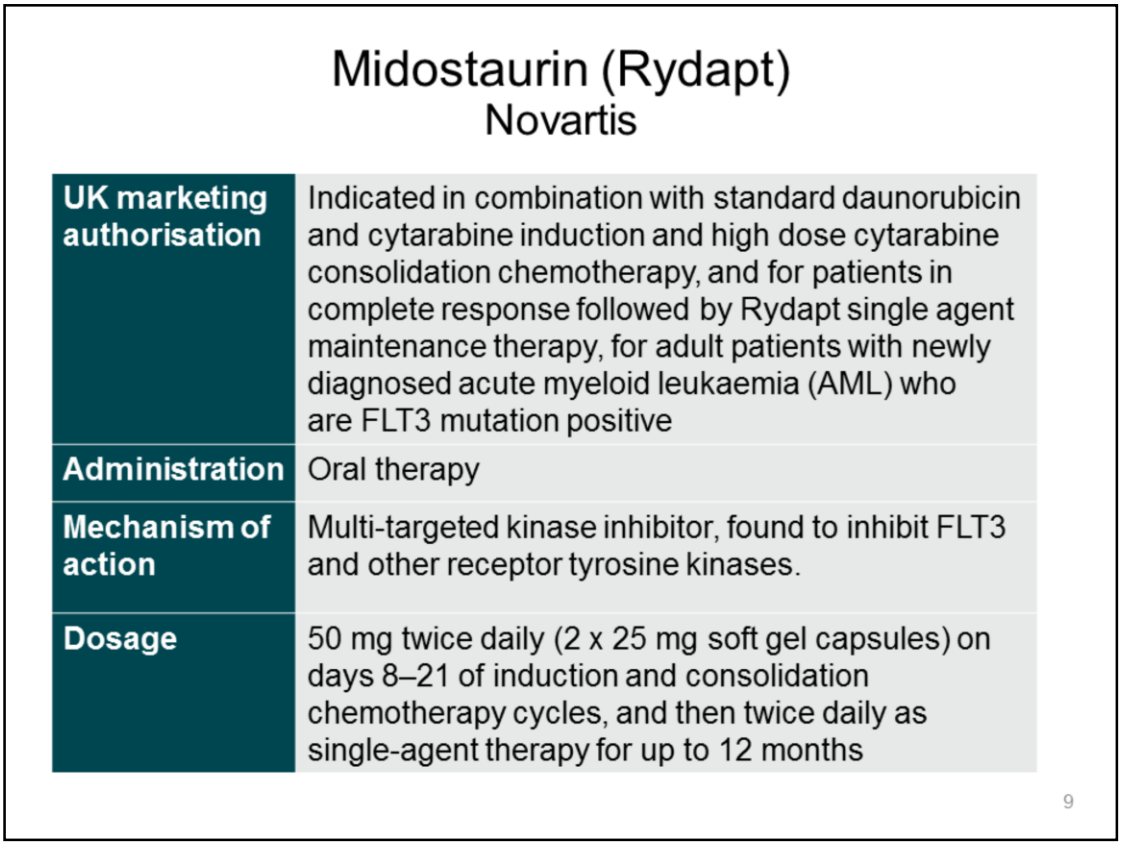
7

Comments from patient and professional groups

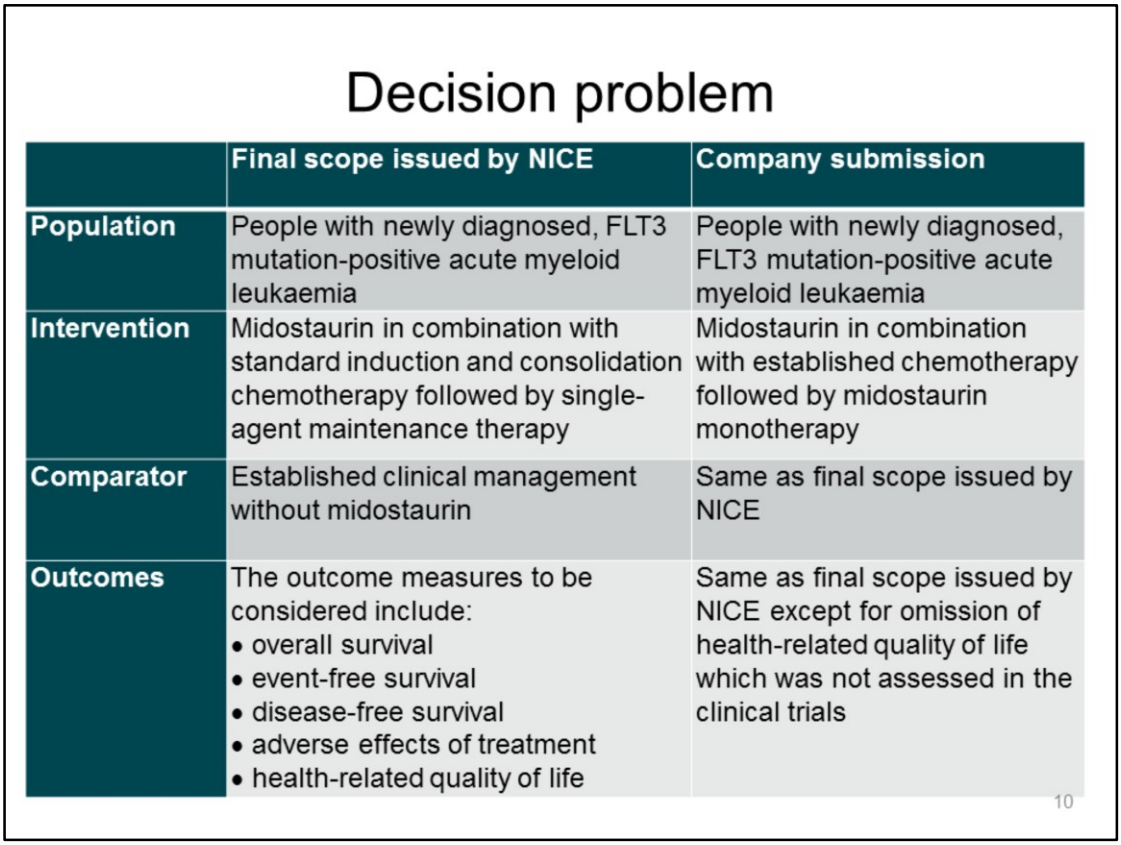
- Patient groups
  - AML has a large emotional impact for patients, families and carers
  - Practical impact – many people with AML have difficulty moving around or performing daily routines
  - Extremely poor prognosis and no recent progress in treatment
  - Common side effects from current treatments include fatigue, hair loss, neutropenia, diarrhoea, sore mouth, nausea and vomiting
  - Overall survival in placebo group of RATIFY trial may be an overestimate for UK clinical practice
- Professional groups
  - FLT-3 mutation testing done at diagnosis but results may not be available when therapy is initiated
  - 20-25% patients have FLT3-ITD mutation – increased relapse rate and poorer overall survival. 5-8% have FLT3-TKD mutation – better prognosis
  - Some differences between numbers of chemotherapy cycles and length of induction treatment in RATIFY and NHS practice

8

Source: submissions from Leukaemia CARE and NCRI-ACP-RCP



Source: company submission section 2.3 and midostaurin summary of product characteristics

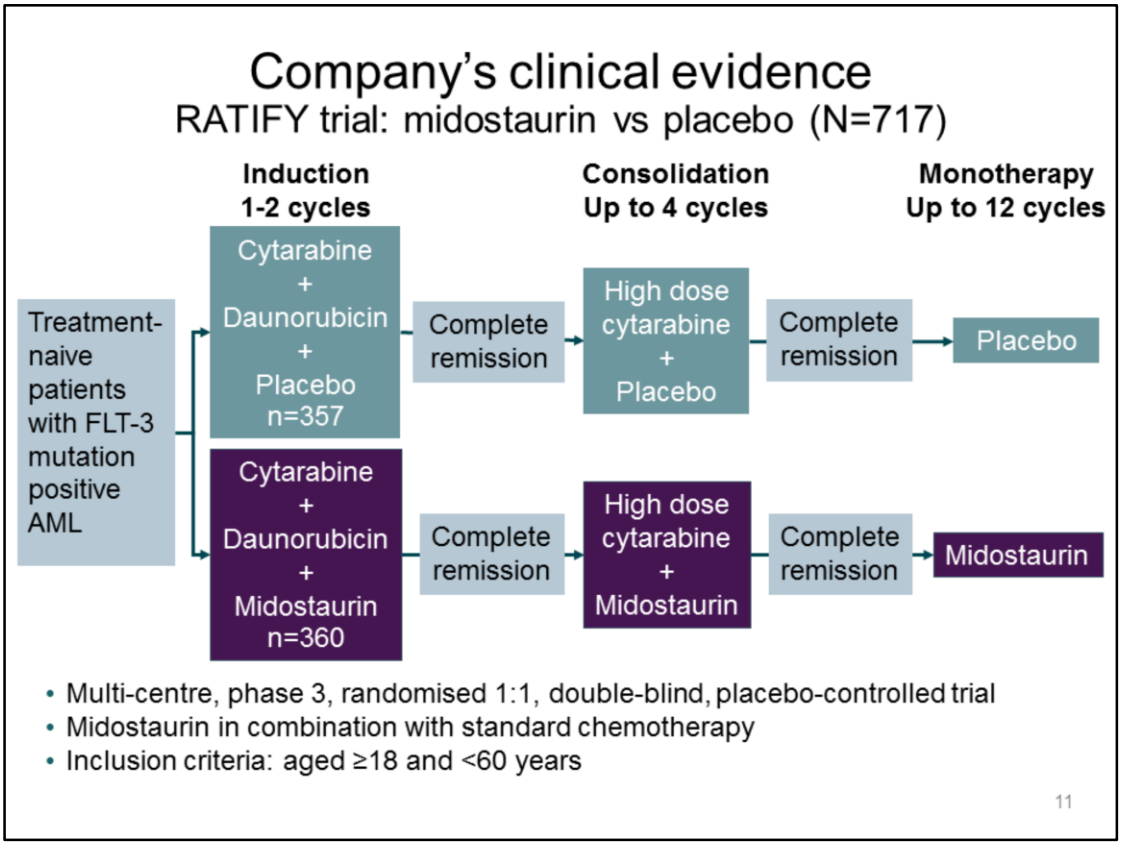


Decision problem

	Final scope issued by NICE	Company submission
Population	People with newly diagnosed, FLT3 mutation-positive acute myeloid leukaemia	People with newly diagnosed, FLT3 mutation-positive acute myeloid leukaemia
Intervention	Midostaurin in combination with standard induction and consolidation chemotherapy followed by single-agent maintenance therapy	Midostaurin in combination with established chemotherapy followed by midostaurin monotherapy
Comparator	Established clinical management without midostaurin	Same as final scope issued by NICE
Outcomes	The outcome measures to be considered include: • overall survival • event-free survival • disease-free survival • adverse effects of treatment • health-related quality of life	Same as final scope issued by NICE except for omission of health-related quality of life which was not assessed in the clinical trials

10

Source: company submission section 1.1



Source: company submission section 4.3.1-4.3.3, figure 6, table 8
To note:

- 3 definitions of complete remission were used in analysis
    - CR achieved within 60 days of the start of study treatment
    - CR achieved during induction phase after 1 or 2 induction cycles
    - CR achieved from randomisation up to 30 days after the end of treatment
- No crossover between groups permitted
- Progression to next stage dependent on achieving complete remission – if not achieved, study treatment discontinued but patient followed for overall survival.
- Induction: patients who did not achieve complete remission after first cycle underwent second cycle
- Consolidation: each cycle minimum 4 weeks.

Baseline characteristics in RATIFY (1)

Full population

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)

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group

12

Source: company submission, table 9

Baseline characteristics in RATIFY (2)

Full population

Characteristic	Midostaurin (N = 360)	Placebo (N = 357)	Total (N = 717)
Race, n (%)			
White	147 (40.8)	128 (35.9)	275 (38.4)
Black or African American	8 (2.2)	9 (2.5)	17 (2.4)
Asian	8 (2.2)	5 (1.4)	13 (1.8)
American Indian or Alaskan native	0	1 (0.3)	1 (0.1)
Not reported	1 (0.3)	2 (0.6)	3 (0.4)
More than one race	2 (0.6)	1 (0.3)	3 (0.4)
Unknown	194 (53.9)	211 (59.1)	405 (56.5)
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 (%)			
Tyrosine kinase domain (TKD)	83 (23.1)	80 (22.4)	163 (22.7)
Internal tandem duplication (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)

13

Source: company submission, table 9

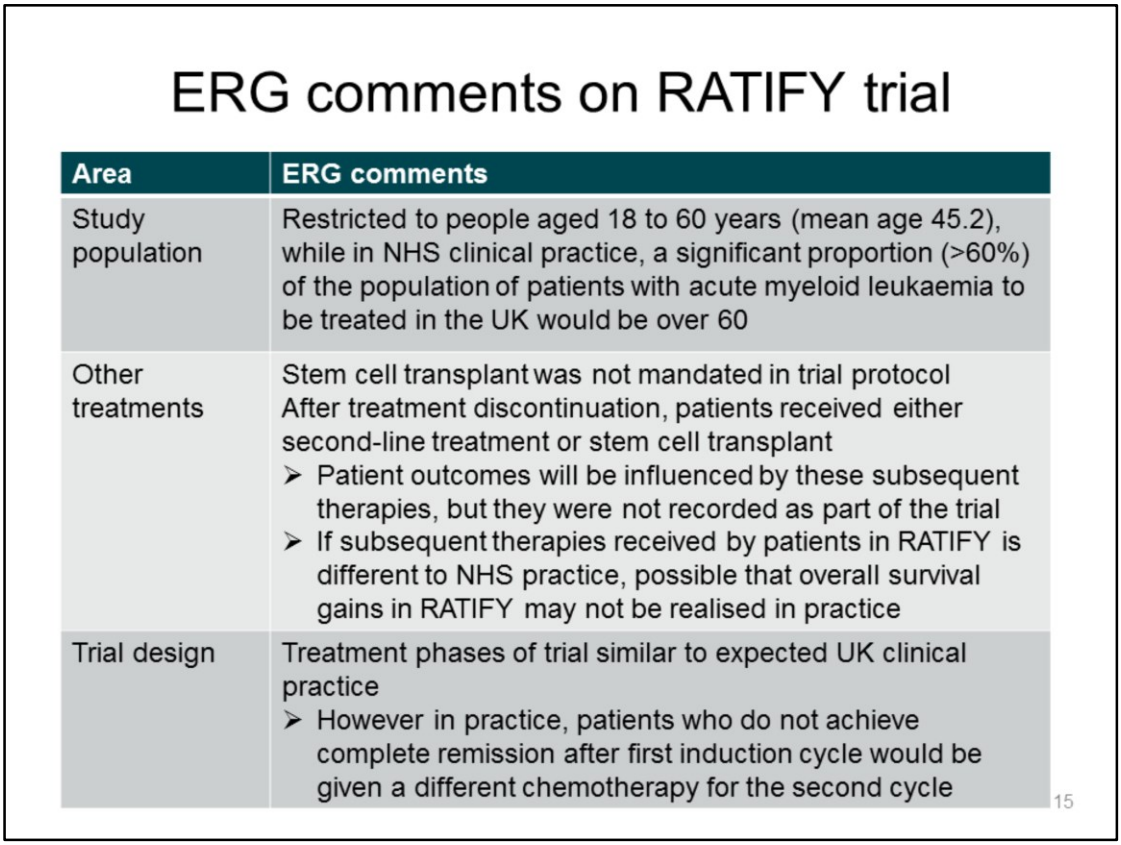
Stem cell transplantation

- Stem cell transplant was permitted at the discretion of the investigator, but patients could not resume midostaurin/placebo therapy afterwards
- Outcomes of SCT or complications related to SCT were not recorded

Patients undergoing SCT, n (%)	Midostaurin, n=360	Placebo, n=357
Overall	214 (59.4)	197 (55.2), p=0.250
Following treatment failure	[redacted]	[redacted]
In first complete remission (during induction)	[redacted]	[redacted]
After relapse	[redacted]	[redacted]

14

Source: company's submission section 4.3.1 and response to clarification, table 3
To note:
- Study was not designed to assess any benefit for midostaurin over placebo in enabling patients to receive SCT

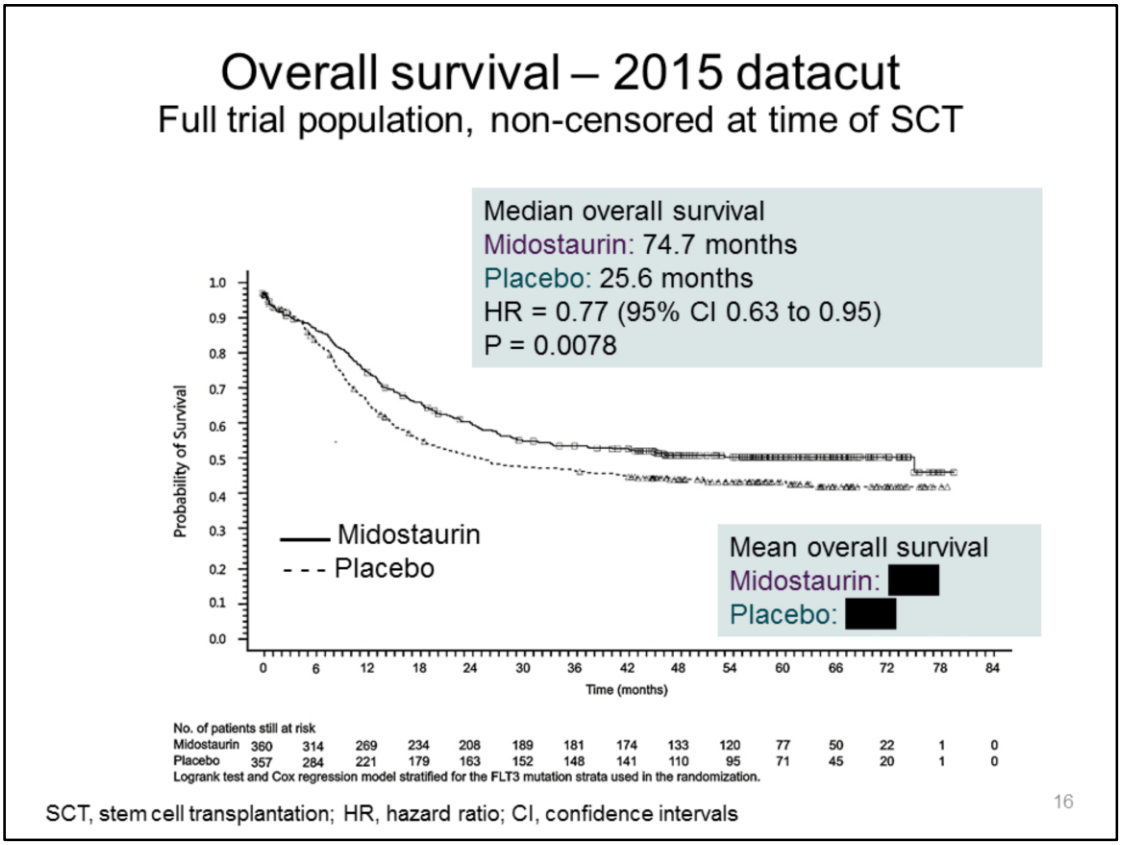


ERG comments on RATIFY trial

Area	ERG comments
Study population	Restricted to people aged 18 to 60 years (mean age 45.2), while in NHS clinical practice, a significant proportion (>60%) of the population of patients with acute myeloid leukaemia to be treated in the UK would be over 60
Other treatments	Stem cell transplant was not mandated in trial protocol After treatment discontinuation, patients received either second-line treatment or stem cell transplant ➢ Patient outcomes will be influenced by these subsequent therapies, but they were not recorded as part of the trial ➢ If subsequent therapies received by patients in RATIFY is different to NHS practice, possible that overall survival gains in RATIFY may not be realised in practice
Trial design	Treatment phases of trial similar to expected UK clinical practice ➢ However in practice, patients who do not achieve complete remission after first induction cycle would be given a different chemotherapy for the second cycle

15

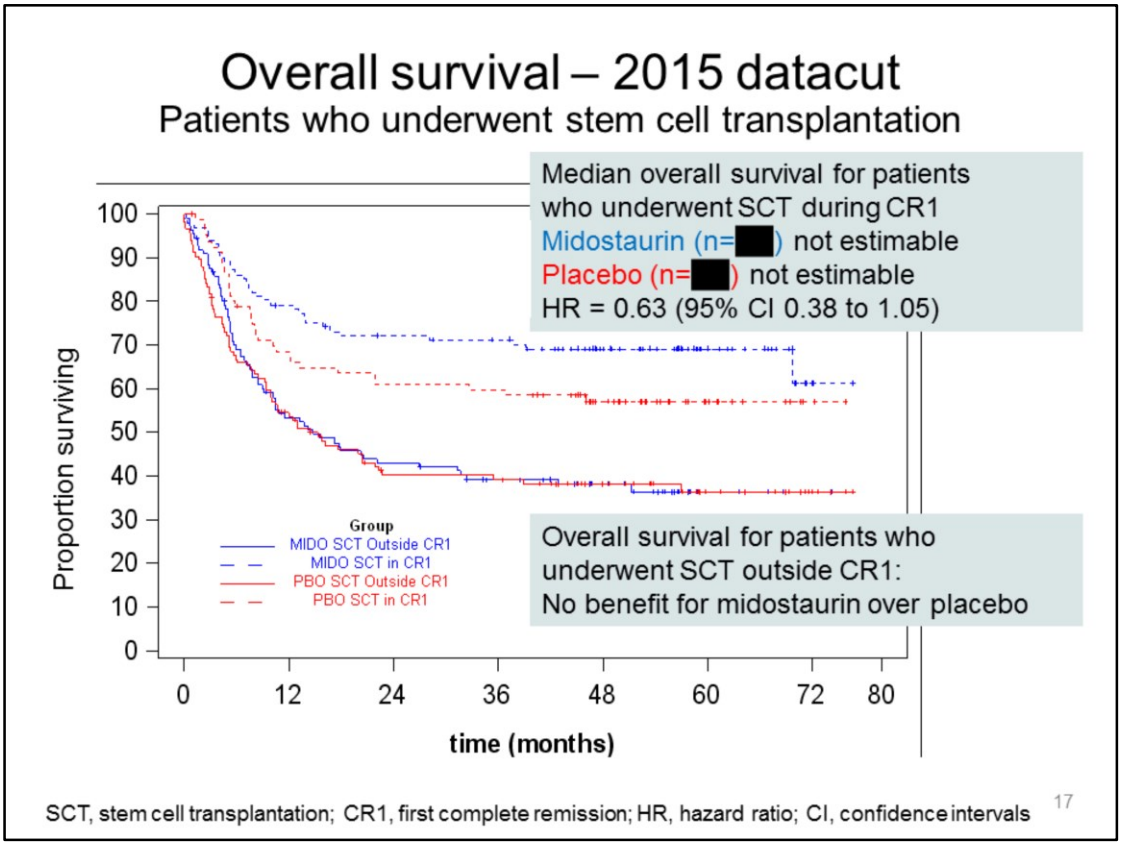
Source: ERG report, section 4.2.2



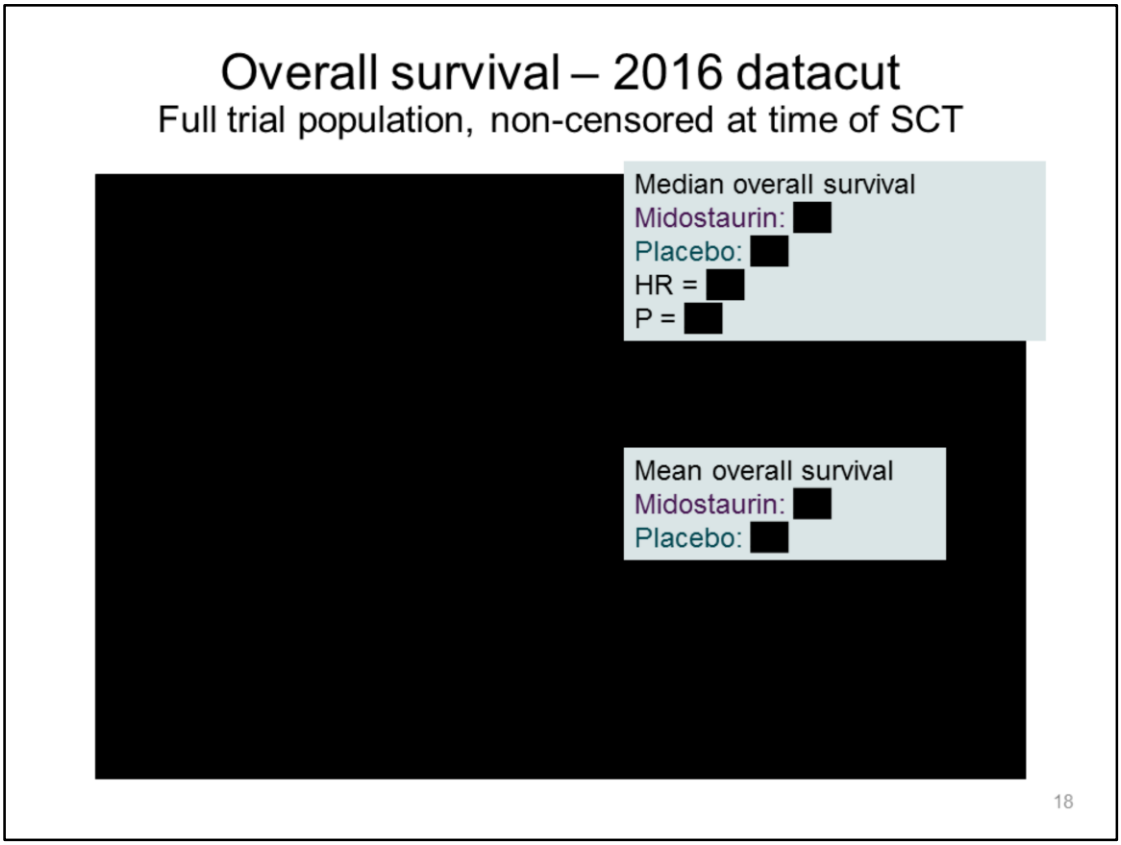
Source: company submission, figure 10

To note:

- Results for sensitivity analysis of overall survival censored by stem cell transplantation were consistent with the results of the primary endpoint
- Datacut 1st April 2015



Source: company submission, figure 11

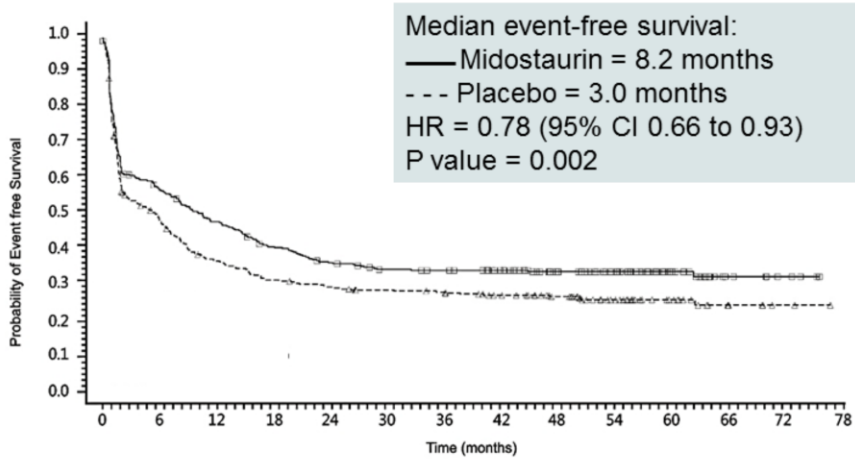


Source: company's response to clarification, figure 2 and ERG report section 4.2.2
To note:

- Datacut 5th September 2016
- Mean overall survival calculated by ERG

Event-free survival – 2015 datacut

Non-censored at time of stem cell transplant



No. of patients still at risk

Midostaurin	360	190	153	124	106	95	92	83	65	51	27	9	4	0
Placebo	357	153	106	86	78	73	70	60	49	32	18	8	2	0

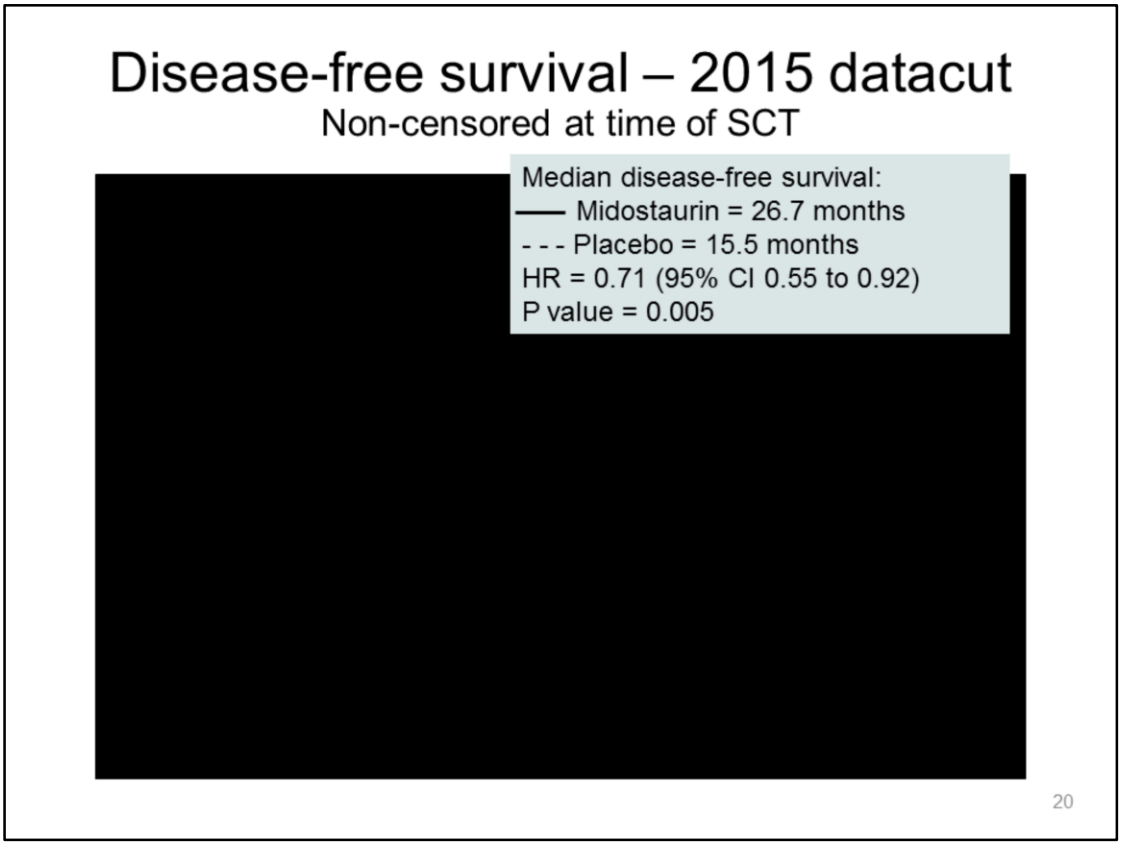
Logrank test and Coxregression model stratified for the FLT3 mutation strata used in the randomization.

19

Source: company submission, section 4.7.5, figure 12

To note

- Event-free survival defined as failure to obtain complete remission within 60 days of treatment initiation
- All patients were followed up for EFS irrespective of when they stopped study treatment



Source: company submission, section 4.7.7, figure 13

To note

- Disease-free survival defined as period from complete remission to relapse or death from any cause

Adverse effects (1)

- Summary of key adverse events reported from the RATIFY trial

	Grade 3/4 AEs suspected be related to treatment	SAEs	Grade 3/4 infections	Withdrawal due to grade 3/4 AEs	Death within 30 days of starting treatment	Deaths at any time
Placebo (N=335)	[redacted]	163 (48.7%)	[redacted]	15 (4.5%)	21 (6.3%)	[redacted]
Midostaurin (N=345)	[redacted]	162 (47%)	[redacted]	21 (6.1%)	15 (4.3%)	[redacted]

Key: AEs, adverse events; SAEs, serious adverse events; SCT, stem cell transplant

21

Source: ERG report table 10

To note

- Safety profile of midostaurin is similar to that of placebo

Adverse effects (2)

Grade 3/4 treatment-related AEs reported in ≥5% of patients receiving midostaurin across the randomised groups

System organ class AEs	Midostaurin (N=345)	Placebo (N=335)
Non-haematological grade 3/4 AEs in ≥5% of patients in either group, n (%)		
Diarrhoea	[redacted]	[redacted]
Dermatitis exfoliative	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]
Device-related infection	[redacted]	[redacted]
Haematological grade 3/4 AEs in ≥5% of patients in either group, n (%)		
Thrombocytopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]

Dermatitis exfoliative occurred more frequently in midostaurin group – 4 patients in midostaurin group discontinued treatment due to this adverse effect

22

Source: company submission, table 21

Company's additional evidence (1)

Submitted after ERG report received

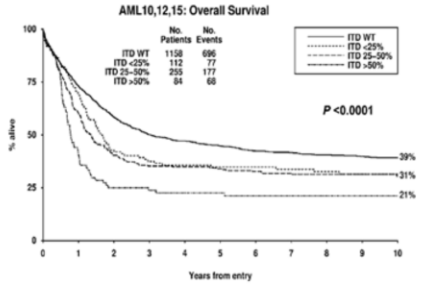
- After receiving the ERG report, company submitted additional evidence about the efficacy of midostaurin in patients over 60

1. Biology of FLT3-positive AML is the same regardless of age group, unlike patients with AML as a whole – therefore patients in target population will not have different prognosis based on age

2. Prognosis of patients with FLT3-positive AML is similarly poor across age groups – comparison of 2 cohorts

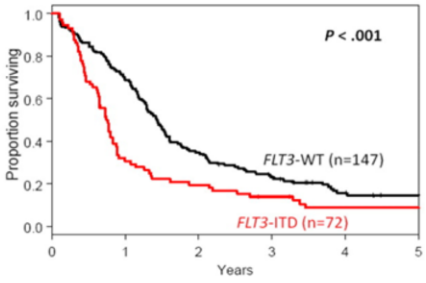
Patients ≤60 years

Linch, Hills & Brunett 2014



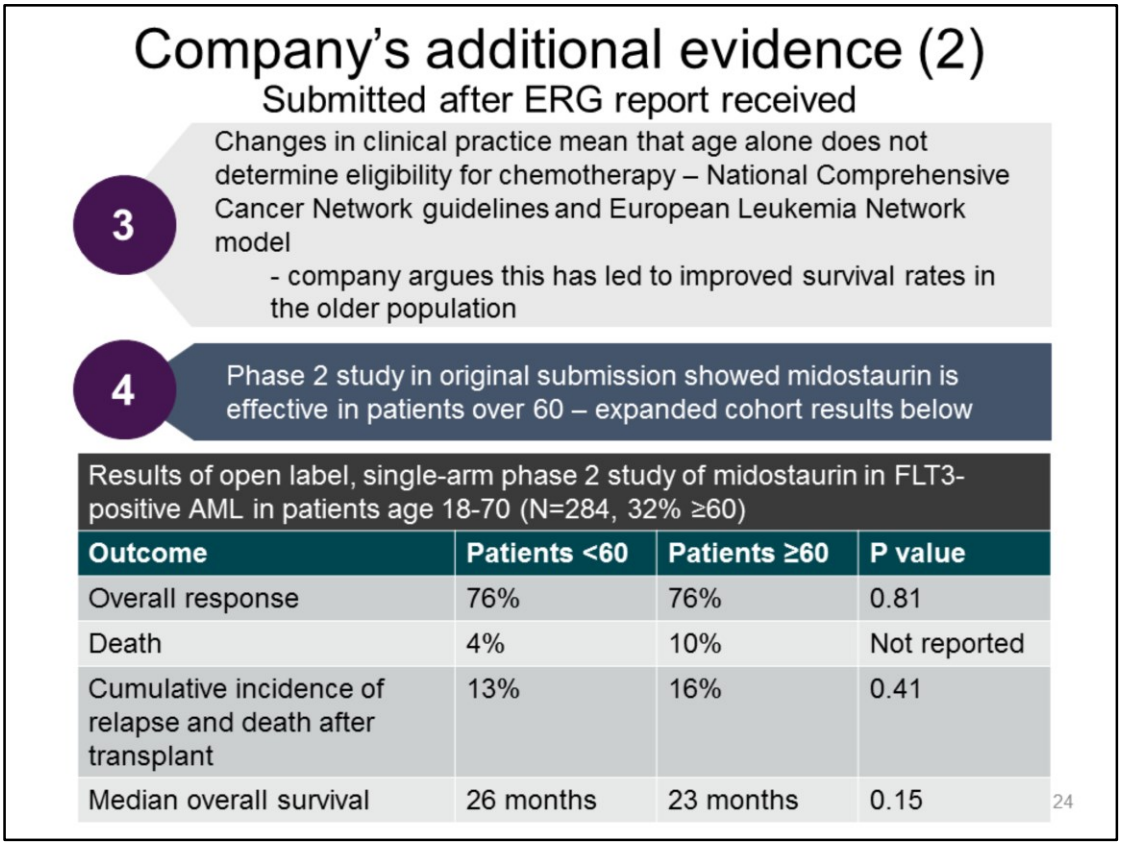
Patients >60 years

Whitman, Maharry & Radmacher 2010



23

Source: company's submission addendum



Source: company's submission addendum
Phase 2 study: Schlenk, Fiedler, & Salih, Impact of age and midostaurin-dose on response and outcome in acute myeloid leukemia with FLT3-ITD: interim-analyses of the AMLSG 16-10 trial., 2016

Company's additional evidence (3)

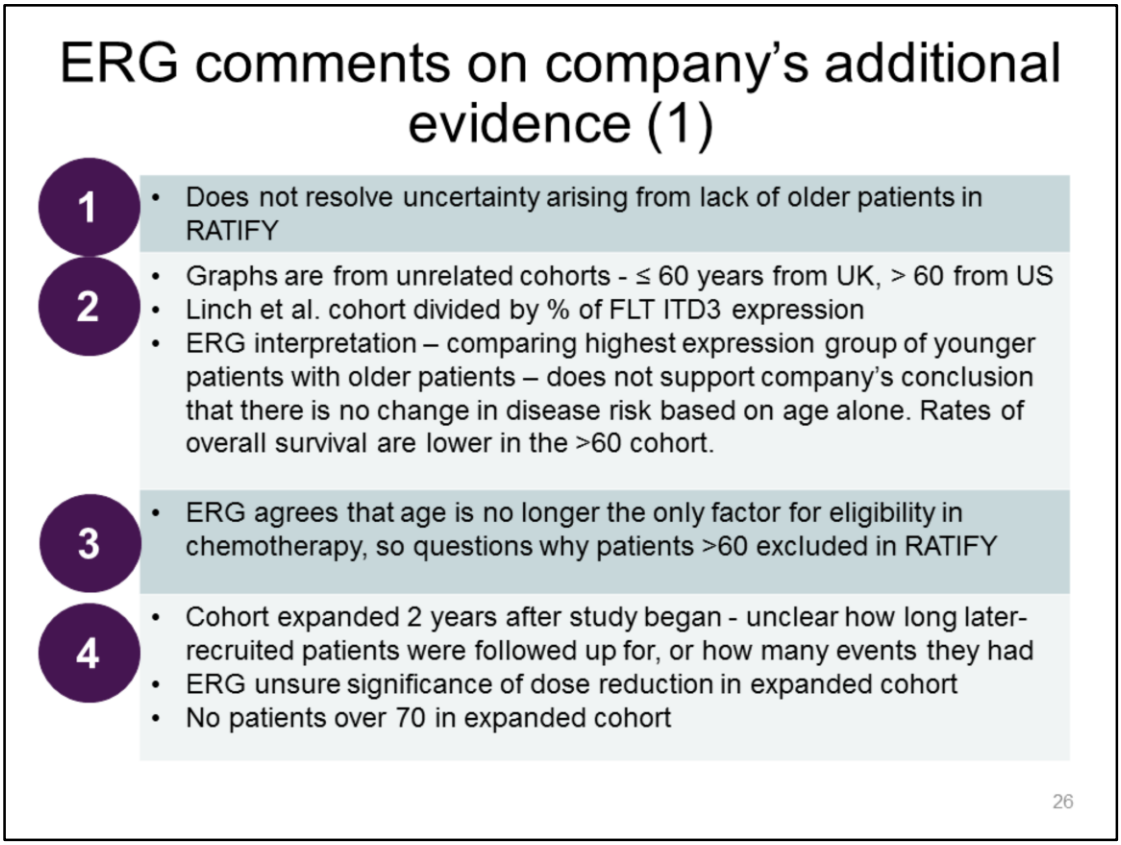
Submitted after ERG report received

5

Comparing phase 2 trial data with propensity score-matched historical controls shows efficacy of midostaurin in patients over 60

- Historical controls selected from 5 clinical trials of patients with AML treated with intensive chemotherapy (n=[redacted])
- Compared to [redacted] patients in phase 2 study (16-10) using propensity scoring

Source: company's submission addendum



Source: ERG addendum section 2

ERG comments on company's additional evidence (2)

5

- Phase 2 study: patients could receive midostaurin after stem cell transplant – not permitted in RATIFY
- ERG stated it could only check 2 of the 5 historical trials as no citation provided for other 3*
- Information about the 2 studies suggests historical controls may not be representative of current clinical practice e.g. treatment regimen different to RATIFY trial
- Patient characteristics not provided, but no patients over 70
- Observational study so subject to bias
- Unclear if analysis of overall survival censored for stem cell transplant
- Results are more favourable to midostaurin than the results of RATIFY – appears to be due to poorer survival in historical cohort compared with control group in RATIFY

*amended after committee meeting

27

Source: ERG addendum section 2

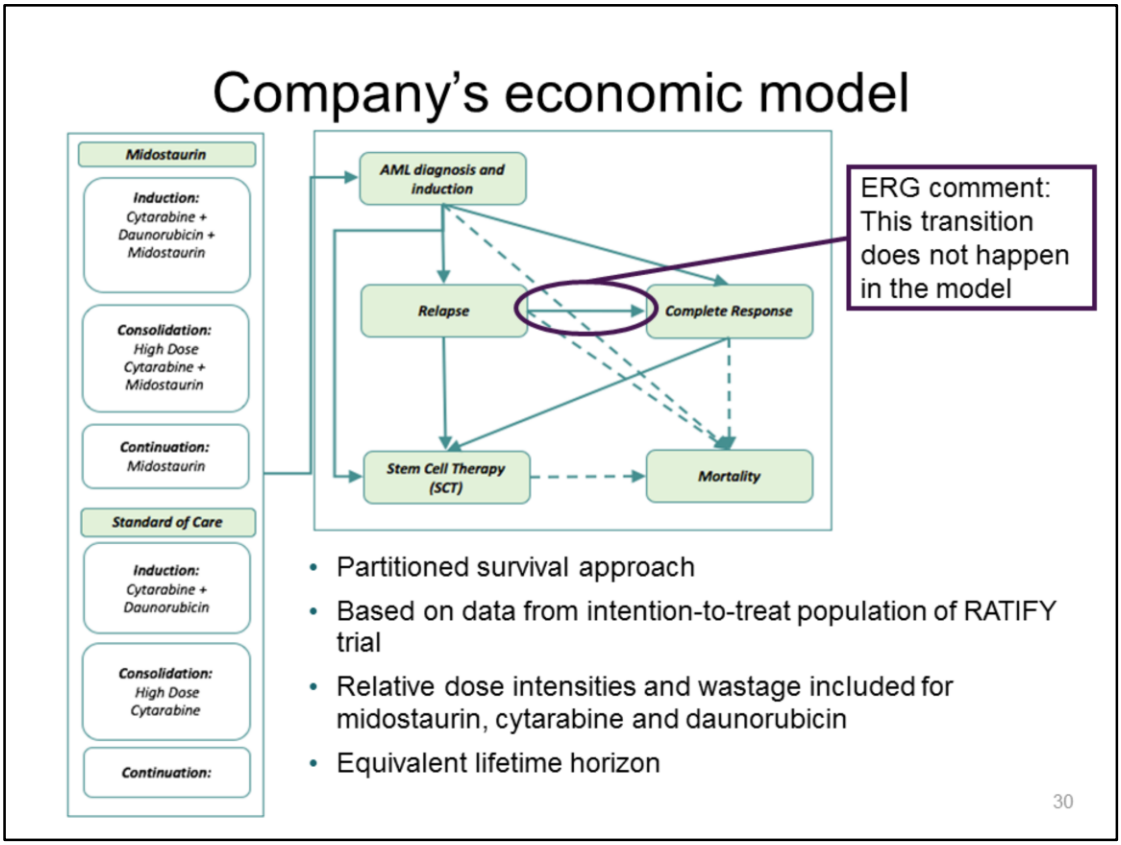
Key issues – clinical effectiveness

- Is the treatment schedule used in RATIFY representative of clinical practice in the NHS?
- Is the population in the trial relevant to clinical practice in the NHS?
- Will midostaurin be used for older patients (over 60)?
- Is midostaurin clinically effective?
- Are the adverse effects of midostaurin acceptable compared to standard of care?
- Is there uncertainty in the results because subsequent therapies were not recorded in the trial (including subsequent chemotherapy and stem cell transplant data)?
- Does the company's phase II trial provide evidence that midostaurin is effective across different age groups?

28

Cost effectiveness

29



Source: company submission section 5.2.2

To note

- 700 28-day cycles or approximately 54 years, equivalent to a lifetime horizon
- Complete response state is split into 3 sub-states that indicate the phase of treatment a patient is in: consolidation, monotherapy, and post-discontinuation of primary treatment

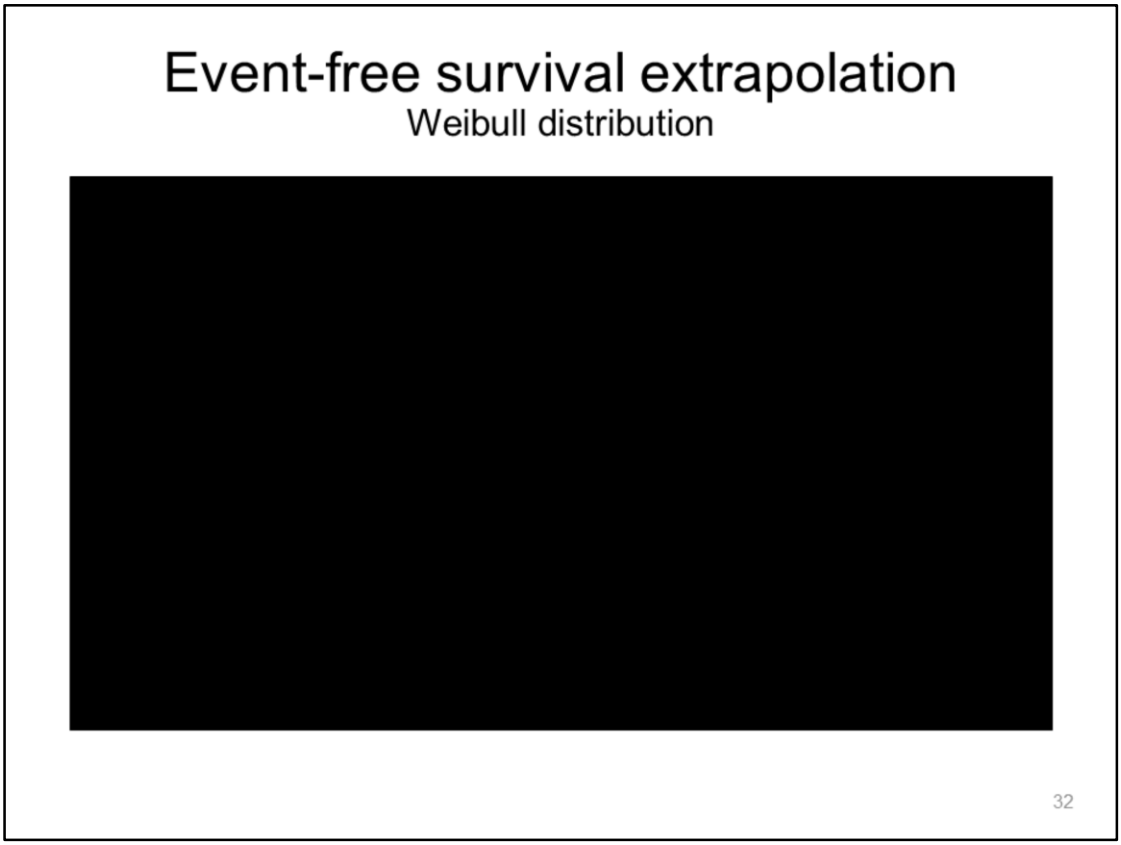
Overall survival extrapolation

- Cure model used in base case, assuming rate of death of general population after trial end (approx. 6.2 years), using mortality data from Office for National Statistics adjusted for age and sex

31

Source: company submission, section 5.3.2, figure 26

- Company explored range of non-parametric and parametric extrapolation methods
- Assessed distribution using visual fit to observed Kaplan-Meier, Akaike Information Criteria and Bayesian Information Criteria to assess statistical goodness of fit, and assessing plausibility of long-term extrapolation
- None provided reasonable extrapolation
- Clinical experts considered that patients still alive at the end of the trial period would typically experience same rate of death as general population, with a slightly higher risk of secondary cancers



Source: company submission, section 5.3.2, figure 27

- Time to complete response following trial cut-off was based on the extrapolated event-free survival curves
- Proportion of patients switching to subsequent therapy derived from subtracting both proportion of stem cell transplant uptake and mortality from extrapolated event-free survival curves
- Curve selection methods used for overall survival also applied to event-free survival
- Company state Weibull is conservative as complete response lost quicker using Weibull compared to log-logistic or gamma distributions

Company's model inputs (1)

Health-related quality of life

- Health-related quality of life data not collected in RATIFY so values from literature used in economic model

Utility state	Values used in base case (literature)	Values used in scenario analysis (TTO)	Source (literature values)
Induction treatment*	0.648	[redacted]	Uyl-de Groot _Br J Haematol_1998
Consolidation treatment*	0.710	[redacted]	Batty et al 2014
Monotherapy treatment*	0.810	[redacted]	Batty et al 2014
Complete remission post-first line (no relapse)	0.830	[redacted]	Leunis et al 2014
Relapse	0.530	[redacted]	Pan et al 2010

*Includes treatment disutility
TTO, time trade off

33

Source: company submission section 5.4, table 29
To note:
- Utility values from time trade off study used in scenario analysis
- Health-related quality of life varied among the different treatment phases but was assumed to remain constant within each phase
- Utility values were assumed to include the disutilities for toxicities during treatment

Company's model inputs (2)

Health-related quality of life

Utility state	Values used in base case (literature)	Values used in scenario analysis (TTO)	Source (literature values)
SCT Treatment *	0.613	[redacted]	Source for Algorithm - Crott et al 2010; Source of QLQC30 data – Grulke et al 2012
SCT Recovery	0.810	[redacted]	Source for Algorithm - Crott et al 2010; Source of QLQC30 data – Grulke et al 2012
Post-SCT Recovery	0.826	[redacted]	Source for Algorithm - Crott et al 2010; Source of QLQC30 data – Grulke et al 2012

*Includes treatment disutility
TTO, time trade off; SCT, stem cell transplantation

34

Source: company submission section 5.4, table 29
To note:
- Utility values from time trade off study used in scenario analysis
- Health-related quality of life varied among the different treatment phases but was assumed to remain constant within each phase
- Utility values were assumed to include the disutilities for toxicities during treatment

Costs and resource use

Cost	Source
Midostaurin	Data on file
Cytarabine Daunorubicin Secondary therapy	British National Formulary https://www.bnf.org/
Stem cell therapy Routine care Adverse events	National Schedule of Reference Costs (2014-1015). NHS Trusts and NHS Foundation Trusts
Mortality	Georghiou, Theo, and Martin Bardsley. "Exploring the cost of care at the end of life." Report, Nuffield Trust, London (2014).

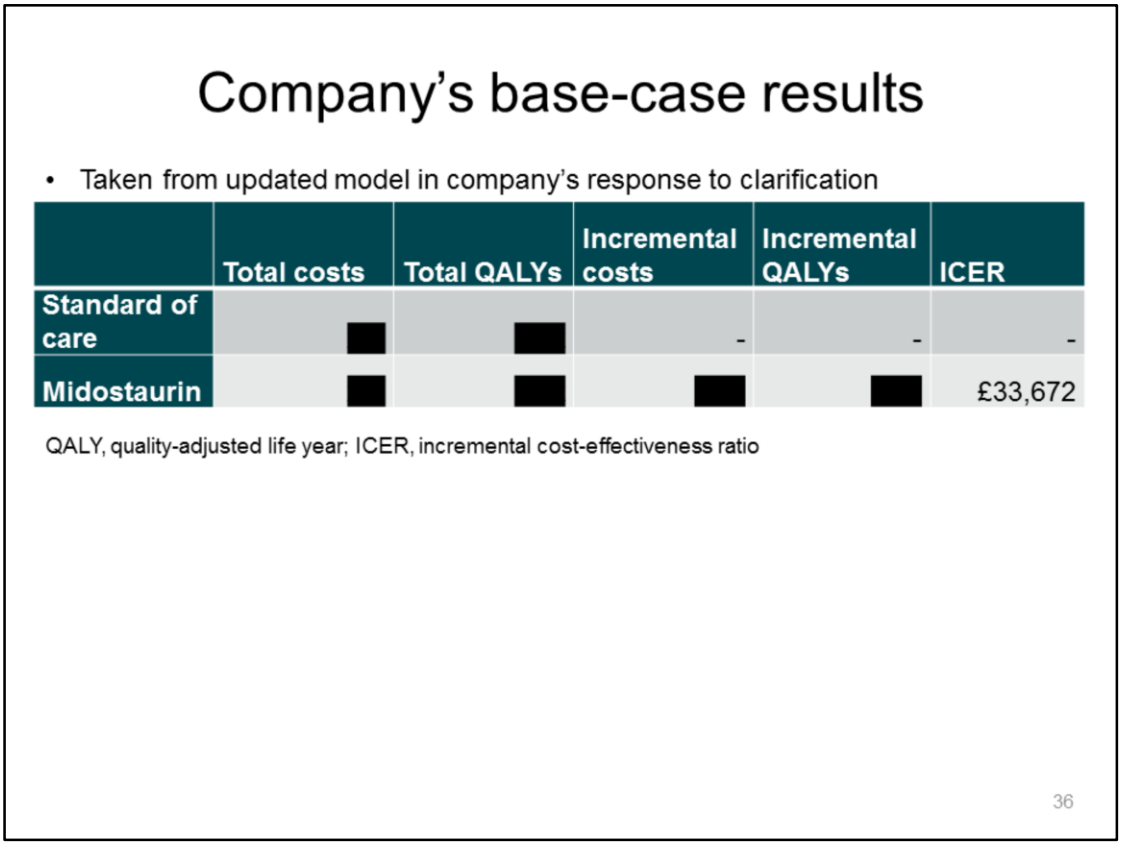
- Routine care use based on data used in TA399 azacitidine – includes administration costs for chemotherapies
- Patients could receive subsequent therapy (FLAG-IDA - clinical expert opinion) after primary therapy only if they had an event (including relapse or no complete remission) not related to mortality
  - Includes drug cost and routine care cost

35

Source: company submission section 5.5, table 31

To note

- Wastage included in costs of midostaurin
- FLAG-IDA: fludarabine, cytarabin, granulocyte-colony stimulating factor, idarubicin
- Costs of adverse events included grade 3/4 events with a prevalence ≥5% in any treatment phase
- Duration of SCT (cycles) based on estimates from clinical experts



Source: company's response to clarification, ERG report table 23

To note

- In response to clarification, company updated the model:
  - Implemented half-cycle correction
  - Weighted outcomes to account for patients being in different treatment phases at different time points in the model
  - Applied cycle transition formula to adverse event rates
  - Included drug monitoring tests and outpatient procedure costs

Costs included in the model

Costs in base case	Midostaurin	Standard of care	Difference
Induction	[redacted]	[redacted]	[redacted]
Consolidation	[redacted]	[redacted]	[redacted]
Maintenance	[redacted]	[redacted]	[redacted]
Secondary therapy	[redacted]	[redacted]	[redacted]
Adverse events induction	[redacted]	[redacted]	[redacted]
AE consolidation	[redacted]	[redacted]	[redacted]
AE maintenance	[redacted]	[redacted]	[redacted]
Routine care costs during treatment	[redacted]	[redacted]	[redacted]
Routine care costs after drug treatment	[redacted]	[redacted]	[redacted]
Stem cell transplant	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

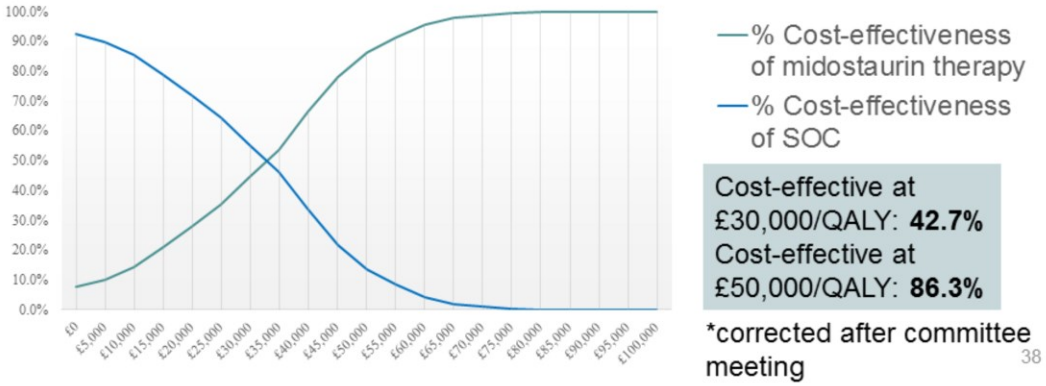
37

Source: company's response to clarification model

Company's probabilistic sensitivity analysis

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Standard of care (SOC)	[redacted]	[redacted]	-	-	-
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	£33,273* (-£5,780 to £58,254)

Cost-effectiveness acceptability curve

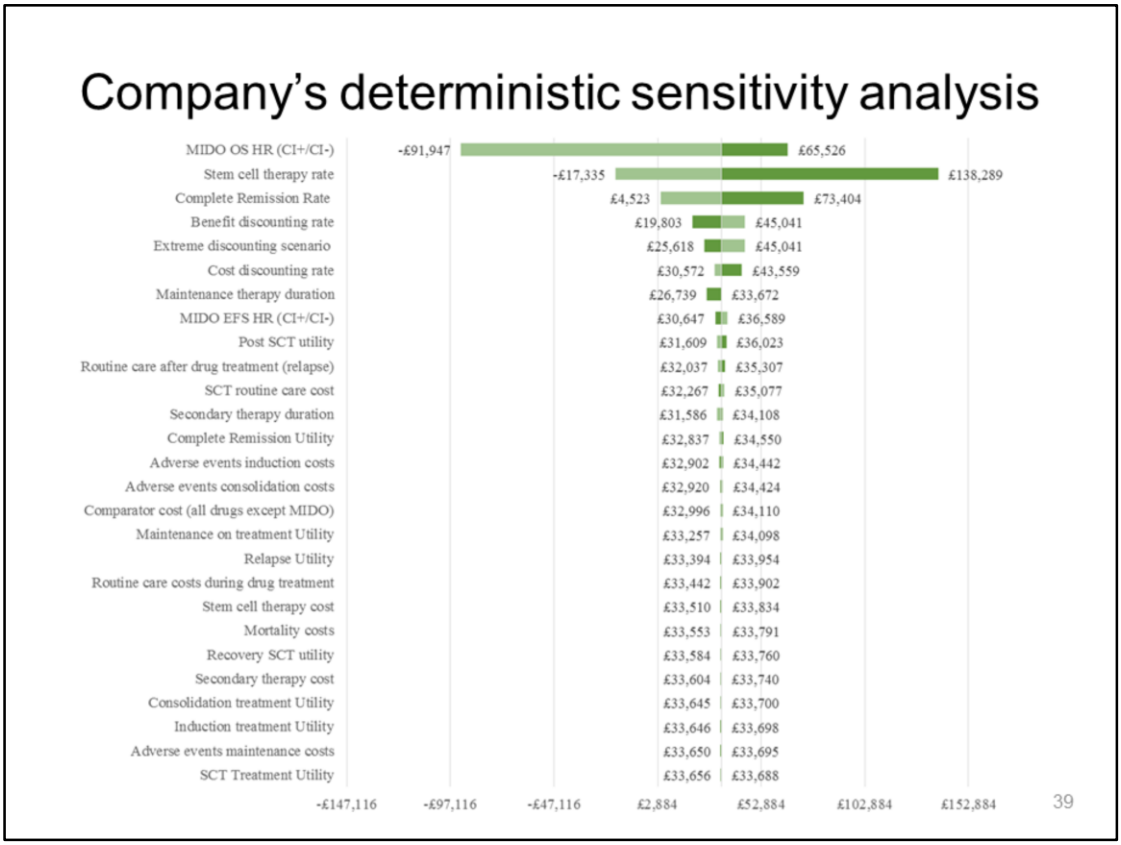


Cost-effective at £30,000/QALY: **42.7%**
Cost-effective at £50,000/QALY: **86.3%**

*corrected after committee meeting

38

Source: company's response to clarification, ERG report section 5.2.11.2



Source: company's response to clarification, ERG report figure 6

To note

- Results most sensitive to variations in stem cell transplant rate, midostaurin therapy overall survival hazard ratio, complete remission rate and discounting rates

Company's scenario analyses results

	Technique	Midostaurin vs SOC		
Scenarios		Inc. costs	Inc. QALYs	ICER
Base case		[redacted]	[redacted]	**£33,672**
Cure model	Individual parametric curves with Gompertz distribution	[redacted]	[redacted]	£22,042
	Piecewise model with last observation as extrapolation cut-off	[redacted]	[redacted]	Mido is dominant
	Cure model including adjustment for elderly	[redacted]	[redacted]	£26,225
Transition model	Using transition model after month 40 (transition based on patient level data)	[redacted]	[redacted]	£33,321
	Transition model with elderly adjustment	[redacted]	[redacted]	£38,599
Natural mortality rate	Standardised mortality ratio at 200% of the general population	[redacted]	[redacted]	£26,167
Utility	Utility values from the TTO study	[redacted]	[redacted]	£23,547
Time horizon	Trial horizon	[redacted]	[redacted]	£68,198
	10 years	[redacted]	[redacted]	£44,146

40

Source: company's response to clarification updated model, ERG report table 25

Company's additional scenario analyses

Presented in response to clarification

Scenario	Midostaurin vs Standard of care		
	Inc. costs	Inc. QALYs	ICER
Base case	[redacted]	[redacted]	**£33,672**
CR time to event data replaced with data on the proportion of patients in CR during trial follow-up	[redacted]	[redacted]	£26,507
SCT time to event curve replaced by a SCT time to event curve censored for both OS and relapse	[redacted]	[redacted]	£33,306
Relevant adverse events added	[redacted]	[redacted]	£36,339
Patients allowed to transition from relapse, SCT or CR to any of the other health states in the model	[redacted]	[redacted]	£42,109
Higher SMR (RR of 2.00) for long-term survival	[redacted]	[redacted]	£34,102
Cycle transition formula applied to AE rates	[redacted]	[redacted]	£33,905
Inclusion of elderly patients	[redacted]	[redacted]	£33,994
SCT costs based on NHS Blood and Transplant, 2014	[redacted]	[redacted]	£29,419
Reduced routine care costs in the long run (e.g., reduction of 50% after 26 cycles)	[redacted]	[redacted]	£31,791
Drug monitoring test and outpatient procedure costs included	[redacted]	[redacted]	£33,672

Inc, incremental; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; SMR, standardised mortality ratio; AE, adverse effects; SCT, stem cell transplantation

41

Source: company's response to clarification updated model, ERG report table 25

ERG's adjustments to company's base-case model

- ERG used later datacut from RATIFY as increase in patients observed at later part of Kaplan-Meier curve reduces uncertainty at base-case cure point, where overall survival differences are estimated
- Updated company model included new complete response data censored for SCT events – lacks face validity so ERG revert to original, uncensored complete response data

	ICER
Company's base case (response to clarification)	**£33,672**
1. Correction of errors and inconsistencies	£28,270
2. Use of 2016 data cut of RATIFY	£25,137
3. Use of original complete response data	£31,531
1, 2 and 3	£28,465

42

Source: ERG report section 6.2 and appendix 2

ERG's exploratory analyses

1a. Model structure - response to subsequent therapy

- Model doesn't accommodate response to subsequent therapy – patients remain in relapse state
- Sustained low health-related quality of life and high health care costs over a long time period
- ERG add new cured health state, where patients accrue same costs and QALYs as in CR 1L health state
- Scenario 3 used in ERG base case – see next slide

Scenario	Midostaurin vs standard of care		
	Inc. cost	Inc. QALY	ICER
Company base case* (corrected)	[redacted]	[redacted]	£28,465
1. Addition of cured health state	[redacted]	[redacted]	£30,821
2. Enter cured health state after 3 years	[redacted]	[redacted]	£36,555
3. Enter cured health state after discontinuing first-line treatment	[redacted]	[redacted]	£49,720

*All ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; QALY, quality adjusted life year

43

Source: ERG report section 5.2.1, 6.3.1.1

To note

- CR 1L: complete remission after discontinuation of primary therapy

ERG exploratory analyses

1b. Model structure - ongoing costs in CR 1L and post-stem cell transplant

- Health states CR 1L and SCT recovery are associated with ongoing costs of approximately £8,000 per annum
- ERG considers costs unjustified and inconsistent with previous TAs
- Company's response to clarification included scenario where routine care costs reduced by 50% after 26 cycles
- Scenario 3 used in ERG base case

Scenario	Midostaurin vs SOC		
	Inc. cost	Inc. QALY	ICER
Company base case* (corrected)	[redacted]	[redacted]	£28,465
1. Zero costs after cure point	[redacted]	[redacted]	£21,201
2. Zero costs after 3 years	[redacted]	[redacted]	£19,263
3. Zero costs after discontinuing first-line treatment	[redacted]	[redacted]	£16,772
ERG preferred model structure – both scenario 3s combined	[redacted]	[redacted]	**£39,720**

*All ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; QALY, quality adjusted life year; SOC, standard of care

Source: ERG report section 5.2.1, 6.3.1.2

ERG's exploratory analyses

2. Cure assumption

- Surviving patients assumed to be cured after cycle 80
- General population mortality rates applied after cure point
- ERG considers assumption is uncertain – studies have reported higher mortality rates than general population for survivors of acute myeloid leukaemia
- 4-fold increased risk used in ERG base case (most conservative)

Scenario	Midostaurin vs SOC		
	Inc. cost	Inc. QALY	ICER
Company base case* (corrected)	[redacted]	[redacted]	£28,465
4-fold increase in mortality risk	[redacted]	[redacted]	£28,899
9-fold increase in mortality risk	[redacted]	[redacted]	£29,205

*All ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; QALY, quality adjusted life year; SOC, standard of care

45

Source: ERG report, section 5.2.8, 6.3.2

To note:

- Mortality risk for people who had haematopoietic cell transplantation was reported in Martin et al. (2010)

ERG's exploratory analyses

3 and 4. Duration of treatment

- 3. Maximum number of cycles of monotherapy in model is 12, as in draft SPC for midostaurin – in RATIFY trial patients received up to 18 cycles
- 4. Total units of treatment received changed when model updated at clarification stage – ERG unsure why or which is correct, so explored impact of revisions in exploratory analysis

Scenario	Midostaurin vs SOC		
	Inc. cost	Inc. QALY	ICER
Company base case* (corrected)	[redacted]	[redacted]	£28,465
Up to 18 cycles of monotherapy permitted	[redacted]	[redacted]	£28,569
Reverting to original total units of treatment	[redacted]	[redacted]	£30,904

*All ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; QALY, quality adjusted life year; SOC, standard of care

46

Source: ERG report section 5.2.5, 6.3.3

ERG's exploratory analyses

5 and 6. Utility values

- 5. Utilities in CR 1L and post-stem cell transplant (SCT) recovery states were not adjusted for age – health-related quality of life in general population naturally declines with age
- 6. Disutilities and costs for adverse effect of SCT (graft versus host disease) were not included

Scenario	Midostaurin vs SOC		
	Inc. cost	Inc. QALY	ICER
Company base case* (corrected)	[redacted]	[redacted]	£28,465
Age-adjusted utilities applied	[redacted]	[redacted]	£30,354
Adverse effects of SCT applied	[redacted]	[redacted]	£30,869

*All ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio; Inc. incremental; QALY, quality adjusted life year; SOC, standard of care

47

Source: ERG report section 5.2.9, 6.3.4, 6.3.5

Summary of ERG's exploratory analyses and base case

Amendment	ICER	Cumulative ICER
Company's base case (response to clarification) - corrected by ERG	**£28,465**	**£28,465**
1. Using ERG's preferred model structure (new cured state on discontinuing first-line treatment, zero health state costs in CR 1L and post-SCT recovery states)	£39,720	£39,720
3. Maximum number of cycles of monotherapy increased to 18 (based on RATIFY)	£28,569	£39,835
5. Age-adjusted utilities applied	£30,354	£42,734
4. Units of treatment received based on company's original model (discrepancy corrected)	£30,904	£45,937
6. Adverse events associated with SCT applied	£30,869	£49,778
2. Applying 4 fold risk to general population mortality	£28,899	£62,810
1 to 6: ERG's base case	**£62,810**	**£62,810**

Table corrected after committee meeting

48

Source: ERG report section 6.3.1, ERG exploratory analyses document table 1
To note:
- Scenario 1 from table 33 in ERG report – scenario 3 from slides 43 and 44

ERG's exploratory analyses applied to ERG's preferred model structure

Amendment	ICER
Company's base case (response to clarification) - corrected by ERG	**£28,465**
Amendment 1. Using ERG's preferred model structure (new cured state on discontinuing first-line treatment, zero health state costs in CR 1L and post-SCT recovery states)	£39,720
Amendment 1 **and** 2. Applying 4 fold risk to general population mortality	£51,163
Amendment 1 **and** 3. Maximum number of cycles of monotherapy increased to 18 (based on RATIFY)	£39,835
Amendment 1 **and** 4. Units of treatment received based on company's original model (discrepancy corrected)	£42,694
Amendment 1 **and** 5. Age-adjusted utilities applied	£42,611
Amendment 1 **and** 6. Adverse events associated with SCT applied	£43,107
1 to 6: ERG's base case	**£62,810**

Table corrected after committee meeting

49

Source: ERG report section 6.3.1, ERG exploratory analyses document table 2

ERG further comments on cost effectiveness model (1)

Issue	Comments
Relapse after stem cell transplant (SCT)	• Literature suggests 25-40% of patients experience relapse after SCT – not possible in model • Resulting lower health-related quality of life and health care and drug costs not taken into account in model • Lack of data so issue cannot be explored further
Rate of stem cell transplant	• In model, higher rate of SCT in midostaurin group attributed only to primary therapy – leads to additional QALYs due to improved prognosis after SCT • Not clear in RATIFY that midostaurin increases rate of SCT so in practice, the increase in OS benefits may not be realised if due to SCT rather than midostaurin • Due to model structure, issue cannot be explored further
Extrapolation of complete remission	• Weibull distribution fitted to tail of Kaplan-Meier curve • ERG finds problematic, but considers extrapolation unnecessary if assuming cure after 80 cycles • Issue not explored further

50

Source: ERG report section 5.2.1

ERG further comments on cost effectiveness model (2)

Issue	Comments
Mortality beyond trial follow up	• Choice of cure point important as survival gains at this point are extrapolated over lifetime • ERG explores alternative cure points (see next slide)
Utility values	• Company did not justify why sources of utility values were chosen when other sources were available • ERG explores alternative sources (see next slide)
Population	• Population in RATIFY may be younger than population eligible for midostaurin in practice • Company's scenario analysis not accepted by ERG – assumption that complete remission, stem cell transplant and overall survival before cycle 80 would be same for younger and older patients is not justified by data • ERG presents additional scenario analysis (next slide)

51

Source: ERG report section 5.2.1, 5.2.4, 5.2.8.2, 6.5.1

ERG's base case - further exploratory analyses

Amendment	ICER
ERG's preferred base case	**£62,810**
Alternative cure point	
• At 4 years	£70,160
• At 5 years	£64,207
• At 7 years	£84,161
Alternative assumptions of utility values for CR 1L and SCT post-recovery health states	
• Kurosawa 2014 (pessimistic assumption)	£66,429
• Novartis time trade off study (optimistic assumption)	£53,718
Mean age of population on entry to trial (base case 45 years)	
• 50 years	£70,513
• 55 years	£80,325
• 60 years	£92,619

52

Source: ERG report section 6.5

To note:

- Observed difference in overall survival is larger at 80 cycles (6.2 years) than alternative cure points considered, so alternatives increase ICER
- Increasing mean age increases the ICER because it reduces the benefits of cure due to reduced life expectancy in older patients (treatment efficacy not changed)

Company's additional evidence

Age adjustment in model

6a

- Younger population: Overall survival data based on intention-to-treat population from RATIFY, using initial cure model
- Older population: Overall survival data from historical comparison, extrapolated with cure model – average age at baseline considered to be 65 (45 used in initial model)

Pooled Kaplan-Meier:

- Weight of 59% applied to older population
- Weight of 41% applied to younger population

6b Model adjusted to assume mean age of patients receiving midostaurin is 65

53

Source: company's submission addendum

To note

- Only overall survival data used in model is changed – all other clinical data sourced from RATIFY as in original base case.

Company's additional evidence

New base case

6

	ICER
Previous base-case ICER (Clarification response)	**£33,672**
Using initial complete response data (uncensored for stem cell transplant)*	£18,712
Total unit of treatment as in original submission*	£19,820
Include graft versus host disease complications from stem cell transplant‡*	£21,548
Stem cell transplant costs from NHS blood and transplant 2014‡	£17,398
Routine care costs: 50% reduction after 26 cycles‡	£25,503
Updated overall survival data cut (extracted using digitalisation)*	£13,588
Age-related adjustment (based on new historical comparison) **- company's new base case including all adjustments**	**£27,754**

*Assumption consistent with ERG base case
‡Previously a company scenario analysis

54

Source: company's submission addendum

ERG comments on company's revised base case

Model changes	• ERG unsure why company has adopted some changes from ERG base case and not others, and why some previous scenario analyses are now incorporated in the base case
	  • ERG's corrections of calculation error not included
	  • NHS blood and transplant used for stem cell transplant costs, although company previously stated preference for NHS reference costs – ERG agreed and used NHS reference costs in base case

Age adjustment	• Response/relapse, rate of stem cell transplant and time on treatment likely to be different between younger and older patients – only overall survival adjusted for >> significant uncertainty in results of analysis • Proportion of older patients based on incidence of AML in patients over 60 – likely to overestimate proportion of older patients who would be eligible for treatment with midostaurin • Mean age of cohort used to determine mortality of patients after cure point – company assume mean age is 65. ERG estimates mean age is 56.8 >> reducing mean age reduces ICER

Overall: likely that new OS data in the model overestimates benefits of midostaurin.

55

ERG addendum section 2.6.1, 2.6.2

Incorporating company's age adjustment into ERG base case

- When age adjustment made to company's base case, ICER increases
- In ERG base case, ICER decreases

	Midostaurin vs standard of care		
Scenarios	Inc. cost	Inc. QALY	ICER
Company revised base case without age related adjustment	[redacted]	[redacted]	£13,588
Company revised base case (with age related adjustment: mean age 57)	[redacted]	[redacted]	£24,001
Company revised base case (with age related adjustment: mean age 65)	[redacted]	[redacted]	**£27,754**
ERG's preferred base case (without age related adjustment)	[redacted]	[redacted]	£62,810
ERG's preferred base case (with new adjustment: mean age 57)	[redacted]	[redacted]	£35,999
ERG's preferred base case (with new adjustment: mean age 65)	[redacted]	[redacted]	£45,060

56

Source: ERG addendum table 5

End of life considerations

Criterion	Data source	Indication	Age	Overall survival	
				Median (months)	Mean (months)
Short life expectancy, normally < 24 months	Maynadie (2013)	AML	15-70+	9.1	18
	Recher (2014)	AML	15-60	33	45
	Ohtake (2011)	AML	15-64	53	46
	Mandelli (2009)	AML	15-60	17	41
	Stone (2015) - RATIFY April 2015 cut off	FLT3+ve AML	18-60	26	[redacted]
	Company submission - RATIFY Sept 2016 cut off	FLT3+ve AML	18-60	[redacted]	[redacted]
Extension to life, normally of a mean value of ≥ 3 months				Increase with midostaurin (months)	
				Median	Mean
	RATIFY trial			49	[redacted]

ERG question relevance of Maynadie (2013) as data from 1995-2002 cancer registry. ERG reconstructed individual patient-level data using Kaplan-Meier graphs (except median overall survival in RATIFY trial) so figures may not be exact

57

Source: company's submission table 23, ERG report table 43

To note

- FLT3 positive AML have lower median OS than general AML population
- Older patients with AML may have a lower life expectancy
- Treatment benefit may not be as great if population treated in practice is older

Innovation and equality

- Company considers midostaurin to be innovative:
  - Induction therapy for people newly-diagnosed with FLT3-positive acute myeloid leukaemia has not changed substantially in past 30 years
  - Midostaurin is first targeted therapy and first tyrosine kinase inhibitor therapy for newly-diagnosed FLT3-positive acute myeloid leukaemia
  - Mode of action of inhibiting FLT3 activity is innovative
  - Offers a bridge to potentially curative stem cell transplant
  - Oral therapy that requires no additional hospital visits when used with standard-of-care therapy

- Age is highlighted as a potential equality issue, as the trial only recruited people up to 60 years
  - NICE will appraise midostaurin in line with the marketing authorisation, which does not have restrictions by age. Any recommendations will not make it more difficult to access midostaurin based on age compared with other groups.

58

Key issues – cost effectiveness

- Is the model structure appropriate for decision-making?
- Should response to subsequent therapy (including stem cell transplant) be incorporated into the model?
- What long-term routine care costs should be included in the CR-1L (complete remission after first-line treatment discontinuation) and stem cell transplant recovery health states?
- What increase in mortality risk should be assumed after the cure point for patients with AML compared to the general population?
- Should utility values be adjusted for age?
- Should disutilities for adverse effects of stem cell transplant be included?
- What is the most plausible cure point?
- Is it appropriate to extrapolate the cost-effectiveness results to an older population?
- Are the end-of-life criteria met?
- Is midostaurin an innovative treatment?

59

Authors

- **Kirsty Pitt**
  Technical Lead
- **Sally Doss**
  Technical Adviser
- with input from the Lead Team (Derek Ward, Stephen O'Brien and David Chandler)

60

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Midostaurin for newly diagnosed acute myeloid leukaemia [ID894]

Company evidence submission

2 March 2017

File name	Version	Contains confidential information	Date
Midostaurin manufacturer's submission ID894ACIC_2-Mar-17.docx	**Final**	**Yes/no**	**2.3.17**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

Tables and figures

List of tables

List of figures

Abbreviations

AD	cytarabine and daunorubicin
AE	adverse events
AIC	akaike information criteria
AKT/PI3	protein kinase B/phosphatidylinositol-3-kinase
alloSTC	allogeneic STC
AML	acute myeloid leukaemia
ANC	absolute neutrophil count
AZA	azacitidine
BIC	Bayesian Information Criteria
BID	twice daily
BNF	British national formulary
BSA	body surface area
BSC	best supportive care
CCR	conventional care
CCRs	conventional chemotherapy regimens
CEA	cost-effectiveness analysis
CLL	chronic lymphocytic leukaemia
CML	chronic myeloid leukaemia
CMML	chronic myelomonocytic leukemia
CR	complete remission
CSR	clinical study report
DC	dendritic cell
DEC	decitabine
DEL5Q	deletion 5Q
DFS	disease-free survival
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
ELN	European Leukaemia Network
EMA	European Medicines Agency
EORTC	European organization for research and treatment of cancer
EQ5D	Euro-QoL 5D
ERG	Evidence Review Group
FAS	full analysis set
FGFr 1-3	Fibroblast growth factor receptor
FLAG-IDA	Fludarabine Arabinofuranosyl cytidine Granulocyte colony stimulating factor IDArubicin
FLT3	FMS-like tyrosine kinase 3
GM-CSF	granulocyte-macrophage colony-stimulating factor

GP	general practitioner
GVHD	graft-versus-host disease
HCRU	health-care resource use
HCT	hematopoietic stem cell transplantation
HIDAC	high-dose cytarabine
HMA	hypomethylating agent
HR	hazard ratio
HRG	healthcare resource group
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplant
ICER	incremental cost-effectiveness ratio
ICT	induction and consolidation chemotherapy
ITD	internal tandem duplication
IV	intravenous
LDC	low-dose chemotherapy
LYs	life-years
MAP	mitogen-activated protein
MDS	myelosdysplastic syndrome
NE	not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOS	not otherwise specified
ONS	Office for National Statistics
OS	overall survival
PE	point estimate
PKC	protein kinase C
post-1L	post first-line therapy
PPS	per protocol set
PR	partial remission
PSA	probabilistic sensitivity analysis
PSS	personal social services
PSSRU	personal social services research unit
QALY	quality-adjusted life-year
QLQ-C30	quality of life questionnaire-C30
RBC	red blood cell
RCT	randomised controlled trial
RFS	relapse-free survival
RTK	receptor tyrosine kinases
SAE	serious adverse event
SCT	stem cell transplantation

SD	standard deviation
SDC	standard dose chemotherapy
SOC	standard of care
STA	single technology appraisal
STAT5	signal transducer and activator of transcription 5
TFI	treatment-free intervals
TKD	tyrosine kinase domain
TKI	tyrosine kinase inhibitor
TTO	time trade-off
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
WHO	World Health Organization

1 Executive summary

AML is the most common acute leukaemia in adults and has the lowest survival rate of all adult leukaemia's, with FMS-like tyrosine kinase 3 (FLT3) mutation conferring an even poorer prognosis. FLT3 mutation-positive acute myeloid leukaemia (AML) is an aggressive haematological malignancy associated with a median overall survival (OS) of less than 12 months with current standard treatments. Midostaurin, an oral, tyrosine kinase inhibitor that targets FLT3 and other receptor tyrosine kinases, represents a breakthrough for the treatment of newly diagnosed FLT3 mutation-positive AML.

As demonstrated conclusively in the largest international, multicentre, phase 3, randomized, double-blind, placebo-controlled trial, in FLT3 +ve AML patients, midostaurin is the first targeted therapy that significantly improves OS versus standard-of-care chemotherapy alone. Midostaurin in combination with standard chemotherapy followed by midostaurin monotherapy significantly extended median OS by approximately 4 years and prolonged the duration of remission from 22 to 61 months over standard-of-care chemotherapy. These efficacy gains were achieved without a significant increase in the overall incidence of grade 3/4 AEs or serious AEs and few patients discontinued therapy.

Midostaurin meets the NICE end of life criteria and is a cost-effective treatment for newly-diagnosed patients with FLT3 mutation-positive AML, having an ICER of £34,327 per QALY over standard-of-care chemotherapy. Probability sensitivity analysis indicates that midostaurin in combination with chemotherapy plus midostaurin monotherapy has an ICER of £31,550 per QALY over standard-of-care, with a 39.2% probability of being cost-effective at a threshold of £30,000 per QALY and a 97.3% probability at a threshold of £50,000 per QALY. Midostaurin thus represents a new paradigm in the management of FLT3 mutation-positive AML and is the first breakthrough in the management of AML achieved in the last 30 years.

Acute myeloid leukaemia (AML) is an aggressive haematological malignancy and is considered a clinical emergency.[1,2]

- Estimates of 5-year overall survival (OS) for patients with newly diagnosed AML in the UK range from 12–27% overall and may be as low as 5% in individuals aged 65 years or older.[3,4] An analysis of registry data for 20 European countries estimated median OS in 2000–2002 to be approximately 10 months and reported a lower estimated 5-year OS for patients in the UK compared with data for Europe as a whole (12% vs. 17%).[4]
- Patients with mutations in the FMS-like tyrosine kinase 3 (FLT3) gene, noted in around 30% of all AMLs[5,6], have a particularly aggressive form of the disease with inferior OS and duration of remission.[7] An analysis of data for a UK cohort (median age, 43 years) reported a 5-year OS of 15–31% among patients with FLT3 mutations compared with 42% among those without such mutations.[7]
- Taken together, these data suggest that median OS for patients with newly diagnosed FLT3 mutation-positive AML is less than 12 months with current standard treatments.

There have been no significant advances in the management of AML in recent decades despite efforts to find new treatments conferring improved OS.[8]

- Current guidelines recommend the use of intensive induction chemotherapy in fit patients able to tolerate such therapy and use of less intensive therapy for less fit patients.[9] In the UK, induction therapy generally comprises an anthracycline (most frequently daunorubicin) and cytarabine; patients who achieve a complete remission (CR) then receive consolidation chemotherapy (usually high-dose cytarabine) and possibly undergo allogeneic stem cell transplantation (SCT).[10-12]
- SCT is associated with significant mortality and morbidity. As a result, SCT is particularly recommended for intermediate- and high-risk patients, such as patients with FLT3 mutation-positive disease, because of the high risk of disease recurrence in these patients.[11,12] For favourable-risk patients, consolidation chemotherapy is preferred over SCT as the lower risk of recurrence makes the mortality risk associated with SCT less justifiable.

There is thus a need for better treatments that can induce long-term remissions and prolong OS in patients with intermediate- and high-risk disease, such as those with FLT3 mutation-positive AML.

1.1 Statement of decision problem

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
Population	People with newly diagnosed, FLT3 mutation-positive acute myeloid leukaemia	People with newly diagnosed, FLT3 mutation-positive acute myeloid leukaemia	
Intervention	Midostaurin in combination with standard induction and consolidation chemotherapy followed by single-agent maintenance therapy	Midostaurin in combination with established chemotherapy followed by midostaurin monotherapy	
Comparator (s)	Established clinical management without midostaurin	Same as final scope issued by NICE	
Outcomes	The outcome measures to be considered include: • overall survival • event-free survival • disease-free survival • adverse effects of treatment • health-related quality of life	Same as final scope issued by NICE except for omission of health-related quality of life which was not assessed in the clinical trials	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	In line with NICE reference case	

	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The use of midostaurin is conditional on the presence of FLT3 mutation. The economic modelling should include the costs associated with diagnostic testing for FLT3 mutation in people with acute myeloid leukaemia who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		
Subgroups to be considered	No subgroups mentioned	Same as final scope issued by NICE	
Special considerations including issues related to equity or equality			

1.2 Description of the technology being appraised

Midostaurin represents a new paradigm for the treatment of newly diagnosed FLT3 mutation-positive AML and is the first targeted therapy that significantly improves OS versus standard-of-care chemotherapy.[13]

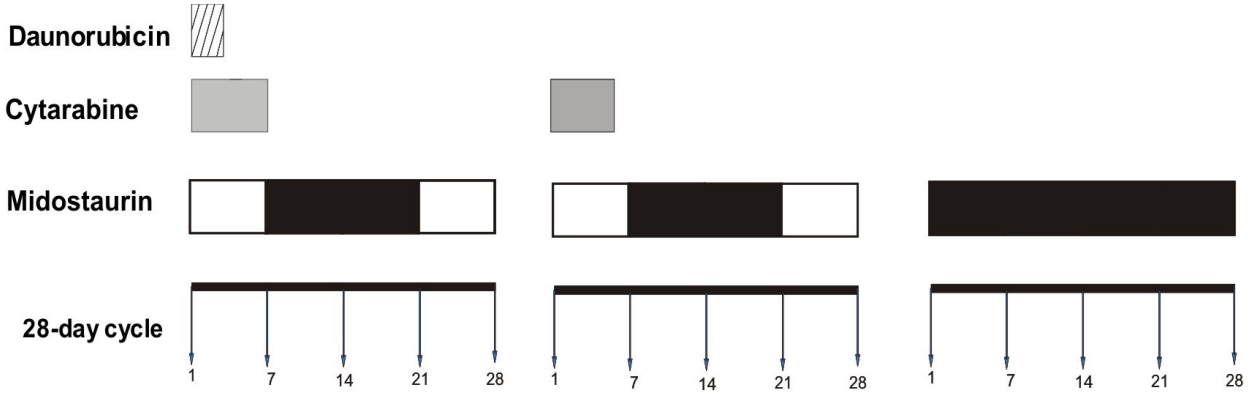
- Midostaurin is an oral, type III, multi-target receptor tyrosine kinase inhibitor (TKI) with antiproliferative activity.
- It inhibits FLT3 and other receptor tyrosine kinases (RTKs) leading to inhibition of cell signalling. This in turn leads to cell cycle arrest and apoptosis in leukaemic cells overexpressing wild-type FLT3 receptors.[14,15]

Midostaurin is given in combination with chemotherapy followed by midostaurin monotherapy for up to a year post-combination therapy (Table 1).

- It is anticipated midostaurin will be indicated for treatment of adult patients with newly diagnosed AML who are FLT3 mutation-positive.

- Being an oral therapy, midostaurin is convenient for patients to administer and requires no additional hospital visits over and above those required for standard-of-care therapy.
- Midostaurin is taken orally twice daily on days 8–21 of 28-day induction and consolidation chemotherapy cycles, and twice daily as single-agent therapy for up to 12 months following combination treatment (Figure 1).[14]

Figure 1 Dosing schedule for treatment with midostaurin in RATIFY



Induction therapy, given for 1–2 cycles, consists of daunorubicin plus cytarabine plus midostaurin.
Consolidation therapy, given for up to 4 cycles, consists of cytarabine plus midostaurin.
Midostaurin monotherapy is given for up to 12 months.

Table 1 Technology being appraised

UK approved name and brand name	Approved name: Midostaurin (PKC412)[14] Brand name: Rydapt®[14]
Marketing authorisation/CE mark status	Midostaurin does not currently have UK marketing authorisation and does not have regulatory approval outside the UK Anticipated UK launch: October/November 2017
Indications and any restriction(s) as described in the summary of product characteristics	A marketing authorisation application for midostaurin, for use in combination with standard induction and consolidation chemotherapy, followed by use as monotherapy, as treatment for adult patients with newly diagnosed AML who are FLT3 mutation-positive, was submitted to the EMA in July 2016.
Method of administration and dosage	Oral: 50 mg twice daily, with each 50 mg dose being administered as 2 x 25 mg soft gel capsules on days 8–21 of 28-day induction and consolidation chemotherapy cycles, and twice daily as monotherapy for up to 12 months following consolidation.[14] Dose-interruption is permitted to manage treatment-related adverse events.

1.3 Summary of the clinical effectiveness analysis

Midostaurin represents a clinically significant advance in the management of newly diagnosed AML, being the first therapy demonstrated to significantly prolong OS in recent decades. Results of the international, multicentre, phase 3, randomized, double-blind, placebo-controlled trial, RATIFY,

(n=717) have shown that, in patients with FLT3 mutation-positive AML, added to chemotherapy, midostaurin:[13,16]

- Significantly reduced the risk of death by approximately 23% (HR 0.77 [95% CI 0.63–0.95]; p=0.0078), prolonging median OS from 25.6 months (95% CI 18.6–42.9) for placebo to 74.7 months (95% CI 31.5–not estimable [NE]) for midostaurin
- Significantly prolonged event-free survival (EFS) from 3 months (95% CI 1.9–5.9) for placebo to 8.2 months (95% CI 5.4–10.7) [HR of 0.78 (95% CI 0.66–0.93); p=0.002]
- Significantly prolonged disease-free survival (DFS) from 15.5 months [95% CI 11.3–23.5) to 26.7 months (95% CI 19.4–NE),
- Significantly prolonged the duration of remission from [redacted] and
- Increased treatment-free interval (TFI) by [redacted] months ([redacted] months to [redacted] months).

Sensitivity analyses indicated that the improvements in OS, EFS and DFS were robust to censoring of patients who underwent SCT and use of an alternative definition for complete remission (CR). Subgroup analyses indicated that the improvements in OS and EFS achieved with midostaurin were generally consistent across all subgroups considered.

The benefits of midostaurin added to standard chemotherapy are further confirmed in the results of an ongoing single-arm phase 2 study, which is assessing midostaurin in combination with chemotherapy (induction chemotherapy followed by consolidation chemotherapy or SCT) followed by midostaurin monotherapy.

- Results for the initial analysis involving 145 patients showed a statistically significant improvement in relapse-free survival compared with historical controls, both in patients aged 18–<60 years and those aged 60–70 years.[17]
- A further analysis involving 284 patients showed that at a median follow-up of 19 months, there was [redacted] difference in OS between younger and older patients.[18]
- The results of this study thus confirm the benefits for the addition of midostaurin to chemotherapy and indicate that these are seen both in younger and older patients who are fit enough to undergo intensive chemotherapy.

Taken together, the results from these two trials provided robust evidence for the benefits of midostaurin in the management of newly diagnosed FLT3-mutated AML patients.

- The addition of midostaurin to current standard-of-care chemotherapy thus represents a new paradigm in the management of FLT3 mutation-positive AML, significantly prolonging OS by approximately 4 years, as well as extending the median duration of remission by over [redacted].
- Extending the duration of remission can be expected to improve HRQoL for patients and reduce the burden on caregivers.

1.3.1 Safety

Midostaurin added to standard chemotherapy is generally well tolerated and does not significantly increase the overall incidence of grade 3/4 AEs or SAEs.[17-20]

- In RATIFY, AEs were generally manageable with few patients in either group withdrawing from therapy due to grade 3/4 AEs (midostaurin, 6.1%; placebo, 4.5%).[13,16]
- The median dose intensity was 95% for midostaurin, indicating few patients required dose adjustments or treatment interruptions.
- The median relative dose intensity for daunorubicin and cytarabine was [redacted] for both induction and consolidation therapy, indicating that midostaurin did not compromise the chemotherapy dose that could be given.
- The incidence of grade 3/4 AEs was similar for both treatment groups, both overall and for each phase of treatment.
- In particular, the incidence of grade 3/4 AEs during chemotherapy (induction and consolidation) was approximately 100% in both treatment groups, whereas during midostaurin monotherapy the incidence of grade 3/4 AEs was 42% compared with 47% in the placebo group.
- The incidence of on-treatment deaths was 4.3% for the midostaurin group compared with 6.3% in the placebo group.

AEs observed in RATIFY corresponded to the safety profile associated with standard chemotherapy with the addition of midostaurin having minimal impact on the overall safety profile.

- The most commonly observed AEs during induction and consolidation treatment in RATIFY in both treatment groups were haematological (≥89% of patients reported grade 3/4 thrombocytopenia, anaemia and neutropenia AEs in both treatment groups),
- The most frequently reported grade 3/4 non-haematological AEs (> 10%) were device-related infection, diarrhoea, rash, hypokalaemia, pneumonia and elevated alanine aminotransferase (ALT), and the incidence was similar in both treatment groups.
- Neutropenia (incidence, 8.3%) was the only grade 3/4 AE reported in >5% of patients during midostaurin monotherapy and compared with an incidence of 9% in the placebo group, further indicating that midostaurin is generally well tolerated and adds little to the toxicities associated with standard chemotherapy.

Results for the phase 2 study were in general consistent with those from RATIFY.

- Haematological events were the most frequently reported grade 3/4 treatment-related AEs.[17-20] The only other grade 3/4 AEs reported in >10% of patients were febrile neutropenia (24%) and nausea (12%). Most non-haematological AEs were grade 1/2 in severity.
- This study involved patients aged 18–70 years and compared the safety profile for younger (<60 years) and older (≥60 years) patients. The safety profile was generally similar in both

subgroups although more of the older patients died on study [redacted] and discontinued midostaurin therapy due to AEs ([redacted]).[19]

- Overall approximately [redacted] of patients withdrew from midostaurin therapy due to AEs and [redacted] patients died during study treatment.

Results from this study suggest that the addition of midostaurin to standard induction and consolidation therapy together with use as monotherapy is as feasible in fit elderly patients as for younger patients.

1.3.2 Conclusions

- Results from the phase 3 RATIFY study, supported by those of the phase 2 study, demonstrate that the addition of midostaurin to current standard-of-care chemotherapy significantly improves outcomes for patients with FLT3 mutation-positive AML.
- For a disease generally associated with a median OS of less than 12 months in routine clinical practice in the UK, midostaurin in combination with chemotherapy followed by midostaurin monotherapy provided a statistically and clinically meaningful prolongation of OS of approximately 4 years in RATIFY.
- Patients included in RATIFY were younger than those routinely diagnosed with AML in the UK, as reflected in the median OS of 26 months in the placebo group. Despite this, midostaurin is expected to provide clinically meaningful prolongation of OS of at least 3 months in patients with FLT3 mutation positive AML in routine clinical practice.
- Thus midostaurin for the management of FLT3 mutation-positive AML meets the NICE end of life criteria.

1.4 Summary of the cost-effectiveness analysis

A cost-effectiveness analysis performed based on data from RATIFY from the perspective of the NHS has demonstrated that midostaurin in combination with chemotherapy followed by midostaurin monotherapy is a cost-effective treatment for newly diagnosed patients with FLT3 mutation-positive AML.

- According to the base-case analysis, midostaurin provides a gain of [redacted] life years (LYs) and [redacted] quality-adjusted life years (QALY) over standard chemotherapy at an additional cost of [redacted], resulting in incremental cost-effectiveness ratios (ICERs) of £30,263 per LYs and £34,327 per QALY (Table 2).
- Additional costs largely reflect an increase in drug costs and costs for SCT, and are partially off-set by a reduction in costs for routine care after drug treatment and in mortality costs.
- Probability sensitivity analysis (PSA) indicates that the probability of midostaurin in combination with chemotherapy plus midostaurin monotherapy being cost-effective is approximately 39.2% at a threshold of £30,000 and 97.3% at a threshold of £50,000.
- Results of deterministic sensitivity analysis indicate that ICER is robust to changes in most parameters considered and that the ICER is most sensitive to variations in stem cell therapy

rate, variations in the midostaurin overall survival hazard ratio, difference in CR rate, and discounting rates.

- Scenario analysis indicated that the ICER is particularly sensitive to variations in the time horizon used.
- A budget impact analysis estimates that the introduction of midostaurin for the treatment of FLT3 mutation-positive AML in newly diagnosed patients is expected to be approximately £16M over the 5 year period. This figure is the maximum budget impact as UK clinical expert feedback states that midostaurin will be used in the UK as part of clinical trials as a comparator to novel agents. Thus as many as 75–50% of the biologically appropriate patients used for this budget impact calculations may not in fact be prescribed midostaurin.
- This is based on consideration of the direct drug and administration costs and does not take into account any savings made as a result of reduced severity or number of AEs, or potential savings resulting from a reduced need for other medical care required after the introduction of midostaurin (e.g. hospitalizations avoided).

Table 2 Incremental cost-effectiveness results

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (A)	Incremental analysis
Chemotherapy	[redacted]	8.93	6.32					
Midostaurin plus chemotherapy followed by midostaurin monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,327	

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

2 The technology

2.1 Description of the technology

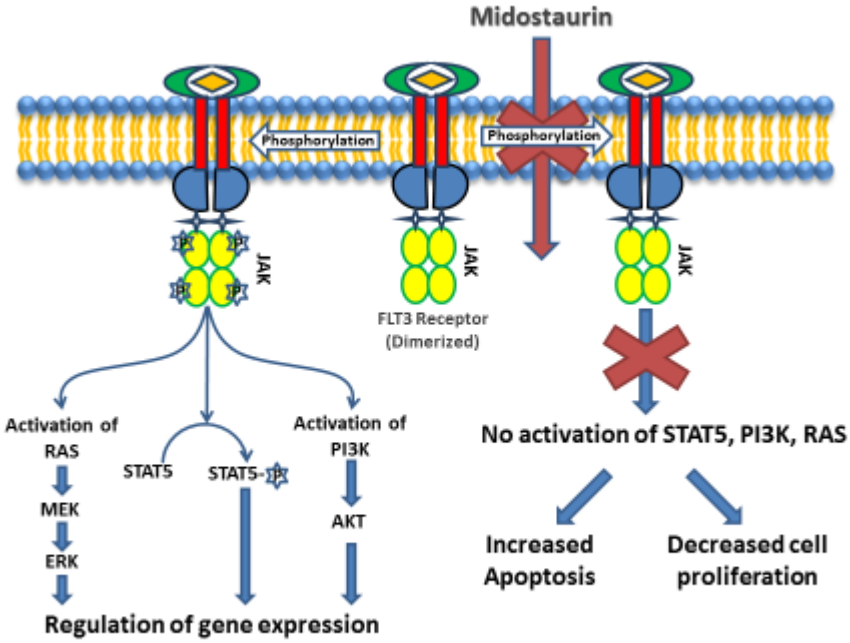
- Brand name: Rydapt®[14]
- Approved name: Midostaurin (PKC412)[14]
- Pharmacotherapeutic group: Protein kinase inhibitors[14]

Midostaurin is a potent multi-targeted receptor tyrosine kinase inhibitor

Midostaurin is an oral, type III, multi-target receptor tyrosine kinase inhibitor (TKI) with antiproliferative activity. The actions of midostaurin include the inhibition of FMS-like tyrosine kinase 3 (FLT3) and multiple other receptor tyrosine kinases (RTKs), including fibroblast growth factor receptor 1-3 (FGFr 1-3), KIT and vascular endothelial growth factor receptor (VEGFR2).[14,15] Specifically, midostaurin effects its inhibitory actions by competing with adenosine triphosphate for binding to the active pocket of these RTKs, resulting in the inability of the target kinase to phosphorylate substrate proteins.[21]

Through its multi-antikinase activity, midostaurin exhibits antiproliferative activity in a number of cancer cell lines and xenografts, and the inhibition of FLT3 by midostaurin contributes substantially towards growth-inhibitory effects in myeloid cells.[15] By inhibiting the catalytic domain of key kinases, midostaurin interferes with mitogenic signalling and causes cell growth arrest at clinically achievable doses (Figure 2).[14] Importantly, midostaurin inhibits FLT3-receptor signalling in leukaemic cells that express FLT3 internal tandem duplication (ITD) or tyrosine kinase domain (TKD) mutant receptors, leading to cell cycle arrest and apoptosis. Midostaurin has also been shown to induce cell growth arrest in leukaemic cells overexpressing wild-type FLT3 receptors.[14] Additional actions of midostaurin that contribute to its antiproliferative activity include inhibition of aberrant signalling of KIT, as well as inhibition of fibroblast growth factor receptor, VEGFR2, and members of the serine/threonine kinase family protein kinase C (PKC). In FLT3-ITD-expressing acute myeloid leukaemia (AML) cell lines, midostaurin in combination with chemotherapeutic agents displays synergistic growth inhibition.[14]

Figure 2 Mechanism of action of midostaurin



ERK1/2, extracellular signal-regulated kinases 1/2; FLT3, FMS-like tyrosine kinase 3; MEK, mitogen-activated protein kinase; STAT5, signal transducer and activator of transcription 5.

2.2 *Marketing authorisation/CE marking and health technology assessment*

Midostaurin does not currently have UK marketing authorisation and does not have regulatory approval outside the UK. Midostaurin was granted orphan status for the treatment of acute AML by the European Medicines Agency (EMA) in 2004, and by the US Food and Drug Administration in 2009.

A marketing authorisation application for midostaurin in combination with chemotherapy followed by midostaurin monotherapy as treatment for adult patients with newly diagnosed AML who are FLT3 mutation-positive, was submitted to the EMA in July 2016.

A marketing authorisation application for midostaurin for treatment of adult patients with advanced systemic mastocytosis has also been submitted to the EMA. This indication is not relevant for this submission.

An opinion from the EMA (Committee for Medicinal Products for Human Use) for midostaurin, for use in combination with chemotherapy, followed by use as monotherapy, as treatment for adult patients with newly diagnosed AML who are FLT3 mutation-positive, is anticipated in October 2017.

The anticipated UK launch for midostaurin for the treatment of newly diagnosed FLT3-positive AML is November 2017.

A possible health technology submission to the Scottish Medicines Consortium in combination with chemotherapy followed by midostaurin monotherapy as treatment for adult patients with newly diagnosed AML who are FLT3 mutation-positive, is planned in June/July 2017.

2.3 Administration and costs of the technology

Considerations related to the cost of midostaurin therapy are summarized in Table 3.

Midostaurin is an oral therapy and the recommended dose of midostaurin is 50 mg twice daily, with each 50 mg dose administered as 2 x 25 mg soft gel capsules.[14] In the treatment of adult patients with newly diagnosed AML who are FLT3 mutation-positive, midostaurin is given on days 8–21 of induction and consolidation chemotherapy cycles, and is then taken twice daily as single-agent therapy for up to 12 months.[14]

During midostaurin monotherapy, in the event of grade 4 neutropenia (absolute neutrophil count [ANC] <0.5 x 10^9/L), it is recommended to interrupt midostaurin treatment until the ANC is ≥1.0 x 10^9/L, and then to resume midostaurin 50 mg twice daily. If neutropenia (ANC <1.0 x 10^9/L) persists for >2 weeks and is suspected to be related to midostaurin, it is recommended to discontinue midostaurin treatment.

Midostaurin is administered as an oral therapy. Therefore, there are no additional administration costs over and above those incurred during current standard treatment of newly diagnosed AML.

No additional tests over those required for initiating standard chemotherapy will be associated with midostaurin. Testing for FLT3 mutations is recommended and is often performed routinely in the prognostication of patients with AML.[10,12,22,23]

No additional monitoring, over standard practice, is required during midostaurin treatment.

Table 3 Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Soft capsule	SmPC
Acquisition cost (excluding VAT) [a]	[redacted] (112 pills of 25mg)	Novartis data on file
Method of administration	Oral	SmPC
Doses	50 mg BID	SmPC
Dosing frequency	Days 8–21 of 28-day chemotherapy cycles (induction and consolidation) and daily during midostaurin monotherapy	SmPC
Average length of a course of treatment	136 days	
Average cost of a course of treatment	[redacted]	
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 a complete remission and not going on to have a stem cell transplant, then receive midostaurin monotherapy for up to 12 months	SmPC
Anticipated number of repeat courses of treatments	Not applicable	
Dose adjustments	Treatment with midostaurin should be interrupted in patients with ANC <0.5 x 10^9/L and resumed when ANC is ≥1.0 x 10^9/L If ANC <1.0 x 10^9/L persists for >2 weeks and is suspected to be related to midostaurin, therapy with midostaurin should be discontinued	SmPC
Anticipated care setting	Secondary care	

[a]List price. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

ANC, absolute neutrophil count; BID, twice daily; SmPC, Summary of Product Characteristics.

2.4 Changes in service provision and management

No additional tests or investigations are needed for the selection of patients, use, administration and monitoring of midostaurin as a treatment for AML. Use of midostaurin in the management of newly diagnosed AML will not adversely impact or alter current infrastructure and service provision requirements. There are no concomitant therapies specified in the Summary of Product Characteristics or used in the pivotal phase 3 trial that differ from those used with standard therapy in the relevant setting.

2.5 Innovation

Midostaurin is a targeted therapy that inhibits a number of receptor tyrosine kinases, including FLT3, implicated in the pathogenesis of AML

Midostaurin is an innovation in the treatment of newly diagnosed AML. Midostaurin has a diverse kinase inhibition profile. It is a type III receptor TKI with multi-antikinase actions affecting FLT3, FGFr 1-3, KIT and VEGFR2 activity.[14,15] The action of midostaurin to inhibit FLT3 activity represents a particular therapeutic innovation, and is considered important in conferring much of the observed antineoplastic activity of midostaurin in haematopoietic tumours such as AML.[15] It is known that FLT3 is expressed in haematopoietic cell precursors and that FLT3 is important in the regulation of normal cell development, differentiation, survival and expansion.[15] Study of cell lines indicates that when FLT3 is overexpressed, the result is increased proliferation and decreased apoptosis.[15] Clinically, mutations in FLT3 occur in around 25–30% of AMLs and these mutations lead to FLT3 overexpression, with deleterious effects on the regulation of haematopoietic cell growth.[15,24,25] Both FLT3 ITD mutations and point mutations (FLT3 TKD, Asp835 or D835) cause the constitutive activation of FLT3. This in turn triggers the activation of a number of intracellular mediators such as signal transducer and activator of transcription 5 (STAT5), mitogen-activated protein (MAP) kinase and protein kinase B/phosphatidylinositol-3-kinase (AKT/PI3), resulting in a downstream signalling cascade of dysregulated cell growth, characterized by increased cell proliferation and suppressed apoptosis.[1,15,24]

The FLT3-ITD mutation is considered a driver-lesion in human AML,[26] and the presence of FLT3 mutations in patients with AML is uniformly associated with an adverse prognosis.[1,10,12,22,23,27] By inhibiting FLT3 and multiple key RTKs involved in activation of signalling pathways essential to the proliferation and differentiation of haematopoietic precursor cells, midostaurin can effect cell-cycle arrest at clinically achievable doses and has been shown to display potent antiproliferative activity in a number of cancer cell lines and xenografts.[15]

Preclinical study of midostaurin has shown that the inhibition of FLT3 substantially contributes towards the growth inhibitory effects of this agent in myeloid cells, yet research also highlights that midostaurin has antiproliferative effects in cell lines not specifically engineered to overexpress mutant FLT3.[15] As well as its effects on FLT3, directly and indirectly, midostaurin inhibits other molecular targets involved

in AML pathogenesis, and its administration is associated with decreased activity of FGFr 1-3, KIT and VEGF, effects that are considered to contribute to its overall antiproliferative profile in haematopoietic progenitor cells.[15] It has also been reported that midostaurin can, through its inhibitory effects on FLT3 and other RTKs, potentially reverse the multidrug resistant phenotype that has been associated with the failure of other potential TKI therapies that may be and have been used in management of haematological malignancies. The emergence of the F691L gatekeeper mutation, for example, has been a reported cause of clinical resistance to a number of investigative TKI molecules.[15,26,28,29] Studies have shown that midostaurin continues to have partial inhibitory activity against this mutant FLT3 and also blocks the ability of mutants to continue to signal via STAT5, AKT and MAP kinase.[28]

Midostaurin is the first targeted therapy to offer benefits over standard of care in newly diagnosed patients with AML

Induction therapy, and the treatment of newly diagnosed patients with FLT3 mutation-positive AML, has not changed or advanced substantially over the past 30 years, despite active clinical research efforts to find new treatments with improved OS benefit .[8] With standard chemotherapy, between 20% and 40% of AML patients fail to achieve CR and as many as 50% to 70% of those who do achieve CR relapse within 3 years.[8]

Midostaurin has a different mechanism of action to chemotherapy, targeting RTKs, including FLT3, to effect its antiproliferative activity in AML. When administered in addition to induction chemotherapy, midostaurin has the potential to deepen and potentially prolong responses.[15] Midostaurin is the first targeted therapy and the first TKI therapy for newly diagnosed FLT3 +ve AML, that significantly extends overall survival (OS) versus standard-of-care treatment.[13] Midostaurin has been studied as add-on therapy during standard induction and consolidation phases followed by use as self-administered monotherapy in patients with newly diagnosed AML.

As described in section 4.7, midostaurin has been studied in the largest phase 3, randomized, double-blind, placebo-controlled, international study ever conducted in patients with FLT3 mutation-positive AML (RATIFY).[13] In this study, patients were randomised to receive midostaurin or placebo in combination with chemotherapy (one or two cycles of induction therapy consisting of daunorubicin plus cytarabine, with patients who achieved a CR then receiving up to four cycles of high-dose cytarabine consolidation therapy). Patients remaining in remission after chemotherapy received up to twelve 28-day cycles of midostaurin (or placebo) as monotherapy. In this study, midostaurin in combination with chemotherapy followed by midostaurin monotherapy was found to significantly prolong OS, event-free survival (EFS), disease-free survival (DFS) and remission duration, as well as increasing the proportion of patients achieving CR after one cycle of induction therapy. Furthermore, midostaurin in combination with chemotherapy increased the treatment-free interval (TFI) by [redacted] months.[30]

These significant improvements in OS and EFS with the addition of midostaurin to standard of care were achieved with no increase in the incidence or severity of grade 3/4 adverse events (AEs) or serious adverse events (SAEs).

The prolongation in EFS and duration of remission with no increase in the incidence of grade 3/4 AEs means that the addition of midostaurin should not adversely affect patients' health-related quality of life (HRQoL) during treatment over and above what might be expected in patients receiving standard chemotherapy, as well as increasing the treatment-free interval, a period during which HRQoL is anticipated to be better. Furthermore, the addition of midostaurin prolongs OS in this typically aggressive, life-threatening leukaemia (see section 3).

A further innovation is that, being an oral therapy, midostaurin is convenient for patients to administer and requires no additional hospital visits when used with standard-of-care therapy. Midostaurin does not require special storage conditions, which is likely to be of further benefit for patients.

Midostaurin offers an improved treatment option for newly diagnosed patients with FLT3 mutation-positive (ITD or TKD) AML who are fit enough for intensive chemotherapy bridging more patients to curative therapy and offering better outcomes to patients who do not proceed to SCT

In patients with newly diagnosed FLT3 mutation-positive AML who achieve CR after induction therapy, a common post-remission strategy and goal for fitter patients is to enable them to undergo potentially curative haematopoietic stem cell transplantation (SCT) (see section 3.3).[11] In RATIFY 59.4% (midostaurin) and 55.2% (placebo) of patients underwent SCT and, for those who underwent SCT during the first CR, a [redacted] reduced risk of death was observed in the midostaurin group compared with the placebo group (see section 4.7.4).[13] In a phase 2 study of midostaurin, which included patients with FLT3 mutation-positive AML aged up to 70 years, 71 of 149 patients who received induction chemotherapy and midostaurin received an allogeneic STC (allogeneic SCT).[17]

3 Health condition and position of the technology in the treatment pathway

3.1 Disease overview and pathogenesis

AML is an aggressive haematological malignancy that requires immediate treatment

AML is an aggressive haematological malignancy and is considered a clinical emergency.[1,2] Untreated AML is a fatal disease. Without treatment, patients would die within 11–20 weeks of diagnosis, with mortality being due to complications (such as serious infection and haemorrhage) that are associated with the fundamental bone marrow failure that defines this leukaemia.[31] Treatment should therefore be initiated as soon as possible – ideally within a matter of days – after diagnosis.[11]

AML is a heterogeneous haematological malignancy

The term AML refers to a group of haematopoietic stem cell disorders characterized 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%.[23]

Current staging and classification systems for the condition recognise that there are two major aetiologies of AML: de novo AML and AML secondary, or iatrogenic, to exposure to chemotherapy or radiotherapy.[32] This submission 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.[33]

AML is a condition of dysregulated haematopoiesis

AML develops as a consequence of a series of genetic changes in haematopoietic precursor cells. In AML, immature monocytes and granulocytes are overproduced by the bone marrow and do not develop into leukocytes. Normal white blood cells (WBCs) are therefore replaced by leukaemic cells that have a diminished ability to defend against infection. The production of normal blood cells is decreased – resulting in anaemia, thrombocytopenia and neutropenia – and the overproduction of abnormal, immature cells, leads to an accumulation of leukaemic blood cells in the bone marrow, peripheral blood, spleen and liver.

AML is a condition of dysregulated haematopoiesis. Study of normal and aberrant haematopoiesis has identified that normal haematopoiesis is highly regulated by cytokine-induced stimulation of

multiple signal transduction pathways,[24] and that the activation of signalling pathways via RTKs plays a key mediator role in the placebo of proliferation and differentiation of normal haematopoietic precursor cells.[24,25] The RTK, FLT3, is expressed primarily in haematopoietic precursor cells, where it regulates cell development, differentiation, survival and expansion.[15] When FLT3 is overexpressed, this triggers the activation of intracellular mediators such as STAT5, MAP kinase and AKT/PI3, resulting in a downstream signalling cascade of dysregulated cell growth, characterized by increased cell proliferation and suppressed apoptosis.[1,15,24]

Research into understanding the role of FLT3 and factors that may cause its overexpression have identified that genetic alterations to the FLT3 gene (FLT3 ITD and FLT3 TKD mutations) are common in a number of haematological malignancies, implicating this RTK in AML pathogenesis. Indeed FLT3 mutations are noted in around 30% of all AMLs.[5,6]

Diagnosis and assessment of AML rely on molecular and genetic characterisation

The presenting early signs and symptoms of AML can be vague and non-specific and may 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 may be asymptomatic at diagnosis.[34] Often, cases of AML are discovered through routine blood tests, which reveal abnormalities requiring further investigation. However, not all cases of AML present with non-specific symptoms or asymptomatically, and some patients may be very ill at presentation. For example, around 5–30% of AML cases will present with hyperleukocytosis (WBC counts >100,000/mm^3), and such patients require immediate referral for emergency leukapheresis.[35]

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.[12]

The patient's age or fitness, initial leukocyte count and comorbidities are important risk factors. Age or fitness has an influence on survival and prognosis, in part related to the fact that initial treatment with intensive chemotherapy may not be tolerated by many older and less healthy patients.[36,37] History of previous cerebrovascular disease, rheumatologic disease, psychiatric disease and, in particular, renal disease have all been shown to affect and increase the risk of all-cause and cancer-specific mortality in patients with AML.[38]

In the assessment of patients with AML, molecular and genetic risk stratification are the key principles to guide therapy.[11,12] Mutations in the genes for FLT3, nucleophosmin 1 and CCAAT/enhancer binding protein α have been identified as important prognostic factors, with the latter two mutations conferring a favourable prognosis when present as single molecular aberrations, while FLT3 alterations presenting as a single molecular abnormality, or with a high allelic ratio, predict for a high and early relapse rate.[11,12]

Patients with FLT3 mutations have a particularly aggressive disease phenotype and worse prognosis than those without this mutation

Patients with FLT3 mutations (e.g. FLT3-ITD) have an aggressive disease phenotype with inferior outcomes. The expected 5-year survival for younger patients with AML is lower among those with FLT3 mutation-positive AML than among those without such mutations (wild-type FLT3 AML) (see section 3.4).[7]

3.2 Effects of AML on patients and carers

AML is a potentially life-threatening condition with as many as 50–70% of patients relapsing within 3 years following chemotherapy; prognosis is particularly poor for patients with FLT3 mutation-positive disease

AML is a potentially life-threatening condition that requires urgent treatment with standard-of-care chemotherapy. Despite early intervention after diagnosis, induction chemotherapy may not help all patients achieve remission and as many as 50–70% of those who do achieve remission following chemotherapy relapse within 3 years.[8] This is particularly the case for patients with FLT3 mutation-positive disease; one study has reported the 5-year relapse rate to increase from 49% for patients with wild-type FLT3 to 82% for patients with a high ITD burden (odds ratio 1.35 [95% confidence interval (CI) 1.24–1.47]; p<0.001).[7] Furthermore complications of the disease at presentation (such as anaemia, persistent infections and bleeding risk) and severe myelosuppression that is both a consequence of the disease and of induction chemotherapy negatively impact on patients.

Receiving a diagnosis of AML can be traumatic, with little time for patients to adjust to their diagnosis before treatment needs to be initiated, and the current standard-of-care treatments used in management of AML can have a significant impact on patient short-term and long-term HRQoL.[39,40] Patients report high rates of fatigue when receiving induction treatment. For example, as many 64% of patients in one study experienced moderate to severe fatigue, and high rates of moderate to severe non-functional symptoms (including dysgeusia, decreased appetite, dry mouth, diarrhoea, insomnia, daytime sleepiness, nausea, hair loss, dry skin and mouth ulcers) were reported.[41] Consistent with this, the effects of AML and its treatment were found to have a substantial negative impact on patients' physical and functional well-being. Indeed, the findings of a systematic review underline the substantial impact of diagnosis and induction therapy on patient HRQoL, and highlight that multiple HRQoL domains are affected, including physical, psychological, emotional and sexual.[40] In particular, the period during which patients may require inpatient treatment is associated with poor HRQoL.[42 43]

Caregivers also face burdens from living with, caring for and supporting a patient with AML. Caregivers find the period of supporting patients during chemotherapy a time of high burden, describing this period as disruptive.[44] Carers have reported that activities of daily living are affected, including time for self or leisure activities, time for maintenance of functions outside the home, and

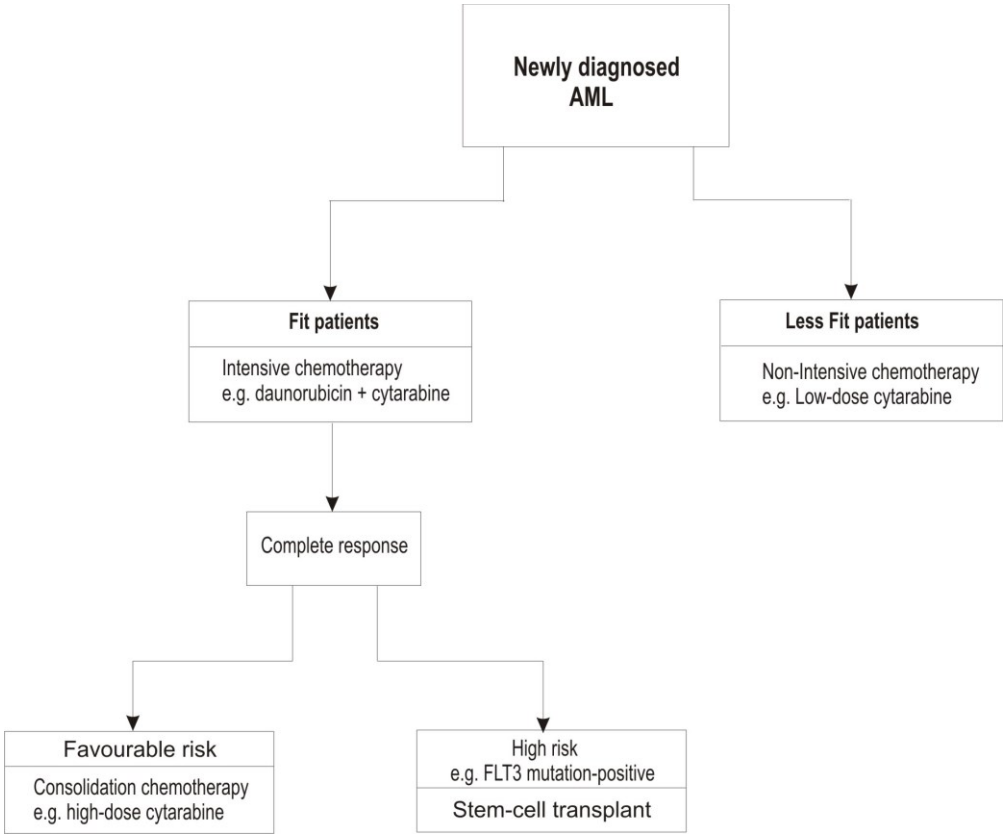
time to give general family support and undertake household tasks. Carers have also reported financial concerns as factors affecting their (caregiver) quality of life. Caregivers continue to face burdens across the patient treatment journey, and there are studies showing that when patients are undergoing 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.[45,46]

3.3 Clinical pathway, current guidelines and the role of midostaurin in the management of newly diagnosed FLT3 mutation-positive AML

The often vague and non-specific symptoms of AML can complicate and delay diagnosis; however, prompt recognition and treatment are priorities. [34] In the UK, patients typically seek help within ~10 days of symptom onset and the reported interval to diagnosis is ~4 days. Thus, patients with this medical emergency diagnosed in the UK are generally recognized early and will be assessed for appropriate management. The overarching goals of treatment in AML are to achieve remission and prevent disease relapse, so improving the survival outlook for patients.[10-12,47]

Treatment pathways for the care of patients with AML in the UK typically follow current UK or European guidelines. These guidelines note that treatment should be planned with curative intent whenever possible.[12] Available European and UK guidelines concur in their suggested treatment pathway for patients with newly diagnosed AML.[10-12] Figure 3 summarises the treatment pathway for patients with AML.[10-12]

Figure 3 Treatment pathway for management of AML



Dohner et al 2010, Fey et al 2010[11,12]

Management of newly diagnosed AML generally involves induction therapy aimed at inducing CR

It is recommended that treatment should be initiated without undue delay and ideally within 5 days of diagnosis.[11] For otherwise healthy patients, intensive induction chemotherapy is the standard of care and typically includes a chemotherapy regimen comprising an anthracycline and cytarabine. The European LeukemiaNet and European Society for Medical Oncology guidelines recommend a "3 + 7" induction regimen and the European LeukemiaNet guidelines recommend personalised choice of therapy for patients older than 75 years.[11,12] The current British Committee for Standards in Haematology UK guidelines state that a "3 + 10" induction chemotherapy regimen may be used as an alternative to a "3 + 7" regimen, while noting that there is no evidence for superiority over "3 + 7".

Patients achieving remission receive consolidation chemotherapy and/or allogeneic SCT to extend remission

For AML patients who achieve a CR, current guidelines note that, post remission, patients may continue chemotherapy as consolidation (often high-dose cytarabine chemotherapy) or receive high-dose chemotherapy conditioning as a bridge to SCT, typically allogeneic SCT, with the role of

autologous SCT being less clear.[10-12] The choice of therapy depends on the patient's fitness for consolidation chemotherapy and/or potentially curative SCT and on key cytogenetic and molecular genetic risk factors.[11] In general patients receive 4–6 cycles of induction-consolidation therapy. Results of the Medical Research Council AML15 trial indicate that there is no benefit for 5 cycles over 4 cycles.[48] Consolidation chemotherapy is generally recommended for patients with intermediate- or favourable-risk AML.[12] In patients with favourable risk, current guidelines consider that allogeneic SCT may be less justified because of the risk of treatment-related mortality, but for intermediate-risk or high-risk disease, allogeneic SCT should be considered or is generally recommended given the poorer outcomes achieved with chemotherapy.[11] Both intermediate- and high-risk groups can include patients with FLT3 mutation-positive disease.[11,12] Thus for patients with FLT3 mutation-positive disease there is a need for better treatment options that improve survival and avoid the need for SCT.

In most patients who achieve a CR following induction chemotherapy, the disease will recur within 3 years. Prognosis after relapse is generally poor and there is no standard or accepted therapy for AML relapse. Today, treatment options for relapsed patients typically include second-line treatment with cytarabine (intermediate or high dose) or anthracyclines. Once a CR is achieved then allogeneic SCT is again a preferred option and autologous SCT can also be an option. Better first-line treatments are needed to reduce the risk of relapse and prolong remission. Meanwhile, all current guidelines recommend that patients with AML be considered for entry into clinical trials.

Midostaurin fits within current clinical pathways as an addition to first-line chemotherapy followed by use as monotherapy for treatment of newly diagnosed patients with FLT3 mutation-positive AML

Midostaurin fits within current clinical pathways as an addition to first-line chemotherapy followed by use as monotherapy, for management of newly diagnosed patients with FLT3 mutation-positive AML, a group of patients having a poor outlook with current treatment options. Midostaurin in combination with chemotherapy followed by midostaurin monotherapy for up to 12 months has been shown to significantly extend OS, EFS, DFS, duration of remission and treatment-free interval, as well as increasing the proportion of patients achieving CR after one induction cycle versus standard-of-care treatment.[13]

3.4 Life expectancy and potential patient population

Approximately 30% of patients with AML have FLT3 mutation-positive disease

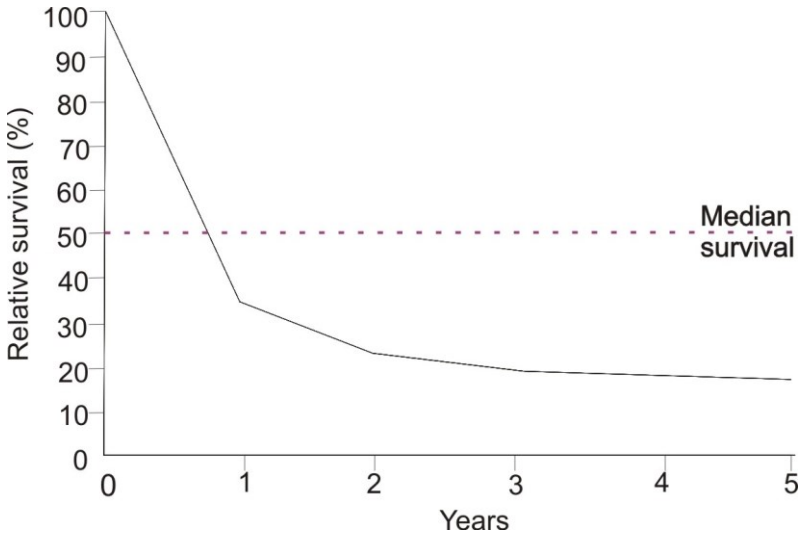
AML is a rare condition and traditionally has one of the lowest survival rates among the leukaemias due to poor prognosis and limited treatment options.[31] AML is primarily a disease of later adulthood and is rarely diagnosed before the age of 40 years.[31] The incidence of AML is approximately 1.3 to 1.5 times greater in men than in women.[49,50]

In 2013, there were 2,467 new cases of AML in England and 196 in Wales, and the age-standardised incidence for the UK was 5.0 per 100,000 population.[50,51] Approximately 55% of patients were aged 70 years or older, according to data for 2011–2013.[51] In terms of the potential population of newly diagnosed AML patients who may be candidates for midostaurin therapy, FLT3 mutations are estimated to occur in approximately 30% of patients with AML.[5,6] Furthermore, approximately 85% of patients with AML receive systemic therapy, and approximately three-quarters of these receive intensive chemotherapy.[52]

Median overall survival is less than 12 months for patients with AML and is lower in patients with FLT3 mutation-positive disease

Data from the National Cancer Intelligence Network for patients diagnosed with AML in England between 2006 and 2012 report that the 5-year survival rate was 27%. For people with AML aged 25–64 years the 5-year survival rate was 40%, but was 5% in people aged 65 years and older (data for 2008–2010).[3] A further study estimating 5-year survival for incident cases between 1995 and 2002 based on 48 population-based registries for 20 European countries reported a relative 5-year OS of 17% for AML and ranging from 47% for patients aged 15–49 years, to 15% for patients aged 50–69 years and 3% for patients aged 70 or older.[4] These authors estimated age-adjusted 5-year relative survival to be approximately 12% in the UK and Ireland. Thus the median survival for patients with newly diagnosed AML is less than 12 months (Figure 4). This is further supported by data from SEER (Surveillance, Epidemiology, and End Results) for 1988–2012 which reports a median OS of less than 12 months for the overall population of patients with AML; analysis according to age indicated that median OS is less than 12 months in patients aged 50 years or older and is 2–4 years in patients aged <50 years.[53]

Figure 4 Relative survival in 2000–2002 for patients with newly diagnosed AML from analysis of data from population-based registries for 20 European countries



Maynadie et al 2013[4]

Data for a UK cohort (median age, 43 years) suggest that the expected 5-year survival for younger patients with AML is lower among those with FLT3 mutations than among those without such mutations (wild-type AML) (15–31% vs. 42%).[7] A further UK study has reported a 5-year survival of 32% for FLT3-ITD versus 44% for FLT3 wild type disease.[22] There are also studies reporting 5-year survival for patients with unfavourable cytogenetic risk (i.e. including patients with FLT3 mutations) as ranging from 2–14%, as compared with 35–65% for patients with favourable cytogenetics.[54-57]

Available data therefore suggest that the median overall survival for patients with FLT3 mutation-positive AML is less than 12 months.

3.5 NICE guidance

Current National Institute for Health and Care Excellence (NICE) guidance relating to the care and management of people with AML includes NICE guidance 47 (May 2016): *Haematological cancers: improving outcomes*, which covers integrated diagnostic reporting of haematological cancers and the organisation of care.[58] This guidance does not make any specific recommendations regarding treatment.

There have been no significant advances in the management of AML in recent decades. There is only one positive NICE recommendation regarding AML treatment options and that relates to the management of patients with relapsed disease – a population different to the group of relevance to this submission. The technology appraisal, published in 2011, relates to azacitidine as a therapy for myelodysplastic syndromes and considers this agent in AML as a treatment option for adults not eligible for SCT. [59]

3.6 Clinical guidelines

The clinical guidelines typically followed in the UK are those described in section 3.3.

3.7 Issues relating to current clinical practice

There is currently no standard therapy for the management of newly diagnosed AML. The majority of newly diagnosed patients are enrolled in clinical trials which use standard chemotherapy.

3.8 Equality

There is no evidence to suggest there is inequality in the management of AML in England and Wales.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

A systematic review was performed to identify all published RCTs and non-RCTs concerning the efficacy and safety of midostaurin for treatment of patients with newly diagnosed FLT3-positive AML. Searches were devised to identify studies relating to any pharmacological therapy for this patient population and were screened to identify relevant publications. Identified publications were then further screened to exclude those relating to treatments other than midostaurin. Details of the search strings, databases searched and the supplementary searches performed are summarised in Appendix 8.2.1. Electronic searches were performed on 12 October 2016, and identified abstracts were independently screened by two reviewers and disagreements were resolved by a third independent reviewer. For the abstracts that potentially met the criteria, publications were obtained if available. Based on these full text reports, two reviewers evaluated whether each study met the selection criteria and disagreements were once again resolved by the third independent reviewer.

Table 4 summarises the inclusion and exclusion criteria used for the initial screening, including the full text review. In the final step, publications relating to pharmacotherapies other than midostaurin were excluded.

Figure 5 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram relating to the identification of relevant studies reporting data for the efficacy and safety of midostaurin. A list of the references included and excluded in the initial screen is provided in Appendix 8.2.2.

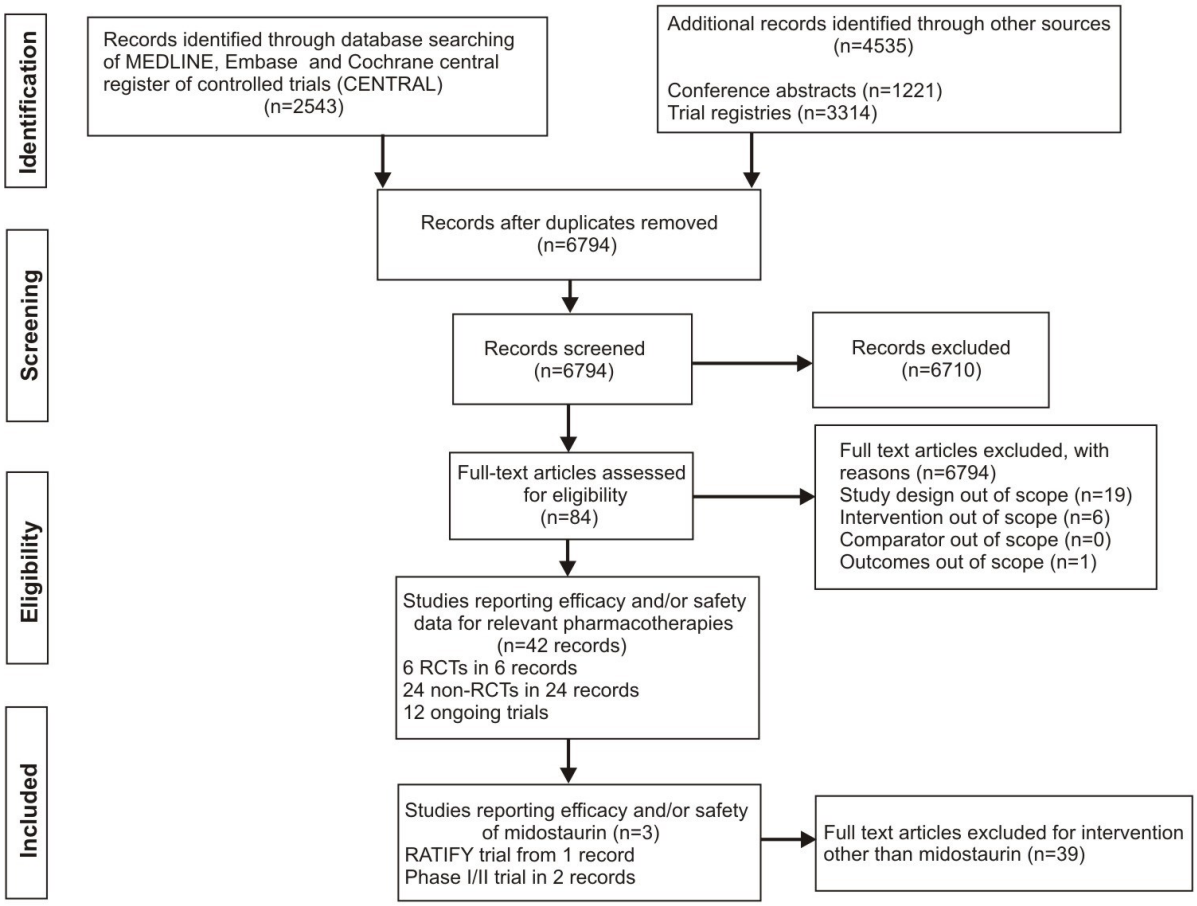
Table 4 Eligibility criteria used in the initial screening to identify studies relating to any pharmacological therapy for patients with newly diagnosed FLT3 mutation-positive AML

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with newly diagnosed FLT3 mutation-positive AML	*In vitro* studies, biomarker or genetic studies, studies in animals or other preclinical studies
Intervention	Midostaurin, cytarabine + daunorubicin; cytarabine + idarubicin; azacitidine; mitoxantrone; sorafenib; quizartinib; gemtuzumab ozogamicin/Mylotarg®	Other active treatments not provided by Novartis as comparators of interest
Comparators	Any active comparator including dose–dose comparisons; placebo; best supportive care	NA

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Outcomes	*Efficacy*: rates and mean duration of objective response (including overall, partial, and complete response), OS, PFS, clinically relevant PFS, disease-free survival, time to progression or treatment failure, HRQoL *Safety*: rates and duration of AEs, treatment discontinuations due to AEs or treatment-related AEs, treatment interruptions due to AEs, and dose modifications due to AEs	NA
Study design	RCTs, including crossover studies RCT substudies were included only if they reported additional outcomes of interest (e.g. separate HRQoL report) or long-term follow-up data (e.g. open label extensions). Non-RCTs; observational studies (prospective and retrospective cohort studies); case-placebo and single-arm studies	Publications that are duplicates, narrative reviews, editorials, letters, case reports, commentaries, interview-based research, legal cases, newspaper articles, debates, general or independent central reviews, opinions, protocols, workshops, assay studies, cytogenetic studies, surgical studies or patient educational material Studies on the prevention or detection of AML
Language restrictions	English language	NA

AE, adverse events; AML, acute myeloid leukaemia; FLT3, FMS-like tyrosine kinase 3; HRQoL, health-related quality of life; NA, not applicable; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial.

Figure 5 PRISMA flow diagram for clinical evidence relating to the efficacy and safety of midostaurin



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

4.2 List of relevant randomised controlled trials

The systematic review identified one relevant RCT, RATIFY, as is summarised in Table 5. Results from RATIFY have been published as an abstract.[13] Full details of the results for this study as presented in this submission are taken from the CSR[16] as the primary paper reporting the results for this study has yet to be published.

Table 5 List of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
CALGB 10603/ CPKC412A2301 (RATIFY) Phase-3 randomized, double-blind, placebo-controlled study (NCT00651261)	Adults (18–60 years) newly diagnosed with FLT3 mutation-positive AML	Cytarabine Daunorubicin Midostaurin	Cytarabine Daunorubicin Placebo	Stone *et al.,* 2015[13]

AML, acute myeloid leukaemia; CSR, clinical study report; FLT3, FMS-like tyrosine kinase receptor-3; ITD, internal tandem duplication; RCT, randomised controlled trial.

4.3 Summary of methodology of the relevant RCT RATIFY

RATIFY, an international, multi-centre, phase 3, 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, was the only relevant RCT identified (summarised in Table 6).[13,16]

Table 6 Comparative summary of trial methodology

Trial number (acronym)	CPKC412A2301, CALGB 10603 (RATIFY)[13,16]
Location	Multicentre international study; 225 sites in 17 countries (including USA, Germany, Italy, Canada, Australia, Spain, Netherlands)
Trial design	A phase 3, 1:1 randomised, double-blind, placebo-controlled trial Patients stratified by FLT3 mutation subtype (TKD vs. ITD high allelic mutation fraction [≥0.7] vs. 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

Trial number (acronym)	CPKC412A2301, CALGB 10603 (RATIFY)[13,16]
	• 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 x ULN • History of antecedent MDS in patients who had prior cytotoxic therapy (e.g. azacitidine or decitabine) • Pregnant or nursing patients
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) Intervention(s) (n=) and comparator(s) (n=) 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 midostaurin 50 mg BID (days 8–21) Consolidation phase (4 cycles): IV cytarabine 3 g/m^2 every 12 hours (days 1–7) + oral midostaurin 50 mg BID (days 8–21) Maintenance phase (up to 12 cycles): oral midostaurin 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, non-steroidal 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 Patients who underwent SCT were not to resume midostaurin/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 rate within 60 days of the start of treatment • DFS

Trial number (acronym)	CPKC412A2301, CALGB 10603 (RATIFY)[13,16]
	• DFS rate 1 year after completion of the continuation phase • SCT rate • OS censored at the time of SCT • Additional secondary endpoints: • EFS censored at the time of SCT • DFS censored at the time of SCT • Remission duration • Further objectives • To assess the safety of the treatment combination
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 x 10^9/L vs. ≥50 x 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

Stone *et al.,* 2015;[13] RATIFY CSR.[16]

AML, acute myeloid leukaemia; BID, twice daily; CNS, central nervous system; CR, complete response; CSF, cerebrospinal fluid; CYP, cytochrome P450; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FLT3, FMS-like tyrosine kinase receptor-3; ITD, internal tandem duplication; IV, intravenous; MDS, myelodysplastic syndrome; OS, overall survival; SCT, stem cell transplantation; TKD, tyrosine kinase domain; WBC, white blood cell; WHO, World Health Organisation; ULN, upper limit of normal.

4.3.1 Design

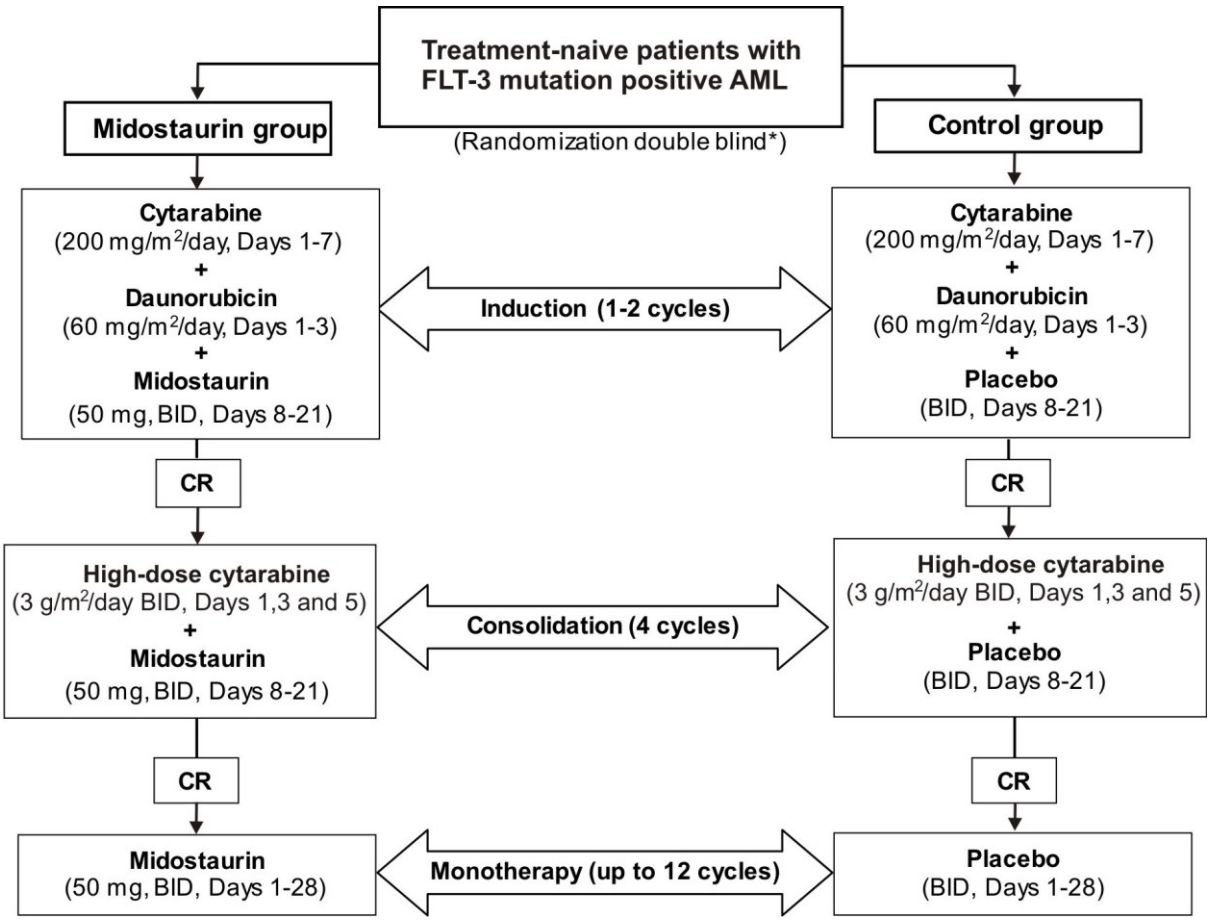
RATIFY was a multicentre, randomised, double-blind, placebo-controlled study assessing the addition of midostaurin to standard chemotherapy followed by midostaurin monotherapy for the treatment of FLT3 mutation-positive AML.

The trial consisted of three treatment phases (summarised in Figure 6 and described in detail below):

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

Figure 7 summarises the dosing schedule used in each part of the treatment pathway.

Figure 6 RATIFY study design



RATIFY CSR.[16]

AML, acute myeloid leukaemia; BID, twice daily; CR, complete remission; CSR, clinical study report; FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; TKD, tyrosine kinase domain.

* Central randomization within 3 strata: FLT3-TKD, FLT3-ITD with allelic ratio ≥ 0.7; FLT3-ITD with allelic ratio <0.7. ** Up to 12 cycles.

No cross over between study groups was permitted. Progression from one phase to the next was based on the patient achieving CR at the end of each phase. A CR was defined as all of the following criteria by 60 days after initial induction therapy was started, unless otherwise specified:

- Peripheral blood counts:
  - ANC ≥1000/µL
  - Platelet count ≥100,000/µL
  - No leukaemic blasts in the peripheral blood
  - Adequate erythroid recovery so that RBC transfusions were not necessary
- Bone marrow:
  - Adequate cellularity
  - No Auer rods

    - <5% blast cells
- No extramedullary leukaemia (such as central nervous system or soft tissue involvement).

Induction therapy

Patients received the following treatment schedule:

- Cytarabine 200 mg/m^2/day by continuous intravenous (IV) infusion on days 1–7
- Daunorubicin 60 mg/m^2/day by IV (push or short infusion) on days 1–3.
- Either midostaurin 50 mg OR placebo twice daily (BID), orally on days 8–21.

Patients not achieving CR after the first cycle underwent a second induction cycle. Those who did not achieve a CR after the second induction cycle were discontinued from the study treatment, but were followed for OS at least every 2 months for years 1 and 2, every 3 months for years 3 and 4 and then annually for a maximum of 10 years from study entry. Patients achieving CR after one or two induction cycles proceeded to consolidation therapy.

Consolidation therapy

Patients received the following treatment schedule:

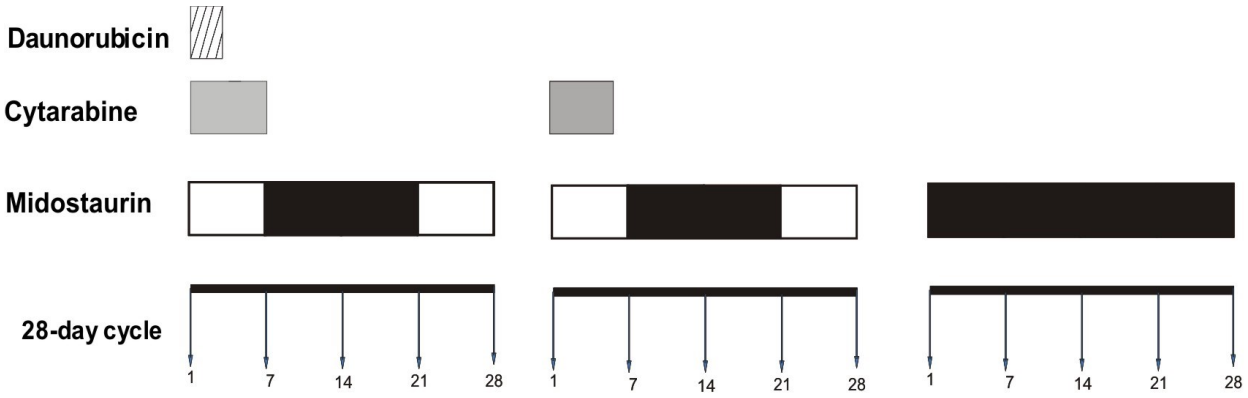
- High-dose cytarabine 3 g/m^2 IV every 12 hours on days 1, 3, and 5 of each cycle
- Midostaurin 50 mg OR placebo BID on days 8–21.

Each consolidation cycle was a minimum of 4 weeks in duration and was to begin within 2 weeks following haematologic recovery (ANC ≥1000/μL and platelet count ≥100,000/μL), but not sooner than 4 weeks from the beginning of the previous cycle. Patients who remained in CR after up to four cycles of consolidation therapy proceeded to monotherapy. Patients unable to complete four courses of high-dose cytarabine consolidation therapy because of toxicity could still be eligible for monotherapy, but this required discussion with the Study Chair.

Midostaurin monotherapy

Patients received midostaurin 50 mg OR placebo BID given continuously on days 1–28 of each 28-day cycle for up to 12 cycles or until leukaemia relapse.

Figure 7 Dosing schedule for treatment with midostaurin in RATIFY



Induction therapy, given for 1–2 cycles, consists of daunorubicin plus cytarabine plus midostaurin.
Consolidation therapy, given for up to 4 cycles, consists of cytarabine plus midostaurin.
Midostaurin monotherapy is given for up to 12 months.
RATIFY CSR.[16]
CSR, clinical study report.

Follow-up

Patients continued with study treatment until one of the following occurred:

- Completion of all protocol-specified treatments
- Failure to achieve CR after two courses of induction therapy
- Presence of leukaemic cells in cerebrospinal fluid
- Leukaemic regrowth: absolute peripheral leukaemic cells that were previously absent and then reappeared to a level of 1000/μL
- Relapse during post-remission therapy, with relapse defined as any of the following, occurring after either CR or partial remission (PR):
  - The reappearance of circulating blast cells not attributable to “overshoot” following recovery from myelosuppressive therapy
  - >5% blasts in the marrow, not attributable to another cause (e.g. bone marrow regeneration)
  - Development of extramedullary leukaemia.

Patients who completed study treatment were followed up for long-term survival and SCT status. Those who were still in remission on completing treatment were also followed up for remission status until relapse. Patients who discontinued study treatment also remained in the study and were followed up for response status (if in CR when discontinuing), long-term survival and SCT status.

Patients who underwent SCT were followed for relapse and survival. In the event that a patient received non-protocol therapy (including SCT) directed against their leukaemia, midostaurin/placebo therapy was not resumed.

4.3.2 Randomisation and blinding

Following confirmation of FLT3 mutation status and eligibility criteria, patients were randomised in a 1:1 ratio to midostaurin or placebo, stratified by mutation status (ITD allelic ratio <0.7, ITD allelic ratio ≥0.7 or TKD). Patients and all study-site personnel (investigators, pharmacists and people performing the study assessments) were blinded to the treatment from randomisation until after database lock. Alliance statisticians and programmers, as well as the Data Safety Monitoring Board (DSMB) members, were the only personnel not blinded to the treatments.

4.3.3 Inclusion and exclusion criteria

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 with symptomatic congestive heart failure were excluded, as were patients who had received prior chemotherapy for myelodysplasia. Inclusion and exclusion criteria are summarised in Table 6.

.

4.3.4 Treatment

Study treatments

Midostaurin or matched placebo was administered as two capsules taken orally BID. Doses were to be taken with food with an interval of approximately 12 hours between morning and evening doses. Dose adjustments or interruptions were allowed in the following cases:

- Pulmonary infiltration ≥grade 3
- QTc prolongation events >470 ms
- Non-haematologic toxicity grade 3–4 considered to be at least possibly related to midostaurin/placebo
- Neutropenia grade 4 during continuation therapy
- Persistent non-haematologic toxicity grade 1–2 that patients deemed unacceptable during continuation therapy.

Concomitant therapies

Patients were to receive full supportive care, including blood transfusions and products during the study. As ocular toxicity (including photophobia and conjunctivitis) is described with cytarabine, patients received dexamethasone 0.1% or corticosteroid ophthalmic solution starting 6–12 hours before the initiation of the high-dose cytarabine infusion, with therapy continuing for at least 24 hours after the last cytarabine dose.

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 with prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection.

Use of the following concomitant drugs was to be recorded: antibiotic/antiviral/antifungal agents, proton pump inhibitors or H_2-receptor antagonists, non-steroidal anti-inflammatory drugs, opioids, antiemetic agents, antihistamines, corticosteroids, growth factors, diuretics, antihypertensives, and other cytochrome P450 (CYP) 3A4 inhibitors and CYP3A4 inducers.

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) and other chemotherapeutic agents were not permitted. SCT (allogeneic or autologous) was permitted, although patients who underwent SCT were not to resume midostaurin/placebo therapy following treatment.

4.3.5 Overview of efficacy endpoints and sensitivity analyses

The primary endpoint for the study was OS. EFS was a key secondary endpoint and other secondary efficacy endpoints included: CR rate, DFS and remission duration.
Additional secondary endpoints included:

- OS for the subgroup of patients who underwent SCT
- OS and DFS from the start of maintenance therapy for patients receiving maintenance therapy
- DFS from the completion of maintenance therapy for patients who completed 1 year of maintenance therapy.

Furthermore, the following sensitivity analyses were included:

- Censoring at SCT for OS, EFS, DFS and remission duration
- Considering all CRs rather than just using the protocol-specified definition of a CR (a CR within 60 days of treatment initiation) – for EFS and DFS

4.3.6 Overall survival – primary efficacy endpoint

The primary efficacy evaluation tested the superiority of midostaurin compared to placebo on OS using a non-censoring analysis at the time of SCT. An event was defined as a death from any cause and was measured as the time between randomisation plus 1 day and death. All patients were followed up for this endpoint irrespective of when they stopped study treatment.

All deaths up to and including the cut-off date of 01 April 2015 were considered as OS events. Patients known to be alive at their last contact and whose vital status was not updated during the data sweep were censored at their date of last contact before 01 April 2015. The remaining patients were considered as alive on 01 April 2015 and were censored for the OS analysis on this date.

4.3.7 Complete remission

CR rate was analysed as a secondary endpoint. Two definitions of CR rate were employed. The primary measure was the proportion of patients achieving a CR within 60 days of treatment initiation. A secondary measure was the proportion of patients achieving a CR at any time.

4.3.8 Event-free survival – key secondary endpoint

An EFS event was defined as a failure to obtain a CR within 60 days of initiation of protocol therapy, or relapse from CR, or death from any cause, whichever occurred first, and was measured as the time from randomisation plus 1 day to the event. All patients were followed up for this endpoint irrespective of when they stopped study treatment.

4.3.9 Disease-free survival

This analysis included patients who achieved CR by day 60 after study treatment initiation; patients were not censored at the time of SCT. DFS was measured from the date of the first CR to relapse or death from any cause, whichever occurred first.

4.3.10 Remission duration

The duration of remission was measured for patients who achieved CR in 60 days and was defined as the time between the first CR and relapse or death due to AML, whichever occurred first. Two analyses were performed, one non-censored for SCT and the other censored at the time of SCT. Patients who died due to other reasons were censored at their date of death with the duration measured as the time between the first CR plus 1 day and the event.

4.3.11 Stem cell transplant rates

The overall number and percentage of patients who received SCT during the study were summarized by treatment arm and according to whether SCT was performed in first CR or later. However, outcomes of SCT or complications related to SCT were not recorded.

4.3.12 Pre-planned subgroup analyses

OS and EFS (non-censored for SCT) were analysed according to the following subgroups in order to assess the homogeneity of the treatment effect:

- **FLT3 mutation status 1:** 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/ITD mutation-positive patients
- **Gender:** Male/female
- **Region:** North American/non-North American
- Prior MDS: Yes/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 x 10^9/L/≥50 x 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)
- Eastern Cooperative Oncology Group (ECOG) Performance Status (ECOG/Zubrod scale): 0–1/≥2.

4.3.13 Safety outcomes

AEs and SAEs were recorded with their severity and relationship to study treatment both for overall treatment and for each phase of treatment. Laboratory tests (haematology, blood biochemistry, coagulation and thyroid function) multiple gated acquisition/echocardiogram and electrocardiogram were performed at local laboratories.

The recording of AEs differed between North American and non-North American regions. In non-North American centres, all AEs were required to be reported regardless of grade. However, in North American centres, grade 1–5 AEs were only recorded for 13 pre-specified expected AEs (neutrophils/granulocytes, platelets, haemoglobin, febrile neutropenia, ataxia [incoordination], rash/desquamation, diarrhoea, nausea, vomiting, keratitis, fatigue, left ventricular systolic dysfunction and mucositis/stomatitis) and other AEs were only recorded if they were ≥ grade 3 in severity.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trial, RATIFY

4.4.1 Populations

Three study populations were considered: the full analysis set (FAS), the per protocol set (PPS) and the safety set.

The FAS included all consenting patients randomised to a treatment group and patients were analysed according to the treatment to which they were randomised. The FAS was used for analysis of the baseline characteristics and efficacy endpoints.

The PPS included all consenting patients randomised to a treatment arm who received at least one dose of study medication (midostaurin or placebo) and who had no major protocol deviation regarding inclusion/exclusion criteria or randomisation that could affect response to treatment. The PPS was used in a sensitivity analysis of EFS.

The safety set included all consenting patients who received at least one dose of study drug (midostaurin or placebo). Patients randomised in one arm, but who only received the study drug of the

other arm were analysed according to the study drug they received. The safety set was used for the analyses of the safety endpoints, concomitant medications and treatment exposure.

4.4.2 Sample size calculation

Sample size and power calculations for RATIFY are summarised in Table 7.

4.4.3 Statistical tests

Statistical analyses employed in RATIFY are summarised in Table 7.

Interim analyses

One formal interim efficacy analysis was planned to be conducted when 50% of the OS events had been accrued in order to determine whether to stop the study for early efficacy. As pre-specified in the study protocol, an alpha of 0.5% was to be spent at the interim analysis, meaning the one-sided test of the primary endpoint OS was significant if the p-value was less than 0.005.

Conservative futility analyses (conducted twice annually) were also planned for the OS primary endpoint with a conditional probability of <0.10 being grounds for stopping the study early. Conditional power was calculated as the probability of having a significant p-value at the primary analysis assuming an underlying hazard ratio (HR) of 0.78 on OS, given the interim effect observed at the futility analysis. Interim futility analyses were conducted only after all patients had been enrolled and CR status was available from all patients.

Key safety data were analysed every 6 months by the DSMB who could recommend additional safety analyses.

The interim efficacy analysis, which occurred in June 2012, included 255 events, 115 in the midostaurin arm and 140 in the placebo arm. The one-sided p-value associated with the analysis was 0.0126. The DSMB recommended continuing the study without changes.

Final analysis

In March 2015, 350 events had been observed with only one death in the previous 6 months. Based on this, the required number of events was not expected to occur in a reasonable timeframe. In June 2015, the protocol was amended to perform the final analysis with a data cut off of 01 April 2015. The secondary endpoint EFS was promoted to a key secondary endpoint to be tested in a hierarchical manner if the OS endpoint was significant. The critical value to declare statistical significance would consider the total information for the number of events retrieved in April 2015 and the alpha already spent (fixed at 0.5%) at the interim analysis. Using the joint distribution of the test statistics at the interim and the final analysis the critical value would be derived to maintain a one-sided type I error of 0.025 for the study.

Table 7 Summary of statistical analyses in the RCT

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
CALGB 10603 CPKC412A2301 (RATIFY)[16]	To evaluate the effect on OS of adding midostaurin to standard chemotherapy (induction therapy – daunorubicin/cytarabine – and consolidation therapy – high-dose cytarabine), followed by midostaurin monotherapy in patients with newly diagnosed FLT3 mutation-positive AML	• Stratified log-rank tests adjusting for the FLT3 mutation strata were used to test the null hypothesis and calculate the one-sided p-value • Stratified Cox regression models adjusting for FLT3 mutation were used to estimate HRs and Wald 95% CIs • Kaplan-Meier plots were used to depict OS in each treatment arm • Median survival and 95% CIs were calculated using the method of Brookmeyer and Crowley (1982)[60] • Kaplan-Meier estimates with 95% CIs at specific time points were summarized every 6 months using Greenwood's formula for the standard error of the Kaplan–Meier estimate. • The primary efficacy evaluation tested the superiority of midostaurin compared to placebo on OS using an analysis non-censoring at the time of SCT. An interim analysis was planned to be conducted when 50% of the OS events were entered into the database. In case of positive results the DSMB was to decide whether to stop the study for early efficacy. The test was significant if the associated one-sided p-value was <0.005	• 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%	• 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 01 April 2015 were censored on 01 April 2015

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		• Only if the test of the primary endpoint, OS, was significant was the test of the key secondary efficacy endpoint that determines the superiority of midostaurin on EFS performed in a formal confirmatory setting at the alpha level 0.025. If OS was not significant, the nominal p-value was still to be produced for this endpoint. This was the only secondary endpoint with confirmatory testing for which the type I error was controlled		

RATIFY CSR.[16]

AML, acute myeloid leukaemia; CI, confidence interval; CR, complete remission; CSR, clinical study report; DSMB, Data Safety Monitoring Board; EFS, event-free survival; FLT3, FMS-like tyrosine kinase 3; HR, hazard ratio; ITT, intent to treat; OS, overall survival; RCT, randomised controlled trial; SCT, stem cell transplantation; TKD, tyrosine kinase domain.

4.5 Participant flow in the relevant RCT, RATIFY

4.5.1 Analysis sets

The FAS population consisted of 717 patients, 360 randomised to midostaurin and 357 randomised to placebo (Table 8).[16] The PPS set consisted of 610 patients with 307 and 303 in the midostaurin and placebo groups, respectively. The safety set consisted of 680 patients with 343 and 337 patients in the midostaurin and placebo groups, respectively.

Table 8 Analysis sets

Analysis Sets	Midostaurin N=360 n (%)	Placebo N=357 n (%)	Total N=717 n (%)
Full analysis set	360 (100)	357 (100)	717 (100)
ITD <0.7	171 (47.5)	170 (47.6)	341 (47.6)
ITD ≥0.7	108 (30.0)	106 (29.7)	214 (29.8)
TKD	81 (22.5)	81 (22.7)	162 (22.6)
Per protocol set	307 (85.3)	303 (84.9)	610 (85.1)
Safety set[a]	343 (95.3)	337 (94.4)	680 (94.8)

[a] Two patients randomised to placebo received only midostaurin. These patients are considered randomised and analysed in the midostaurin arm for the safety analyses.
CSR, clinical study report; ITD, internal tandem duplication; TKD, tyrosine kinase domain.
RATIFY CSR.[16]

4.5.2 Patient disposition

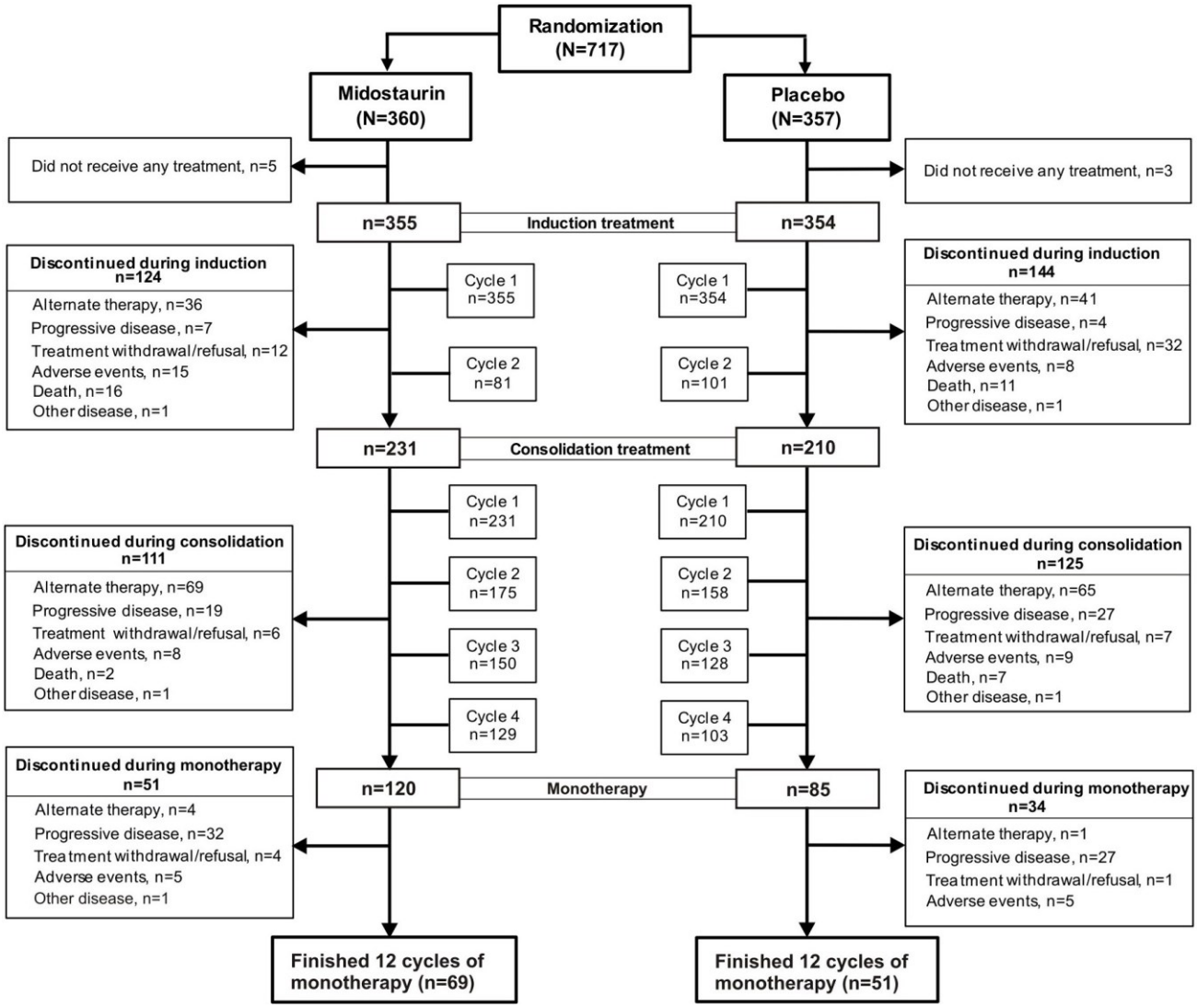
A total of 355 (98.6%) and 354 (99.2%) patients randomised to midostaurin and placebo, respectively, received induction therapy (Figure 8). Approximately one-quarter of patients (182/709 = 26.7%) required a second induction cycle (i.e. did not achieve a CR after the first cycle) with more patients requiring a second cycle in the placebo group (101/354 = 28.5%) compared to the midostaurin group (81/ 355 = 22.8%).

A greater proportion of the midostaurin versus placebo group, respectively, subsequently progressed to each key stage of the trial:

- Proceeded to consolidation phase (i.e. achieved a CR after induction therapy): 64.2% (231/360) versus 58.8% (210/357)
- Completed all four consolidation treatment cycles: 55.8% (129/231) versus 49.0% (103/210)
- Proceeded to receive monotherapy: 33.3% (120/360) versus 23.8% (85/357)
- Completed monotherapy: 19.2% (69/360) versus 14.3% (51/357).

Over the three phases of the study, the main reasons for discontinuation were receiving an alternative therapy (30% for both groups), and progressive disease (16% for both groups). Discontinuation for patient withdrawal was more frequent in the placebo group (11.2% vs. 6.1%) and discontinuation for AEs/complications was more frequent in the midostaurin group (8.9% vs. 6.2%).

Figure 8 Patient disposition (FAS population)



RATIFY CSR.[16]
CSR, clinical study report; FAS, full analysis set.

4.5.3 Baseline patient demographics and clinical characteristics

Baseline patient demographics and clinical characteristics are presented in Table 9 and were largely well balanced between groups, except that there was a higher proportion of men in the midostaurin arm compared with the placebo arm (48.3% vs. 40.6%, respectively). Most patients (88.3%) had a performance status of 0 or 1, and median age was 47.0 years (range 19–59 years) for midostaurin and 48.0 years (range 18–60 years) for placebo. Overall, 23% of patients had FLT3-TKD, 46% had FLT3-ITD <0.7 and 31% had FLT3-ITD ≥0.7. Approximately one-third of patients were from North American centres.

Table 9 Baseline patient demographics and clinical characteristics (FAS population)

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)
Race, n (%)			
White	147 (40.8)	128 (35.9)	275 (38.4)
Black or African American	8 (2.2)	9 (2.5)	17 (2.4)
Asian	8 (2.2)	5 (1.4)	13 (1.8)
American Indian or AN	0	1 (0.3)	1 (0.1)
Not reported	1 (0.3)	2 (0.6)	3 (0.4)
More than one race	2 (0.6)	1 (0.3)	3 (0.4)
Unknown	194 (53.9)	211 (59.1)	405 (56.5)
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)

RATIFY CSR.[16]

AN, Alaskan native; BSA, body surface area; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; FLT3, FMS-like tyrosine kinase receptor-3; ITD, internal tandem duplication; SD, standard deviation; TKD, tyrosine kinase domain.

4.6 Quality assessment of the relevant RCTs

Table 10 summarises the assessment of the risk of bias for the RCT, RATIFY. Overall, the risk of bias was considered to be low given that randomisation and blinding were performed adequately, both treatment groups were well matched at baseline and there were no unexpected imbalances in withdrawals during the course of the study. Furthermore, evidence suggests that most planned outcome measures were analysed and reported and most efficacy analyses used an ITT approach.

Table 10 Quality assessment results for the RCT, RATIFY

Study question	How is the question addressed in the study?	Risk of bias (High, Low, Unclear)
Was randomisation carried out appropriately?	Randomisation was performed using a robust, validated block approach with treatment allocation concealed	Low
Was the concealment of treatment allocation adequate?	Yes, patients receive midostaurin or matching placebo as soft capsules	Low
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were no significant differences between the arms in age, race, FLT3 subtype, or baseline CBC except for gender (p=0.04)	Low
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients and all site study personnel including investigators, pharmacists and people performing the study assessments remained blinded to the identity of the treatment from the time of randomization until after database lock	Low
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. The main reasons for discontinuation were the same for both groups, i.e. receiving an alternative therapy (30% for both groups), and progressive disease (16% for both groups). Discontinuation for patient withdrawal was more frequent in the placebo group (11.2% vs. 6.1%) and discontinuation for AEs/complications was more frequent in the midostaurin group (8.9% vs. 6.2%)	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The CSR lists all planned outcomes and results are reported for most efficacy outcomes described	Low
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, most efficacy data are reported for the FAS, which includes all patients randomised to therapy and who were analysed according to ITT. The per protocol set is used for some sensitivity analyses	Low

RATIFY CSR.[16]

AE, adverse event; CBC, complete blood count; CSR, clinical study report; FAS, full analysis set; FLT3, FMS-like tyrosine kinase receptor-3; ITT, intention-to-treat; OS, overall survival; RCT, randomised controlled trial.

4.7 Clinical effectiveness results of the relevant RCTs

4.7.1 Overview

A summary of the key efficacy endpoints is presented in Table 11.[16] Midostaurin significantly prolonged OS, EFS and DFS, as well as these parameters when censored at SCT (i.e. demonstrating the benefit of midostaurin, independent of any effect on allowing patients to receive SCT). Midostaurin was also associated with a significantly higher CR rate and a numerically greater proportion of patients undergoing SCT.

Table 11 Summary of efficacy data for the phase 3 RCT

Endpoint	Midostaurin (N=360)	Placebo (N=357)	p-value or HR
Median overall survival, months	74.7	25.6	HR 0.77, p=0.0078
3-year, %	54	47	
5-year, %	51	43	
Complete remission, %			
Protocol defined[a]	58.9	53.5	p=0.073
Expanded definition[b]	65.0	58.0	p=0.027
Median event-free survival, months	8.2	3.0	HR=0.78, p=0.002
1-year, %	43	31	
5-year, %	28	19	
Median disease-free survival, months	26.7	15.5	HR=0.714, p=0.0051
1-year, %	71	57	
5-year, %	48	37	
Patients undergoing SCT			
All patients, %	59.4	55.2	p=0.250
Patients with SCT in the 1st CR	[redacted]	[redacted]	[redacted]
Median overall survival censored at SCT, months	NE	NE	HR=0.749, p=0.0373
3-year, %	65	58	
5-year, %	64	56	
Median event-free survival censored at SCT, months	8.3	2.8	HR=0.81, p=0.0124
1-year, %	43	30	
5-year, %	25	21	
Median disease-free survival censored at SCT, months	[redacted]	[redacted]	[redacted]
3-year, %	[redacted]	[redacted]	
5-year, %			
Median duration of remission, months	[redacted]	[redacted]	[redacted]
Median duration of remission censoring for SCT, months			

RATIFY CSR.[16]

[a] CRs within 60 days of therapy initiation.

[b] All CRs during protocol treatment and those in the 30 days following treatment discontinuation.

CR, complete remission; CSR, clinical study report; HR, hazard ratio; NE, not estimable; NR, not reported; RCT, randomised controlled trial; SCT, stem cell transplantation.

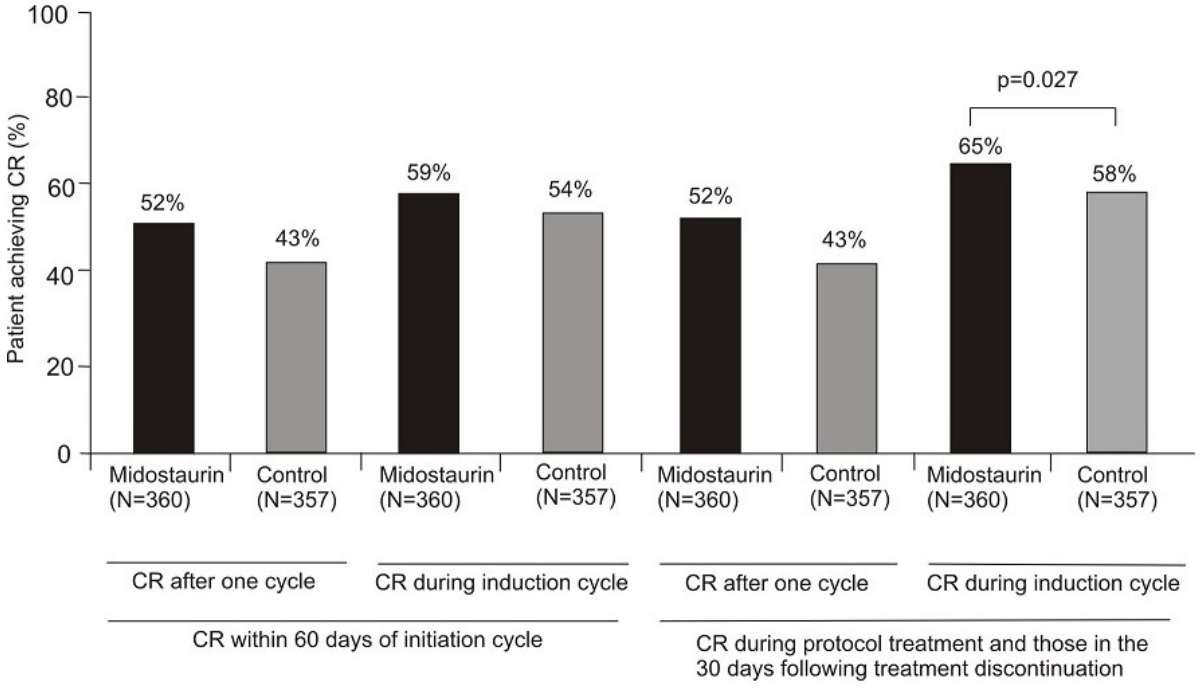
4.7.2 Rates of complete remission

Midostaurin increased the proportion of patients achieving CR after one cycle of induction therapy

Using the protocol-specified definition of a CR (a CR within 60 days of treatment initiation), a numerically higher proportion of patients in the midostaurin arm compared with the placebo arm achieved a CR (58.9% vs. 53.5%. respectively; one-sided p value = 0.073; Figure 9). Similarly, more patients treated with midostaurin compared with placebo achieved a CR after a single induction cycle (51.7% vs. 43.1%, respectively). The proportion of patients achieving a CR after the second induction cycle (i.e. patients who did not achieve a CR after the first cycle) was low for both groups (3.9% for midostaurin and 7.3% for placebo). The median time to CR was 35 days in both groups.

Using an expanded CR definition (CRs during protocol treatment and those in the 30 days following treatment discontinuation), the CR rate was significantly higher in patients randomised to midostaurin compared with placebo (65.0% vs. 58.0%; one-sided p value = 0.027; Figure 9). The proportion of patients achieving CRs after one cycle of induction therapy remained higher in the midostaurin group compared with placebo (51.7% vs. 43.1%). The median time to CR was 37 days for midostaurin and 36 days for placebo.

Figure 9 CR rates achieved after one or two cycles of induction therapy for a) CR achieved within 60 days of treatment initiation and b) CR achieved during protocol treatment and those in the 30 days following treatment discontinuation



RATIFY CSR.[16]
CR, complete remission; CSR, clinical study report.

4.7.3 Overall survival – primary efficacy outcome

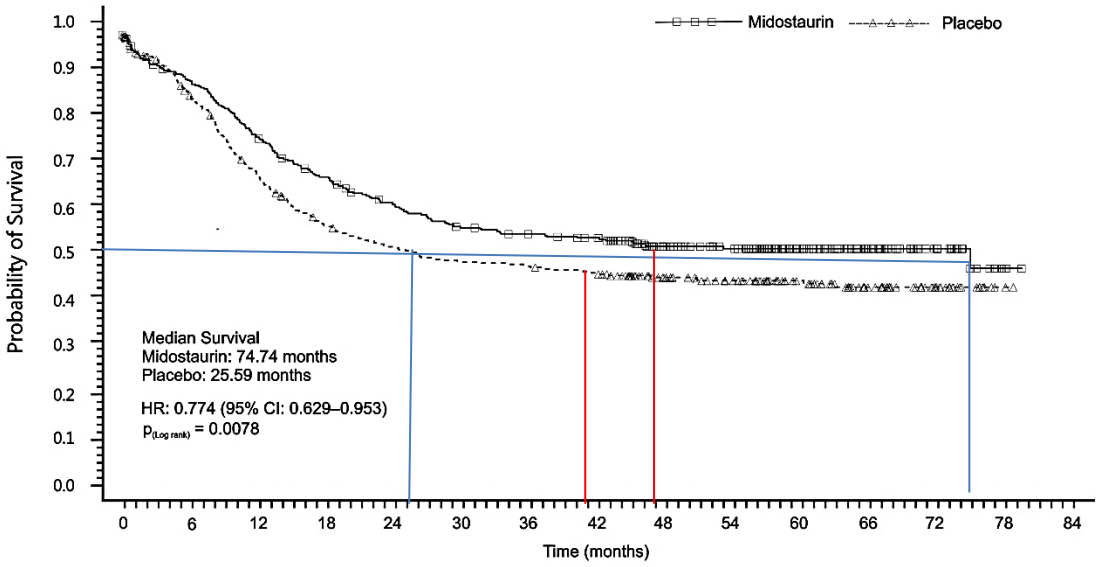
Midostaurin significantly reduced the risk of death by approximately 25%; benefits were largely seen within the first 18 months of therapy and were then sustained

Median follow-up was 60.2 months for both groups. RATIFY CSR[16] The risk of death was significantly reduced by 23% for midostaurin versus placebo (HR 0.77 [95% CI 0.63–0.95]; p=0.0078) and the estimated probability of being alive was higher for midostaurin versus placebo at 3 and 5 years:

- Three years – 54% (95% CI 0.49–0.59) versus 47% (95% CI 0.41–0.52), respectively
- Five years – 51% (95% CI 0.45–0.56) versus 43% (95% CI 0.38–0.49), respectively.

As evident from the Kaplan–Meier plot, the impact of midostaurin was largely seen in the first 18 months of the study (Figure 10). This was then followed by a plateau phase during which the survival benefit achieved with midostaurin was maintained, as evident by the parallel curves for survival. Median OS was 74.7 months (95% CI 31.5–not estimable [NE]) for midostaurin and 25.6 months (95% CI 18.6–42.9) for placebo. The large difference in median OS between treatment groups reflects the effect of the plateau phase observed in the Kaplan–Meier plot. Mean OS [redacted] from [redacted] months for the placebo group to [redacted] months for the midostaurin group.

Figure 10 Overall survival – non-censored at the time of SCT (FAS population)



RATIFY CSR.[16]
Median is indicated by blue lines and mean by red lines.
CI, confidence interval; CSR, clinical study report; FAS, full analysis set; FLT3, FMS-like tyrosine kinase 3; SCT, stem cell transplantation.

4.7.4 Overall survival – secondary analyses and sensitivity analyses

Midostaurin consistently reduced the risk of death in all secondary analyses and sensitivity analyses

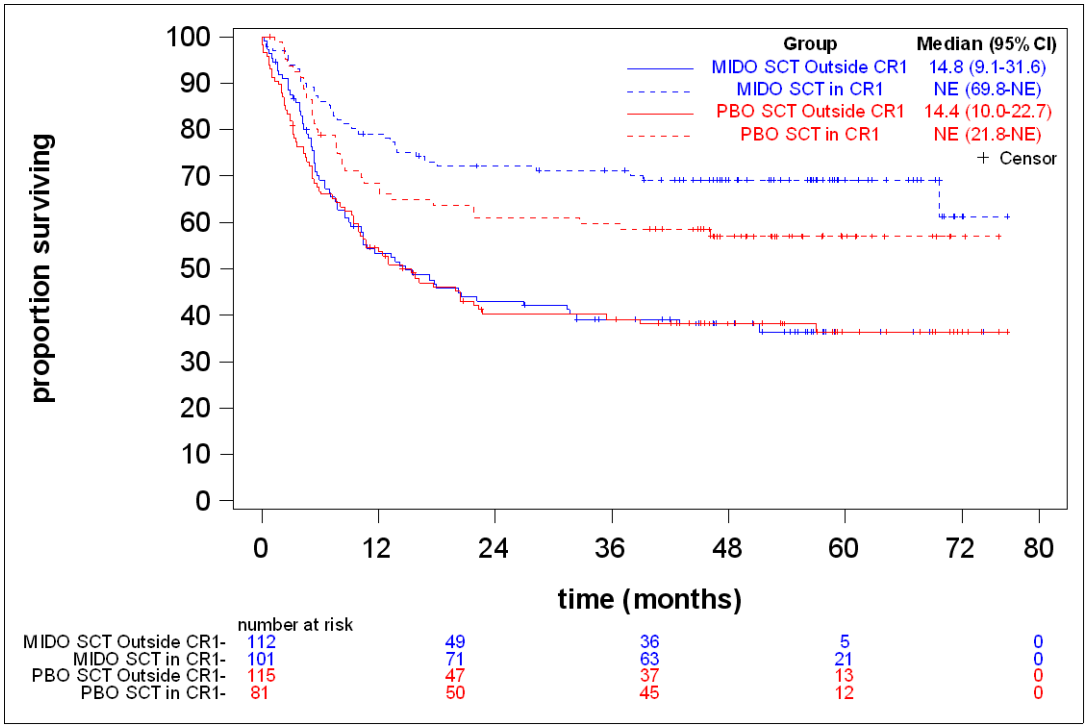
Sensitivity analysis: Overall survival censored at SCT

During the study, 57% of the patients received an SCT, which exceeded the pre-study estimated rate of 15%. Overall SCT rates were similar in the midostaurin and placebo groups (59.4% and 55.2%, respectively) with approximately [redacted] of patients ([redacted] and [redacted], respectively) receiving an SCT in the first CR. Results for OS censored by SCT were consistent with the results of the primary endpoint. Median OS was not reached for either treatment arm. However, there was a significantly reduced risk of death for midostaurin over placebo (HR 0.75 [95% CI 0.54–1.03]; p=0.0373), with a 5-year OS of 64% (95% CI 0.56–0.71) for midostaurin and 56% (95% CI 0.47–0.63) for placebo.

Overall survival in patients who underwent SCT

OS was assessed in patients who received SCT during the first CR (those occurring within 30 days of the last treatment). The analysis included [redacted] patients in the midostaurin arm and [redacted] patients in the placebo arm and demonstrated a reduced risk of death by 37% for patients receiving midostaurin over placebo (HR 0.63 [95% CI 0.38–1.05]) (Figure 11). No benefit for midostaurin over placebo was observed for patients who underwent SCT outside the first CR.

Figure 11 Overall survival post-SCT in patients undergoing SCT



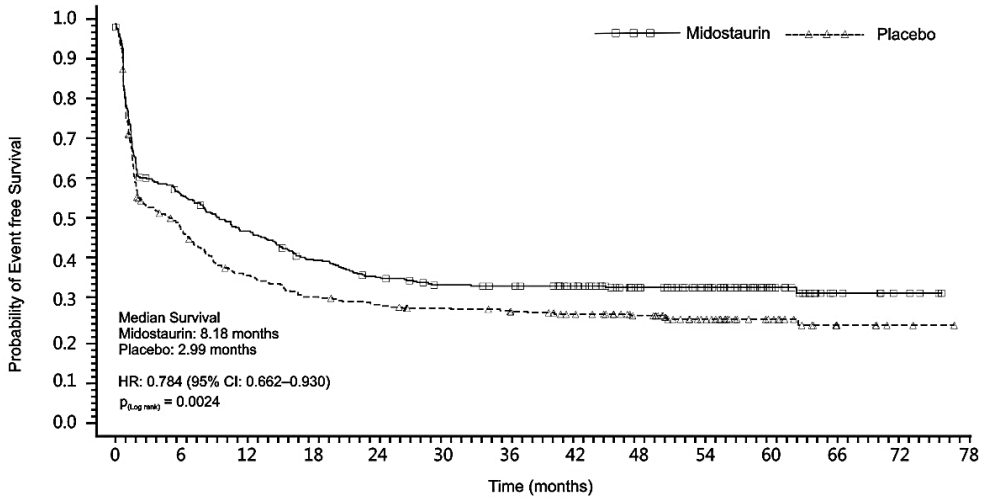
SCT, stem cell transplantation.

4.7.5 Event-free survival – key secondary endpoint

Midostaurin significantly prolonged EFS compared to placebo; the benefits of midostaurin were evident at 1 year and sustained at 5 years

Using the protocol-specified definition of a CR (a CR within 60 days of treatment initiation), median EFS was significantly longer for midostaurin (8.2 months [95% CI 5.4–10.7 months]) than placebo (3.0 months [95% CI 1.9–5.9 months]) with an HR of 0.78 (95% CI 0.66–0.93; p=0.002) (Figure 12). The improvement in EFS for midostaurin over placebo was evident from approximately 3 months. At 1 year EFS was 43% [95% CI 0.38–0.49) for midostaurin versus 31% [95% CI 0.27–0.36] for placebo, and the difference was sustained at 5 years (28% [95% CI 0.23–0.33] vs. 19% [95% CI 0.15–0.24], respectively).

Figure 12 Event-free survival – non-censored at the time of SCT (FAS population)



RATIFY CSR.[16]
CI, confidence interval; CSR, clinical study report; FAS, full analysis set; FLT3, FMS-like tyrosine kinase 3; SCT, stem cell transplantation.

4.7.6 Event-free survival sensitivity analyses

Sensitivity analyses censoring at SCT and varying the definition of a CR support the primary EFS analysis

Event-free survival censored at SCT

Consistent with results from the key secondary endpoint (EFS), median EFS when censored at SCT demonstrated superiority for midostaurin over placebo (8.3 months vs. 2.8 months, respectively) with an HR of 0.81 (95% CI 0.68–0.98; p=0.0124). Superiority for EFS for midostaurin over placebo was

maintained at 1 year (43% [95% CI 0.38–0.49]) vs. 30% [95% CI 0.25–0.35], respectively) and 5 years (25% [95% CI 0.20–0.31] vs. 21% [95% CI 0.16–0.27], respectively).

Event-free survival using different CR definitions

Sensitivity analyses using different definitions for EFS are presented in Table 12. Results for EFS when considering all CRs (rather than those occurring within 60 days of treatment initiation) were consistent with those for the main EFS assessment (median 10.2 months for midostaurin vs. 5.6 months for placebo; HR 0.73 [95% CI 0.61–0.87]) demonstrating significant prolongation of EFS with midostaurin. These data are considered to reflect the treatment benefit that would be seen in clinical practice more accurately than the primary EFS analysis as, in routine clinical practice, the time to achieve CR is not taken into consideration. Other sensitivity analyses also consistently demonstrated a statistically significant benefit for midostaurin over placebo (Table 12).

Table 12 EFS sensitivity analyses (FAS and PPS populations)

Sensitivity analysis (population assessed)	Median EFS (95% CI), months		HR (95% CI)
	Midostaurin N=307	Placebo N=303	
Considering all CRs (FAS)	10.2 (8.1–13.9)	5.6 (2.9, 6.7)	0.73 (0.61–0.88)
Considering all CRs up to 30 days after treatment discontinuation (FAS)	11.4 (8.7–15.3)	6.2 (4.8–7.5)	0.74 (0.62–0.88)
EFS (PPS)	8.05 (5.3–0.7)	4.6 (2.0–6.2)	0.82 (0.69–0.99)
Not considering relapse events if observed after ≥2 consecutive missing assessments (FAS)	8.2 (5.4–10.7)	3.0 (1.9–5.9)	0.79 (0.67–0.94)
Considering all treatment failures as occurring on date of randomisation + 1 day (FAS)	8.2 (5.4–10.7)	3.6 (0.0–5.9)	0.78 (0.66–0.93)

RATIFY CSR.[16]

CI, confidence interval; CR, complete remission; CSR, clinical study report; EFS, event-free survival; FAS, full analysis set; HR, hazard ratio; PPS, per protocol set.

4.7.7 Disease-free survival

Midostaurin significantly increased DFS by approximately 11 months

Using the protocol-specified definition of a CR (a CR within 60 days of treatment initiation), median DFS was significantly prolonged with midostaurin (26.7 months [95% CI 19.4–NE]) versus placebo (15.5 months [95% CI 11.3–23.5]) with an HR of 0.71 (95% CI 0.55–0.92; p = 0.005; Figure 13). The superiority of midostaurin over placebo for DFS was evident at 1 year (71% [95% CI 0.64–0.76] vs. 57% [95% CI 0.49–0.64], respectively) and was maintained at 5 years (48% [95% CI 0.41–0.54) vs. 37% [95% CI 0.29–0.44], respectively).

[redacted]

RATIFY CSR.[16]
CI, confidence interval; CSR, clinical study report; FAS, full analysis set; FLT3, FMS-like tyrosine kinase 3; SCT, stem cell transplantation.

4.7.8 Disease-free survival secondary analyses and sensitivity analyses

Midostaurin significantly prolonged DFS from 14 to 28 months when considering all CRs

Sensitivity analysis: Disease-free survival considering all CRs

A sensitivity analysis considering all CRs demonstrated a greater benefit for midostaurin over placebo than was observed in the primary DFS analysis (median DFS: 28.1 months vs. 14.1 months, respectively; HR 0.66 [95% CI 0.52–0.85]; p=0.0006 one-sided). These data are more reflective of clinical practice where any CR would be considered.

Sensitivity analysis: Disease-free survival censored at SCT

Results for DFS when censoring at SCT were consistent with those without censoring. Median DFS was [redacted] months for midostaurin and [redacted] months for placebo, with patients receiving midostaurin experiencing a [redacted] reduced risk of death or relapse compared with those receiving placebo (HR [redacted] [95% CI [redacted]; p=[redacted]). The improvements in DFS for midostaurin over placebo were maintained up to 5 years ([redacted] [95% CI [redacted]] vs. [redacted] [95% CI [redacted]], respectively).

4.7.9 Remission duration

Midostaurin increased the duration of remission and significantly reduced the risk of relapse or death

The risk of relapse or death due to AML for patients in the midostaurin arm who had achieved a CR was reduced by [redacted] (HR [redacted] [95% CI [redacted]) compared to those who had achieved a CR in the placebo arm. The median duration of remission for midostaurin was [redacted] months (95% CI [redacted]–NE) and [redacted] months (95% CI [redacted]–NE) for placebo. Censoring for SCT, midostaurin was associated with reduction in the risk of relapse or death of [redacted] (HR [redacted] [95% CI [redacted]) and median duration of remission was [redacted] months (95% CI [redacted]–NE) in the midostaurin arm versus [redacted] months (95% CI [redacted]–NE) in the placebo arm.

4.7.10 Treatment-free interval

Midostaurin provided a clinically meaningful prolongation of the treatment-free interval of almost [redacted] months compared with placebo

A post hoc analysis assessed the impact of midostaurin on treatment-free interval (TFI), calculated as the difference between mean EFS and mean treatment period. Midostaurin increased the TFI from [redacted] months to [redacted] months, representing a clinically significant prolongation of [redacted] months.[30]

4.8 Subgroup analysis

The benefits of midostaurin over placebo were evident across all subgroups considered

Subgroup analyses were conducted for OS and EFS endpoints. Subgroups assessed included breakdown by FLT3 randomisation/mutation/subtype, gender, region, race, WBC count and cytogenetics. For both endpoints a consistent benefit was observed for midostaurin over placebo amongst most subgroups except for certain subgroups where the population size was small with large variability.

4.9 Meta-analysis

Only one relevant RCT was identified. Thus a meta-analysis could not be performed.

4.10 Indirect and mixed treatment comparisons

The RCT identified compares midostaurin (added to cytarabine plus daunorubicin) versus cytarabine plus daunorubicin, the relevant comparator for the economic evaluation. Therefore an indirect treatment comparison was not performed.

4.11 Non-randomised and non-controlled evidence

List of relevant non-randomised and non-controlled evidence

Two relevant non-randomised controlled trials for midostaurin in patients with newly diagnosed AML were identified (summarised in Table 13). The first was a phase 1b study assessing the efficacy, safety and pharmacokinetics of several dosing schedules for midostaurin (100 mg BID for 14, 21 and 28 days and 50 mg BID for 14 days) in addition to standard chemotherapy.[61] This study identified midostaurin 50 mg BID given sequentially with daunorubicin plus cytarabine as an appropriate regimen for further investigation.

The second was a phase 2 open-label single-arm assessment of the efficacy and safety of midostaurin in addition to standard chemotherapy followed by midostaurin monotherapy in patients with newly diagnosed FLT3-ITD-positive AML.[17,18] This study demonstrated the feasibility and activity of midostaurin 50 mg BID in combination with daunorubicin and cytarabine – the regimen investigated further in the phase 3 RATIFY trial – for patients with newly diagnosed FLT3–ITD-positive AML.

Quality assessment for the two studies is provided in Table 14 and results for the two studies are summarised in Table 15.

Table 13 List of relevant non-randomised and non-controlled evidence

Study number (acronym)	Intervention	Population	Objective	Primary study reference	Justification for inclusion
Phase 1b study Novartis-CPKC412A2106 NCT00093600	Midostaurin, daunorubicin, cytarabine	Patients with previously untreated AML 18–60 years of age with Karnofsky Performance Status ≥70.	Primary objectives: • To evaluate the safety and tolerability of midostaurin (50 mg and 100 mg BID) in combination with daunorubicin and cytarabine (administered concomitantly or sequentially) • To determine the effect of midostaurin on the pharmacokinetics of daunorubicin and cytarabine Secondary objectives: • To evaluate the efficacy of midostaurin by measuring the response rate, DFS, and OS. • To investigate the effect of FLT3 mutational status on the rate of patient response	Stone *et al*., 2012[61]	Provides data for the efficacy, safety and tolerability of midostaurin in combination with daunorubicin and cytarabine
Open-label, single-arm, phase 2 study AMLSG 16-10 (NCT01477606)	Midostaurin, daunorubicin, cytarabine	Patients 18-70 years of age with newly diagnosed FLT3-ITD positive AML	To assess the feasibility and efficacy of midostaurin in combination with intensive induction therapy and as single-agent maintenance therapy after allogeneic SCT or HiDAC.	Schlenk *et al*., 2015; [17] Schlenk *et al*., 2016[18]	Provides data for the efficacy of midostaurin in combination with intensive induction therapy

Stone *et al*., 2012;[61] Schlenk *et al*., 2015; [17] Schlenk *et al*., 2016[18]

allogeneic SCT, allogeneic STC; AML, acute myeloid leukaemia; BID, twice daily; DFS, disease-free survival; FLT3, FMS-like tyrosine kinase receptor-3; HiDAC, high dose cytarabine; ITD, internal tandem duplication; NR, not reported; OS, overall survival; SCT, stem cell transplantation.

Table 14 Quality assessment for relevant non-RCTs

Study question	How is the question addressed in the study?	Risk of bias (High, Low, Unclear)
Phase 1b study, Stone *et al.*, 2012[61]		
Is there concern that the target condition as defined by the reference standard does not match the review question? [Concern: Low, Concern: High, Unclear]	Efficacy and safety data were reported for patients with FLT3-ITD	Low
Were eligibility criteria clear?	Inclusion and exclusion criteria were clearly described	Low
Was a consecutive or random sample of patients enrolled?	Not explicitly stated	Unclear
Is there a low risk of sampling bias due to a low enrollment of population of potentially eligible people and no other concern about "sampling frame"?	Data were provided separately for FLT3-ITD AML patients included in the study	Low
Were the groups similar at baseline regarding the most important prognostic indicators?	Not reported in record	Unclear
Were interventions adequately described?	The interventions were well described within each treatment schedule	Low
Were co-interventions avoided or similar?	Co-interventions were similar for all patients	Low
Appropriate statistical analysis?	No information was provided on statistical methods	Unclear
Intention to treat analysis	No information was provided on statistical methods	Unclear
If multicenter, was this accounted for in analysis?	No information was provided on statistical methods	Unclear
Were potential confounders properly accounted for?	No information was provided on statistical methods	Unclear
Were the outcome measures valid and reliable (consistent and reproducible)?	Outcomes measures were well defined and considered reliable	Low
What is the risk of reporting bias due to selective outcome reporting?	Results from all pre-specified outcomes were reported	Low
Clear reporting with no discrepancies	No discrepancies were found	Low
Are there other risks of bias?	No additional risks of bias	Low
Phase 2 study, AMLSG 16-10; Schlenk *et al*., 2015;[17] Schlenk *et al*., 2016[18]		
Is there concern that the target condition as defined by the reference standard does not match the review question? [Concern: Low, Concern: High, Unclear]	All patients had FLT3-ITD AML	Low
Were eligibility criteria clear?	The study enrolled adult patients (age 18–70 years) with newly diagnosed FLT3-ITD-positive AML. Patients with acute promyelocytic leukaemia were not eligible	Low
Was a consecutive or random sample of patients enrolled?	Not explicitly stated but assume was a random sample	Unclear

Study question	How is the question addressed in the study?	Risk of bias (High, Low, Unclear)
Is there a low risk of sampling bias due to a low enrollment of population of potentially eligible people and no other concern about "sampling frame"?	All enrolled patients had FLT3-ITD AML	Low
Were the groups similar at baseline regarding the most important prognostic indicators?	NA, single-arm study	Low
Were interventions adequately described?	Yes, dose, frequency, and duration were well defined	Low
Were co-interventions avoided or similar?	NA, single-arm study	Low
Appropriate statistical analysis?	Yes, appropriate methods were used for analysis of the primary and secondary endpoints	Low
Intention to treat analysis	Yes, analysis of efficacy was based on the full analysis set	Loq
If multicenter, was this accounted for in analysis?	Not reported in record	Unclear
Were potential confounders properly accounted for?	Not reported in record	Unclear
Were the outcome measures valid and reliable (consistent and reproducible)?	Death and response outcomes are valid and reproducible	Low
What is the risk of reporting bias due to selective outcome reporting?	No outcomes were listed *a priori*	Unclear
Clear reporting with no discrepancies	No discrepancies were found	Low
Are there other risks of bias?	No additional risks of bias	Low

Schlenk *et al*., 2015;[17] Schlenk *et al*., 2016[18]; Stone *et al*., 2012.[61]

AML, acute myeloid leukaemia; FLT3, FMS-like tyrosine kinase receptor-3; ITD, internal tandem duplication; NA, not applicable; RCT, randomised controlled trial.

Table 15 Summary of outcomes for the relevant non-RCTs

Study	Patients	Treatment/ Duration of follow-up	Efficacy outcome 1	Efficacy outcome 2	Efficacy outcome 3	Safety (and information on dose modification)
Stone *et al.,* 2012[61] Phase 1b dose-ranging study Novartis-CPKC412A2106	N=69 Patients receiving dose schedule III (N=40) Male, 60% Median age, 48.5 years Karnofsky PS: 100, 20% 90, 35% Cytogenetics: Favourable, 13% Normal, 38%	**Midostaurin plus chemotherapy** Midostaurin 50 mg or 100 mg, oral, BID concomitant or sequential with chemotherapy Induction therapy: Daunorubicin 60 mg/m^2 IV plus cytarabine 200 mg/m^2 Consolidation therapy: Cytarabine 3 g/m^2 IV	CR rate Overall, 80% FLT3 mutation-positive: 92% FLT3 wild-type: 74%	OS: FLT3 mutation-positive vs. wild-type: 1-year: 85% vs. 78% 2-year: 62% vs. 52%	1-year DFS: FLT3 mutation-positive vs. wild-type: 50% vs. 60%	Grade 3/4 AEs in >10%: Neutropenia: 73% Thrombocytopenia: 73% Anaemia: 43% Hypokalaemia: 18% Pyrexia: 15%
Schlenk *et al.,* 2015[17,19] Open-label single-arm phase 2 study AMLSG 16-10 (NCT01477606)	N=149 Median (range) age, 54 (25–70) years Male, 42%	**Midostaurin plus chemotherapy followed by midostaurin monotherapy:** Induction therapy (1–2 cycles): Daunorubicin 60 mg/m^2 IV days 1–3 and cytarabine 200 mg/ m^2 continuously days 1–7, midostaurin 50 mg BID (from day 8 to 48 hours	Response to induction therapy cycle 1: CR rate, 58.5% PR rate, 20.4% Refractory disease, 15.0% Death, 6.1%	Overall response to induction therapy: CR rate, 74.8% Refractory disease, 17.7% Death, 7.5% At 25 months: Overall CR, [redacted] <60 years, [redacted] ≥60 years, [redacted]	Cumulative incidence of relapse at 12 months: allogeneic SCT, 9.2% HiDAC, 12%	Grade ≥3 toxicities in ≥10% of patients during 1st induction phase, % (n=125) Infection: 79.2 Gastrointestinal: 37.5 Metabolic: 32.8 Midostaurin interruption, dose-reduction or stopping during induction therapy: 55%

Study	Patients	Treatment/ Duration of follow-up	Efficacy outcome 1	Efficacy outcome 2	Efficacy outcome 3	Safety (and information on dose modification)
		before start of next cycle) Consolidation therapy: allogeneic SCT or age-adapted HiDAC and midostaurin (from day 6) Monotherapy: Midostaurin 50 mg and 100 mg, oral, BID for 1 year				Premature termination of midostaurin maintenance therapy: 80% Toxicity during maintenance phase: Haematological: 33% Gastrointestinal: 19% Fatigue: 9.5%
Schlenk *et al.,* 2016[18] Open-label single-arm phase 2 study AMLSG 16-10 (NCT01477606) second report	N=284 Median (range) age, 54 (18–70) years, Aged ≥ 60 years, 32%	**Midostaurin plus chemotherapy followed by midostaurin monotherapy:** As above, but with a dose reduction of 12.5% from the initial dose of midostaurin in case of comedication with strong CYP3A4 inhibitors	Response to induction therapy cycle 1: CR rate, 60% PR rate, 20% Refractory disease, 15% Death, 5%	Overall response to induction therapy: CR rate, 76% (same for <60 vs. ≥60 years) Refractory disease, 17.7% Death, 7.5% <60 years, 4% ≥60 years, 10%	Cumulative incidence of relapse and death after transplant at median follow-up of 18 months: 13% and 16%, respectively, and no significant difference between age groups Median OS: 25 months <60 years, 26 months ≥60 years, 23 months, p=0.15	55 grade 3/4 AEs attributed to midostaurin

References: Stone *et al*., 2012[61], Schlenk et al., 2015

AE, adverse event; allogeneic SCT, allogeneic SCT; AML, acute myeloid leukaemia; BID, twice daily; CR, complete remission; CYP, cytochrome P450; DFS, disease-free survival; FLT3, FMS-like tyrosine kinase receptor-3; HiDAC, high-dose cytarabine; IV, intravenous; OS, overall survival; PR, partial remission; PS, performance status; RCT, randomised controlled trial; SCT, stem cell transplantation.

4.11.1 Phase 1b study

Design and objectives

This was a phase Ib trial in newly diagnosed patients with FLT3 wild-type or mutation-positive AML to examine the safety, efficacy, and pharmacokinetics of combining midostaurin with an induction regimen of daunorubicin plus cytarabine followed by high-dose cytarabine consolidation.[61]

Patients

The study included patients aged 18–60 years with AML (as defined by WHO criteria) and Karnofsky Performance Status score of ≥70. Patients with impaired gastrointestinal function, ejection fraction of <50%, pulmonary infiltrates, history of or newly diagnosed myelodysplastic syndrome, history of myeloproliferative disease or secondary AML, and those who had received any previous chemotherapy (other than hydroxyurea) or radiation therapy, or an investigational agent within 30 days of day 1 or surgery within 14 days of day 1 were excluded.

Endpoints

Efficacy endpoints included the CR rate (definition not provided), OS (defined as the time from first dose of any study drug to death; otherwise, patients were censored at the date last known to be alive) and DFS (defined as the time from first CR to relapse or death and was not censored for SCT). For safety analyses, all AEs were recorded regardless of causality.

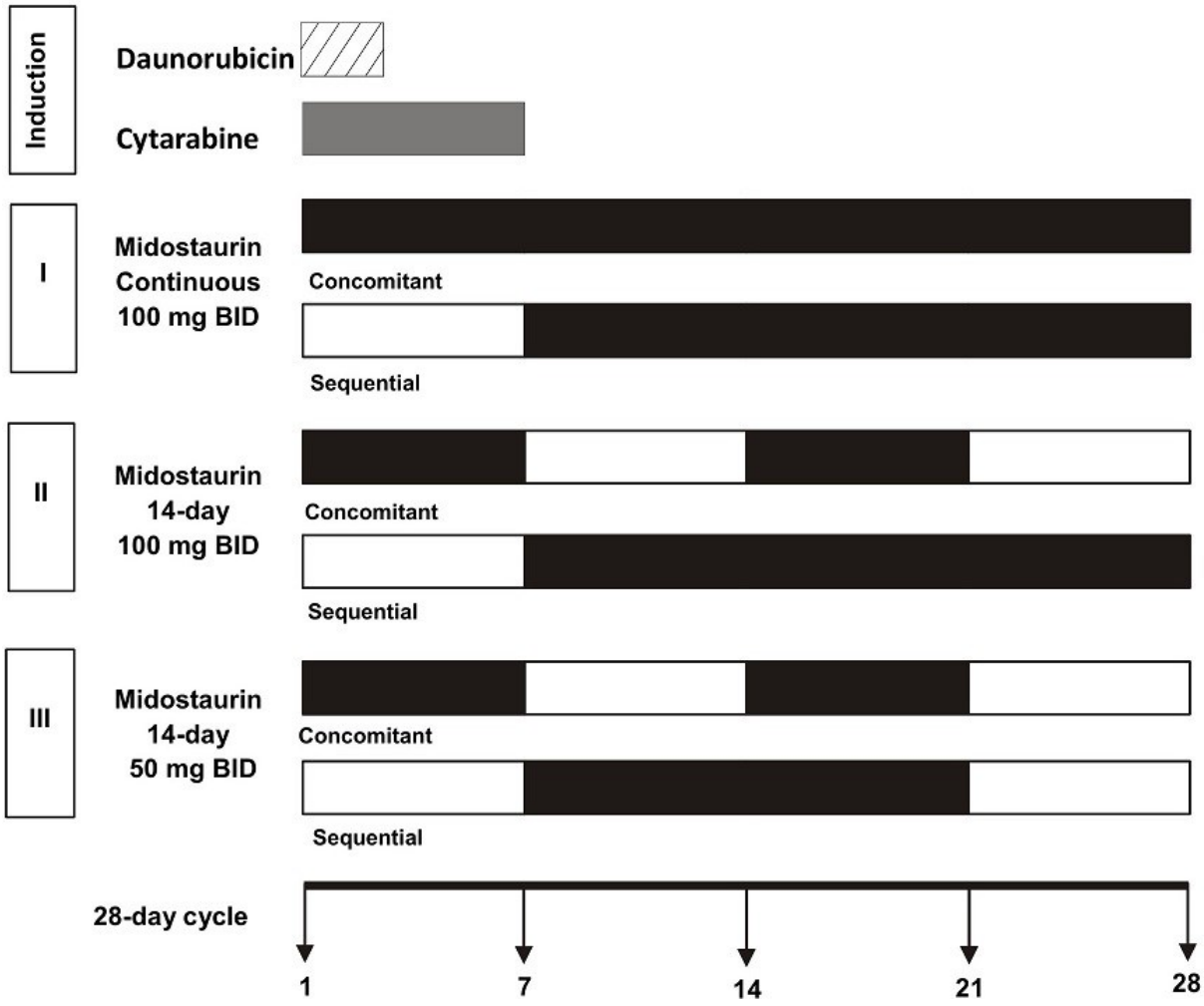
Treatment

Treatment consisted of induction therapy administered as one of three dosing schedules, consolidation therapy followed by midostaurin monotherapy.

Induction therapy consisted of midostaurin either concomitant or sequential to conventional chemotherapy (daunorubicin 60 mg/m^2 [days 1–3] and cytarabine 200 mg/m^2 [days 1–7]) according to the following three schedules (Figure 14):

- Dosing schedule 1: midostaurin 100 mg BID days 1–28 days (concomitant) or days 8–28 days (sequential)
- Dosing schedule 2: midostaurin 100 mg BID for 14 days (concomitant [days 1–7 and 14–21] or sequential [days 8–21])
- Dosing schedule 3: midostaurin 50 mg BID for 14 days (concomitant [days 1–7 and 14–21] or sequential [days 8–21]).

Figure 14 Dosing schedules for induction therapy in the phase 1b trial



Stone et al., 2012[61]
Schema of dose and schedule of midostaurin administration. Daunorubicin and cytarabine induction (3 + 7) and high-dose cytarabine post-remission therapy was administered on a standard schedule. In addition, patients received midostaurin (indicated by red bars) on one of three dose schedules: I. midostaurin 100 mg twice daily (BID) for 21 or 28 days; II. midostaurin 100 mg twice daily for 14 days; or III. midostaurin 50 mg twice daily for 14 days. Within each dose schedule, patients were assigned to receive midostaurin on day 1 (concomitant with chemotherapy, days 1-7; 14-21 in dose schedules II and III) or day 8 (sequential with chemotherapy; days 8-21 in dose schedules II and III).

A bone marrow biopsy was done to determine whether a second cycle of induction therapy (daunorubicin 60 mg/m^2 [days 1–2]; cytarabine 200 mg/m^2 [days 1–5]; and midostaurin [as above]) should be administered. Patients who did not achieve CR at the end of cycle 2 were discontinued from the study.

Consolidation therapy was administered to patients achieving a CR at the end of induction cycles 1 or 2. Consolidation therapy consisted of three cycles of high-dose cytarabine 3 g/m^2 IV over 3 hours every 12 hours on days 1, 3, and 5 for six doses in addition to midostaurin administered according to the schedule assigned during induction. After completion of planned chemotherapy, patients could

receive midostaurin monotherapy for 14 days in each 28-day cycle according to the patient's original assignment.

Patients and patient disposition

A total of 69 patients were included in the study; 29 patients received midostaurin 100 mg BID (schedule 1 or 2) and 23 (79%) of these patients discontinued therapy early. A total of 40 patients received midostaurin 50 mg BID (20 as sequential therapy to chemotherapy and 20 as concomitant therapy) with 18 (45%) discontinuing therapy early. Of these 40 patients, 31 and 9 patients received one and two cycles of induction therapy, respectively, and 26 received one or more cycles of consolidation therapy. Five patients received midostaurin monotherapy (two for <2 months [both of whom were in CR, although one relapsed] and three for >2 months [all three were in CR and remained in CR at the last follow-up]). Of the 40 patients who received midostaurin 50 mg BID, mean (median) age was 39 (48.5) years, over half (55%) had a Karnofsky Performance Status score of ≥90, and 52% had a cytogenetic profile that was either favourable or normal. There were 13 and 27 patients in the FLT3 mutation-positive and FLT3 wild-type groups, respectively.

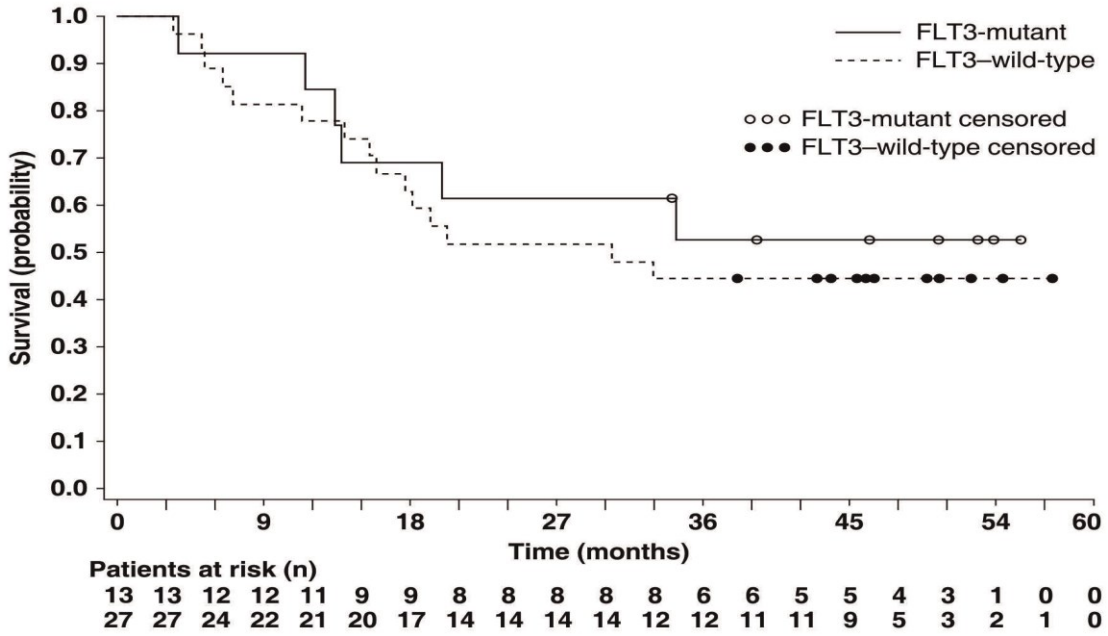
Efficacy results

Midostaurin 50 mg BID in combination with daunorubicin plus cytarabine demonstrated promising activity in patients with newly diagnosed AML providing an overall CR rate of 80%

Note that efficacy results are presented for dosing schedule 3 (midostaurin 50 mg BID) unless specified. The overall CR rate was 80%, and there was no difference between the concomitant and sequential dosing schedules. Most patients (92%) in the FLT3 mutation-positive group achieved a CR and 74% of patients in the FLT3 wild-type group achieved a CR. In both the FLT3 mutation-positive and wild-type groups, 75% of patients achieving a CR did so after one treatment cycle. For patients receiving dosing schedule 1, the overall CR rate was 45%, with 83% (5/6 patients) and 35% (8/23 patients) in the FLT3 mutation-positive and FLT3 wild-type groups, respectively, achieving CR).

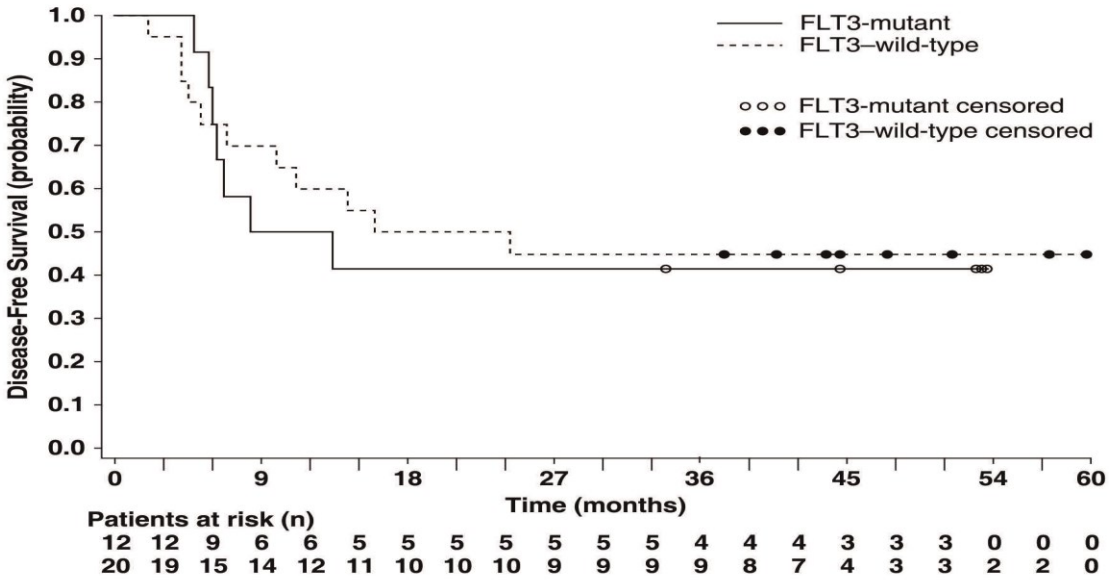
OS probabilities for the FLT3 mutation-positive and FLT3 wild-type groups were similar at 1 year (0.85 [95% CI 0.65–1.0] and 0.78 [95% CI 0.62–0.93], respectively) and 2 years (0.62 [95% CI 0.35–0.88] and 0.52 [96% CI 0.33–0.71], respectively) (Figure 15). There was also little difference between the groups in DFS at 1 year (0.50 [95% CI 0.22–0.78] for the FLT3 mutation-positive group and 0.60 [95% CI 0.39–0.81] for the FLT3 wild-type group; Figure 16).

Figure 15 OS in the phase 1b study



Stone *et al*., 2012.[61]
OS, overall survival.

Figure 16 DFS in the phase 1b trial



Stone *et al*., 2012.[61]
DFS, disease-free survival.

Safety results

Midostaurin 50 mg BID was generally well tolerated with 14/20 (70%) patients in each arm completing therapy. More patients in the sequential and concomitant arms completed all three cycles of consolidation therapy (75% vs. 50%, respectively), although the discontinuation rate was higher in the concomitant arm (55%) than in the sequential arm (35%). Median exposure to midostaurin was 130 days (range 7–975 days) for the sequential arm and 89 days (range 8–1,016 days) for the concomitant arm.

Nausea (grade 1/2, 83%), diarrhoea (grade 1/2, 68%; grade 3/4, 3%) and vomiting (grade 1/2, 65%) were the most common non-haematologic AEs during the induction and consolidation phases (Table 16). One episode of grade 3 diarrhoea was observed, lasting 1 day and resolving without treatment. No grade 3/4 nausea or vomiting occurred, grade 3/4 hepatic toxicity was infrequent and no grade 3/4 peripheral oedema was observed. Overall, the toxicity reported was similar in the sequential and concomitant schedules. No deaths were recorded in either arm on treatment or within 28 days of the last dose of study drug.

Table 16 All AEs occurring during the induction and consolidation treatment phases of the phase 1b trial

Event, n (%)	Concomitant (N = 20)		Sequential (N = 20)		Total (N = 40)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Nausea	16 (80)	0	17 (85)	0	33 (83)	0
Neutropenia (including febrile)	2 (10)	16 (80)	0	13 (65)	2 (5)	29 (73)
Thrombocytopenia	1 (5)	13 (65)	0	16 (80)	1 (3)	29 (73)
Diarrhoea	13 (65)	0	14 (70)	1 (5)	27 (68)	1 (3)
Vomiting	12 (60)	0	14 (70)	0	26 (65)	0
Hypokalaemia	10 (50)	3 (15)	8 (40)	4 (20)	18 (45)	7 (18)
Pyrexia	8 (40)	0	9 (45)	6 (30)	17 (43)	6 (15)
Headache	9 (45)	1 (5)	11 (55)	0	20 (50)	1 (3)
Anaemia	1 (5)	6 (30)	1 (5)	11 (55)	2 (5)	17 (43)
Insomnia	10 (50)	0	9 (45)	0	19 (48)	0
Constipation	9 (45)	0	9 (45)	0	18 (45)	0
Chills	8 (40)	0	9 (45)	0	17 (43)	0
Petechiae	5 (25)	2 (10)	10 (50)	0	15 (38)	2 (5)
Cough	6 (30)	0	9 (45)	0	15 (38)	0
Hypomagnesaemia	9 (45)	0	6 (30)	0	15 (38)	0
Rash	8 (40)	1 (5)	6 (30)	0	14 (35)	1 (3)
Abdominal pain	3 (15)	0	10 (50)	1 (5)	13 (33)	1 (3)
Peripheral oedema	9 (45)	0	5 (25)	0	14 (35)	0
Epistaxis	5 (25)	0	4 (20)	3 (15)	9 (23)	3 (8)
Hypotension	8 (40)	0	4 (20)	0	12 (30)	0
ALT increased	4 (20)	0	4 (20)	3 (15)	8 (20)	3 (8)
Alopecia	7 (35)	0	4 (20)	0	11 (28)	0
Decreased appetite	5 (25)	0	5 (25)	1 (5)	10 (25)	1 (3)
Hypocalcaemia	7 (35)	1 (5)	2 (10)	1 (5)	9 (23)	2 (5)
Pruritus	6 (30)	1 (5)	4 (20)	0	10 (25)	1 (3)
Anorexia	4 (20)	0	5 (25)	1 (5)	9 (23)	1 (3)

Event, n (%)	Concomitant (N = 20)		Sequential (N = 20)		Total (N = 40)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Anxiety	4 (20)	0	5 (25)	1 (5)	9 (23)	1 (3)
AST increased	3 (15)	1 (5)	3 (15)	3 (15)	6 (15)	4 (10)
Depression	2 (10)	0	8 (40)	0	10 (25)	0
Fatigue	5 (25)	0	5 (25)	0	10 (25)	0
Mucosal inflammation	4 (20)	1 (5)	5 (25)	0	9 (23)	1 (3)
Blood bilirubin increased	4 (20)	1 (5)	3 (15)	1 (5)	7 (18)	2 (5)
Transfusion reaction	4 (20)	1 (5)	2 (10)	2 (10)	6 (15)	3 (8)

Stone *et al*., 2012.[61]
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

A total of 18 gastrointestinal grade 3/4 AEs were experienced with the 100 mg dose, with seven (24%) patients experiencing each of nausea and vomiting, and four (14%) patients experiencing diarrhoea. Intolerable grade 2 gastrointestinal AEs led to discontinuation in two patients.

Conclusions

Midostaurin 50 mg BID in combination with daunorubicin plus cytarabine demonstrated promising activity in patients with newly diagnosed AML providing an overall CR rate of 80%. The sequential regimen was better tolerated than the concomitant regimen and was recommended for further study. In contrast, the higher dose of 100 mg BID lead to discontinuation in approximately 80% of patients.

4.11.2 Phase 2 study

Design and objectives

This study was a single-arm phase 2 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.[17-20] A specific stated primary objective was to compare outcomes for patients aged 18–60 years with those aged 61–70 years.

Patients

The study included patients aged 18–70 years with newly diagnosed FLT3-ITD-positive AML, with a WHO Performance Status of ≤2 who were considered eligible for intensive chemotherapy and had received no prior chemotherapy for leukaemia except hydroxyurea to placebo hyperleukocytosis (received for ≤7 days).

Patients with specific recurrent genetic abnormalities (*RUNX1-RUNX1T1, CBFB-MYH11* and *PML-RARA)*, an ejection fraction [redacted] within [redacted] days of day, organ insufficiency, uncontrolled infection, severe neurological or psychiatric disorder interfering with ability to give informed consent, a “currently

active" second malignancy other than non-melanoma skin cancers, HIV, a bleeding disorder independent of leukaemia, and pregnant or nursing women were excluded.

Endpoints

The primary endpoint was EFS after [redacted] 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). Relapse-free survival (RFS) was defined as the time to relapse or death in CR for patients achieving a CR. Other endpoints included OS and CR rate.

Treatment

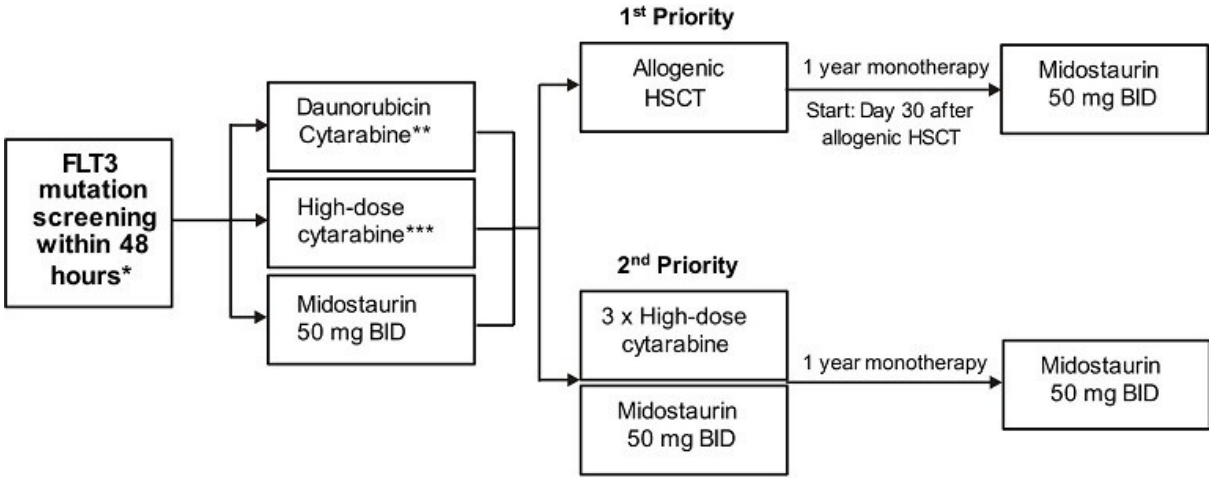
Treatment consisted of induction and consolidation followed by midostaurin monotherapy given for up to 1 year (Figure 17). Induction therapy consisted of daunorubicin 60 mg/m² (days 1–3), cytarabine 200 mg/m² (continuously, days 1–7) and midostaurin 50 mg BID (from day 8 to 48 hours before start of the next treatment cycle).

Response (evaluated using standard criteria defined by the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukaemia[62]) was assessed by performing a bone marrow aspiration between day 21 and day 28. Patients achieving a PR could receive an optional second induction cycle. Those achieving a CR after either induction cycle could receive a single cycle of consolidation therapy (consolidation cycle 1) consisting of high-dose cytarabine (total dose 18 g/m^2 and 6 g/m^2 for patients aged 18–65 and >65 years, respectively, given on days 1, 3 and 5) plus midostaurin 50 mg BID (from day 6 until 48 hours before progressing to further consolidation therapy).

As a first priority, further consolidation therapy consisted of allogeneic SCT from a matched donor. Patients ineligible for allogeneic SCT (i.e. with WHO Performance Status >2, European Group for Bone Marrow Transplantation Score >4, creatinine clearance <40 mL/minute, left ventricular ejection fraction <40%, pulmonary diffusion capacity <40%, bilirubin >2 x upper limit of normal, aspartate aminotransferase and alanine aminotransferase >3 x upper limit of normal) or those with no compatible donor or not giving consent, received consolidation therapy consisting of three cycles of high-dose cytarabine plus midostaurin (consolidation cycles 2–4).

Following consolidation therapy, all patients were to receive midostaurin monotherapy (50 mg BID) for 1 year so long as the patient remained in CR (assessed every 3 months).

Figure 17 Design of the phase 2 trial



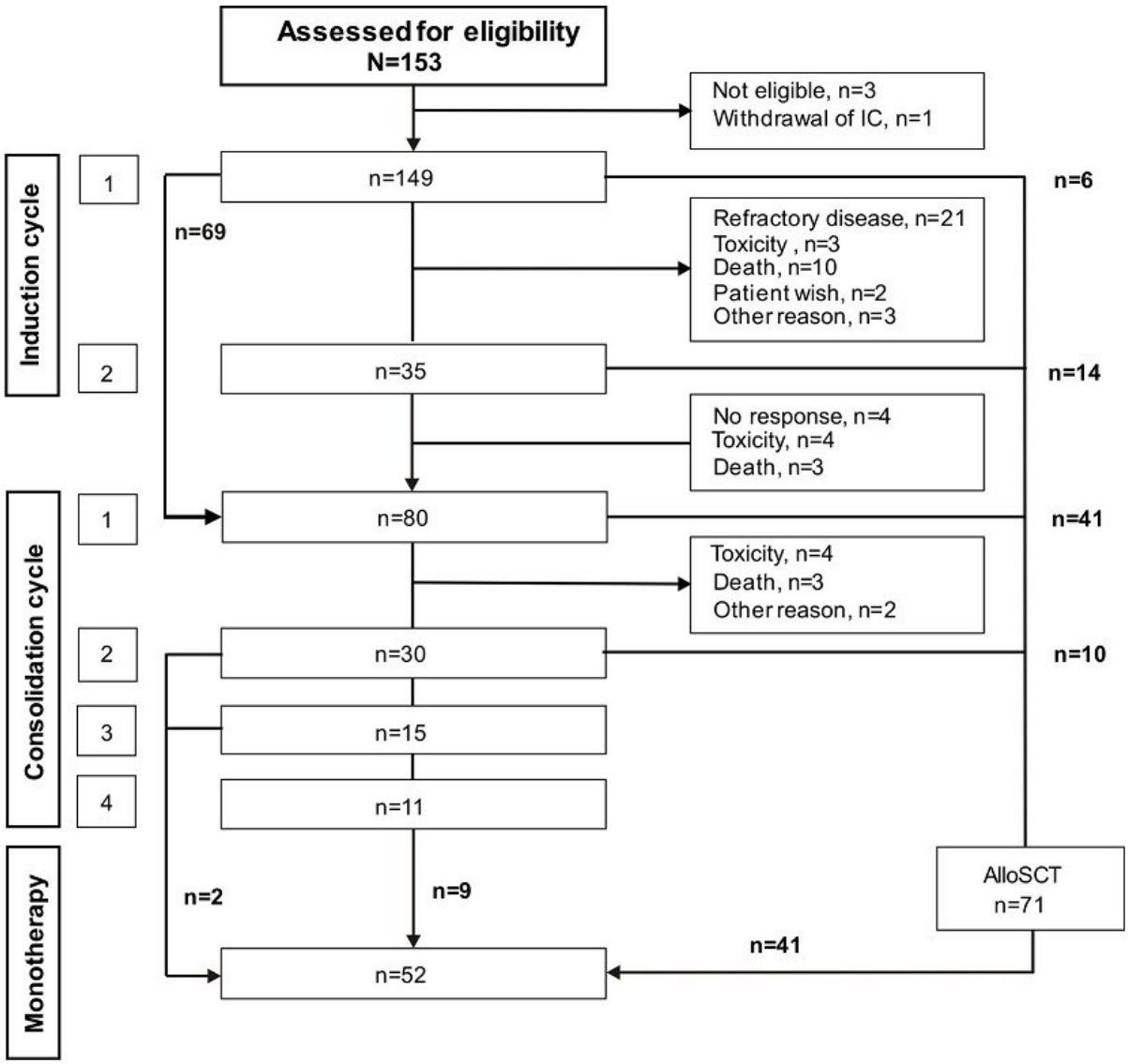
Phase 2 study protocol[20] and CSR[19]
* Patients may receive hydroxyurea during screening phase
** Optional 2nd cycle in patients achieving PR after cycle I
*** Cytarabine: 18-65 years, 3g/m², q12hr, day 1, 3, 5; >65 years, 1g/m², q12hr, day 1, 3, 5; optional for patients before allogeneic SCT.

BID, twice daily; CSR, clinical study report; HSCT, haematopoietic stem cell transplantation; PR, partial remission; q12hr, every 12 hours; SCT, stem cell transplantation.

Patient disposition and baseline demographics

Patient disposition in the study is presented in Figure 18. A total of 149 patients received induction therapy; of these, six proceeded straight to allogeneic SCT, 69 proceeded to consolidation cycle 1, 35 patients received a second induction cycle and the rest withdrew from the study. Of the 35 patients receiving a second induction cycle, 14 progressed to allogeneic SCT and 11 progressed to consolidation cycle 1 (in total 80 patients received consolidation cycle 1). A total of 41 patients who received consolidation cycle 1 and 10 who received consolidation cycle 2 progressed to allogeneic SCT (in total 71 patients received allogeneic SCT). A total of 52 patients received maintenance therapy (41 after receiving allogeneic SCT and 11 after receiving additional consolidation therapy). The main reasons for withdrawal from induction or consolidation chemotherapy included refractory disease/relapse (n=25, 16.7%), death (n=12, 8.0%) and AEs (n=10, 6.7%). Thus therapy was generally well tolerated.

Figure 18 Patient disposition in the phase 2 trial



Allogeneic SCT, allogeneic stem cell transplant; IC, informed consent.

Table 17 Baseline demographics and disease characteristics in the phase 2 trial

Demographic variables	All patients (N=145)	Patients ≤60 years old (N=99)	Patients >60 years old (N=46)
Age, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Men	[redacted]	[redacted]	[redacted]
Women	[redacted]	[redacted]	[redacted]
ECOG Performance status, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
FLT3 mutation status TKD, n (%)			
FLT-3 TKD	[redacted]	[redacted]	[redacted]
FLT-3 ITD ratio ≤0.50	[redacted]	[redacted]	[redacted]
FLT-3 ITD ratio >0.50	[redacted]	[redacted]	[redacted]

Phase 2 study CSR.[19]

CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FLT, FMS-like tyrosine kinase; ITD, internal tandem duplication; SD, standard deviation; TKD, tyrosine kinase domain.

Baseline demographics and disease characteristics are presented in Table 17. A total of [redacted] patients were included in the study, [redacted] were aged ≤60 years (median [redacted] years) and [redacted] were aged >60 years (median [redacted] years). Men and women were evenly distributed in the >60 years group, but there were more women ([redacted]) than men in the ≤60 years group. Approximately [redacted] of both groups had ECOG Performance Status 0 or 1. Only [redacted] of each group carried the FLT3 TKD mutation with the rest being evenly distributed between the high (>0.50) and wild-type (≤0.50) ITD allelic ratios.

Efficacy results

Midostaurin 50 mg BID sequential therapy in combination with daunorubicin plus cytarabine is feasible for newly diagnosed FLT-mutation-positive AML in patients up to 70 years of age; induction therapy achieves CR in approximately [redacted] of patients

Data are reported for a median follow-up of [redacted] months and are summarised in Table 18.

Table 18 Summary of efficacy results for the phase 2 trial

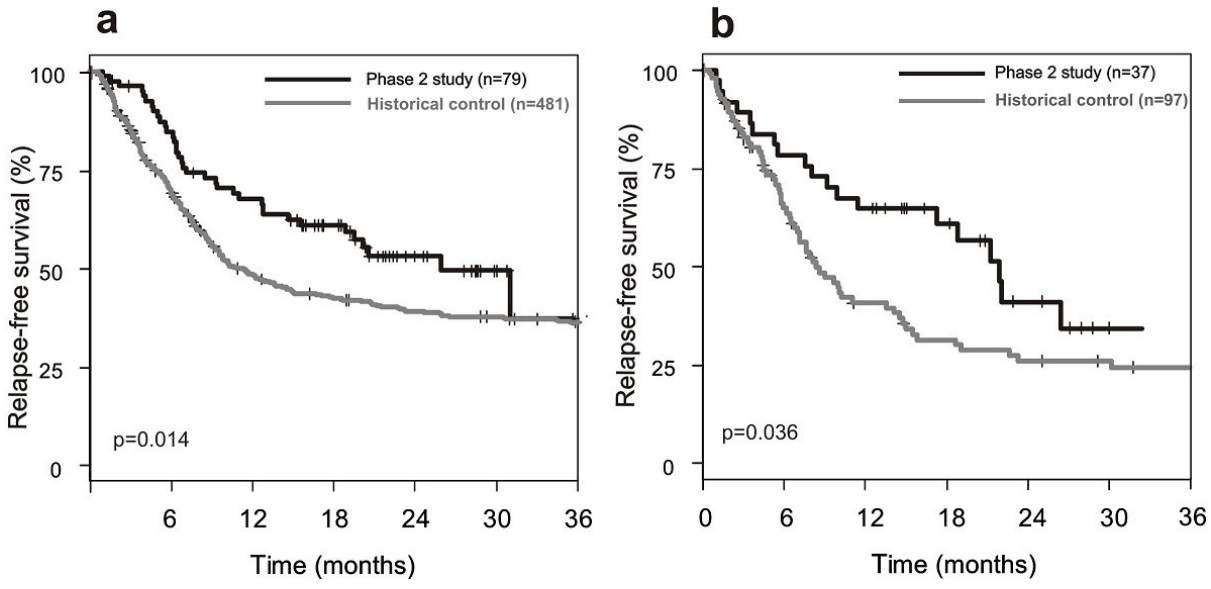
Endpoint	All patients (N=145)	Aged ≤60 years (N=99)	Aged >60 years (N=46)
CR, n (%)	[redacted]	[redacted]	[redacted]
EFS			
Median EFS, months	[redacted]	[redacted]	[redacted]
2-year EFS, %	[redacted]	[redacted]	[redacted]
OS			
Median OS, months	[redacted]	[redacted]	[redacted]
2-year OS, %	[redacted]	[redacted]	[redacted]
RFS			
Median RFS, months	[redacted]	[redacted]	[redacted]
2-year RFS, %	[redacted]	[redacted]	[redacted]
Cumulative incidence of relapse, %	[redacted]	[redacted]	[redacted]
Cumulative incidence of death, %	[redacted]	[redacted]	[redacted]

Phase 2 study CSR.[19]

CR, complete remission; CSR, clinical study report; EFS, event-free survival; OS, overall survival; RFS, relapse-free survival.

Overall, [redacted] ([redacted]) patients achieved a CR, with [redacted] and [redacted] of the younger and older patients, respectively, achieving a CR. For all efficacy endpoints, outcomes were somewhat better in the younger patients. However, an exploratory analyses comparing trial data with historical controls found that RFS was significantly better in patients treated with midostaurin than controls both for patients aged 18–≤60 years (p=0.014) and for those aged >60 years (p=0.036) (Figure 19).[17] Thus, the addition of midostaurin to standard chemotherapy improves outcomes in both older and younger patients.

Figure 19 RFS in patients treated with midostaurin in the phase 2 trial and historical controls: a) 18–<60 years; b) 60–70 years



Schlenk *et al.,* 2015.[17]

RFS, relapse-free survival.

Safety analysis

The median (range) duration of treatment during the study was [redacted] months ([redacted] months) for the total population, and was longer for younger patients ([redacted] months [[redacted] months]) than for older patients ([redacted] months [[redacted] months]).

Analysis of AEs is presented in Table 19. Most patients experienced treatment-related AEs ([redacted]) and [redacted] of patients discontinued midostaurin therapy due to AEs. The most frequently reported non-haematological treatment-related AEs were gastrointestinal AEs (nausea, vomiting and diarrhoea), but most were grade 1/2 in severity, and the only other non-haematological grade 3/4 AEs reported in more than 5% of patients overall was lung infection. Haematological AEs were the most frequently reported grade 3/4 treatment-related AEs, with decreased platelet counts, decreased haemoglobin and leukopenia being reported in [redacted], [redacted] and [redacted] of patients, respectively. Furthermore, grade 3/4 febrile neutropenia was reported in [redacted] of patients. The pattern of treatment-related AEs and their severity was largely similar in patients aged ≤60 years and >60 years, although the incidence of serious AEs and discontinuation of midostaurin for AEs were higher in older patients, and there were more on-study deaths in the older age group.

Table 19 Summary of the incidence of AEs and incidence of grade 3/4 treatment-related AEs occurring in ≥5% of patients in the phase 2 trial

Endpoint	All patients (N=144)	Aged ≤60 years (N=98)	Aged >60 years (N=46)
Any AE	[redacted]	[redacted]	[redacted]
Deaths (during study treatment and 30-day follow up period)	[redacted]	[redacted]	[redacted]
Other serious AEs	[redacted]	[redacted]	[redacted]
Withdrawn from midostaurin treatment due to AEs	[redacted]	[redacted]	[redacted]
Treatment-related AEs	[redacted]	[redacted]	[redacted]
Non-haematological treatment-related grade 3/4 AEs reported in ≥5% of patients, n (%)			
Nausea	[redacted]	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]	[redacted]
QT prolongation	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]
Device-related infection	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]
Gastrointestinal inflammation	[redacted]	[redacted]	[redacted]
ALT elevation	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Haematological treatment-related grade 3/4 AEs reported in ≥5% of patients, n (%)			
Decreased platelet count	[redacted]	[redacted]	[redacted]
Decreased haemoglobin	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]

Phase 2 study CSR.[19]

AE, adverse event; ALT, alanine aminotransferase; CSR, clinical study report;

Further follow-up

A later follow-up of this study reports the results for inclusion of a further 137 patients.[18] The total cohort consisted of 284 patients having a median age of 54 years, of whom approximately one-third (32%) were ≥60 years of age. The overall response rate after induction therapy was 76% and was the same in older (≥60 years) and younger patients; mortality was slightly higher in older patients (10% vs. 4%). However, at a median follow-up of 19 months, there was [redacted] in OS for older (n=93) and younger patients (n=191) ([redacted]) and this was [redacted] when considering only patients who underwent SCT in first CR (older patients, n=35, younger patients, n=106, [redacted]). These data provide further evidence to suggest that the benefits of adding midostaurin to standard therapy improve the outlook in both older and younger patients with newly diagnosed AML.

Conclusions

Midostaurin 50 mg BID sequential therapy in combination with daunorubicin plus cytarabine is feasible for management of newly diagnosed FLT mutation-positive AML in patients up to 70 years of age. A CR was achieved in approximately 75% of patients, with [redacted] and [redacted] of the younger and older patients, respectively, achieving a CR. The potential benefit for midostaurin in treating patients <60 years and aged ≥60 years was demonstrated in a favourable comparison of RFS with historical controls. Haematologic and non-haematologic AEs were within the expected range and were considered manageable in both age groups. This study identified this regimen as warranting further investigation. As a result this regimen was investigated in the phase 3 RATIFY trial. Thus the phase 2 study provides supporting evidence for the efficacy and safety of midostaurin in combination with chemotherapy followed by midostaurin monotherapy in patients with FLT3 mutation-positive AML.

4.12 Adverse reactions

Data from RATIFY provide a detailed assessment of the safety profile of midostaurin in combination with chemotherapy (daunorubicin plus cytarabine) followed by midostaurin monotherapy.[16]

4.12.1 Drug exposure

Dosage

A total of 345 patients received at least one dose of midostaurin during the study, and 335 patients received at least one dose of placebo. The median relative dose intensity was high (95%) in both treatment groups and was maintained throughout all treatment phases. The overall median daily dose was 95.1 mg/day (range 4–108 mg/day) and 94.8 mg/day (range 2–107 mg/day) for midostaurin and placebo, respectively, and the median cumulative dose was 4150 mg (range 50–80,800) and 2800 mg (range 50–43,250), respectively.

The median relative dose intensity for daunorubicin was 100% for both induction cycles for both treatment groups indicating that midostaurin did not compromise delivery of the full dose of daunorubicin. Similarly, the median relative dose intensity for cytarabine was 100% for both induction cycles and all four consolidation cycles indicating that the addition of midostaurin did not compromise the dose of chemotherapy that could be given either as induction or consolidation therapy.

Duration of exposure

Median duration of drug exposure was [redacted] days for both treatments during both induction cycles and was longer for midostaurin compared with placebo during the consolidation phase ([redacted] and [redacted] days for midostaurin and placebo, respectively). The median duration of midostaurin monotherapy following consolidation was [redacted] days and the treatment duration following consolidation therapy was the same for the placebo group. More patients in the midostaurin group compared with the placebo group received monotherapy (midostaurin or placebo) for ≥3 months ([redacted] vs. [redacted], respectively), ≥6 months ([redacted] vs. [redacted], respectively) and ≥12 months ([redacted] vs. [redacted], respectively).

4.12.2 Safety profile

Overview of AEs

A summary of the AEs recorded in the RATIFY study is provided in Table 20. There were 36 deaths during the study (15 and 21 in the midostaurin and placebo arms, respectively). Approximately half of the patients in both groups experienced a SAE and approximately three-quarters of patients in both groups reported at least one grade 3/4 AE considered related to treatment. However few patients (6.1% for midostaurin and 4.5% for placebo) discontinued therapy due to grade 3/4 AEs. The incidence of any grade 3/4 AE was similar for the midostaurin and placebo groups during all three treatment phases, being approximately 100% for induction and consolidation, and [redacted] during midostaurin monotherapy compared with [redacted] during placebo therapy (Table 20).

AEs regardless of relationship to midostaurin or placebo

Haematologic AEs were the most frequently reported AEs in both treatment groups with ≥89% of patients in both groups reporting grade 3/4 thrombocytopenia, anaemia and neutropenia (Table 20). The incidence of febrile neutropenia was 83% in both groups, and the incidence of grade 3/4 infection (54% and 53%) and grade 3/4 bleeding (12% and 10%) was also similar for both treatment groups. Thus, the addition of midostaurin to standard chemotherapy did not increase the incidence of grade 3/4 haematologic AEs. Consistent with this, the incidence of grade 3/4 haematologic AEs during midostaurin monotherapy was considerably lower than during induction and consolidation treatment with only neutropenia and lymphopenia being reported in >5% of patients receiving midostaurin monotherapy. Only one patient in the midostaurin group and two patients from the placebo group discontinued due to febrile neutropenia. Platelet and RBC transfusions were given to [redacted] of patients in both induction cycles and to [redacted] of patients in the consolidation phase. [redacted] patient received G-CSF.

The most frequent non-haematologic grade 3/4 AEs in the midostaurin group were device-related infections (16.2%), diarrhoea (15.7%) and exfoliative dermatitis (13.6%), and in the placebo arm were hypokalaemia (17.0%), diarrhoea (15.2%) and pneumonia (14.0%). Grade 3/4 AEs were generally balanced across the two treatment groups, and there were only two grade 3/4 AEs occurring more frequently (>5%) in the midostaurin group than in the placebo group. The first was dermatitis exfoliative (experienced by 13.6% vs. 7.8% of the midostaurin and placebo groups, respectively). The higher levels for midostaurin over placebo can be attributed to higher levels during induction (11.6% vs. 6.7%, respectively), as the incidence during consolidation was similar between groups (2.6% vs. 2.0%, respectively). Only four patients (in the midostaurin group) discontinued due to this AE. The second was device-related infection (experienced by 16.2% and 10.1% of the midostaurin and placebo groups, respectively). No grade 3/4 non-haematologic AEs were reported in ≥5% of patients while receiving midostaurin monotherapy (Table 20).

Grade 3/4 infections (54.2% in the midostaurin group, 52.5% in the placebo group) and grade 3/4 bleeding events (11.9% in the midostaurin group, 9.9% in the placebo group) were balanced between both treatment groups. Only two patients in each group discontinued due to infections, while four patients (three treated with midostaurin and one treated with placebo) discontinued due to bleeding events.

Table 20 Summary of grade 3/4 AEs reported in ≥10% of patients receiving midostaurin regardless of relationship to study drug across the randomised groups in RATIFY (overall study)

System organ class AEs	CALGB 10603/ CPKC412A2301 (RATIFY)							
	Overall		Induction phase		Consolidation phase		Monotherapy phase	
	Mido N=345	Placebo N=335	Mido N=345	Placebo N=329	Mido N=227	Placebo N=205	Mido N=120	Placebo N=85
Death, n (%)	15 (4.3)	21 (6.3)	[redacted]	11 (3.3)	[redacted]	9 (4.4)	[redacted]	1 (1.2)
SAEs, n (%)	162 (47.0)	163 (48.7)					14 (11.7)	9 (10.6)
Grade 3/4 AEs, n (%)	344 (99.7)	335 (100.0)	344 (99.7)	329 (100.0)	225 (99.1)	204 (99.5)	50 (41.7)	40 (47.1)
Grade 3/4 AEs suspected to be related to treatment, n (%)	[redacted]	[redacted]	-	-	-	-	-	-
Withdrawal due to grade 3/4 AEs, n (%)	21 (6.1)	15 (4.5)	-	-	-	-	[redacted]	[redacted]
Grade 3/4 AEs reported in >10% of patients in the midostaurin group								
Non-haematological AEs, n (%)								
Device related infection	56 (16.2)	34 (10.1)	-	-	39 (17.2)	16 (7.8)	0	0
Diarrhoea	54 (15.7)	51 (15.2)	43 (12.5)	43 (13.1)	12 (5.3)	13 (6.3)	1 (0.8)	2 (2.4)
Dermatitis exfoliative	47 (13.6)	26 (7.8)	40 (11.6)	22 (6.7)	6 (2.6)	4 (2.0)	1 (0.8)	0
Hypokalaemia	47 (13.6)	57 (17.0)	37 (10.7)	43 (13.1)	14 (6.2)	19 (9.3)	0	1 (1.2)
Pneumonia	45 (13.0)	47 (14.0)	32 (9.3)	33 (10.0)	16 (7.0)	22 (10.7)	0	0
ALT increased	44 (12.8)	32 (9.6)	21 (6.1)	18 (5.5)	22 (9.7)	13 (6.3)	5 (4.2)	4 (4.7)
Haematological AEs, n (%)								
Thrombocytopenia	337 (97.7)	325 (97.0)	332 (96.2)	315 (95.7)	223 (98.2)	199 (97.1)	2 (1.7)	13 (15.3)
Neutropenia	329 (95.4)	326 (97.3)	317 (91.9)	311 (94.5)	218 (96.0)	201 (98.0)	10 (8.3)	8 (9.4)
Anaemia	321 (93.0)	297 (88.7)	304 (88.1)	267 (81.2)	194 (85.5)	167 (81.5)	1 (0.8)	0
Febrile neutropenia	287 (83.2)	279 (83.3)	259 (75.1)	259 (78.7)	141 (62.1)	120 (58.5)	1 (0.8)	0

System organ class AEs	CALGB 10603/ CPKC412A2301 (RATIFY)							
	Overall		Induction phase		Consolidation phase		Monotherapy phase	
	Mido N=345	Placebo N=335	Mido N=345	Placebo N=329	Mido N=227	Placebo N=205	Mido N=120	Placebo N=85
Leukopenia	92 (26.7)	101 (30.1)	78 (22.6)	86 (26.1)	54 (23.8)	60 (29.3)	3 (2.5)	0
Lymphopenia	68 (19.7)	76 (22.7)	47 (13.6)	55 (16.7)	46 (20.3)	53 (25.9)	8 (6.7)	2 (2.4)

RATIFY CSR.[16]
AE, adverse event; ALT, alanine aminotransferase, Mido, midostaurin.

[redacted] patients ([redacted]) in the midostaurin group and [redacted] patients ([redacted]) in the placebo group had notable liver function abnormalities. All of these cases occurred in the induction ([redacted] cases) or consolidation phases ([redacted] cases). [redacted] treatment discontinuations due to newly occurring liver function test elevations and [redacted] deaths due to liver toxicities occurred. Based on an individual case review [redacted] of these were considered to be Hy's law cases.

Overall, considering the individual treatment phases, the only grade 3/4 AEs reported more frequently in the midostaurin group were anaemia and device-related infection in the induction phase, lymphopenia and device-related infection in the consolidation phase and thrombocytopenia in the monotherapy phase.

Grade 3/4 AEs suspected to be related to midostaurin or placebo

Approximately [redacted] of patients in either treatment group experienced at least one grade 3/4 AE suspected to be related to study treatment. Most of these AEs occurred at similar frequencies between the treatment groups (Table 21). The only grade 3/4 AE that was ≥5% more prevalent in the midostaurin group compared with the placebo group was dermatitis exfoliative ([redacted] and [redacted] for midostaurin and placebo, respectively).

Table 21 Summary of grade 3/4 treatment-related AEs reported in ≥5% of patients receiving midostaurin across the randomised groups in RATIFY (overall study)

System organ class AEs	CALGB 10603/ CPKC412A2301 (RATIFY)	
	Midostaurin (N=345)	Placebo (N=335)
Non-haematological grade 3/4 AEs in ≥5% of patients in either group, n (%)		
Diarrhoea	[redacted]	[redacted]
Dermatitis exfoliative	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]
Device-related infection	[redacted]	[redacted]
Haematological grade 3/4 AEs in ≥5% of patients in either group, n (%)		
Thrombocytopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]

RATIFY CSR.[16]
AE, adverse event; alanine aminotransferase.

SAEs

Almost half of the patients (47% and 49% of patients in the midostaurin and placebo arms) experienced at least one SAE and over half of these were suspected to be related to study treatment. Febrile neutropenia, neutrophil count decreased, platelet count decreased, device-related infection and pneumonia were the most frequently occurring SAEs in the midostaurin group, each with incidences >5% (Table 22). Only 12% of patients experienced a SAE while receiving midostaurin monotherapy (compared with 11% for placebo).

The incidence of SAEs was generally balanced between the two treatment groups with the exception of dermatitis exfoliative (10 [2.9%] patients on midostaurin and 1 [0.3%] patient on placebo) and hypotension (10 [2.9%] patients on midostaurin and 1 [0.3%] patient on placebo).

Table 22 SAEs reported in >2% of patients in the midostaurin group regardless of relationship to midostaurin or placebo in RATIFY

SAE, n (%)	Overall		Monotherapy phase	
	Midostaurin (N=345)	Placebo (N=335)	Midostaurin (N=120)	Placebo (N=85)
Any event	162 (47.0)	163 (48.7)	14 (11.7)	9 (10.6)
Febrile neutropenia	54 (15.7)	53 (15.8)		
Neutrophil count decreased	28 (8.1)	33 (9.9)	3 (2.5)	1 (1.2)
Platelet count decreased	24 (7.0)	28 (8.4)	0	2 (2.4)
Haemoglobin decreased	12 (3.5)	9 (2.7)	0	0
Dermatitis exfoliative	10 (2.9)	1 (0.3)	-	-
Device-related infection	23 (6.7)	13 (3.9)	-	-
Pneumonia	23 (6.7)	23 (6.9)	0	0
Sepsis	16 (4.6)	14 (4.2)	-	-
Pneumonitis	11 (3.2)	8 (2.4)	-	-
Hypotension	10 (2.9)	1 (0.3)	0	0
Aspartate aminotransferase increased	9 (2.6)	1 (0.3)	1 (0.8)	0
Neutropenic infection	9 (2.6)	6 (1.8)	-	-
Alanine aminotransferase increased	8 (2.3)	3 (0.9)	0	0
Infection	8 (2.3)	3 (0.9)	1 (0.8)	0
Leukopenia	8 (2.3)	7 (2.1)	1 (0.8)	0
Neutropenic sepsis	8 (2.3)	1 (0.3)	-	-
Renal failure	8 (2.3)	2 (0.6)	-	-
Colitis	7 (2.0)	9 (2.7)	0	0

RATIFY CSR.[16]

Deaths

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 were due to AML/disease progression (one for midostaurin and two for placebo) and most deaths were due to 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 multi-organ failure, infectious colitis, acute respiratory failure, colitis, myocardial infarction, neutropenic sepsis, pulmonary haemorrhage and septic shock in one patient each.

Overall there were fewer deaths during the study (all deaths that occurred by the time of the data cut-off date on 01 April 2015) in the midostaurin arm compared with the placebo arm ([redacted] [redacted] and [redacted] [redacted] patients, respectively). The reasons for death were generally similar in the two treatment groups with the most common cause of death being AML ([redacted] on midostaurin vs. [redacted] on placebo).

Deaths following SCT

A total of [redacted] patients ([redacted] in the midostaurin group and [redacted] in the placebo group) received SCT within 2 months of study drug discontinuation. Among these patients, midostaurin did not increase mortality rates post-SCT over placebo, with similar proportions of patients dying following SCT within 30 days (3 [3.4%] and 3 [3.5%] patients, respectively) and 100 days (6 [6.8%] and 11 [12.8%] patients, respectively).

4.13 Interpretation of clinical effectiveness and safety evidence

AML is the most common acute leukaemia in adults and has the lowest survival rate of all adult leukaemia's, with FMS-like tyrosine kinase 3 (FLT3) mutation conferring an even poorer prognosis. FLT3 mutation-positive acute myeloid leukaemia (AML) is an aggressive haematological malignancy associated with a median overall survival (OS) of less than 12 months with current standard treatments. Midostaurin, an oral, tyrosine kinase inhibitor that targets FLT3 and other receptor tyrosine kinases, represents a breakthrough for the treatment of newly diagnosed FLT3 mutation-positive AML.

As demonstrated conclusively in the largest international, multicentre, phase 3, randomized, double-blind, placebo-controlled trial, in FLT3 +ve AML patients, midostaurin is the first targeted therapy that significantly improves OS versus standard-of-care chemotherapy alone. Midostaurin in combination with standard chemotherapy followed by midostaurin monotherapy significantly extended median OS by approximately 4 years and prolonged the duration of remission from 22 to 61 months over standard-of-care chemotherapy. These efficacy gains were achieved without a significant increase in the overall incidence of grade 3/4 AEs or serious AEs and few patients discontinued therapy.

4.13.1 Efficacy

The addition of midostaurin to standard chemotherapy significantly extends OS, EFS, DFS and remission duration versus standard of care for patients with newly diagnosed FLT3 mutation-positive AML

The efficacy and safety of midostaurin in combination with standard chemotherapy (daunorubicin plus cytarabine) followed by midostaurin monotherapy was assessed in RATIFY, the largest phase 3, randomised, double-blind, placebo-controlled, international study ever conducted in patients with FLT3 mutation-positive AML.[16] These data are supported by results of a phase 2, open-label, single-arm study assessing the efficacy and safety of the same regimen in patients with newly diagnosed FLT3-ITD-positive AML,[17,18] and a phase 1b study assessing the feasibility of several dosing schedules for midostaurin in combination with daunorubicin plus cytarabine.[61]

RATIFY met its primary endpoint, demonstrating a significant reduction in the risk of death of 23% (HR 0.77 [95% CI 0.63–0.95]; p=0.0078) for midostaurin plus standard chemotherapy followed by midostaurin monotherapy over standard chemotherapy alone. The benefits of midostaurin over placebo were evident over the first 18 months during which patients received therapy and were sustained thereafter. The OS benefit achieved with midostaurin versus placebo was seen across all subgroups considered, including gender, race, cytogenetics and WBC count. Midostaurin also [redacted] the risk of death following SCT by [redacted] for patients who underwent SCT in the first CR (HR [redacted] [95% CI [redacted]]). Thus midostaurin provides a particular benefit for patients undergoing SCT. When OS was measured from the start of monotherapy and censored by patients receiving SCT ([redacted] and [redacted] patients receiving midostaurin and placebo, respectively) the reduced risk

of death with midostaurin over placebo was [redacted] (HR [redacted] [95% CI [redacted]]). This indicates that in patients who cannot undergo SCT, midostaurin monotherapy following consolidation yields significant benefits.

The prolongation in OS achieved with midostaurin is likely, in part, to reflect the improvement in overall CR rate achieved with midostaurin over placebo (58.9% vs. 53.5%, respectively p = 0.073) and, in particular, the increased proportion of patients achieving a CR following a single cycle of induction therapy (51.7% vs. 43.1%, respectively).

Median OS for patients receiving midostaurin was 74.7 months, compared with 25.6 months for placebo. Thus midostaurin provided a highly clinically meaningful increase in median OS of over 4 years. Considering mean OS, this increased from [redacted] months with standard chemotherapy to [redacted] months with midostaurin plus chemotherapy, an improvement of [redacted] months.

Consistent with the prolongation in OS seen with midostaurin, RATIFY also demonstrated statistical superiority for midostaurin over placebo for prolongation of EFS and DFS, and reduced risk of relapse or death due to AML:

- Median EFS: extended from 3.0 months (95% CI 1.9–5.9) to 8.2 months (95% CI 5.4–10.7), respectively
- Median DFS: extended from 15.5 months [95% CI 11.3–23.5) to 26.7 months (95% CI 19.4–NE), respectively
- Median duration of remission: extended from [redacted] months (95% CI: [redacted]) to [redacted] months (95% CI: [redacted]), respectively.

Improvements in EFS, DFS and duration of remission achieved with midostaurin over placebo were found to be robust based on a number of sensitivity analyses, including censoring for SCT and using alternative definitions for CR. Midostaurin also increase the TFI from [redacted] months to [redacted] months, representing a clinically significant prolongation of [redacted] months.[30]

Results from the phase 2 study, which involved 149 patients, confirmed the benefits achieved with the addition of midostaurin to standard chemotherapy, reporting a CR rate of 74%, and a reduced risk of relapse (when midostaurin therapy is followed by allogeneic SCT or high-dose cytarabine) compared to historical controls. Furthermore, this study involved patients aged 18–70 years and demonstrated that the benefits for midostaurin extend to elderly patients (those aged ≥60 years).[17,18] Results for the phase 1b study established a regimen of midostaurin 50 mg BID for 14 days administered sequentially to chemotherapy to be feasible and to provide clinically meaningful activity.[61]

4.13.2 Safety

Midostaurin added to standard chemotherapy is generally well tolerated and does not significantly increase the overall incidence of grade 3/4 AEs, SAEs or grade 3/4 AEs considered related to treatment. In RATIFY, during induction and consolidation therapy the incidence of grade 3/4 AEs was approximately 100% in both treatment groups, whereas during the following period of monotherapy the incidence of grade 3/4 AEs was 42% in the midostaurin group and 47% in the placebo group. Haematologic AEs were the most frequently reported AEs in both treatment groups with ≥89% of patients in both groups reporting grade 3/4 thrombocytopenia, anaemia and neutropenia. This is consistent with the known safety profile for standard chemotherapy and the mechanism of action for midostaurin. The incidence of febrile neutropenia was 83% in both groups and the incidence of grade 3/4 infection ([redacted] and [redacted]) and grade 3/4 bleeding events ([redacted] and [redacted]) were also similar for both treatment groups. Thus, the addition of midostaurin to standard chemotherapy did not increase the incidence of grade 3/4 AEs. There was a slight trend toward greater use of platelet infusions and RBC transfusions in the midostaurin group.

The most frequently reported non-haematologic AEs (>10%) were device-related infection, diarrhoea, rash, hypokalaemia, pneumonia and elevated ALT and the incidence was similar in both treatment groups. The only grade 3/4 AEs reported more frequently (>5%) overall with the addition of midostaurin were dermatitis exfoliative (14% vs. 8%) and device-related infection (16% vs. 10%). However, only four patients (receiving midostaurin) discontinued therapy for dermatitis exfoliative and one for device-related infection.

Few patients discontinued therapy for grade 3/4 AEs and the incidence was similar for the two treatment groups (6.1% vs. 4.5%). The only grade 3/4 AEs leading to discontinuation in ≥2 patients were dermatitis exfoliative (midostaurin, [redacted] patients), elevated ALT (midostaurin, [redacted] patients; placebo, [redacted] patient), elevated AST (midostaurin, [redacted] patients), renal failure (midostaurin, [redacted] patients), febrile neutropenia (midostaurin, [redacted] patient; placebo, [redacted] patients).

Results for the phase 2 study were in general consistent with those from RATIFY with haematological events being the most frequently reported grade 3/4 treatment-related AEs.[17] The only other grade 3/4 AEs reported in >10% of patients were febrile neutropenia ([redacted]) and nausea ([redacted]). Most non-haematological AEs were grade 1/2 in severity. This study involved patients aged 18–70 years and compared the safety profile for younger (<60 years) and older (≥60 years) patients. The safety profile was generally similar in both subgroups although more of the older patients died on study ([redacted] vs. [redacted]) and discontinued midostaurin therapy due to AEs ([redacted]).[19] Overall approximately one-quarter ([redacted]) of patients withdrew from midostaurin therapy due to AEs and [redacted] patients died during study treatment. Results from this study suggest that midostaurin in combination with chemotherapy followed by midostaurin monotherapy is as feasible in fit elderly patients as for younger patients.

Thus, the prolongation of OS, EFS, DFS, duration of remission and TFI provided midostaurin in combination with chemotherapy are achieved with minimal increase in the incidence of grade 3/4 AEs and no need for modification of the chemotherapy regimen. The safety profile observed largely corresponds to that expected for daunorubicin + cytarabine chemotherapy and clinically impactful haematological AEs were generally managed by platelet and RBC transfusions. Few patients required dose reductions or treatment interruptions for management of AEs. Only 21 (6.1%) patients discontinued therapy for grade 3/4 AEs.

4.13.3 Strengths of the evidence base

Evidence for the efficacy and safety of midostaurin in combination with chemotherapy followed by midostaurin monotherapy comes from a robust multicentre, randomised, double-blind placebo-controlled study, RATIFY. This study involved 717 patients from centres in Europe and North America, included both patients with FLT3-TKD (23% of patients) and patients with FLT3-ITD (77% of patients), and patients generally representative of those anticipated to be eligible to receive midostaurin in clinical practice in the UK. The study enrolled patients with similar baseline characteristics across the treatment arms. Randomisation was performed using a robust, validated block approach with treatment allocation concealed. Sample size was determined based on an estimation of the number of patients required to achieve a clinically meaningful increase in OS for midostaurin versus placebo. Investigators and patients were blinded to treatment, and assessment of outcomes was also performed by blinded independent central review.

RATIFY compared midostaurin added to daunorubicin plus cytarabine, with daunorubicin plus cytarabine alone, the standard chemotherapy regimen used in management of newly diagnosed AML and hence the most relevant comparator. The chemotherapy regimen used – cytarabine plus daunorubicin – on a 3 +7 day schedule corresponds to the induction regimen most widely used in the UK. Thus the comparator used in RATIFY is the most relevant to the clinical practice in the UK. In the trial, up to 4 cycles of consolidation therapy were given. This contrasts with current UK practice where in general patients receive 4–6 cycles of consolidation therapy. However, results of the Medical Research Council AML15 trial indicate that there is no benefit for 5 cycles over 4 cycles.[48]

The primary and key secondary efficacy outcomes (OS and EFS) are well recognised and appropriate endpoints for assessing the efficacy of treatments for AML. Sensitivity analyses were included to investigate the effect of the high rate of SCT on efficacy outcomes, and the effect of using a less stringent but more clinically meaningful measure of CR.

The study has a median follow-up of 5 years, thus data are sufficiently mature to demonstrate effects of midostaurin on OS as well as EFS, DFS and remission duration. Subgroup analyses demonstrate consistent effects across subgroups defined by various clinical and demographic characteristics as well as FLT3 mutation type. Safety data collected over each treatment phase of the study provide

detailed data on the safety profile of midostaurin as part of induction and consolidation therapy and as monotherapy following chemotherapy.

Evidence from RATIFY are further supported by the results of a single-arm phase 2 study involving 284 patients, which investigated the same regimen and compared the efficacy and safety profile for younger (<60 years) and older (≥60 years) patients,[17,18] and a phase 1b study, which established midostaurin 50 mg BID administered sequentially after daunorubicin plus cytarabine as a feasible induction regimen for newly diagnosed AML.[61]

4.13.4 Weaknesses of the evidence base

One possible limitation of RATIFY was that patients >60 years were excluded, whereas many patients newly diagnosed with AML in the UK are >60 years. However, the phase 2 study involved patients aged 25–70 years who achieved a CR rate of approximately [redacted], which was consistent with the results from RATIFY. In addition, results for patients aged >60 years were broadly similar to those aged ≤60 years in the phase 2 trial (see Table 18), and comparison of older patients treated with midostaurin to historical controls also indicated significant benefit in these patients in terms of RFS (see Figure 19). Furthermore, the cumulative incidence of relapse following consolidation therapy (SCT or high-dose cytarabine) was low providing evidence for the efficacy of midostaurin-based therapy in older patients.

In addition, approximately 55% of patients in both treatment groups underwent SCT, meaning that survival outcomes may reflect the impact of SCT as well as the investigational therapy. To address this issue, sensitivity analyses were performed for all the main endpoints censoring for SCT and results were found to be similar to those for the primary analysis. A final limitation was that HRQoL was not assessed in RATIFY.

4.13.5 Relevance of the evidence to the decision problem

Evidence from RATIFY is highly relevant to the decision problem as the study involved patients with newly diagnosed FLT3 mutation-positive AML (the population relevant for the economic assessment) and the comparator (daunorubicin plus cytarabine) is considered the standard of care in UK clinical practice. In addition, the main efficacy (OS and EFS) and safety (grade 3/4 AEs occurring during each phase of therapy) endpoints are used in the economic model, as are data on the use of RBC and platelet transfusions during treatment.

4.13.6 End-of-life criteria

As described in Table 23, this submission meets the criteria for end of life as:

- the life expectancy for patients with newly diagnosed FLT3 mutation-positive AML is estimated to be less than 12 months (see section 3.4) and
- the addition of midostaurin to standard-of-care chemotherapy has been shown to extend median OS by approximately 4 years (see section 4.7.3).

Table 23 End of life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median survival for patients with AML has been reported to be less than 12 months for patients in Europe,[4] and is shorter in patients with FLT3 mutation-positive disease compared with those without such mutations.[7] For example, a study involving a cohort of younger patients (median age 43 years) reported a 5-year OS of 15–31% in patients with FLT mutation-positive disease compared with 42% in patients without FLT3 mutations.[7]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	In RATIFY, at a median follow-up of 60 months, midostaurin increased median OS from 25.6 months in the placebo group to 75 months in the midostaurin group (HR 0.77, p=0.0078).[16] Thus the addition of midostaurin to standard-of-care chemotherapy prolongs median OS by approximately 49 months, ie over 4 years.

NHS, National Health Service.

4.14 Ongoing studies

Table 24 lists the ongoing midostaurin studies in patients with newly diagnosed AML. Only RATIFY and the phase 2 study (Schlenk et al) described earlier in this submission are likely to report additional data over the next 12 months.

Table 24 List of ongoing midostaurin studies in patients with newly diagnosed AML

Trial (NCT number)	Status	Therapy (drugs)	Phase of study	Patients	Expected date of reporting	
					Primary completion	Study completion
NCT02634827	Recruiting	Midostaurin, decitabine	2	Newly diagnosed AML with FLT3 mutation	April 2020	–
NCT01846624	Active, not recruiting	Midostaurin, decitabine	2	Older patients with newly diagnosed AML	December 2020	December 2024
NCT02624570 (US56X)	Recruiting	Midostaurin	–	Newly diagnosed FLT3 (ITD or TKD) mutation-positive AML adult patients	–	Will close when midostaurin in commercialized
NCT01830361	Currently recruiting participants	Midostaurin	2	Newly diagnosed c-KIT or FLT3-ITD mutated t(8;21) AML	May 2018	September 2018
NCT01093573	Ongoing, but not recruiting participants	Midostaurin, azacitidine	1/2	Elderly patients with untreated AML	June 2016	–
NCT00651261 (RATIFY)	Completed	Midostaurin, cytarabine, daunorubicin	3	Newly diagnosed patients < 60 years of age with FLT3 mutation-positive AML	October 2021	-
NCT01477606 (Phase 2, Schlenk et al)	Currently recruiting participants	Midostaurin, SCT	2	Intensive induction, consolidation including allogeneic hematopoietic stem cell transplantation and single agent maintenance therapy on event-free survival (EFS) in adult patients with AML exhibiting a FLT3-ITD	December 2019	December 2019

AML, acute myeloid leukaemia; FLT3, FMS-like tyrosine kinase receptor-3; ITD, Internal tandem duplication; TKD, tyrosine kinase domain.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

5.1.1 Identification of studies

A systematic review was conducted to retrieve relevant information from the published literature regarding the cost-effectiveness of other systemic therapies in AML. Results from this review were used to help contextualise the cost-effectiveness results from our model by comparing cost per QALY (or LYs) of other systemic treatments. Due to a sparsity of economic data in AML and potential relevance of economic analyses in myelodysplastic syndromes (MDS), studies in MDS patients were included in the economic literature review. In many cases, these economic evaluations followed patients as they progressed to AML and death. As such these studies were considered potentially relevant to the review (see section 8.11, Appendix 11 for details of methodology and results of the literature review).

5.1.2 Description of identified studies

Among the nine selected studies, four evaluate azacitidine, two decitabine, one lenalidomide, one salvage therapy and one a combination of dendritic cell vaccination with chemotherapy. Countries from which the economic data were derived included US (3), UK (2), Canada (1), Belgium (1), Mexico (1) and Spain (1). Four studies considered the treatment of patients with MDS, two studies were in patients with high-risk MDS and AML and three studies were in newly diagnosed AML.

Among the nine selected studies, six were cost-utility analyses and reported an ICER. Among these studies, only two evaluated treatment of AML patients compared to intensive chemotherapy (decitabine US analysis and azacitidine UK analysis in patients with >30% blasts). With regard to the model structures used, these two studies constructed Markov models with four health states: active disease, remission, progression and death. Both studies assumed a payer perspective. The time horizon was 1 year in the decitabine model and a lifetime time horizon was employed in the azacitidine model.

Table 25 Summary list of published cost-effectiveness studies

Study	Year, country	Interventions	Summary of model	Patient population	QALYs/LYS (intervention, comparator)	Cost (intervention, comparator)	ICER (per QALY (per LYS, if QALY not available)
Crespo_Health Economics Review_2013[63]	2012, Spain	Azacitidine, low-dose chemo, standard dose chemo, BSC	A lifetime Markov model with 3 health states: MDS, AML and death. Comparators: BSC, low and standard dose chemo. NHS perspective. Discount 3%.	High risk MDS	AZA vs. BSC: 3.06 vs. 1.24; AZA vs. LDC: 3.39 vs. 1.26; AZA vs. SDC: 2.94 vs. 0.98	AZA vs. BSC: €107,168 vs. €35,090; AZA vs. LDC: €115,537 vs. €53,184; AZA vs. SDC: €106,422 vs. €59,725	AZA vs. BSC: €39,610/QALY; AZA vs. LDC: €30,531/QALY; AZA vs. SDC: €23,804/QALY
Levy_Current Oncology_2014[64]	2012, Canada	Azacitidine vs. low-dose chemo and standard dose chemo	A lifetime Markov model with 3 health states: MDS, transformation to AML with >30% blasts and death. Comparators: BSC, low and standard dose chemo. Public payer	High risk MDS and Low Blast AML	AZA vs. BSC: 2.50 vs. 1.48; AZA vs. LDC: 2.53 vs. 1.55 AZA vs. SDC: 2.23 vs. 1.36	AZA vs. BSC: $111,414 vs. $33.517; AZA vs. LDC: $114,368 vs. $41,032; AZA vs. SDC: 110,337 vs 108,486	AZA vs. BSC: $86,973/QALY; AZA vs. LDC: $84,829/QALY; AZA vs. SDC: $2,152/QALY

Study	Year, country	Interventions	Summary of model	Patient population	QALYs/LYS (intervention, comparator)	Cost (intervention, comparator)	ICER (per QALY (per LYS, if QALY not available)
			perspective. Discount 3%.				
Batty_J Canc Reseach_2014[65]	2012, US	Decitabine vs. cytarabine+daunorubicin (AD)	Semi-Markov model with 4 HS: AML Active, AML Remission, AML Relapse, Death. Comparator: cytarabine+daunorubicin. Payer perspective. 1year horizon.	Newly Diagnosed AML, >= 60 years old.	DEC vs. AD: 0.61. vs. 0.47	DEC vs. AD: $108,084 vs. $168, 863	AZA vs. AD: $433,756/QALY
Pan_Clinical Therapeutics_2010[66]	2009, US	Decitabine vs. BSC	Markov model with 3 HS: MDS, AML, and death. Comparator: BSC. US payer perspective. 4-week cycles, 5-year horizon.	Intermediate/High risk MDS	DEC vs. BSC: 0.938 vs. 0.886	DEC vs. BSC: $122,940 vs. 122.666	DEC vs. BSC: $5,277/QALY

Study	Year, country	Interventions	Summary of model	Patient population	QALYs/LYS (intervention, comparator)	Cost (intervention, comparator)	ICER (per QALY (per LYS, if QALY not available)
Ramos_Value in Health_2016 (Abstract)[67]	2016, Mexico	Lenalidomide vs. placebo	Markov model with 5 HS: MDS transfusion-dependent, MDS transfusion-independence, complications from transfusion, AML and death. Public health care perspective. Horizon 5 years. Discount rate 5%.	DEL5Q MDS	NR	NR	ICER per LYS w/o transfusion dependence: USD$14,072
Cogle_Blood_2014 (Abstract)[68]	2013, US	Salvage therapy: low-intensity chemo, high-intensity chemo, HMA treatment, HSCT, and BSC	Markov model with 4 HS: rMDS, AML, treatment- or disease-related AE (thrombocytopenia, anaemia and neutropenia), discontinue treatment, or die. Comparators: low-and high-intensity chemo; switching	Relapsed MDS	LYS: BSC: 0.48; HMA: NR; Low int. chemo: 0.88; high int. chemo: 1.08; HSCT: 2.26	BSC: $55,343; HMA: $84,625; low-int. chemo: $89,877; high int. chemo: $146,519; HSCT: $492,359	NR

Study	Year, country	Interventions	Summary of model	Patient population	QALYs/LYS (intervention, comparator)	Cost (intervention, comparator)	ICER (per QALY (per LYS, if QALY not available)
			HMA treatment; HSCT; and BSC. 4-week cycle, payer perspective.				
Van de Velde_Leukemia Research_2016[69]	2010, Belgium	Chemo (ICT) vs. chemo+HCT (HCT) vs. chemo+dendritic cell (DC) vaccination	CEA of total costs and OS. Cost and effect (OS) pairs from each of the three comparators were bootstrapped (10,000 iterations using Latin Hypercube sampling with replacement) to explore uncertainty around estimates.	Newly diagnosed AML	OS days: ICT 57; HCT 339; DC 477.	ICT: €32,649; HCT: €134,112; DC: €109,856	ICER NR. At a willingness to pay of €40,000/LYG, there is 75% probability of making a cost-effective choice if DC is chosen over HCT.
Edlin et al 2010[70] (NICE_Azacitidine HTA_2011)	2011, UK	Azacitidine vs. conventional care (BSC, low-dose chemo (LDC) or	Two arm health state transition model with 2 health states: MDS and death. Lifetime horizon was used.	Adult patients who are not eligible for SCT	QALY: 2.04 vs. 1.03 (BSC); 2.44 vs. 1.10 (LCL), 1.91 vs. 0.98 (SDC)	€91,753 vs. 27,998 BSC, €101,355 vs. 35,684 LCL,	Per QALY: £63,177 BSC, £49,030 LDC, £51,252 SDC.

Study	Year, country	Interventions	Summary of model	Patient population	QALYs/LYS (intervention, comparator)	Cost (intervention, comparator)	ICER (per QALY (per LYS, if QALY not available)
		standard dose chemo (SDC))		with Int-2/HR MDS, CMML or AML with 20–30% blasts.		€91,534 vs. 44,060 SDC)	
NICE_Azacitidine_2016[71]	2016, UK	Azacitidine vs. conventional care (CCR)	Semi-Markov model based on 4 states: remission, non-remission, relapsed or progressive disease, and death, lifetime time horizon of 10 years.	AML with >30% bone marrow blasts in people >=65 years who are not eligible for SCT transplant.	LYS: 1.1820 vs. 0.9041 QALY: NR vs. 0.6365	AZA NR vs. £40,608	Per QALY: £20,648

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years, LYS, life years saved.

5.2 De novo analysis

The cost-effectiveness model was developed according to methods guidance published by NICE[72] and international good research practices for modelling, to ensure that the analysis was as methodologically rigorous as possible.

5.2.1 Patient population

This *de novo* economic evaluation was designed to assess the cost-effectiveness of midostaurin plus standard chemotherapy followed by midostaurin monotherapy (referred to as "midostaurin therapy" throughout section 5), compared to standard of care (referred to as "SOC" throughout section 5), in a population identical to that of the RATIFY (CALGB 10603) clinical trial: newly diagnosed adult patients with FLT3 mutation-positive AML who were eligible to receive SCT (described in section 4.3).

For this analysis, the intention-to-treat population of RATIFY was used, as these patients were considered to be representative of those who would receive midostaurin therapy in the UK, based on the described intended use of midostaurin therapy (i.e. to treat FLT3 mutation-positive adults who have not been previously treated for leukaemia or myelodysplasia and who are eligible to receive standard induction and consolidation therapy).

The RATIFY trial is also broadly reflective of clinical practice in the UK. In RATIFY, the majority of people received one cycle of induction treatment followed by a maximum of 4 cycles of consolidation. A minority of patients received 2 induction cycles (if they did not achieve CR following the first induction cycle) followed by a maximum of 4 cycles of consolidation. Clinical experts considered that typically, in the UK, patients receive one induction cycle followed by 3 cycles of consolidation, with some patients (who do not achieve CR) receiving 2 induction cycles. It should be noted that data from the AML-15 trial in the UK support the use of up to 4 cycles of consolidation.[48]

Furthermore, the FLT3 mutation-positive AML population is a specific subgroup of the AML population. Additional stratifications of this sub-population were not explored in this analysis, as survival was similar across the FLT3 mutation stratification subgroups and stratification would significantly reduce the precision of estimates.

5.2.2 Model structure

Structure overview

A partitioned survival model (PSM) was used due to its intuitive implementation with the patient-level data available, as the model is not deviating from the trial data, and because the patient data was relatively mature (in a sense that most short- and medium-term events occurred during the trial period) and was considered reflective of real clinical practice. This type of model eliminates the need for generating assumptions for the transition of patients between health states and allows for the

direct use of the trial Kaplan–Meier curve in the model. Therefore, the estimation of patients occupying each health state was derived directly from the cumulative survival probabilities. The conceptual model framework is presented in Figure 20. Using the partitioned survival model approach, the proportion of patients in each health state ("health state occupancy") was determined by the area under the curves fitted to the trial outcomes. The model was created using Microsoft Excel and the survival analyses were performed in Stata 14.

Health states

As shown in Figure 20, the model included five health states: AML diagnosis/induction, CR, relapse, SCT, and mortality. These health states were selected based on the clinical pathway and current guidelines for treatment of newly diagnosed FLT3 mutation-positive AML (as described in section 3.3). Each health state was mutually exclusive and defined as follows:

- AML diagnosis/induction: AML diagnosis is the initiating state in the model (i.e. where patients enter the model) and where induction therapy begins. Induction therapy is given with the specific aim of inducing remission in the patient. The AML diagnosis/induction health state is the proportion of people on treatment not in CR. It should be noted that to be eligible for consolidation therapy, patients had to achieve CR. The proportion of patients in the AML diagnosis/induction state was based on (a) the proportion of patients receiving treatment in the RATIFY trial (see section 5.5.2) and (b) the proportion of patients in CR (see section 5.3.1). Patients leave the AML diagnosis/induction health state if any of the following events occurred: relapse (when a patient enters the relapse state), CR (when a patient enters the CR health state and can receive consolidation treatment), SCT (when a patient enters the SCT health state), or mortality.

- Complete remission (CR): In the typical clinical pathway for AML, patients who achieve and sustain CR during induction receive consolidation therapy (and potentially receive SCT, if deemed appropriate). In the RATIFY trial, patients also received monotherapy if they completed consolidation therapy and retained their CR status. In the model, the CR state is based directly on the patient-level data, where a CR variable was collected. Patients entered CR at the date of CR and left CR after relapse (when a patient enters the relapse state) or death. To be considered a CR in the clinical trial, CR had to occur in the 60 days following treatment initiation.

- Relapse: Patients who did not respond, or no longer responded, to treatment were considered to be in the relapsed health state. Those in the relapse state were assumed to be all patients *not* in any other state. Therefore, the proportion of patients in the relapse state was essentially driven by the other health states in the model, and relapse estimates were derived from the area under the curve defined by the other extrapolated health states. It should be noted that these patients are a mix of patients not in remission or with progressive disease.

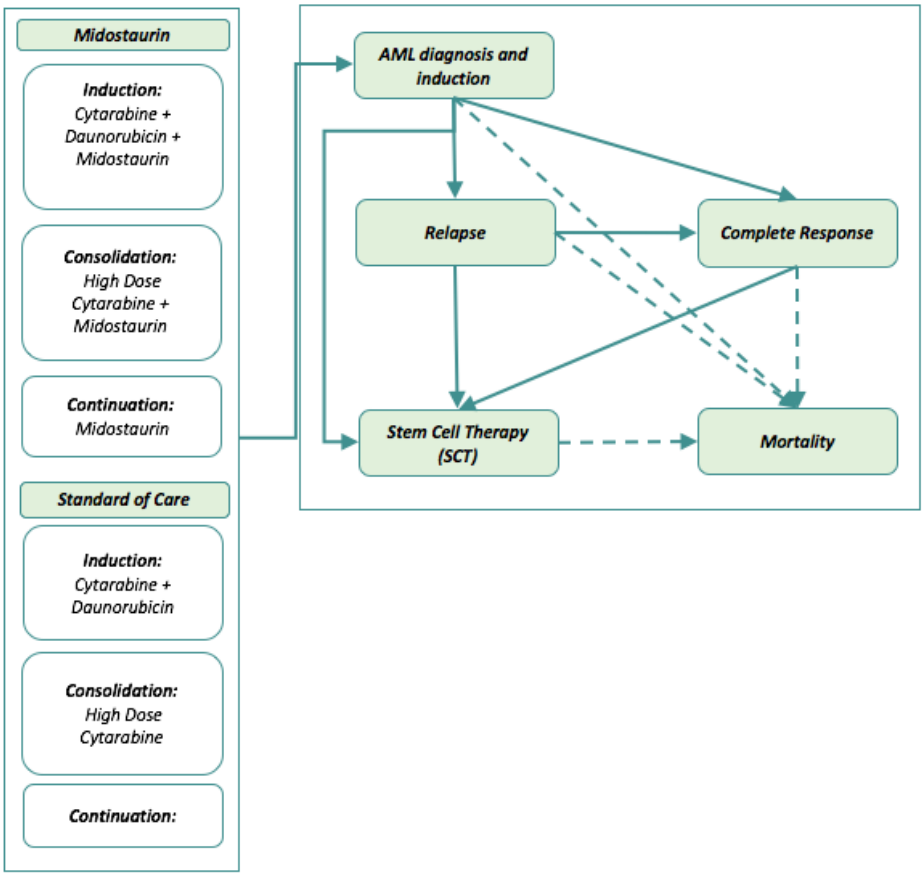
- Stem cell transplant (SCT): When deemed appropriate, AML patients will often receive SCT (typically allogenic) with the goals of preventing relapse and prolonging survival. Time-to-event (SCT initiation) data from the trial were available for SCT status. Patients entering SCT remained in this health state for the entire duration of the model and could only leave the SCT state via mortality. The proportion of patients in the SCT state (cumulative probability of SCT) was therefore derived based on the time between SCT initiation and mortality.

  The model contained three SCT tunnel states to calculate state-specific costs and utilities, as costs and patient utilities vary over the course of SCT. These tunnel states included: SCT treatment (when the patient undergoes SCT), SCT recovery (the initial state following SCT), and post-SCT recovery (the state following recovery, which accounted for the proportion of patients expected to have post-SCT complications).

- Mortality: Mortality was the final, absorbing state in the model and was based on the OS of the clinical trial data.

The duration of treatment (including all phases of treatment) was calculated separately based on the proportion of patients on treatment from the RATIFY trial (see section 5.5.2). It should be noted that given the PSM approach used, the treatment duration is independent of the outcomes for OS, CR and EFS in the economic model.

Figure 20 Model Framework



Proportion of patients occupying each health state

The proportions of patients in each health state were derived from the clinical outcomes of the RATIFY trial: OS, time-to-CR, and time-to-SCT. A 28-day cycle length was used, as the treatment cycles lasted 28 days in the trial.

The model was based on within-trial data, as it reflected UK clinical practice. Since no other comparable treatment is currently approved in the UK, only direct evidence from the RATIFY trial was used. The treatment pathways used in the model are in line with typical clinical pathways (as presented in section 3.3).

Model time horizon

For the base case, a lifetime (700, 28-day cycles, or 53.70 years) time horizon was used, beginning at the time of AML diagnosis/treatment initiation. A lifetime horizon was used given the chronic nature of the disease and in order to capture all the relevant costs and benefits associated with the introduction of midostaurin in England and Wales. The use of a lifetime horizon was supported by clinical experts. In particular, clinical experts indicated that people still alive by the end of the trial duration could be considered to follow the general population mortality and expected the gain in OS observed in the trial

for midostaurin versus SOC to be maintained over the lifetime. Two additional time horizon scenarios (trial horizon and 10-year horizon) were evaluated in sensitivity analyses for transparency and are presented in section 5.8.

Cost and utility estimation

Costs and HRQoL were assumed to be dependent on treatment and expected health state occupancy.

Model perspective

This analysis was conducted from the perspective of the NHS and personal and social services in England and Wales, in line with current NICE guidelines. The analysis excluded patients' out-of-pocket expenses, carers' costs, and lost productivity costs. All costs are reported in pounds sterling.

Other structural characteristics

Discounting: Costs and utilities were discounted at the rate of 3.5% annually, as per NICE guidelines.[72]

Body surface area (BSA) and weight: BSA and weight are important factors for calculating the dose of chemotherapy regimens administered. Based on the RATIFY trial, the mean BSA was assumed to be 1.9 m^2 and mean weight was 70 kg.

Dose intensity: Treatment may have required dose reductions or delays in order to manage AEs. Therefore, patients in the RATIFY trial did not always receive the full intended doses of primary treatment. The dose intensities of the primary therapies (midostaurin, cytarabine, and daunorubicin) were based on RATIFY patient-level data.

Wastage: The available pack sizes of drugs may not allow for the exact dose of drug required. To account for wastage, rounding was applied for dose calculations based on the received doses (i.e. doses were rounded up to the nearest pack/vial size when necessary). For this economic evaluation, the cost of wasted drug was included in the model to be conservative. Wastage and dose reductions were only included for the primary therapies (midostaurin, cytarabine, and daunorubicin).

5.2.3 Intervention technology and comparators

Features of the de novo analysis are summarised in Table 26.

Table 26 Features of the de novo analysis

Factor	Chosen values	Justification
Model year	2017	NA
Time horizon	Lifetime	Sufficient to capture all meaningful differences in technologies compared
Were health effects measured in QALYs; if not, what was used?	Yes. Additionally, life years (LYs) saved were assessed	QALYs were the primary preference-based outcome evaluated
Discount of 3.5% for utilities and costs	Yes	As per NICE reference case
Perspective (NHS/PSS)	An NHS perspective was used	As per NICE reference case

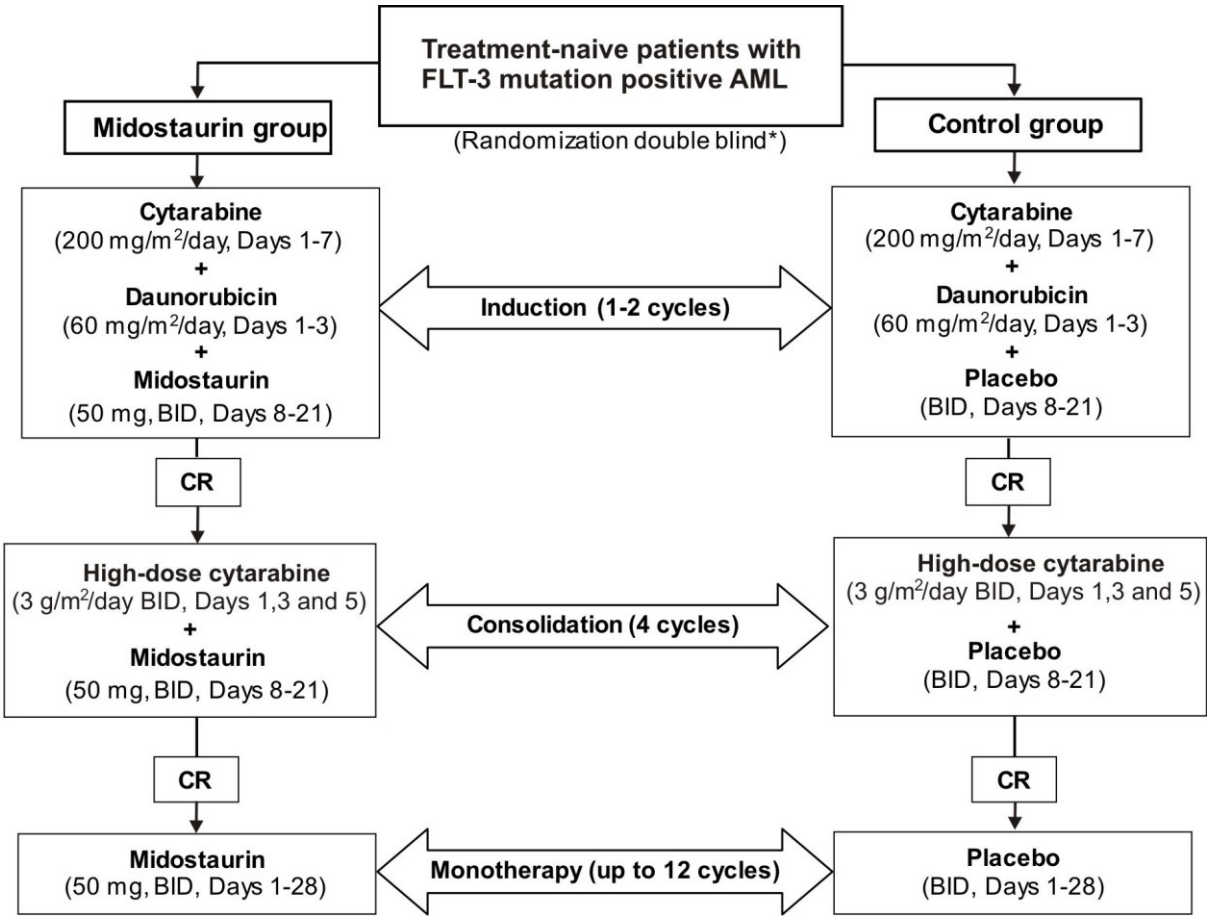
PSS, personal social services; QALYs, quality-adjusted life years

5.2.4 Intervention technology and comparators

A within-trial model was used as the base case and utilized the trial comparators, as the intervention assessed in the RATIFY trial was believed to accurately reflect the intended use of midostaurin therapy in clinical practice. This trial evaluated the addition of midostaurin or placebo to daunorubicin/cytarabine (SOC) in the induction phase (lasting a maximum of 2 cycles), followed by high-dose cytarabine in the consolidation phase (lasting up to 4 cycles); patients who achieved full remission continued treatment with midostaurin or placebo as a single agent for up to 1 year. Dosage in the model was based directly on the RATIFY trial and accounted for wastage and dose reductions.

Figure 21 presents the detailed dosing schedule that was used in the RATIFY trial, and Figure 22 summarizes the scheduled therapy in each treatment step. The number of cycles in RATIFY were applied to the model as the maximum number of cycles for the respective treatment phase (induction, consolidation, and monotherapy).

Figure 21 Dosing used in the RATIFY clinical trial

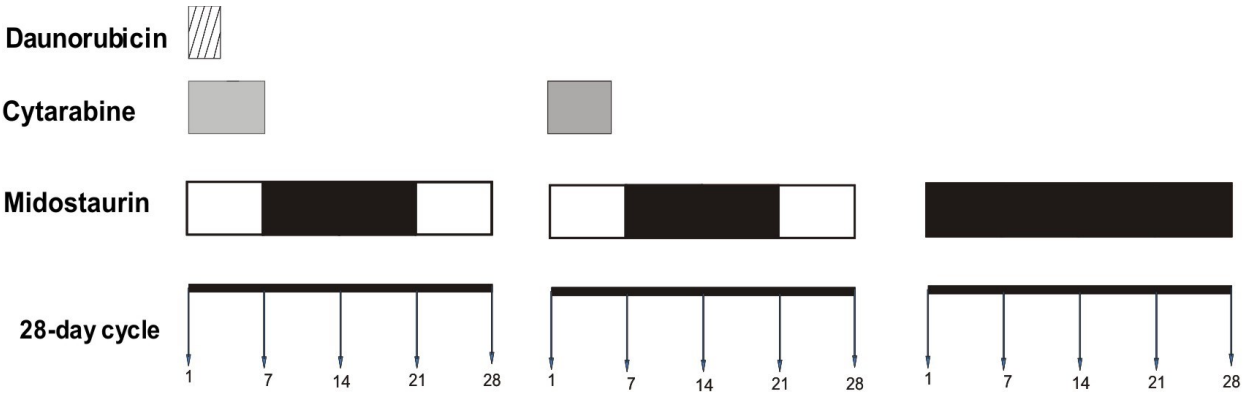


RATIFY CSR.[16]

AML, acute myeloid leukaemia; BID, twice daily; CR, complete remission; CSR, clinical study report; FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; TKD, tyrosine kinase domain.

* Central randomization within 3 strata: FLT3-TKD, FLT3-ITD with allelic ratio ≥ 0.7; FLT3-ITD with allelic ratio <0.7. ** Up to 12 cycles.

Figure 22 Summary of dosing schedule used in RATIFY



Induction therapy, given for 1–2 cycles, consists of daunorubicin plus cytarabine plus midostaurin.

Consolidation therapy, given for up to 4 cycles, consists of cytarabine plus midostaurin.

Midostaurin monotherapy is given for up to 12 months.

RATIFY CSR.[16]

In the model, treatment duration is based on the entire treatment pathway reported in the clinical trial data, meaning that the primary therapy treatment duration included induction, consolidation, and monotherapy (see section 5.5.3). Dose reduction was based on the within-trial distribution of doses for the midostaurin therapy and SOC arms.

5.3 Clinical parameters and variables

The following sections outline how the clinical data from the RATIFY trial were incorporated into the model.

5.3.1 Health outcomes

Based on the clinical trial, the primary health outcomes used in this model included OS, CR, and SCT. The proportion of patients in each health state over time was estimated from the Kaplan–Meier survival functions associated with these clinical outcomes.

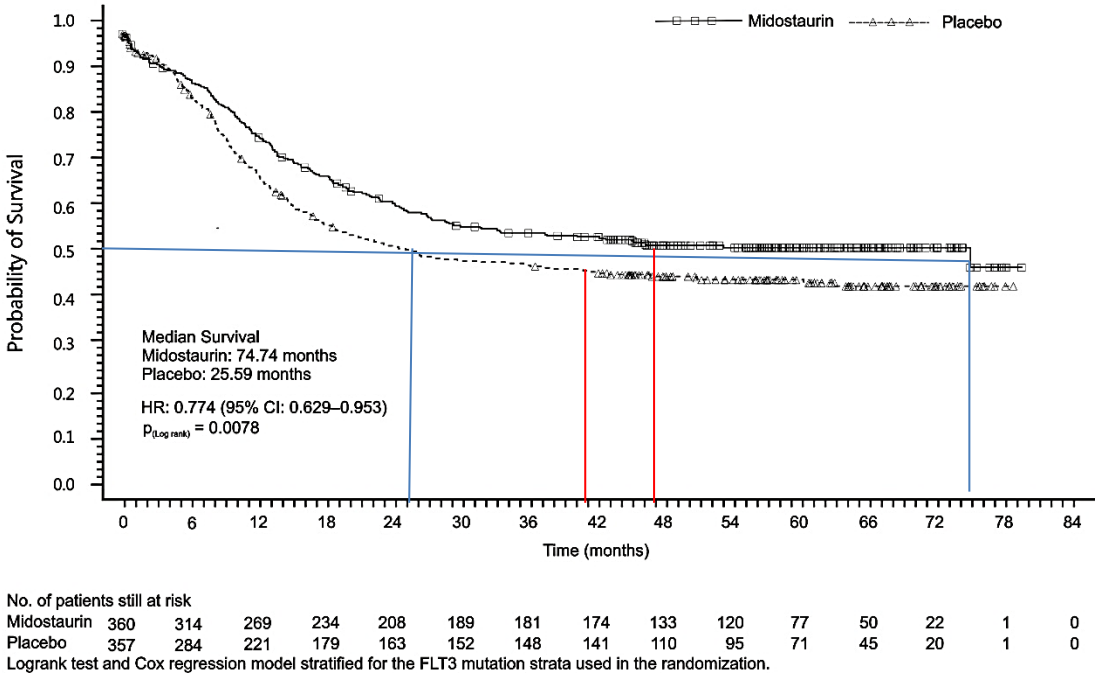
Overall survival

The primary endpoint used in the trial was OS (non-censored at the time of SCT), of which midostaurin therapy showed a statistically significant improvement (p=0.0078) at a one-sided alpha level of 0.0239. Additionally, the estimated probability of being alive at 36 months was higher in the midostaurin therapy arm compared to the SOC arm (54% [95% CI: 0.49, 0.59] vs. 47% [95% CI: 0.41, 0.52]).

Death from any cause was included as an event; patients were censored at their last date of contact. Although available, data for OS with censoring at the time of SCT were not used, as SCT is commonly used in clinical practice to treat patients with AML.

Figure 23 presents the OS Kaplan-Meier curves from the RATIFY trial. OS results were extrapolated beyond the trial horizon using survival extrapolation techniques (see section 5.3.2 for further details on the extrapolation).

Figure 23 Kaplan–Meier curve (midostaurin therapy vs. SOC) for OS (non-censored at the time of SCT)



RATIFY CSR.[16]
Median is indicated by blue lines and mean by red lines.

***OS use in the model**:* OS was the key endpoint contributing to LYs and resulting QALYs. In addition to mortality, the OS curve had an impact on other health states. The relapse state was affected by OS, as relapse would absorb any patients still alive and not in another health state. OS also had an impact on the SCT state, as the only post-SCT event reported in the trial was mortality. Therefore, the proportion of patients occupying the SCT state (i.e. the area between SCT initiation and mortality) was directly based on the OS trend.

Complete remission (CR)

Time-to-CR patient-level data were available and were used in the model for the trial period. Following trial cut-off, the proportion of patients remaining in the CR state were extrapolated based directly on EFS extrapolation data.

Figure 24 presents the proportion of patients in CR at each treatment cycle. Extrapolated CR results were based directly on extrapolated time-to-CR results from the trial.

[redacted]

MIDO, midostaurin therapy
PBO, placebo, i.e. standard of care

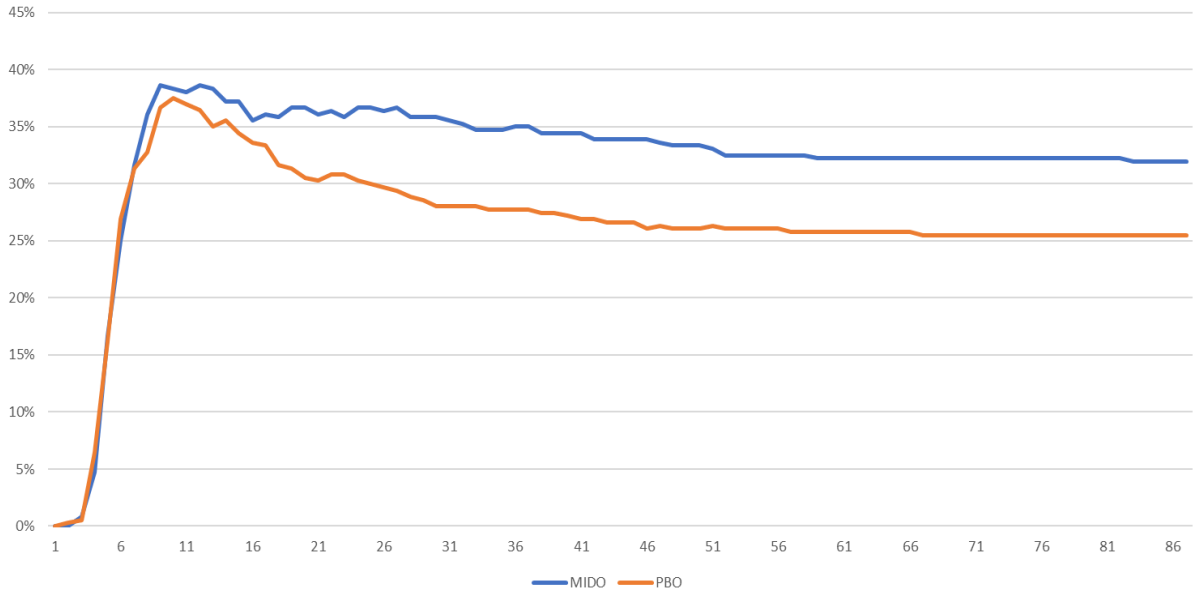
CR use in the model: The primary function of the CR endpoint was to derive the proportion of patients in the CR state. In addition, only patients in CR could receive SCT prior to relapse in the clinical trial, as per current clinical guidelines.[10] This meant that although SCT and CR were independent in the model, dependency was embedded in the patient treatment pathway data. Furthermore, CR affected the relapse state, as patients who were not in AML diagnosis, CR, SCT or mortality health state were considered to be in the relapse health state.

Stem cell transplantation

Data from the RATIFY trial were available for those patients who received SCT. Overall, 57% of patients received SCT in the trial and this proportion was similar between treatment groups (59.4% in the midostaurin therapy arm and 55.2% in the SOC arm, see Figure 25). The slightly higher rate of SCT in the midostaurin therapy arm may be attributed to the higher CR rate seen in this group.

Figure 25 presents the uptake for SCT, *censored for mortality* across the cycles. These mortality-censored values were used in the model for SCT, as patients left the SCT state through mortality.

Figure 25 SCT uptake: midostaurin therapy vs. SOC (censored for mortality)



Extrapolation: By the end of the trial, [redacted]. It was noted by a UK clinical expert that among patients who survive past 6 years, those who received SCT, have similar expected survival as patients who did not. Therefore, SCT survival was based on the OS trend (i.e. it was assumed that SCT patients died at the same rate as the overall surviving population after trial cut-off). It should be noted that no further SCT was assumed in the model after the end of the trial duration. This was supported by clinical experts who felt that most SCT would have occurred within the trial period.

SCT use in the model: The primary function of the SCT endpoint was to derive the state occupancy in the SCT state. SCT also affected the relapse state, as patients who were not in AML diagnosis, CR, SCT or the mortality health state were considered to be in the relapse health state.

5.3.2 Extrapolation

Overall survival extrapolation

Approximately [redacted] (midostaurin therapy) and [redacted] (SOC) of non-censored patients were still alive at trial cut-off, and approximately [redacted] (midostaurin therapy) and [redacted] (SOC) of patients had not progressed by this time.[16] For this reason, a number of extrapolation options were explored using a comprehensive set of techniques (presented in Section 8.16, Appendix 16 in detail).

A range of extrapolation approaches were explored, using (a) non-parametric model (Kaplan–Meier) in addition to a range of parametric functions (exponential, Weibull, Gompertz, log-normal, logistic, gamma) or assuming general mortality (cure model) at the end of the trial or (b) parametric functions for the whole model duration. Parametric models with and without treatment effects were explored. The different approaches are described in further detail in Section 8.16, Appendix 16.

The most appropriate distribution was selected using the following process: (a) assessment of the visual fit to the observed Kaplan–Meier, (b) assessment of the statistical goodness of fit (measured using the Akaike Information Criteria [AIC] and Bayesian Information Criteria [BIC]), and (c) assessment of the plausibility of the long-term extrapolation.

In brief, with the exception of the Gompertz distribution (using a treatment covariate or not), none of the parametric functions provided a reasonable visual fit to the observed period. Similarly, the Gompertz plateaued after approximately 10 years, suggesting no deaths after that time.

Clinical experts considered that none of the single parametric functions (or parametric function in addition to the Kaplan–Meier) examined provided a reasonable extrapolation and that patients still alive by the time the trial ended would 'typically' experience the same rate of death as the general population, but noted patients with AML are at higher risk of secondary cancers, and therefore their rate of death could be slightly higher. More specifically, the key points the clinical experts noted were as follows: (1) following the first 2 years, patients are likely to become more stable depending on their disease status, with relapse and mortality becoming less frequent (i.e. a plateau is expected to occur after the first 2–3 years); (2) after 5 years, patients are likely to follow a natural mortality curve as most of the leukaemia relapse occurred prior to this stage; (3) 10-year survival is likely to be approximately 10% lower than at the end of the trial (about 6.7 years prior), so the mortality trend should not be too aggressively extrapolated after the end of the trial; (4) the aggressive mortality/relapse rate of the first 2–3 years of the trial is not a good base for the long-term extrapolation; (5) the plateau seen at the end of the trial is likely to be relatively constant over time, consistent with the natural mortality of the patients; and (6) continuation of the plateau effect should be considered (i.e. long tail curves should not be automatically discarded).

Thus, a cure model (assuming the rate of death from the general population after the end of the trial) was used in the base case. After trial cut-off, natural mortality was applied to both treatment arms using mortality data from the UK Office for National Statistics (ONS) (2013-2015). Post-trial survival estimates were age- and sex-adjusted based on the average age and proportion of males in the clinical trial population, with increasing mortality as time progressed. Alternative (parametric) models are explored in scenario analysis for transparency.

In the base case, the cure model is used following trial cut-off in addition to the observed Kaplan–Meier prior to trial cut-off. A cure model in addition to the Gompertz distribution fitted to the observed period is used in scenario analysis. Whilst the Gompertz distribution provided a reasonable fit to the data compared with other distributions, the fit of the Gompertz distribution to the observed data is debatable.

Finally, in the base case, the cure model is fitted from the last event. However, it should be noted that for the midostaurin arm, the Kaplan–Meier curve quickly dropped at cycle 81 attributable to one event. This was not observed in the SOC arm. It is unclear whether this is due to an inconsistency in the data, and therefore the cure model has been fitted prior to that event in our base case for midostaurin. It should be noted that fitting the cure model from the last event could be an equally plausible scenario and therefore results are presented in scenario analysis.

Figure 26 presents the extrapolated OS curve using the cure model approach. Given that people still alive by the end of the trial duration are assumed to follow the general population mortality, the gain in OS observed in the trial for midostaurin versus SOC is therefore expected to be maintained over the lifetime. This assumption is supported by clinical opinion. Clinical experts considered that whilst the rate of death at the end of the trial could be more rapid compared with the general population (notably given the development of secondary cancers), clinical experts expected the rate of death to be the same between the two arms from the end of the trial. In particular, clinical experts noted that there was no clinical rationale for using a different rate of death between arms after the end of the trial and that the initial gain would be maintained over the lifetime.

[redacted]

Event-free survival extrapolation

EFS was used for the post-trial extrapolated values of CR, as well as determining the proportion of patients switching to secondary therapy. Time to CR *following the trial cut-off* was based on the extrapolated EFS curves. The proportion of patients switching to secondary therapy were derived from subtracting both the proportion of SCT uptake and mortality from the extrapolated EFS values.

The same curve selection techniques used for OS were applied for EFS. A range of extrapolation approaches were explored, using (a) non-parametric model (Kaplan–Meier) in addition to a range of parametric functions (exponential, Weibull, Gompertz, log-normal, logistic, gamma) or (b) parametric functions for the whole model duration. Parametric models with and without treatment effects were explored. The different approaches are described in further detail in Section 8.16, Appendix 16.

The most appropriate distribution was selected using the following process: (a) assessment of the visual fit to the observed Kaplan–Meier, (b) assessment of the statistical goodness of fit (measured using the AIC and BIC, and (c) assessment of the plausibility of the long-term extrapolation.

In brief, a piecewise approach was used for EFS, where the Kaplan–Meier curve is used prior to the trial cut-off, followed by a parametric tail after the cut-off. However, it is challenging to identify the most appropriate distribution for EFS after the end of the trial. Whilst the log-logistic and gamma distribution provided a plausible visual extrapolation at the end of the trial, these distributions led to EFS being greater than OS. In contrast, the exponential and Weibull distribution did not provide a smooth extrapolation after the end of the trial duration, but led to EFS extrapolation consistent with OS. A conservative approach was used using the Weibull distribution to extrapolate EFS. It should be noted that this is likely to be conservative as CR is lost quicker using the Weibull distribution compared with the log-logistic or gamma distributions.

Figure 27 presents the extrapolated EFS curves using a piecewise, Weibull model approach. Further details on the selection of extrapolation model are provided in Section 8.16, Appendix 16.

[redacted]

Stem cell transplantation

As mentioned, it was noted by a UK clinical expert that among patients who survive past 6 years, those who received SCT have similar expected survival to patients who did not. Therefore, SCT survival after trial cut-off was based on the OS trend (i.e. it was assumed that SCT patients died at the same rate as the overall surviving population after trial cut-off).

Complete remission

Following trial cut-off, the proportion of patients remaining in CR were based directly on the EFS extrapolation.

5.4 Measurement and valuation of health effects

The economic endpoints used in the model were QALYs and LYs saved. Overall LYs were calculated as the sum of OS at each cycle. QALYs were calculated as the sum of the utility-weighted time in each treatment phase and health state (induction, consolidation, monotherapy, CR, relapse, SCT treatment, SCT recovery, post-SCT recovery).

5.4.1 Health-related quality of life data from clinical trials

No within-trial HRQoL data were available from the RATIFY trial, so utility values were obtained from a literature review and a separate time trade-off (TTO) utility study (outlined in Section 8.17, Appendix 17).

5.4.2 Mapping

Mapping was not applicable, as no within-trial HRQoL data were available from the RATIFY trial.

5.4.3 Health-related quality of life studies

A systematic review of the literature was conducted to identify utility values that could be used within the economic model (see Section 8.13, Appendix 13 for further details on the systematic review). In addition, a TTO study was conducted by Novartis. However, due to some inconsistencies in the TTO study (notably for the induction and SCT health state), data from the literature were used in our base case. In particular, clinical opinion was sought and it was felt that the utility values for induction and SCT from the TTO study were not realistic. Details of the TTO study are available in Section 8.17, Appendix 17. Results from the TTO study are used in scenario analysis. It should be noted that the impact on the ICER using the TTO is minimal, and thus, results from the literature were preferred given their face validity.

Overview of the systematic review

A total of 39 studies were selected for full extraction. Of these, we present here the 10 studies that reported specific utility values (Table 27).

Table 27 Relevant HRQOL studies

Reference	Title	Type of Study	Interventions	Study Population	Utility Values
Kurosawa_Blood_2014 (Abstract)[73]	Decision Analysis of Allogeneic Hematopoietic Stem Cell Transplantation Versus Chemotherapy in Cytogenetically Standard-Risk Acute Myeloid Leukaemia in First Complete Remission: The Impact of FLT3-ITD Profile	Decision analysis	Allogeneic HCT vs. CHEMO	Intermediate-/unknown-risk AML	Post SCT overall: 0.74; post SCT with GVHD (complications): 0.67; post chemotherapy overall: 0.70
Levy_Current Oncology_2014[64]	Cost-effectiveness in Canada of azacitidine for the treatment of higher-risk myelodysplastic syndromes	CEA	AZA vs. Conventional Chemotherapy (BSC, low dose chemotherapy, high dose chemotherapy)	High-risk MDS and low-blast AML	AML (>30% blasts): 0.67
Batty_Journal of Cancer Research &Therapy_2014[65]	Decitabine is more cost effective than standard conventional induction therapy in elderly acute myeloid leukaemia patients	CEA	Decitabine vs. conventional induction therapy	Elderly, newly diagnosed AML	Active AML: 0.524 (use Gidwani 2012 study); AML treated with Decitabine: 0.71 (assumption); AML in Remission and on treatment (Consolidation and Monotherapy): 0.81 (assumption); AML in Remission: 0.91(based on Goss study)
Gidwani_Journal of Medical Economics_2012[74]	A cost-effectiveness analysis of using azacitidine vs. decitabine in treating patients with myelodysplastic syndromes.	CEA	Azacitidine vs. Decitabine	Mixed-risk MDS	AML: 0.524 (using blast stage of CML, Dalziel et al, 2005); Remission 0.91 (based on Goss study)

Pan_Clinical Therapeutics_2010[66]	Economic analysis of decitabine versus best supportive care in the treatment of intermediate- and high-risk myelodysplastic syndromes (MDS)	CEA	Decitabine vs. BSC	Intermediate-/high-risk MDS	Transfusion-independent MDS: 0.84; Transfusion-dependant MDS: 0.60 (Szende et al 2009); AML: 0.53 (QLQ-C30 co-Alibhai 2007 converted using mapping)
Uyl de Groot _British Journal of Haematology_1998[75]	Cost- effectiveness and quality-of-life assessment of GM-CSF as an adjunct to intensive remission induction chemotherapy in elderly patients with acute myeloid leukaemia	CEA/QOL	Induction chemo +SCT	Elderly AML	Induction: 64.8; GM-SCF: 53.5; post Immediately SGM-SCF: 68.0; 6 months post GM-SCF 80.6; 12 month after GM-SCF 74.4
Leunis_European Journal of Haematology_2014[76]	Impaired health-related quality of life in acute myeloid leukaemia survivors: A single-centre study	QOL	NR	AML	AML Survivors: 0.82; Survivors - No relapse: 0.83; Survivors after relapse: 0.78
Slovacek_San Paolo Medical Journal_2007[77]	Psychosocial, health and demographic characteristics of quality of life among patients with acute myeloid leukaemia and malignant lymphoma who underwent autologous hematopoietic stem cell transplantation	QOL	Autologous HSCT	AML and ML	AML: 0.715; AML >60 yo: 0.61
Goss_Cancer Control_2006[78]	Cost effectiveness of lenalidomide in the treatment of transfusion-dependent myelodysplastic syndromes in the US	CEA	Lenalidomide	Low-/intermediate-risk MDS	Transfusion independent MDS: 0.91

Grulke_BMT_2012[79]	Quality of life in patients before and after haematopoietic stem cell transplantation measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C30	QOL SLR	HSCT	Variety of cancers (acute leukaemia, CML, solid tumours)	(Results after mapping to EQ-5D using Crott, et al. 2010 algorithm). Before HSCT: 0.826; During hospitalization for HSCT: 0.613; Up to 6 months after HSCT: 0.810; >1 year after HSCT: 0.826

Summary of published utilities by relevant health state

Utilities reported in the literature for specific health states are presented in Table 28, and are ordered in a way to represent the typical course of disease and treatment.

Table 28 Published utility values by health state

Health State	Utility value	Source	Notes
Active AML	0.524	Gidwani et al 2012[74]	CLL considered similar
AML post-MDS	0.53	Pan et al 2010[66]	Mapped from EORTC
Newly Diagnosed	0.67	Levy et al 2014[64]	Measured AML >30% blasts
Induction treatment	0.648	Uyl de Groot et al 1998[75]	Measured
Induction treatment	0.71	Batty et al 2014[65]	Assumption, calculated
Consolidation	0.81	Batty et al 2014[65]	Assumption, calculated
Monotherapy on treatment	0.81	Batty et al 2014[65]	Assumption, calculated
CR off-treatment	0.7	Kurosawa et al 2014[73]	Measured post chemo long term CR
CR off-treatment	0.84	Pan et al 2010[66]	Transfusion-independent MDS
CR off-treatment	0.91	Goss et al 2006[78]	Transfusion-independent MDS
CR post-1L (no relapse)	0.83	Leunis et al 2014[76]	Measured
SCT treatment	0.535	Uyl de Groot et al 1998[75]	Measured
SCT treatment	0.61	Grulke et al 2012[79]	Mapped from EORTC
Recovery SCT	0.68	Uyl de Groot et al 1998[75]	Measured
Recovery SCT	0.810	Grulke et al 2012[79]	Mapped from EORTC
Post RCT with complications	0.67	Kurosawa et al 2014[73]	Measured

Health State	Utility value	Source	Notes
Long-term post-SCT	0.71	Slovacek et al 2007[77]	>60 years old, long term, measured
Post-SCT	0.74	Kurosawa et al 2014[73]	Measured
Post-SCT	0.806	Uyl de Groot et al 1998[75]	Measured
Post-SCT	0.826	Grulke et al 2012[79]	Mapped from EORTC
Relapse	NA	NA	
CR post-relapse	0.78	Leunis et al 2014[76]	Measured

AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; NA, not available; post-1L, post first-line therapy; RCT, randomised controlled trial; SCT, stem cell transplantation.

Mapping of SCT utility

It is important to note that utility values used in the model for SCT treatment, recovery, and post-SCT recovery were mapped from published (EORTC) Quality of Life Core Questionnaire QLQ-C30 data (Grulke, et al. 2012)[79] using an algorithm developed by Crott, et al. (2010),[80] which calculated EQ-5D utility based on QLQ-C30 scores. The QLQ-C30 data published by Grulke, et al. presented scores specific to different stages of stem cell therapy (before SCT, during hospitalization, up to 6 months after SCT, and >1 year after SCT). The algorithm developed by Crott, et al. (presented below) was then applied to these data in order to obtain EQ-5D utility scores:

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

5.4.4 Health-related quality of life data used in cost-effectiveness analysis

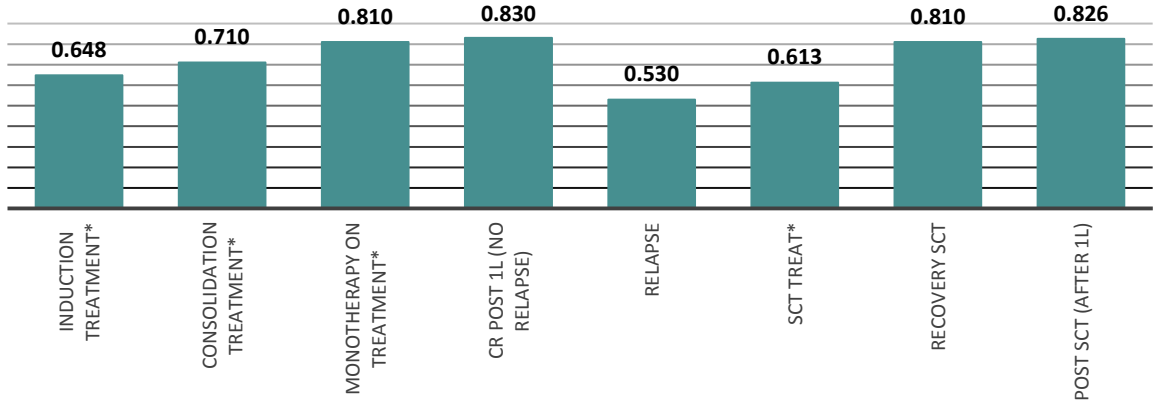
The utility values taken from the literature used in the base case of the economic model, and their sources, are presented in Table 29 and Figure 28. Utility values from the TTO study (see Section 8.17, Appendix 17 for further detail) used in scenario analysis are shown in Table 30. It can be seen that the utility values for induction treatment and SCT are comparatively low and possibly unrealistic.

Table 29 Utility used in the model

Utility state	Utility values used in base case (literature)	Values used in scenario analysis (TTO)	Source (literature values)
Induction treatment*	0.648	[redacted]	Uyl-de Groot _Br J Haematol_1998[75]
Consolidation treatment*	0.710	[redacted]	Batty et al 2014[65]
Monotherapy treatment*	0.810	[redacted]	Batty et al 2014[65]
Complete remission post-1L (No relapse)	0.830	[redacted]	Leunis et al 2014[76]
Relapse	0.530	[redacted]	Pan et al 2010[66]
SCT Treatment *	0.613	[redacted]	Source for Algorithm - Crott et al 2010;[80] Source of QLQC30 data – Grulke et al 2012[79]
SCT Recovery	0.810	[redacted]	Source for Algorithm - Crott et al 2010;[80] Source of QLQC30 data – Grulke et al 2012[79]
Post-SCT Recovery	0.826	[redacted]	Source for Algorithm - Crott et al 2010;[80] Source of QLQC30 data – Grulke et al 2012[79]

*Includes treatment disutility
Post-1L, post first-line; SCT, stem cell transplantation

Figure 28 Utility level per health state



HRQoL in the model varied among the different treatment phases, but was assumed to remain constant within each phase, as no within-state variations were identified. HRQoL values for each treatment arm were determined by applying the state-specific utility values to the proportion of patients in each state.

Adverse reactions

Specific utility values for AEs were not utilised in the model. Instead, utility values specific to each phase (induction, consolidation, CR, etc.) were used and assumed to include the disutilities for toxicities during treatment.

Sensitivity analyses

As part of the sensitivity analysis (presented in section 5.8), utility values were varied by ±20% as shown in Table 30

Table 30 Utility variations used in the sensitivity analysis

Scenarios	Lower-bound value	Base-case value	Upper-bound value
Utility values			
Induction treatment utility	0.58	0.65	0.72
Consolidation treatment utility	0.64	0.71	0.78
Monotherapy treatment utility	0.73	0.81	0.89
Complete Remission utility	0.75	0.83	0.91
Relapse utility	0.48	0.53	0.58
SCT treatment utility	0.55	0.61	0.67
SCT recovery utility	0.73	0.81	0.89
Post-SCT recovery utility	0.74	0.83	0.91

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

Overall resource utilisation and cost calculations associated with each treatment included drug costs (primary and secondary therapy), SCT costs, routine care costs, AE-related costs (grades 3/4 in at least 5% of patients), and mortality costs. Costs were summed for each primary therapy to obtain its total cost. The included costs and their sources are summarised in Table 31.

Table 31 Cost sources

Cost	Source
Midostaurin	Data on file
Cytarabine Daunorubicin Secondary therapy	British National Formulary https://www.bnf.org/

Stem Cell therapy Routine care Adverse events	National Schedule of Reference Costs (2014-1015). NHS Trusts and NHS Foundation Trusts https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016
Mortality	Georghiou, Theo, and Martin Bardsley. "Exploring the cost of care at the end of life." Report, Nuffield Trust, London (2014).

Utilisation of primary therapy and the prevalence of AEs was based directly on patient-level data from the RATIFY trial.

Drug acquisition costs

The drug acquisition cost for midostaurin is not yet available in the BNF. Pack size and price of each pack of midostaurin were based on Novartis data on file. The drug acquisition cost for chemotherapy was taken from the BNF.

Other costs

Routine care utilisation was based on the data used in the NICE STA for azacitidine TA399. Given that administration costs for chemotherapies were accounted for in the HCRU questionnaire utilized in the NICE STA for azacitidine, no separate costs for administration were added to avoid double counting. Midostaurin is also administered orally and, thus, no additional administration costs is assumed.

SCT duration was based on estimates from clinical experts. Secondary therapy ((fludarabine, cytarabine, idarubicin, filgrastim, FLAG-IDA) utilisation was based on Kantar Health (2015)[52] estimates.

5.5.2 Intervention and comparators' costs and resource use

Proportion of patients reaching each treatment cycle

As previously mentioned in the economic model, treatment duration was modelled independently from CR or OS, as it was directly based on the patient-level data. Therefore, treatment duration was derived from the proportion of patients receiving each cycle of treatment within the trial.

The proportion of patients receiving each cycle of treatment is directly based on the patient-level data flag for each treatment cycle. It should be noted that as some patients had treatment-free intervals (TFI) during their treatment pathway, the time-to-event data for treatment duration was not used, as this would mean that patients in TFI would be counted for the cycles when they did not receive treatment. Therefore, the proportion of patients receiving the treatment during a specific cycle was considered as more robust and used for both arms.

Figure 29 shows the proportion of patients who reached each treatment cycle, as indicated on the x-axis. Approximately [redacted] and [redacted] of midostaurin therapy and SOC patients, respectively, reached the last (fourth) cycle of consolidation therapy. While no patients in the SOC arm received monotherapy, approximately [redacted] of those in the midostaurin therapy arm started monotherapy, with [redacted] of all midostaurin patients completing all 12 cycles. A small number of patients received prolonged monotherapy ([redacted]), although the majority of these patients did not receive the full treatment for these additional cycles.

[redacted]

[redacted]

MIDO, midostaurin therapy
PBO, placebo i.e. standard of care

Primary therapy costs

Midostaurin drug acquisition cost

As previously mentioned, the drug acquisition cost for midostaurin is not yet available in the BNF. Pack size and price of each pack of midostaurin were based on Novartis data on file. For the AML indication, midostaurin comes as 25 mg soft capsules and is provided as four packs of 28-day capsules giving 112 capsules at a cost of [redacted]. Midostaurin is also administered orally and thus, no additional administration cost is assumed.

Chemotherapies drug acquisition cost

Drug acquisition costs for chemotherapies were obtained from the BNF. Administration costs are assumed to be already included in the resource use taken from NICE TA399.

Calculation of drug acquisition cost per cycle based on the distribution of dosage given in the trial

Table 32, Table 33, and Table 34 present the distribution of dosage for the primary therapies (midostaurin, cytarabine, and daunorubicin, respectively) at each treatment phase. The costs of

primary therapy are presented in Table 35. Consistent with the clinical trial data, it was assumed that the average patient had a body surface area of 1.9 m^2 and a weight of 70 kg. To obtain total costs per cycle of each therapy, the total dose (mg) of treatment per cycle (including wastage and dose reduction) was divided by the size of pack/vial before being multiplied by the price per pack/vial:

$$Cost\ of\ a\ therapy\ per\ cycle\ (oral) = \frac{(mg\ per\ cycle)}{(pack\ size)} x\ (price\ per\ pack)$$

$$Cost\ of\ a\ therapy\ per\ cycle\ (IV) = BSA\ x\ roundedup\left(\frac{mg}{m2}\right) x\ (price\ per\ vial)\ or$$

$$= KG\ x\ roundedup\left(\frac{mg}{kg}\right) x\ (price\ per\ vial)$$

Wastage was included in the drug costs of midostaurin, meaning it was assumed that no “pill-splitting” occurred (i.e. fractions of doses were rounded up to the nearest whole number). Additionally, dose reduction was accounted for in the drug cost of all primary therapies (midostaurin, daunorubicin, and cytarabine). Costs per cycle with dose reduction for each therapy were calculated by using the within-trial doses received. Wastage used the within-trial doses rounded up to the nearest possible whole pill or vial amount (25 mg pills for midostaurin).

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]

[redacted]

Table 33 Cytarabine dosage (per day)

Dose, mg	Cost of dosing (£)	Midostaurin therapy arm		SOC arm	
		Induction	Consolidation	Induction	Consolidation
100	£4.20	0.85%	0.00%	0.85%	0.00%
200	£8.39	79.32%	0.00%	81.07%	0.00%
300	£12.59	19.83%	0.00%	18.08%	0.00%
1800	£75.53	0.00%	0.43%	0.00%	0.48%
1900	£79.72	0.00%	0.43%	0.00%	0.00%
2300	£96.51	0.00%	0.00%	0.00%	0.48%
2700	£113.29	0.00%	0.00%	0.00%	0.48%
2800	£117.49	0.00%	0.00%	0.00%	0.48%
2900	£121.68	0.00%	1.30%	0.00%	0.00%
3000	£125.88	0.00%	1.30%	0.00%	1.90%
3100	£130.08	0.00%	0.00%	0.00%	1.43%
3200	£134.27	0.00%	0.87%	0.00%	1.43%
3300	£138.47	0.00%	1.30%	0.00%	1.43%
3400	£142.66	0.00%	1.30%	0.00%	1.43%
3500	£146.86	0.00%	4.33%	0.00%	4.76%
3600	£151.06	0.00%	65.37%	0.00%	62.86%
3700	£155.25	0.00%	23.38%	0.00%	20.95%
3800	£159.45	0.00%	0.00%	0.00%	1.90%
Sum		100%	100%	100%	100%
Average		109%	119%	109%	119%

RATIFY patient-level data

Table 34 Daunorubicin dosage (per day)

Dose, mg	Cost of dosing (£)	Midostaurin therapy arm	SOC arm
		Induction	Induction
20	£65	1.40%	0.56%
40	£130	0.00%	0.56%
60	£195	67.42%	68.93%
80	£260	31.18%	29.94%
Sum		100%	100%
Average		213.44	213.36

RATIFY patient-level data

Table 35. Costs of primary therapy

Phase	Arm	Regimen	Dose	mg per cycle	Vial size mg (or tablet)	Price per vial/tablet, £	Cost per cycle as per indication, £	Cost with wastage and dose reduction, £
Induction	Midostaurin therapy arm	Cytarabine	200 mg/m^2/day (1-7)	2660	500	[redacted]	[redacted]	[redacted]
		Daunorubicin	60 mg/m^2/day (1-3)	342	20	[redacted]	[redacted]	[redacted]
		Midostaurin	50 mg (2 X 25) twice per day (8-21)	1400	25	[redacted]	[redacted]	[redacted]
		Total cost per cycle				[redacted]	[redacted]	[redacted]
	Standard of care	Cytarabine	200 mg/m^2/day (1-7)	2660	500	£19.50	£103.74	£112.68
		Daunorubicin	60 mg/m^2/day (1-3)	342	20	£65.00	£1,111.50	£1,216.16
		Total cost per cycle					***£1,215.24***	***£1,328.84***
Consolidation	Midostaurin therapy arm	High-dose cytarabine	3000 mg/m^2/day (1, 3, 5) twice per day	34200	500	[redacted]	[redacted]	[redacted]
		Midostaurin	50 mg (2 X 25) twice per day (8-21)	1400	25	[redacted]	[redacted]	[redacted]
		Total cost per cycle				[redacted]	[redacted]	[redacted]
	Standard of care	High-dose cytarabine	3000 mg/m^2/day (1, 3, 5) twice per day	34200	500	£19.50	£1,333.80	£1,585.32
		Total cost per cycle					***£1,333.80***	***£1,585.32***
Monotherapy	Midostaurin therapy arm	Midostaurin	50 mg (2 X 25) twice per day (1-28)	2800	25	[redacted]	[redacted]	[redacted]
		Total cost per cycle				[redacted]	[redacted]	[redacted]

Cost source: British National Formulary

Secondary therapy drug dosage

Following discussion with UK clinical experts, it was noted that FLAG-IDA is the main regimen used as secondary therapy in the UK. For this reason, FLAG-IDA was the only included secondary therapy in this analysis.

In the analysis, patients could only receive secondary therapy after their primary therapy, but only if they had an EFS event (including relapse or no CR), and if the EFS event was not related to mortality.

Patients receiving secondary therapy in cycle t = Patients with an EFS event in cycle t – patients dying in cycle t

Secondary therapy is a temporary/tunnel state where the patients get (1) a drug cost related to secondary therapy (£3,101 per cycle) and (2) a routine care cost associated with secondary therapy (£5,995 per cycle).

Secondary therapy duration was calculated from Kantar Health (2015)[52] estimates and was rounded up to the nearest whole cycle value. As described in the Kantar CancerMpact Western Europe Report,[52] 76 physicians who treated a total of 2,885 AML patients monthly were asked how many receive second-, third-, and fourth-line systemic therapy. Seventy-five physicians provided data on the proportion of induction patients who relapse and are treated with second-line, 69 physicians provided data for patients moving from second- to third-line (second relapse), and 63 physicians provided data for patients moving from third- to forth-line (third relapse) therapy. Results are presented in Table 36.

Table 36 AML patients who receive later lines of systemic therapy, Western Europe, 2015

Regimen	Induction to first relapse	First to second relapse	Second to third relapse
Patients in remission and received no further systemic therapy	26.7%	26.4%	41.8%
Patients who died before receiving next line of systemic therapy	21.6%	24.0%	19.3%
Patients who are alive but did not receive next line of systemic therapy	19.9%	20.0%	16.8%
Patients who received next line of systemic therapy	31.8%	29.5%	22.1%

Source: Kantar Health. (2015)[52]

Based on the CancerMpact report, the average duration of FLAG-IDA was 2.2 cycles. The duration of secondary therapy was therefore calculated according to the following:

$$Secondary\ therapy = 2.2\ X\ 31.8\% + 2.2\ X\ (31.8\%\ X\ 29.5\%) + 2.2\ X (31.8\%\ X\ 29.5\%\ X\ 22.1\%)$$

$$= 0.95\ additional\ chemotherapy\ cycles\ on\ average\ after\ first\ relapse$$

$$= 1\ additional\ chemotherapy\ cycle\ after\ first\ relapse\ (rounded)$$

Based on this estimate, the duration of secondary therapy in the model was set at 1 cycle and a temporary state (1 cycle) was applied. The proportion of patients in the secondary therapy state was cumulative (temporary/tunnel state), up to the maximum number of cycles of secondary therapy set in the model (1 cycle in the base case).

Costs per cycle of secondary therapy (i.e. therapies received following the first relapse) were calculated the same way as primary costs and are presented in Table 37. One important difference to note is that secondary therapy did not include dose reduction. Instead, the average number of cycles of secondary therapy received was based on Kantar Health (2015)[52] estimates (Table 37).

The average cost per cycle of secondary therapy was calculated by summing the price per 28-day cycle of each FLAG-IDA therapy.

Table 37. Secondary therapy costs

Combination	Regimen	Dose	Body surface area/mass, m^2/kg	Dose	Number of days	mg per cycle	Vial size mg (or µg)	Price per vial, £	Price per cycle, £	Average number of cycles[a]
FLAG-Ida	Fludarabine	30 mg/m^2 IV CI, days 1-5	1.900	30	5	285.00	50.00	£155	£883.50	
	Cytarabine	2000mg/m^2/day (1-7)	1.900	2000	7	26600	500.00	£19.5	£1,037.40	
	Idarubicin	10 mg/m^2/d IV, days 1-3	1.900	10	3	57	10.00	£174.72	£995.90	
	Filgrastim (G-CSF)	5 mcg/kg, days 6-9	70.000	5	3	1050	300.00	£52.70	£184.46	
	Total cost per cycle								£3,101.27	2.2

[a]Source: Kantar Health. (2015)[52]. Table 17 Utilization and number of cycles of systemic therapy at first relapse and second relapse, acute myeloid leukemia, Western Europe, 2015

SCT Costs

Average costs associated with SCT were obtained from NHS Reference Costs, shown in Table 38. These costs included the costs of SCT, peripheral blood stem cell harvest costs, hospitalisation costs, and medical oncologist follow-up costs. Additional costs associated with routine care during SCT recovery are presented below in Table 42. It was assumed that the costs of long-term recovery post-SCT are identical to the costs during CR.

Table 38. NHS reference costs for SCT

Code	Description	Intervention	Cost, £
SA26A	Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over	1,877	£17,344
SA26B	Peripheral Blood Stem Cell Transplant, Autologous, 18 years and under	161	£28,980
SA27A	Peripheral Blood Stem Cell Transplant, Syngeneic, 19 years and over	7	£18,300
SA27B	Peripheral Blood Stem Cell Transplant, Syngeneic, 18 years and under	6	£426
SA38A	Peripheral Blood Stem Cell Transplant, Allogeneic (Sibling), 19 years and over	204	£28,176
SA38B	Peripheral Blood Stem Cell Transplant, Allogeneic (Sibling), 18 years and under	35	£81,622
SA39A	Peripheral Blood Stem Cell Transplant, Allogeneic (Volunteer Unrelated Donor), 19 years and over	379	£33,486
SA39B	Peripheral Blood Stem Cell Transplant, Allogeneic (Volunteer Unrelated Donor), 18 years and under	34	£70,445
SA40Z	Peripheral Blood Stem Cell Transplant, Allogeneic (Donor Type Not Specified)	518	£38,336
		Average SCT cost	**£25,116**

Source: Reference Cost Collection - National Schedule of Reference Costs - Year 2015 - 16 NHS trusts and NHS foundation trusts

The average (total) SCT cost was multiplied by the SCT uptake for each comparator (extrapolated from the time-to-event trial data) to obtain the SCT cost for each comparator. This cost was applied to all patients who received SCT as a “one-off” cost and was added to the included SCT routine care costs. The durations of SCT treatment (3 cycles) and recovery (10 cycles) were obtained from interviews with clinical experts.

5.5.3 Health-state unit costs and resource use

Costs were applied for each treatment phase. In addition to the drug costs (summarised in section 5.5.2), routine care (i.e. non-medication costs) and mortality costs were included and are summarised below.

Routine care costs

Costs were obtained from the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care (2015)[81] with the exception of inpatient day care (obtained from NHS reference costs) and FLT3-ITD testing (obtained from clinical expert interviews). These costs are presented in Table 39.

Table 39 Routine care unit costs

Health states	Unit cost (£)	Cost per minute (£)	Source
CNS Haematologist	£81	1.35	PSSRU, 2015 - (one hour client contact) 10.7 Advanced nurse (includes lead specialist, clinical nurse specialist, senior specialist)
Consultant	£105	1.75	PSSRU, 2015 - (one hour client contact) 115.5 Consultant (medical)
Day care nurse	£44	0.73	PSSRU, 2015 - 10.6 Nurse GP practice (Per hour)
Day care specialist registrar	£41	0.68	PSSRU, 2015 - 1 hour cost - 15.3 Registrar group
District Nurse	£65	1.08	PSSRU, 2015 - 10.4 Nurse specialist (community) (Per hour patient related work)
Doctor	£101	1.68	PSSRU, 2015 - 15.4 Associate specialist (one hour)
Junior doctor	£30	0.50	PSSRU, 2015 -15.2 Foundation house officer 2 (Per hour)
Pharmacist	£63	1.05	PSSRU, 2015 -13.6 Hospital pharmacists (patient related activity) - one hour
Oncology nurse	£81	1.35	PSSRU, 2015 -10.7 Advanced nurse (includes lead specialist, clinical nurse specialist, senior specialist) per hour
Inpatient day	£631	0.44	SA25F, Acute Myeloid Leukaemia without CC (Combined day case / ordinary elective spell tariff (£))[82]
FLT3-ITD testing	£150		Clinical expert assumption

PSSRU 2015[81]

A systematic review of the literature was conducted to identify studies that reported resource utilisation that could be used within the economic model. Whilst a number of studies were identified, details were often lacking on how costs were estimated. Different health states were also used, and it is challenging to robustly map costs from these studies to the health states used in our economic model. Further details of the review are available in Section 8.13, Appendix 13.

In the absence of data, resource utilisation (with the exception of SCT) in the model are based on resource utilisation reported in NICE TA399[83] for azacitidine for the treatment of AML in people aged 65 years or older with more than 30% bone marrow blasts who are not eligible for haematopoietic SCT. It should be noted that whilst the population considered in NICE TA399 is slightly different to the population considered in this appraisal, in that this is an older population not eligible for SCT, clinical experts expected that resource utilisation to be broadly the same between older and younger patients. Clinical experts also considered the items of resource utilisation (described below) in NICE TA399 to be generally appropriate and the range reported to be broadly in line with the expected management of AML in younger patients eligible for SCT.

In brief, in NICE TA399, healthcare resource use was estimated from a clinician survey conducted by the company amongst seven clinicians, with the average of the responses used in the model. A questionnaire was sent to clinicians and included questions regarding resource utilisation in terms of medical staff contacts (doctor, nurse, pharmacist, senior nurse, consultant), monitoring and outpatient procedures, and hospital-related costs (e.g. inpatient stays).

Healthcare resource utilisations were estimated for four health states: (1) induction/pre-response, (2) in remission (CR), (3) not in remission (which could include partial response, stable disease, or not in remission without progressive disease), and (4) progressive disease. Healthcare resource utilisations were also estimated separately by treatment arms in people initiating azacitidine and people initiating conventional chemotherapy regimens (CCRs). Resource use by treatment arms and by health states are reported in the company submission in Table 46 and Table 47.[83]

Following review, the Evidence Review Group (ERG)[84] noted that there "*were significant differences in the costs associated with the relapsed and progressive disease state between the azacitidine and conventional care regimen arms, even though patients in both arms were expected to be receiving best supportive care at this poin*t". The Appraisal Committee also felt that assuming different resource utilisation between treatment arms was inappropriate and considered that taking the average of the resource use estimates for the two treatment arms was more appropriate.

Consequently, in our base case, the average of resource utilisation between azacitidine and CCR was used as recommended by the Appraisal Committee. However, it should be noted that whilst the health state definition for induction and remission in NICE TA399 matches that in our economic evaluation, NICE TA399 uses progressive disease, which includes anyone not in remission with progressive disease only. In contrast, in our economic model, people in the relapsed health state could include people not in remission without progressive disease as well as people with progressive disease. Thus, in the base case, the average resource utilisation estimated from NICE TA399 in people not in remission and with progressive disease was used to represent the resource utilisation in people with relapsed disease in our model.

Resource utilisation from NICE TA399 estimated for the induction/pre-response health state was applied in our model to the induction and secondary health states as this matches our health state definition. Similarly, resource utilisation from NICE TA399 estimated for the remission (in CR) health state was applied to the consolidation and maintenance/remission health states as this matched our health state definition.

For SCT and post-SCT resource utilisation, NICE TA399 estimates for doctor visits in progressive disease were used, with an assumption that patients in both of these phases would require eight visits

per cycle (based on the clinical experts noting that SCT patients would typically be seen twice a week).

The mapping between the health state definitions from NICE TA399 and health states in our economic model used for resource use is summarized in Table 40.

Table 40 Health states applied from NICE TA399

Health states used in model	Health states applied from NICE TA399	Rationale
Induction	'Induction/pre-response'	Identical health states
Second induction and secondary therapy	'Induction/pre-response'	Similar health states
Consolidation	'Remission'	Complete remission is required for reaching consolidation.
Maintenance/complete remission	'Remission'	Similar health states
Relapse	'Progressive disease' and 'not in remission' (midpoint)	Relapse in our model include both patients not in remission with and without progressive disease'.
SCT treatment	'Progressive disease' (doctor visit only)	SCT and recovery require active treatment and monitoring
SCT recovery	'Progressive disease' (doctor visit only)	

NICE TA399[83]

Table 41 presents the healthcare resource utilisation assumed for the health state in our model based on healthcare resource utilisation from NICE TA399. Utilisation for each resource (minutes per cycle) was then multiplied by the corresponding cost per minute to obtain the routine care costs per cycle (Table 42).

Table 41 Health care utilisation used in the model (minutes per cycle)

Health states	Initiation	Induction	Second induction and secondary therapy	Consolidation	Monotherapy/ complete remission	Relapse	SCT treatment	SCT recovery
Clinical nurse specialist Haematologist		66	66	33	33	81	0	0
Consultant		62	62	17	17	36	0	0
Day care nurse		116	116	13	13	138	0	0
Day care specialist registrar		68	68	28	28	54	0	0
District Nurse		42	42	13	13	35	0	0
Doctor		38	38	17	17	20	101	101
Jnr doctor		139	139	11	11	66	0	0
Pharmacist		75	75	2	2	24	0	0
Oncology nurse		16	16	0	0	3	0	0
Inpatient day		12290	12290	828	828	5702	0	0
ITD FLT3 testing	1							

Table 42. Routine care cost (per cycle)

Health states	Initiation costs	Induction	Secondary therapy	Consolidation	Monotherapy /Complete remission	Relapse	SCT treatment*	SCT recovery
Clinical nurse specialist Haematologist		£88.68	£88.68	£44.15	£44.15	£109.59	£0.00	£0.00
Consultant		£108.51	£108.51	£29.22	£29.22	£62.56	£0.00	£0.00
Day care nurse		£85.14	£85.14	£9.30	£9.30	£100.98	£0.00	£0.00
Day care specialist registrar		£46.18	£46.18	£19.33	£19.33	£36.87	£0.00	£0.00
District Nurse		£45.15	£	£13.66	£13.66	£37.50	£0.00	£0.00
Doctor		£63.46	£63.46	£28.35	£28.35	£32.97	£170.62	£170.62
Jnr doctor		£69.40	£69.40	£5.26	£5.26	£32.78	£0.00	£0.00
Pharmacist		£78.88	£78.88	£1.70	£1.70	£24.90	£0.00	£0.00
Oncology nurse		£22.00	£22.00	£0.00	£0.00	£4.17	£0.00	£0.00
Inpatient day		£5385.59	£5385.59	£362.83	£362.83	£2498.76	£0.00	£0.00
ITD FLT3 testing	£150.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
Total cost	**£150.00**	**£5992.99**	**£5992.99**	**£513.78**	**£513.78**	**£2941.04**	**£170.62**	**£170.62**

*Follow-up included in the SCT unit costs

Mortality costs

Mortality-related costs were obtained from Nuffield Trust (2014)[85] data and included acute hospital care (all hospital contacts, emergency inpatient admissions, non-emergency inpatient admissions, outpatient visits, accident and emergency visits), local authority-funded social care, district nursing care, and general practitioner visit costs. These were summed to obtain the cost per mortality event, and were then adjusted for inflation to 2017 values, based on PSSRU inflation rates (Table 43). The overall mortality-associated cost for each comparator was calculated as the sum of the product of the cost per mortality and the estimated mortality (1 − % OS) at each cycle (derived from the extrapolation):

$$Overall\ cost\ of\ mortality = \sum (cost\ per\ mortality) \times (1 - proportion\ of\ patients\ surviving\ at\ cycle\ n)$$

Table 43 Mortality costs

Mortality cost	Cost element	2013 value in the UK (£)
Secondary (acute hospital care)	Cost of all hospital contacts	£5,890
	Cost of emergency inpatient admissions	£4,071
	Cost of non-emergency inpatient admissions	£1,360
	Cost of outpatient visits	£378
	Cost of A&E visits	£80
Local authority funded social care	Cost of local authority-funded social care	£444
District nursing	Cost of district nursing care	£588
GP contacts	Cost of GP visits	£365
Total in 2013		£13,176
Total used in the model (Inflation-adjusted for 2017)		£14,887

Source: Nuffield Trust 2014[85]

5.5.4 Adverse event unit costs and resource use

Grade 3/4 AEs with a prevalence of ≥5% in any of the three treatment phases (induction, consolidation, and monotherapy) were included in the model, as lower grade AEs would likely not bear substantial costs. AE prevalence for the phases were derived from the clinical trial results.[16] To obtain the AE prevalence *per 28-day treatment cycle* for each AE, the trial AE prevalence was divided by the average duration of exposure to treatment in the trial (in cycle numbers):

$$AE\ prevalence\ in\ a\ 28\ day\ cycle = \frac{AE\ prevalence\ in\ clinical\ trial}{average\ duration\ of\ treatment\ exposure}$$

Costs for each AE were based on NHS Healthcare Resource Group (HRG) estimates (Table 44). The cost for all AEs adjusted per 28-day cycle are shown in Table 45 and were calculated for midostaurin therapy and SOC as the sum of products of all AE prevalence and the HRG costs of each AE:

$$Average\ cost\ due\ to\ AEs\ per\ 28\ day\ cycle = \sum(\%\ prevalence\ of\ AE\ in\ 28\ day\ cycle) \times (unit\ costs\ for\ AE)$$

From here, treatment duration (derived from the EFS extrapolations and expressed as the proportion of one cycle) was multiplied by the average cost due to AEs (per 28-day cycle) to obtain the final cost for AEs in each treatment group and treatment phase:

$$Final\ AE\ cost = (treatment\ duration)x(average\ cost\ due\ to\ AEs)$$

Table 44 AE NHS reference costs

Adverse events	HRG unit costs	HRG code	Description
Platelet count decreased	£2,469.87	PA48B + XD43Z	Blood Cell Disorders without CC - Non-elective tariff + Platelet Disorder Drugs, Band 1
Neutrophil count decreased	£1,076.37	PA48B + XD25Z	Blood Cell Disorders without CC - Non-elective tariff + Neutropenia Drugs, Band 1
Haemoglobin decreased	£1,142.90	SA08G-J	Other Haematological or Splenic Disorders, with CC Score 0-6+
Febrile neutropenia	£3,579	PA45Z	Febrile Neutropenia with Malignancy - Non-elective tariff
Leukopenia	£1,076.37	PA48B + XD25Z	Blood Cell Disorders without CC - Non-elective tariff + Neutropenia Drugs, Band 1
Lymphopenia	£1,956.51	WH54A-B	Procedures on the Lymphatic System with CC Score 0-1+
Diarrhoea	£817.76	FZ36Q	Gastrointestinal Infections without Interventions, with CC Score 0-1
Hypokalaemia	£1,320.26	KC05G-N	Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-5+
Liver Failure Disorders without Interventions, with CC Score 0-4	£2,421	GC01B	Liver Failure Disorders without Interventions- Non-elective tariff
Dermatitis exfoliative	£1,057	JC06C	Minor Skin Procedures Category 2, without CC- Non-elective tariff
Fatigue	£664.00	SA25G-M	Acute Myeloid Leukaemia without CC - Non-elective short stay 0-12+
Diabetes with Hyperglycaemic	£1,053.56	KB02G-K	Diabetes with Hyperglycaemic Disorders, 69 years and under without CC- Non-elective tariff
Pneumonia	£892	DZ11R-V	Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-14+ without intervention
Nausea	£664.00	SA25G-M	Acute Myeloid Leukaemia without CC - Non-elective short stay 0-12+
Hyponatraemia	£959	PA48B	Blood Cell Disorders without CC - Non-elective tariff
Blood bilirubin increased	£959	PA48B	Blood Cell Disorders without CC- Non-elective tariff
Infection	£3,630.12	HE81A-C	Infection or Inflammatory Reaction, due to, Internal Orthopaedic Prosthetic Devices, Implants or Grafts, with CC Score 0-6+
Hypophosphataemia	£959	PA48B	Blood Cell Disorders without CC - Non-elective tariff
Gamma-glutamyltransferase increased	£959	PA48B	Blood Cell Disorders without CC - Non-elective tariff

Adverse events	HRG unit costs	HRG code	Description
Hypocalcaemia	£959	PA48B	Blood Cell Disorders without CC - Non-elective tariff
Radiation mucositis	£664.00	SA25G-M	Acute Myeloid Leukaemia without CC - Non-elective short stay 0-12+
Hypoalbuminaemia	£959	PA48B	Blood Cell Disorders without CC - Non-elective tariff
Syncope	£664.00	SA25G-M	Acute Myeloid Leukaemia without CC - Non-elective short stay 0-12+

Table 45 AE cost and prevalence (adjusted per 28-day cycle duration)

	Unit cost	Induction		Consolidation		Monotherapy	
		Midostaurin therapy	SOC	Midostaurin therapy	SOC	Midostaurin therapy	SOC
Platelet count decreased	£1,692.68	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count	£714.63	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemoglobin	£1,077.41	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	£3,057.82	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia NOS	£714.63	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	£1,844.41	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea NOS	£801.95	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	£718.57	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	£1,664.09	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis exfoliative NOS	£302.27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	£586.93	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia NOS	£1,288.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis NOS	£1,870.42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	£586.93	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	£905	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood bilirubin increased	£972	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infection	£3,789.57	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphataemia	£617.12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma-glutamyltransferase increased	£1,664.09	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Unit cost	Induction		Consolidation		Monotherapy	
Hypocalcaemia	£586.93	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radiation mucositis	£586.93	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoalbuminaemia	£586.93	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	£586.93	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost, £		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.5.5 Miscellaneous unit costs and resource use

No other costs were included.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

Model inputs used for the base-case analysis are summarized in Table 46.

Table 46 Summary of variables applied in the economic model*

Variable	Value	Reference in submission
Model characteristics		
Model Year	2017	Section 5.2.2
Inflation rate (used in the adjustment of 2013 mortality costs). Based on NHS planned inflation.	3.1%	
Discounting rate of costs and benefits. Based on NICE HTA Guidelines, 2013.[72]	3.5%	
Average body surface area. Based on trial data.	1.9 m^2	Section 5.5
Average patient weight. Based on trial data.	70 kg	
Therapy Durations		
Maximum duration of induction therapy (cycles). Based on trial dosing schedule.	2	Section 5.5
Maximum duration of consolidation therapy (cycles). Based on trial dosing schedule.	4	
Duration of SCT (cycles). Based on clinical expert interviews.	3.0	
Duration of SCT recovery (cycles). Based on clinical expert interviews.	10.0	
Duration of secondary therapy (cycles). Based on Kantar Health CancerMpact, AML 2015.[52]	1	
Cost of therapy (per cycle)		
Induction midostaurin therapy	[redacted]	Section 5.5.2
Induction SOC	£1,328	
Consolidation midostaurin therapy	[redacted]	
Consolidation SOC	£1,585	
Monotherapy midostaurin therapy	[redacted]	
Secondary therapy cost	£3,101	
Average SCT cost	£25,116	
Routine care costs		
Initiation	£150	Section 5.5.3
Induction	£5,993	
Secondary therapy	£5,993	

Consolidation	£514	
Monotherapy	£514	
Relapse	£2,941	
SCT	£171	
SCT recovery	£171	
Mortality costs		
Cost of all hospital contacts	£5,890	Section 5.5.3
Cost of emergency inpatient admissions	£4,071	
Cost of non-emergency inpatient admissions	£1,360	
Cost of outpatient visits	£378	
Cost of A&E visits	£80	
Cost of local authority-funded social care	£444	
Cost of district nursing care	£588	
Cost of GP visits	£365	
Total mortality cost (inflation-adjusted)	£14,887	
AE costs		
Platelet count decreased	£1,693	Section 5.5.4
Neutrophil count	£715	
Haemoglobin	£1,077	
Febrile neutropenia	£3,058	
Leukopenia NOS	£715	
Lymphopenia	£1,844	
Diarrhoea NOS	£802	
Hypokalaemia	£719	
Alanine aminotransferase increased	£1,664	
Dermatitis exfoliative NOS	£302	
Fatigue	£587	
Hyperglycaemia NOS	£1,289	
Pneumonitis NOS	£1,870	
Nausea	£587	
Hyponatraemia	£905	
Blood bilirubin increased	£972	
Infection	£3,790	
Hypophosphataemia	£617	
Gamma-glutamyltransferase increased	£1,664	
Hypocalcaemia	£587	
Radiation mucositis	£587	
Hypoalbuminaemia	£587	

Syncope	£587	
Utilities		
Induction treatment	0.648	Section 5.4.4
Consolidation treatment	0.710	
Monotherapy treatment	0.810	
Complete remission post 1L (No relapse)	0.830	
Relapse	0.530	
SCT Treatment	0.613	
SCT Recovery	0.810	
Post-SCT Recovery	0.826	

5.6.2 Assumptions

Direct data from the RATIFY trial were not available to inform all model characteristics. A summary of the assumptions used to develop the model are outlined in Table 47.

Table 47 Summary of model assumptions

Model characteristic	Assumption
Model	
Continuous event rates	It was assumed that the efficacy and AE rates were constant throughout each health state, as no time-specific data were available.
Extrapolation technique for OS	OS was extrapolated beyond the trial cut-offs using a "cure model" approach, which was considered the most plausible following discussion with clinical experts. To do this, natural mortality was applied to both treatment arms after the cut-off using mortality data from the Office for National Statistics, UK (2013-2015).[86] The average age and proportion of male patients were based on the clinical trial.
OS gain	Given that people still alive by the end of the trial duration are assumed to follow the general population mortality, the gain in OS observed in the trial for midostaurin vs. current practice is therefore expected to be maintained over the lifetime. This assumption is supported by clinical opinion. Clinical experts considered that whilst the rate of death at the end of the trial could be more rapid compared with the general population (notably given the development of secondary cancers), it is expected the rate of death to be the same between the two arms from the end of the trial. In particular, clinical experts noted that there was no clinical rationale for using a different rate of death between arms after the end of the trial and that the initial gain would be maintained over the lifetime.
Extrapolation technique for EFS	Whilst the Weibull distribution did not provide a smooth fit after the end of trial, the Weibull was selected as this provided a consistent extrapolation to OS. It should be noted that this is likely to be conservative, as the Weibull distribution resulted in a quicker loss of CR compared with other functional forms.
Extrapolation technique for SCT	SCT survival after trial cut-off was based on the OS trend (i.e., it was assumed that SCT patients died at the same rate as the overall surviving population after trial cut-off).
Extrapolation technique for CR	Following trial cut-off, the proportion of patients remaining in complete remission were based directly on the EFS extrapolation.
Extrapolation cut-off	Finally, in the base-case, the cure-model is fitted from the last event. However, it should be noted that for the midostaurin arm, the KM quickly dropped at cycle 81 attributable to one event. This was not observed in the SOC arm. It is unclear whether this is due to an inconsistency in the data, and therefore the cure-model has been fitted prior to that event in our base-case for midostaurin. It should be noted that fitting the cure model from the last event could be an equally plausible scenario and therefore results are presented in scenario analysis.
Utilities	Utility values obtained from a literature review were used in the model for each health state. Values from the TTO are used in scenario analysis due to inconsistencies for the induction and SCT health state supported by clinical opinion.
Treatments	
Dose intensity and wastage	The reported within-trial doses received were used directly as the dose intensities in the model. Additionally, because wastage was included in the drug costs, it was assumed that no vial sharing or pill-splitting occurred (i.e. the reported within-trial doses were rounded up to the nearest possible whole pill or vial amount). See Section 5.5.2 for specific treatment dosages.

Duration of monotherapy	A maximum of 12 cycles of monotherapy was specified in the model, as per trial protocol.
Secondary therapy	Secondary therapy was assumed to be exclusively provided to patients entering the relapse state, and was cumulative up to the maximum number of cycles of secondary therapy set in the model (1 cycle), Secondary therapy only consisted of FLAG-IDA (as per UK recommendations).
Prevalence of SCT	Using the area under the curve from the clinical trial at each cycle, the prevalence of SCT was independently calculated for each treatment arm.
SCT and SCT recovery duration	Durations of SCT (3 cycles) and recovery 10 cycles) were based on UK and Canadian KOL interviews.
Other healthcare utilisation	Utilisation of other health care resources (non-elective hospitalisations, emergency visits, oncologist and generalist visits, and FLT3-ITD testing) were based on a resource use questionnaire; Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts [ID829][71]

5.7 Base-case results

5.7.1 Life years saved and quality-adjusted life years saved

Overall LYs and QALYs are presented in Table 48. Midostaurin therapy resulted in a gain of [redacted] when compared to SOC. A gain in QALYs was also observed for midostaurin therapy patients, with an increase of [redacted]. Figure 30 illustrates the LYs and QALY results.

Table 48 LYs and QALY outcomes

Endpoint	Time horizon	Midostaurin therapy	SOC	Difference
LYs	Lifetime	[redacted]	[redacted]	[redacted]
QALYs	Lifetime	[redacted]	[redacted]	[redacted]

LY, life years; QALY, quality-adjusted life years

[redacted]

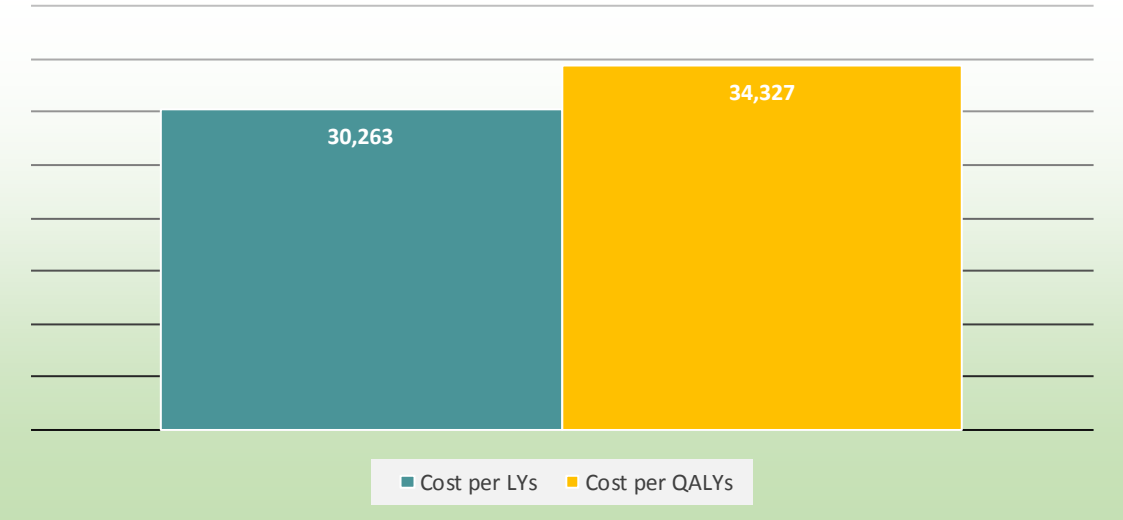
5.7.2 Base-case incremental cost effectiveness analysis results

Incremental cost-effectiveness ratios were calculated based on the total costs and benefits and are presented in Table 49 and Figure 31. When assessing cost per LYs saved, midostaurin therapy showed an ICER of £30,263 over SOC. Regarding cost per QALY, midostaurin therapy showed an ICER of £34,327 over SOC.

Table 49 Base case incremental cost-effectiveness ratios for midostaurin therapy vs. SOC

Endpoint	Time horizon	Midostaurin therapy vs SOC		
		Δ Costs	Δ Benefit	ICER
Cost per LYs saved	Lifetime	[redacted]	[redacted]	£30,263
Cost per QALY	Lifetime	[redacted]	[redacted]	£34,327

Figure 31 Base case incremental cost-effectiveness ratios for midostaurin therapy vs. SOC



LY, life years; QALY, quality-adjusted life years

5.7.3 Clinical outcomes from the model

Model traces

The model traces provide information on patient treatment pathways. Figure 32 and Figure 33 present long-term traces for midostaurin therapy and SOC patients over a lifetime horizon. From these graphs, it is clear that the majority of events occur during the early cycles.

[redacted]

[redacted]

Efficacy

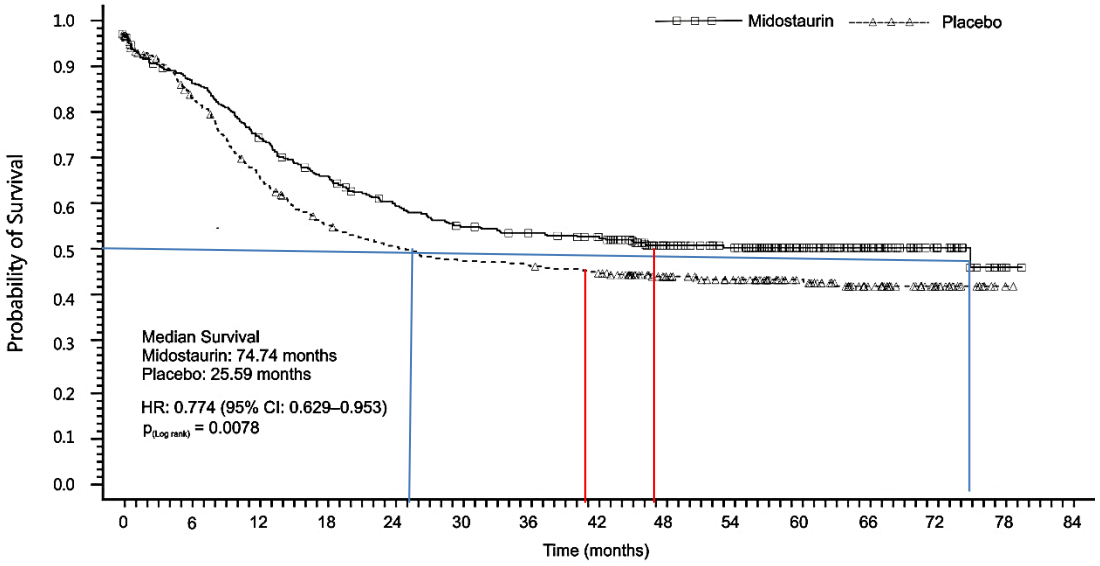
Figure 34 shows the Kaplan–Meier curves for OS from the RATIFY trial. Figure 35 shows the short-term and long-term extrapolated OS Kaplan–Meier curves (see section 5.3.2). As we are using a partitioned survival model approach whereby the Kaplan–Meier is used up to the last event, as expected the model provides an accurate fit to the observed Kaplan–Meier as shown in Figure 35.

As previously described in section 5.3.2, the curves used in the model follow the RATIFY Kaplan–Meier curves until trial cut-off, and then continue as a cure model.

As previously mentioned in section 5.3.2, given that people still alive by the end of the trial duration are assumed to follow the general population mortality, the gain in OS observed in the trial for midostaurin versus current practice is therefore expected to be maintained over the lifetime. This assumption is supported by clinical opinion. Clinical experts considered that whilst the rate of death at the end of the trial could be more rapid compared with the general population (notably given the development of secondary cancers), it is expected that the rate of death will be the same between the two arms from the end of the trial. In particular, clinical experts noted that there was no clinical rationale for using a different rate of death between arms after the end of the trial and that the initial gain would be maintained over the lifetime.

In the base case we also fitted the cure model prior to the last event for midostaurin given the inconsistency in the data. However, a scenario analysis is presented fitting the cure model after the last event despite the sharp drop at the end of the trial.

Figure 34 Kaplan–Meier curve for OS from RATIFY (non-censored at the time of SCT)



No. of patients still at risk

Midostaurin	360	314	269	234	208	189	181	174	133	120	77	50	22	1	0
Placebo	357	284	221	179	163	152	148	141	110	95	71	45	20	1	0

Logrank test and Cox regression model stratified for the FLT3 mutation strata used in the randomization.

RATIFY CSR.[16]
Median is indicated by blue lines and mean by red lines.
CI, confidence interval; CSR, clinical study report; FAS, full analysis set; FLT3, FMS-like tyrosine kinase 3; SCT, stem cell transplantation.

[redacted]

[redacted]

5.7.4 Disaggregated results of the base case incremental cost-effectiveness analysis

Table 50 presents the disaggregated benefit (QALY) results for the base case analysis, and Table 51 presents the disaggregated costs for the base case analysis.

Table 50 Summary of QALY gain by health state

Treatment phase	QALY midostaurin therapy	QALY SOC	Increment	Absolute increment	% absolute increment
Induction	0.0582	0.0597	[redacted]	[redacted]	[redacted]
Consolidation	0.1022	0.0893	[redacted]	[redacted]	[redacted]
Monotherapy	0.1929	0.0000	[redacted]	[redacted]	[redacted]
Secondary therapy	0.0141	0.0182	[redacted]	[redacted]	[redacted]
Complete remission	0.6210	0.1817	[redacted]	[redacted]	[redacted]
Relapse	1.6033	1.7788	[redacted]	[redacted]	[redacted]
SCT	5.2005	4.1960	[redacted]	[redacted]	[redacted]
Total	7.7921	6.3238	[redacted]	[redacted]	[redacted]

SCT, stem cell transplantation; SOC, standard of care

Table 51 Summary of costs by health state

			£50,404		

Costs, broken down by category, are summarised in Table 52. The overall cost per arm was estimated at [redacted] for midostaurin therapy, and [redacted] for SOC.

[redacted]

			£50,404

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis (PSA)

A PSA was conducted to help gauge the uncertainty of the results. Probabilistic distributions were directly applied to the base case model to generate the PSA results.

The PSA parameters and statistical distributions are presented in Table 53.

Table 53 Probabilistic sensitivity analysis parameters

	Point estimate		Standard deviation/error			
	Midostaurin therapy	**SOC**	**Midostaurin therapy**	**SOC**	**Distribution**	**Source**
Efficacy and events						
OS	0.774		0.083		Log-normal	PE based on model and SE based on restricted mean RATIFY (patient-level data) Note: The OS HR was varied between -1 and +1 SE to avoid crossing with other curves (e.g. EFS)
Event free survival	0.784		0.068		Log-normal	PE based on model and SE based on restricted mean RATIFY (patient-level data) Note: The HR was varied between -1.96 and +1.96 SE to avoid crossing with other curves (e.g. EFS)
Complete remission	[redacted]		0.038		Log-normal	PE and SD from RATIFY CSR, p 78[16] Note: The rate was varied between -1.96 and +1.96 SE to avoid crossing with other curves (e.g. OS)
SCT rate	[redacted]		0.036		Log-normal	PE and SD from RATIFY CSR, p 78[16] Note: The rate was varied between -1.96 and +1.96 SE to avoid crossing with other curves (e.g. OS)
Dosing						
Treatment duration partition	Based on patient-level data		Variable for each time point		Beta	PE for midostaurin therapy and SOC from patient-level data for each cycle (probability of been treated) and SE for each cycle i.e. (sqrt((p*(1-p)/n)))^2
Dose intensity – induction	[redacted]	0.020			Beta	PE from patient-level data; SE based on (sqrt((p*(1-p)/n)))^2
Dose intensity - Consolidation	[redacted]	0.018			Beta	RATIFY CSR, p 96;[16] SE based on (sqrt((p*(1-p)/n)))^2
Dose intensity - Monotherapy	[redacted]	0.030			Beta	RATIFY CSR, p 97;[16] SE based on (sqrt((p*(1-p)/n)))^2
Body surface area	1.90		0.28		Log-normal	RATIFY CSR, p 68; SD based on patient-level data
Kilograms	70.00		21.31		Log-normal	Based on RATIFY patient-level data
Secondary therapy duration	1.000	1.000	1.000	1.000	Log-normal	Assumption
Costs						
Adverse event costs	Variable		+/-20%		Log-normal	PE based on micro-costing, SD based on assumptions
Secondary therapy costs	3,101		+/-20%		Log-normal	PE based on micro-costing, SD based on assumptions
On treatment routine care costs	Variable		+/-20%		Log-normal	PE based on micro-costing, SD based on assumptions
Off-treatment routine care costs	Variable		+/-20%		Log-normal	PE based on micro-costing, SD based on assumptions

SCT costs	25,116	+/-20%	Log-normal	PE based on micro-costing, SD based on assumptions
Utility				
On-treatment utility	Variable	+/-10%	Gamma	Literature review
Off-treatment utility	Variable	+/-10%	Gamma	Literature review
SCT utility	Variable	+/-10%	Gamma	Literature review

EFS, event-free survival; OS, overall survival; PE, Point estimate; SCT, stem cell transplantation; SD, standard deviation; SOC, standard of care

Application of the variability in the model

OS and EFS: OS and EFS are partitions in this model. Often in a partition survival model, the parameters (shape, scale) parametric function will become stochastic. In this model, a cure model with the Kaplan–Meier is used for the extrapolation, which limits the possibility of using shape and scale parameters. In this model, we have used the HR of EFS and OS from the model, and applied a stochasticity in the hazard mapping of the midostaurin therapy arm. For OS, the HR is 0.774 (95% CI: 0.62, 0.95), and, therefore, the efficacy of midostaurin therapy in relation to SOC will vary accordingly in the PSA, following a log-normal law. In sum, we apply the uncertainty to the midostaurin therapy arm in comparison to the standard of care. As per recommendations in Claxton et al. (2008),[87] the HR is the result of the cox survival model (after exp() transformation).

[redacted]

[redacted]

CR and SCT: CR and SCT data were obtained directly from the patient-level data. These health states are important because utility values vary significantly and the routine costs of patients in CR and SCT are quite different from the relapse health state. While the state occupancy in CR and SCT does not affect OS (LYs) results, it has an impact on cost and final QALYs. CR and SCT represent [redacted], respectively, of the QALYs gained, while representing [redacted], respectively, of

the costs. The CR and SCT rates are higher for midostaurin therapy in the clinical trial, though not significantly, so it can be assumed that the CR and SCT rates would not always be fixed compared to the SOC arm. Therefore, assuming a certain stochasticity for these variables was considered important in the PSA. Risk ratios based on the patient-level data were used in the PSA and the standard error (SE) from the clinical trial was used (SE based on Wald confidence intervals presented in the CSR).

Table 54 and Table 55 present the specific point estimates and standard deviations (or SE) for costs and utilities, respectively, used in the PSA.

Table 54 Probabilistic sensitivity analysis: Cost parameters

	Midostaurin therapy		SOC	
	PE	**SD**	**PE**	**SD**
Routine care Costs				
Initiation costs	[redacted]	[redacted]	IDEM	IDEM
Induction	[redacted]	[redacted]	IDEM	IDEM
Secondary therapy	[redacted]	[redacted]	IDEM	IDEM
Consolidation	[redacted]	[redacted]	IDEM	IDEM
Monotherapy	[redacted]	[redacted]	IDEM	IDEM
Relapse	[redacted]	[redacted]	IDEM	IDEM
SCT treatment*	[redacted]	[redacted]	IDEM	IDEM
SCT recovery	[redacted]	[redacted]	IDEM	IDEM
Secondary therapy costs	[redacted]	[redacted]	IDEM	IDEM
SCT costs	[redacted]	[redacted]	IDEM	IDEM
Adverse event costs				
AEs induction costs	[redacted]	£903	4,624	925
AEs consolidation costs	[redacted]	£554	2,838	568
AEs monotherapy costs	[redacted]	£11	0	0

PE, point estimate

Table 55 Probabilistic sensitivity analysis: Utility parameters

	PE	SE
Induction treatment*	0.648	0.032
Consolidation treatment*	0.710	0.036
Monotherapy on treatment*	0.810	0.041
CR post 1L (No relapse)	0.830	0.042
Relapse	0.530	0.027
SCT Treat*	0.613	0.031
Recovery SCT	0.810	0.041
Post SCT (after 1L)	0.826	0.041

PE, point estimate; SE, standard error

Distributions were selected for the PSA as follows:

- As per Briggs, et al. (2012),[88] it is recommended that specifying the distribution and defining the interval for uncertainty analysis should follow standard statistical methods (e.g. beta distributions are a natural match for binomial data; gamma or log-normal for right skew parameters; log-normal for relative risks or HRs; logistic for odds ratios). These principals were applied in distribution selection for this analysis.
- Little information is available regarding the distribution of cost, so we assumed a right-skewed distribution. Therefore, a log-normal distribution was applied for all the cost variables.
- OS (Figure 37) and EFS were right-skewed in this data set, and log-normal was therefore applied for these parameters. Log-normal is also recommended for HRs (as per Briggs, et al. 2012).[88]

[redacted]

Dosing variables (e.g. treatment duration) seemed right skewed (Figure 38), as discontinuation and mortality had higher hazards at the beginning of the trial. The use of beta distribution seemed a good fit for the dose intensity of midostaurin therapy and the treatment duration as proportions were used for these variables. The treatment duration was varied using the proportion (between 0 and 1) of patients using the drug at each cycle using a beta distribution. The SE was generated using the traditional formula for proportions:

sqrt((p(1-p)/n))^2).*

[redacted]

Gamma distribution was applied for utility variables to allow a flexible fit to the theoretical 0–1 boundary of utility values (since SCT treatment is outside the theoretical boundary). As the SEs were not available for the literature values, a standard error of 5% was applied. The utility values were correlated by using the same random draw for each utility value, but each value had its own point estimate and SE. The correlation of utility can avoid creating inconsistency in the health state utility values (e.g. relapse having a higher utility value than CR).

The secondary therapy duration was varied using a log-normal distribution and an assumption of 1 cycle for the SE. The random draw was the same for the secondary therapy of midostaurin therapy versus SOC, to ensure correlation between these costs.

Probability sensitivity analysis results

Results of the PSA are presented in Table 56. Figure 39 displays the resulting cost-effectiveness plane. Additionally, a cost-effectiveness acceptability curve was created to understand the probability of midostaurin therapy being cost effective (Figure 40). Based on this analysis, the average QALYs gained with midostaurin therapy compared to SOC were [redacted]. The average incremental cost was [redacted], resulting in an average ICER of £31,550 (95% CI £7,015, £47,213). The probabilities of being cost-effective at a threshold of £30,000 and £50,000 were 39.2% and 97.3%, respectively.

Table 56 Probabilistic sensitivity analysis results

	CI- 95%	Average	Median	CI+ 95%
Δ QALYs	[redacted]	[redacted]	[redacted]	[redacted]
Cost	[redacted]	[redacted]	[redacted]	[redacted]
ICER	£7,015	£31,550	£33,224	£47,213
% cost effective at 30K		39.2%		
% cost effective at 50K		97.3%		

Figure 39 Cost-effectiveness plane

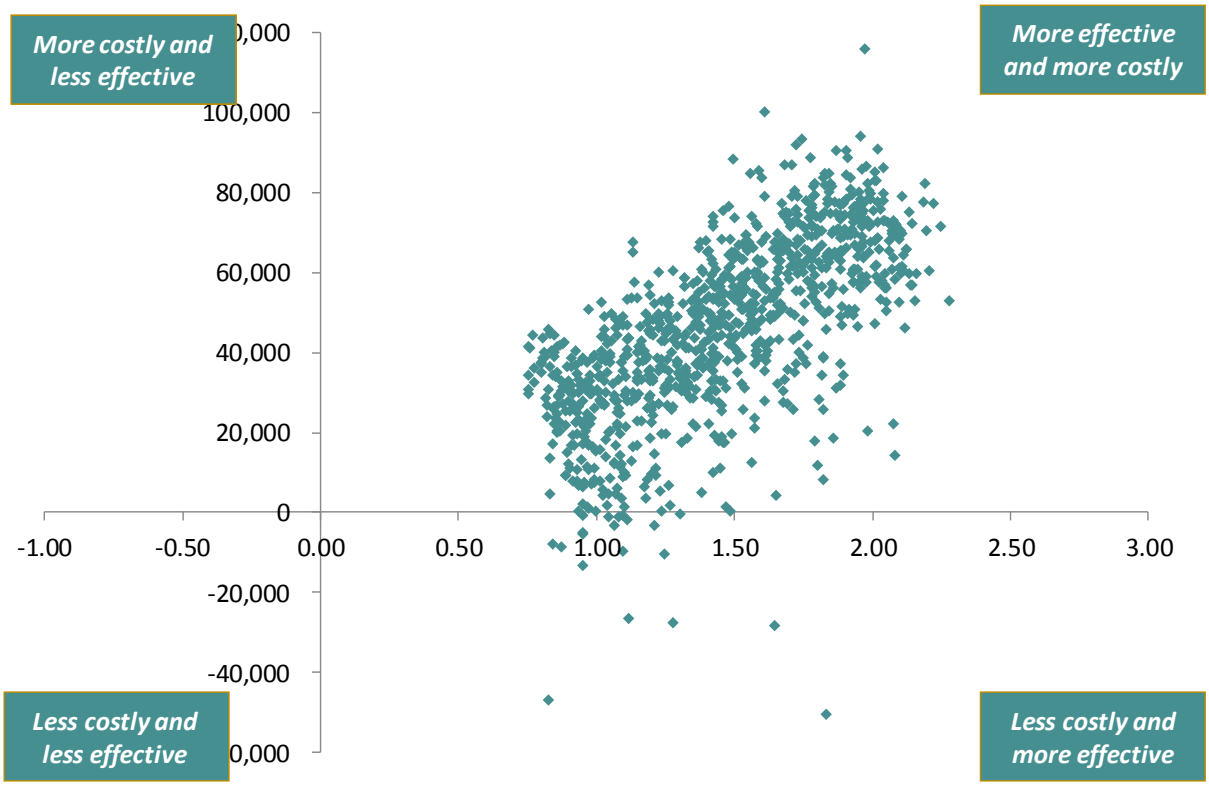


Figure 40 Cost-effectiveness threshold (% probability of being cost effective)

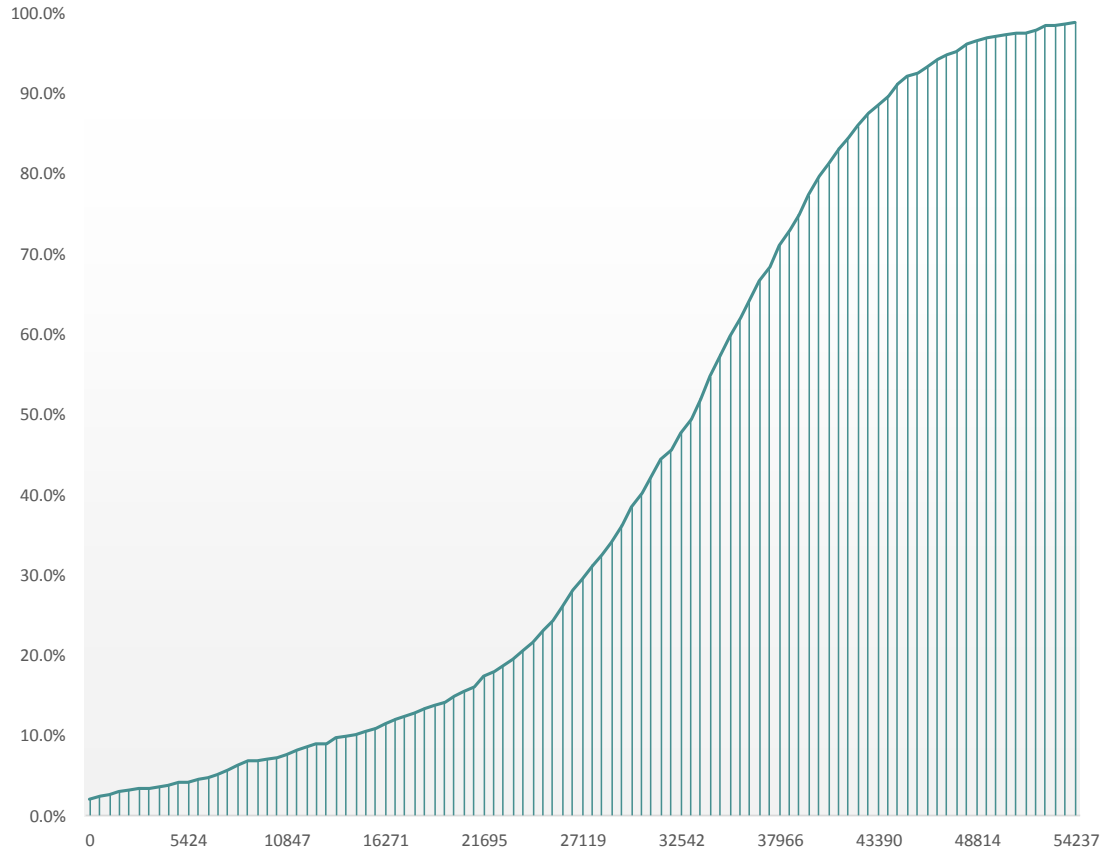
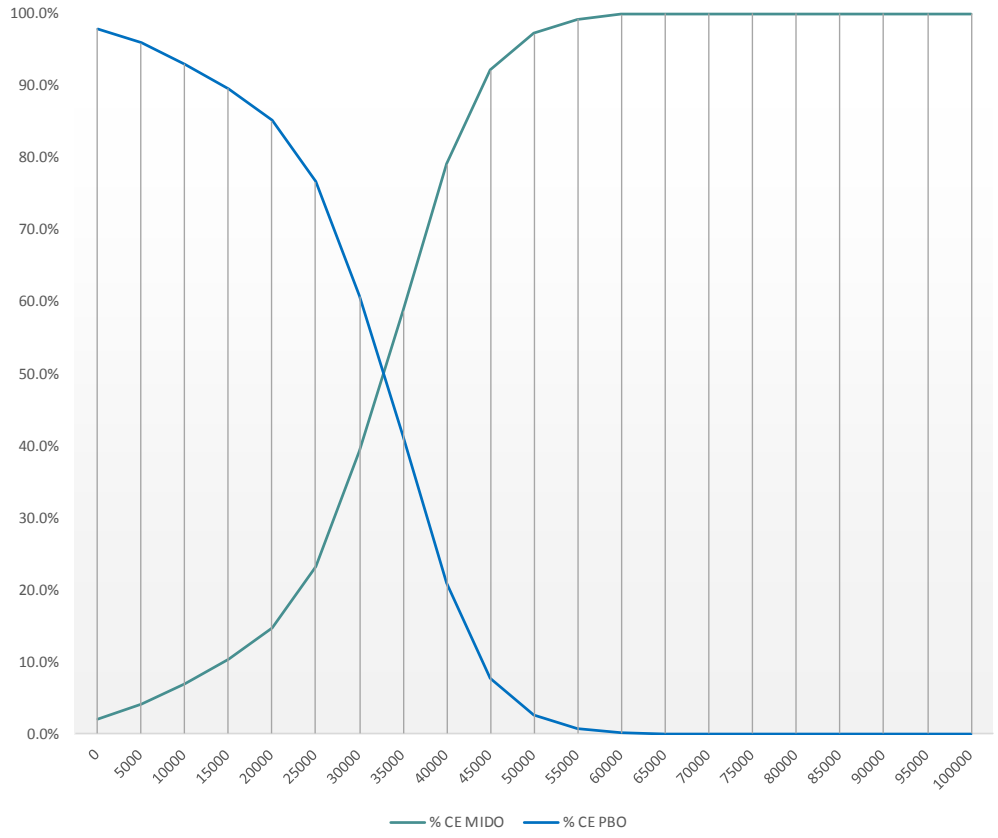


Figure 41 presents the “net benefit threshold” for midostaurin therapy compared to SOC. This graph shows the probability of the net benefit of midostaurin therapy being greater than zero (teal line).

Figure 41 Net benefit threshold



5.8.2 Deterministic sensitivity analysis

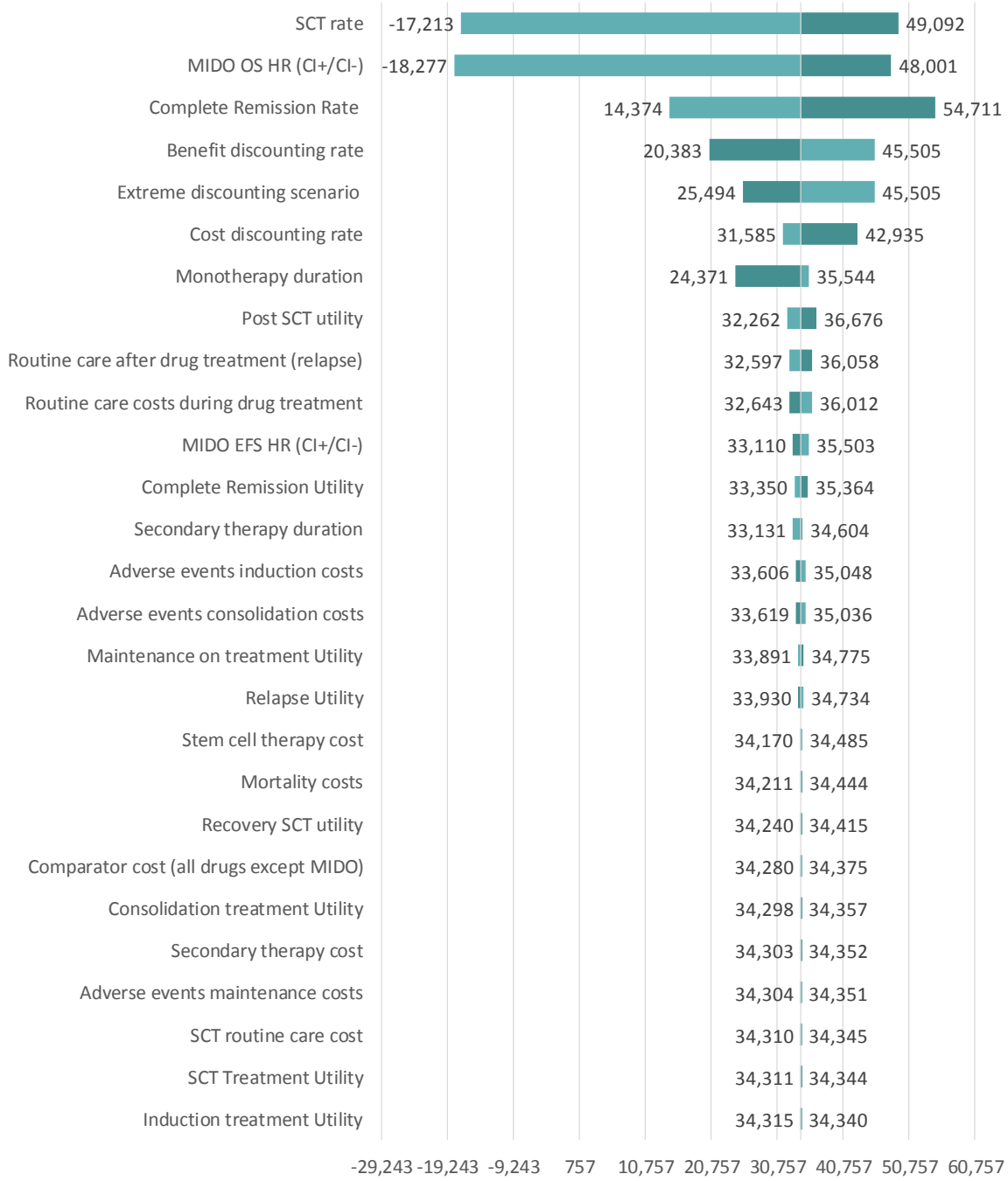
Results from the deterministic sensitivity analysis are shown in Table 57 and plotted in Figure 42. Results were relatively consistent with the base-case findings, but were most sensitive to variations in stem cell therapy rate, variations in the midostaurin therapy OS HR, difference in CR rate, and discounting rates.

Table 57 Deterministic sensitivity analysis results (cost per QALY)

Scenarios	Lower bound scenario	Base case scenario	Upper bound scenario	Lower bound ICER	Base case ICER	Upper bound ICER
Technical assumptions						
Benefit discounting rate	0.0%	3.5%	6.0%	£20,383	**£34,327**	£45,505
Cost discounting rate	0.0%	3.5%	6.0%	£42,935	**£34,327**	£31,585
Extreme discounting scenario	Cost: 6%; Benefit: 0%	C 3.5%; B 3.5%	C 0%; B 6%	£25,494	**£34,327**	£45,505
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	£48,001	**£34,327**	-£18,277
[redacted]	[redacted]	[redacted]	[redacted]	£33,110	**£34,327**	£35,503
[redacted]	[redacted]	[redacted]	[redacted]	£54,711	**£34,327**	£14,374
[redacted]	[redacted]	[redacted]	[redacted]	£49,092	**£34,327**	-£17,213
Therapy duration						
Monotherapy duration	6	12	18	£24,371	**£34,327**	£35,544
Secondary therapy duration	0	1	6	£34,604	**£34,327**	£33,131
Utility values						
Induction treatment Utility	0.58	0.65	0.71	£34,315	**£34,327**	£34,340
Consolidation treatment Utility	0.64	0.71	0.78	£34,357	**£34,327**	£34,298
Monotherapy on treatment Utility	0.73	0.81	0.89	£34,775	**£34,327**	£33,891
Complete Remission Utility	0.75	0.83	0.91	£35,364	**£34,327**	£33,350
Relapse Utility	0.48	0.53	0.58	£33,930	**£34,327**	£34,734
SCT Treatment Utility	0.55	0.61	0.67	£34,344	**£34,327**	£34,311
Recovery SCT utility	0.73	0.81	0.89	£34,415	**£34,327**	£34,240
Post SCT utility	0.75	0.83	0.91	£36,676	**£34,327**	£32,262
Costs						
Comparator cost (all drugs except midostaurin therapy)	80%	100%	120%	£34,280	**£34,327**	£34,375
Secondary therapy cost	2,481	3,101	3,722	£34,352	**£34,327**	£34,303
Routine care costs during drug treatment	80%	100%	120%	£32,643	**£34,327**	£36,012
Routine care after drug treatment (relapse)	80%	100%	120%	£36,058	**£34,327**	£32,597
SCT routine care cost	80%	100%	120%	£34,310	**£34,327**	£34,345
Stem cell therapy cost	20,093	25,116	30,140	£34,170	**£34,327**	£34,485

Scenarios	Lower bound scenario	Base case scenario	Upper bound scenario	Lower bound ICER	Base case ICER	Upper bound ICER
Adverse events induction costs	80%	100%	120%	£33,606	**£34,327**	£35,048
Adverse events consolidation costs	80%	100%	120%	£33,619	**£34,327**	£35,036
Adverse events monotherapy costs	80%	100%	120%	£34,304	**£34,327**	£34,351
Mortality costs	11,910	14,887	17,865	£34,444	**£34,327**	£34,211

Figure 42 Deterministic sensitivity analysis results (cost per QALY)



5.8.3 Scenario analysis

Additional scenarios were explored for cost per QALY and are presented in Table 58 and Figure 43. Results were notably most sensitive to variations in time horizon.

Table 58 QALY results for additional scenarios (lifetime horizon)

	Technique	Midostaurin therapy vs SOC		
Scenarios		**∆ costs**	**∆ Benefit**	**ICER**
Basecase		[redacted]	[redacted]	**£34,327**
Cure model	Individual parametric curves with Gompertz distribution	[redacted]	[redacted]	£32,619
	Piecewise model with last observation as extrapolation cutoff	[redacted]	[redacted]	£21,522
Monotherapy	18 cycles monotherapy therapy	[redacted]	[redacted]	£35,544
Utility	Utility values from the TTO study	[redacted]	[redacted]	£36,364
Time horizon	Trial horizon	[redacted]	[redacted]	£82,451
	10 years	[redacted]	[redacted]	£59,629
Health care resource use	Chemotherapy instead of midpoint	[redacted]	[redacted]	£34,094
Overall Survival - Piecewise (KM + tail)	Weibull	[redacted]	[redacted]	£36,306
	Exponential	[redacted]	[redacted]	£40,589
	Log-normal	[redacted]	[redacted]	£35,239
	Log-logistic	[redacted]	[redacted]	£35,860
	Gamma	[redacted]	[redacted]	£32,789
	Gompertz	[redacted]	[redacted]	£31,662
Overall Survival - Parametric with treatment covariate	Weibull	[redacted]	[redacted]	£34,884
	Exponential	[redacted]	[redacted]	£41,326
	Log-normal	[redacted]	[redacted]	£30,721
	Log-logistic	[redacted]	[redacted]	£33,831
	Gamma	[redacted]	[redacted]	£45,225
	Gompertz	[redacted]	[redacted]	£30,612
Overall Survival - Individual models	Weibull	[redacted]	[redacted]	£34,844
	Exponential	[redacted]	[redacted]	£41,313
	Log-normal	[redacted]	[redacted]	£33,483
	Log-logistic	[redacted]	[redacted]	£35,118
	Gamma	[redacted]	[redacted]	£33,064
	Gompertz	[redacted]	[redacted]	£29,570
Event Free Survival -	Weibull	[redacted]	[redacted]	£34,327

	Technique	Midostaurin therapy vs SOC		
Scenarios		**∆ costs**	**∆ Benefit**	**ICER**
Piecewise (KM + tail)				
	Exponential	[redacted]	[redacted]	£40,396
	Log-normal	[redacted]	[redacted]	£30,918
	Log-logistic	[redacted]	[redacted]	£29,651
	Gamma	[redacted]	[redacted]	£25,331
	Gompertz	[redacted]	[redacted]	£19,681
Event Free Survival - Parametric with treatment covariate	Weibull	[redacted]	[redacted]	£34,491
	Exponential	[redacted]	[redacted]	£40,570
	Log-normal	[redacted]	[redacted]	£31,030
	Log-logistic	[redacted]	[redacted]	£29,741
	Gamma	[redacted]	[redacted]	£25,481
	Gompertz	[redacted]	[redacted]	£19,781
Event Free Survival - Individual models	Weibull	[redacted]	[redacted]	£34,078
	Exponential	[redacted]	[redacted]	£40,570
	Log-normal	[redacted]	[redacted]	£30,221
	Log-logistic	[redacted]	[redacted]	£29,118
	Gamma	[redacted]	[redacted]	£25,662
	Gompertz	[redacted]	[redacted]	£19,768

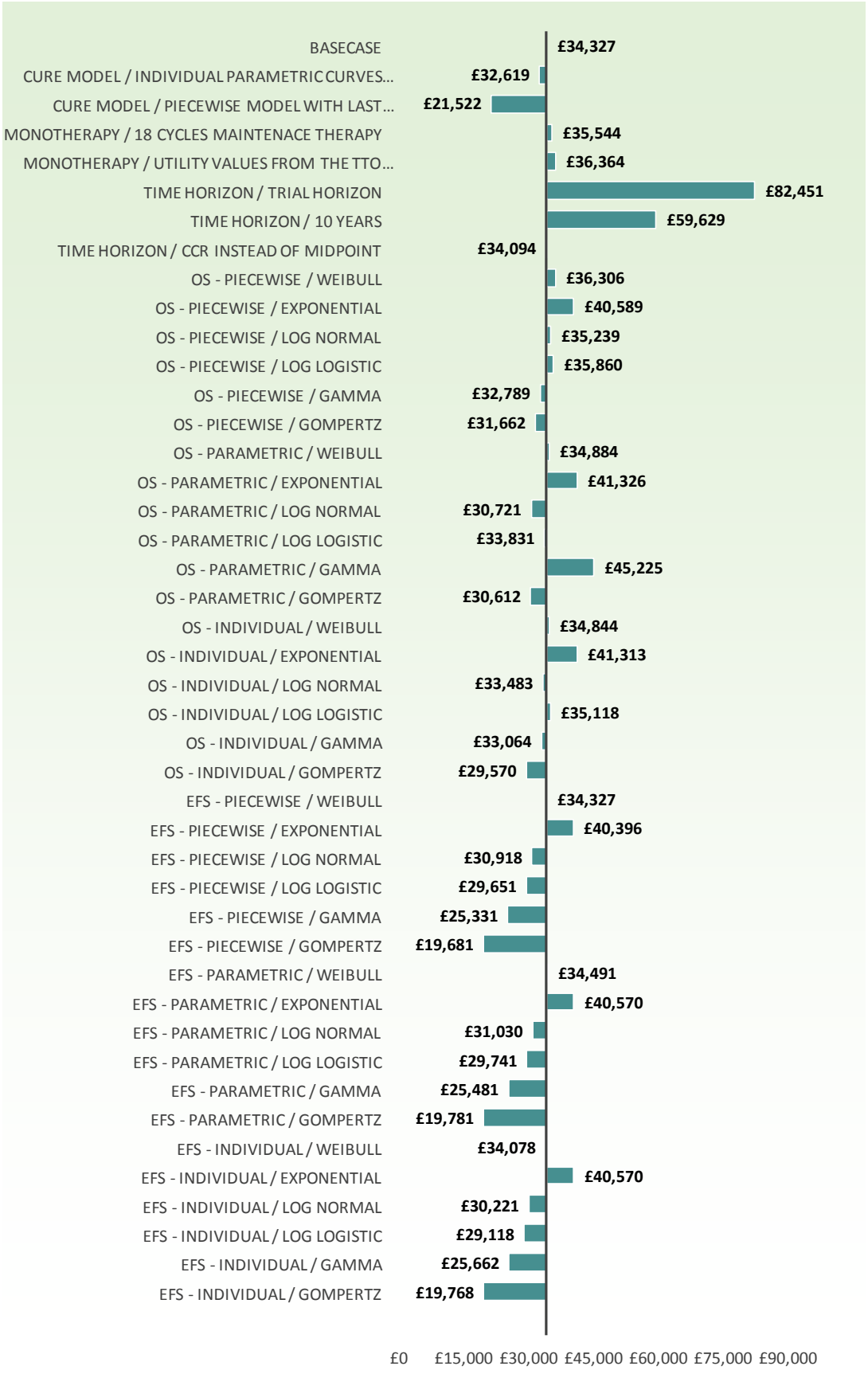
Whilst there was some variation in the ICER depending on the extrapolation functions and method used for OS, the set of plausible extrapolation was limited and the impact modest even under pessimistic assumptions.

Perhaps more importantly, as previously discussed in section 5.3.2, the extrapolation for EFS is challenging. In the base case we used a Weibull distribution, which is conservative. Using alternative distributions (Gamma, log-logistic), which were more plausible in terms of long-term visual extrapolation, but provided an inconsistent extrapolation with OS (curve crossed), the ICER improved.

Similarly, in the midostaurin therapy arm of the trial, there was a sharp drop at the end of the trial for EFS and OS due to one event. In the base case, we fitted a cure model to OS prior to that event given the uncertainty. However, an equally plausible scenario could have been to fit the cure model from the last event irrespective of this inconsistency. By doing so, the ICER reduced from £34,327 to £21,522 per QALY gained.

Finally, utility values from the literature were used in the base case given inconsistencies in the TTO study. Using values from the TTO study had a limited impact on the ICER.

Figure 43 Additional scenario results (cost per QALY)



5.8.4 Summary of sensitivity analyses results

Sensitivity analyses generally showed consistency with base case findings. When additional scenarios were explored, ICERs were most sensitive to variations in the time horizon and fit point from where the cure was fitted. Deterministic sensitivity analysis showed greatest sensitivity to variations in SCT rate, variations in the midostaurin therapy OS HR, difference in CR rate, and discounting rates. The PSA showed that midostaurin therapy was a reasonably efficient use of resources, with a 39.2% probability of being cost effective at a £30,000 cost-effectiveness threshold, and a 97.3% probability of being cost effective at a £50,000 threshold. The average ICER for midostaurin therapy versus SOC according to the PSA was £31,550 per QALY gained.

5.9 Subgroup analysis

Subgroups were not explored in this analysis, as subtypes of FLT3 mutation-positive AML showed similar OS and further stratification would significantly reduce the precision of estimates

5.10 Validation

5.10.1 Validation of the *de novo* cost-effectiveness analysis

Several levels of validation took place. The first evaluated whether the model structure and methods were appropriate. The second assessed whether the model inputs and technical aspects were valid.

Internal validation of the extrapolation: Kaplan–Meier results from the RATIFY trial were used in the model for pre-cut-off estimates. For the tail extrapolation, a cure model was selected and was validated by both economic and clinical experts. In particular, clinical experts indicated that people still alive by the end of the trial duration could be considered to follow the general population mortality. Given that people still alive by the end of the trial duration are assumed to follow the general population mortality, the gain in OS observed in the trial for midostaurin therapy versus current practice is therefore expected to be maintained over the lifetime. This assumption is supported by clinical opinion. Clinical experts considered that whilst the rate of death at the end of the trial could be more rapid compared with the general population (notably given the development of secondary cancers), clinical experts expected the rate of death to be the same between the two arms from the end of the trial. In particular, clinical experts noted that there was no clinical rationale for using a different rate of death between arms after the end of the trial and that the initial gain would be maintained over the lifetime.

External validation of costs: The most recent NHS reference costs (2014–2015) were used in this model. Additionally, mortality-associated costs were obtained from Nuffield Trust (2014) estimates.[85] Both sources were considered to be accurate estimates for their reported costs. To our knowledge, there is limited information on economic evaluations in the population of interest, so an external validation based on published health economic evaluations was not performed.

External validation of utilities: Because HRQoL data were not assessed in the RATIFY trial, utility values specific to treatment type in AML patients were obtained from previously published literature (see Section 8.13, Appendix 13). The utility values were specific to the health states used in the model, and were considered appropriate by clinical experts.

Quality control: Quality control was performed both by Novartis internal HEOR experts and an external health economist.

5.11 Interpretation and conclusions of economic evidence

AML is the most common acute leukaemia in adults and has the lowest survival rate of all adult leukaemia's, with FMS-like tyrosine kinase 3 (FLT3) mutation conferring an even poorer prognosis. FLT3 mutation-positive acute myeloid leukaemia (AML) is an aggressive haematological malignancy associated with a median overall survival (OS) of less than 12 months with current standard treatments. Midostaurin, an oral, tyrosine kinase inhibitor that targets FLT3 and other receptor tyrosine kinases, represents a breakthrough for the treatment of newly diagnosed FLT3 mutation-positive AML.

Midostaurin meets the NICE end of life criteria and is a cost-effective treatment for newly-diagnosed patients with FLT3 mutation-positive AML, having an ICER of £34,327 per QALY over standard-of-care chemotherapy. Probability sensitivity analysis indicates that midostaurin in combination with chemotherapy plus midostaurin monotherapy has an ICER of £31,550 per QALY over standard-of-care, with a 39.2% probability of being cost-effective at a threshold of £30,000 per QALY and a 97.3% probability at a threshold of £50,000 per QALY. Midostaurin thus represents a new paradigm in the management of FLT3 mutation-positive AML and is the first breakthrough in the management of AML achieved in the last 30 years.

In the RATIFY trial[16] and after extrapolation in this analysis, midostaurin therapy showed benefits with respect to both OS and EFS compared to SOC even when censoring for SCT. In the model, this translated into gains in LYs, with midostaurin therapy-treated patients gaining [redacted] when compared to SOC. When applying utility values to the different model health states, midostaurin therapy-treated patients also showed QALY gains, resulting in an incremental gain of [redacted] QALYs versus SOC.

Midostaurin therapy was shown to be cost effective compared to SOC when assessing both LYs and QALYs. The ICER for midostaurin therapy versus SOC was £30,263 per LY gained and £34,327 per QALY.

The model presented in this document, while comprehensive, had some limitations. Due to the unavailability of specific data, the durations of SCT and recovery were based on information provided in interviews with clinical experts, rather than existing validated data. Furthermore, no utility data were collected in the RATIFY trial so this information was derived from previously published literature.

Lastly, the model was designed so that patients in the SCT health state could only transition out through mortality, which inherently dictates that no relapse or subsequent therapy occurred after SCT.

In summary, the clinical trial on which this economic model is based was robust and well conducted in patients representative of the population expected to be treated for newly diagnosed FLT3 mutation-positive AML in the UK. Midostaurin represents a clinically significant advance in the management of newly diagnosed AML, being the first therapy demonstrated to significantly prolong OS in recent decades. Furthermore, midostaurin therapy significantly prolonged event-free survival, disease-free survival, and treatment-free interval when compared with SOC. These results, when applied in the economic analysis, showed cost effectiveness in the base case when comparing midostaurin therapy to SOC. This cost-effectiveness analysis used a validated methodological approach that yielded a cost-effective result for both LYs and QALYs. Sensitivity analyses support the findings and contribute to the robustness of the economic case.

6 Assessment of factors relevant to the NHS and other parties

6.1 Eligible patient population

Table 59 presents the number of patients in England and Wales assumed to be eligible to receive midostaurin in 2017–2022. Estimates of the UK population in 2017 and annual population growth rate (0.78%) were based on ONS 2015[89] data. For the purpose of calculating the eligible patient population and estimating the budget impact, the most conservative approach has been taken. A total of 312 patients could benefit from treatment with midostaurin based on the following selection criteria of age, suitability for intensive chemotherapy, and presence of a FLT3 mutation. Eligible patients were considered to be newly diagnosed, aged between 16 and 75 years (inclusive), as patients younger than 16 years would be treated as paediatric and those older than 75 years would not be likely to receive intensive chemotherapy (clinical expert opinion) and patients also need to be identified as FLT 3 mutation-positive.

Out of the total population in the UK, the incidence of AML was estimated at 0.0048%.[90] Of these, 1688 (56%) patients out of the population incidence statistics of 3,006 AML patients reported by UK Cancer Statistics in 2017 are within the selected age group (16–75 years).[90] A total of 1,246 patients (70% of the age-suitable patients according to clinical expert opinion) are expected to receive intensive chemotherapy, the backbone to which midostaurin therapy has been added. Furthermore, the proportion of the 1,246 patient population identified as FLT3 mutation-positive by UK screening was assumed to be 25%, giving a population of 311.5 (rounded up to 312) based on clinical expert opinion (compared to the 30% prevalence of FLT3 mutations, of which not all would be identified as FLT3 mutation-positive).

An additional layer was applied to the patient flow to account for the patients who would be randomised to FLT3 mutation-positive AML trials. Clinical expert opinion informs us that midostaurin therapy use will likely be as a comparator in National NCRI trials, with midostaurin therapy being considered the SOC. This suggests that, depending on the ratio of randomisation to comparators, populations could be between 25–75% of this figure, e.g. 78–234 patients per year or, at most, 312 (and so the proportion of patients not randomised to other FLT3 trials was estimated at 50% according to clinical expert assumption). This yields a final eligible population of 156 at baseline.

Although the patient flow does not include carry-over, the model is based on 2 years maximum duration and includes cumulative costs. This accounts for patient carry-over. Since not all patients reach all of the treatment cycles (e.g. only 33% reached maintenance in the RATIFY trial), the patient-level data were used for treatment duration.

Table 59 Eligible patient population

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Population in England and Wales (0.78% growth rate)	66,118,190	66,633,242	67,152,306	67,675,414	68,202,596	68,733,885
Incidence of AML in UK (all population)	3,174	3,198	3,223	3,248	3,274	3,299
AML patients between 15-75 years old (56.09%)	1,781	1,794	1,808	1,822	1,837	1,851
AML patients fit for intensive chemotherapy (70%)	1,247	1,256	1,266	1,276	1,286	1,296
FLT3 mutation-positive AML patients (25%) not randomised to other FLT3 clinical trials (50%)	156	157	158	160	161	162

6.2 Assumptions on treatment uptake and market share

It has been assumed that eligible patients currently receive 10+3 cytarabine + daunorubicin or 7+3 cytarabine + idarubicin for induction therapy, and high-dose cytarabine or FLAG-IDA as consolidation therapy (please note that cytarabine 7+3 [trial] was changed to 10+3 for the UK based on clinical expert assumptions). For second-line or continuation therapy, it is assumed that eligible patients receive FLAG-IDA based on clinical expert assumption.

Market share uptake of midostaurin therapy was based on results from the same physician survey (Putnam Quantitative Research, 2016 – data on file), in which 50 UK physicians expressed their willingness to prescribe midostaurin therapy to their FLT3 mutation-positive patients undergoing induction therapy (Table 61).

Table 60 Market share of comparators

Treatment phase	Treatments	Market Share %
Induction	10+3 (Cyta+Dauno):	100.0%
Consolidation	HIDAC	100.0%

Cyta+Dauno, cytarabine plus daunorubicin; HIDAC, high-dose cytarabine

Table 61 Estimated market share uptake for midostaurin therapy

Arm	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Status quo - midostaurin	0%	0%	0%	0%	0%	0%
Base case - midostaurin + cytarabine + daunorubicin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Comparators	100%	87%	73%	60%	46%	33%

Putnam Quant Research, 2016[91]

6.3 Estimates of resource savings

In addition to drug costs, administration costs for both oral and IV drugs were incorporated into the budget impact estimates. Wholesaler mark-up, pharmacy mark-up, inventory allowance, dispensing fees, and co-payments were all assumed to be 0.

6.4 Estimated annual budget impact of introducing midostaurin

Drug prices were obtained from the BNF[92]. Costs per cycle were converted to monthly costs to use in the model. In addition to drug costs, administration costs were included and assumed to be £171.10 per cycle for oral therapies (NHS Reference Costs SB11Z, 2014-2015)[82] and £239.12 per administration day for IV therapies (NHS Reference Costs SB12Z, 2014-2015).[82] Total costs for midostaurin and each comparator therapy are presented in Table 62 and Table 63, respectively.

It should be noted that dose intensity has not been included in the budget impact

Table 62 Midostaurin price and utilization*

Phase	Regimen	Dose	m^2/kg	Dose per day	Number of days	mg per cycle	Vial size mg (or tab)	Price per vial	Number of vials needed	Cost per cycle**	Administration costs	Cost per month
Induction	Cytarabine	200 mg/m^2/day (1-10)	1.90	200	10	3800	100	4.20	38.0	[redacted]		[redacted]
	Daunorubicin	60 mg/m^2/day (1-3)	1.90	60	3	342	20	65	18.0	[redacted]		[redacted]
	Midostaurin	50 mg (2 X 25) twice per day (8-21)				1400	25	100	56.0	[redacted]		[redacted]
	Total cost per cycle				***10***			***10***				
Consolidation	High dose Cytarabine	3000 mg/m^2/day (1, 3, 5) twice per day	1.90	6000	3	34200	100	4.20	342.0	[redacted]		[redacted]
	Midostaurin therapy	50 mg (2 X 25) twice per day (8-21)				1400	25	100	56.0	[redacted]		[redacted]
	Total cost per cycle				***3***			***3***				
Monotherapy	Midostaurin therapy	50 mg (2 X 25) twice per day (1-28)				2800	25	100	112.0	[redacted]		[redacted]
	Total cost per cycle									[redacted]	[redacted]	[redacted]

*Dose intensity not included

**All treatment cycles are 28 days

Table 63 Comparator price and utilization

Treatment Phase	Combination	Regimen	Dose	m^2/kg	Dose per day	Number of days (hospital presence in total)	mg per cycle	Vial size mg (or µg)	Price per vial	Number of vials needed	Cost per cycle*	Administration costs	Cost per month
Induction	10 + 3 (cytarabine, daunorubicin)	Cytarabine	200 mg/m^2/day (1-10)	1.9	200	10	3800	500.00	1.9	200	10		£169.58
		Daunorubicin	90 mg/m^2/day (1-3)	1.9	90	3	513	20.00	1.9	90	3		£1,837.12
		Total cost per cycle				***10***					***1,846.00***	***2391.2***	£***4,606.06***
Induction	HIDAC	High dose Cytarabine	3000 mg/m^2/day (1, 3, 5) twice per day	1.9	6000	3	34200	500.00	19.5	69	1345.5		£1,462.63
		Total cost per cycle				***3***					***1,345.50***	***717.4***	£**1,462.63**

*All treatment cycles are 28 days

Duration of treatment and cost calculations

Treatment duration for each phase was based on the proportion of patients reaching each cycle in the RATIFY trial (presented in Table 64). Based on these results, the months spent in the first and second year of treatment (cycles 1–13 and cycles 14–26, respectively) were derived for each treatment phase (Table 65), converting 28-day cycles into months.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 65 Monthly use of treatment

		Sum of months	
Arm	**Treatment phase**	**First year**	**Second year**
Midostaurin therapy	Induction	1.08	0.00
	Consolidation	1.73	0.00
	Monotherapy	1.86	1.04
	Secondary therapy	0.92	0.00
SOC	Induction	1.11	0.00
	Consolidation	1.52	0.00
	Secondary therapy	0.92	0.00

To calculate total months in each treatment phase, the number of patients receiving each therapy type (midostaurin or SOC), based on estimated market share at each year, was multiplied by the number of months of therapy (Table 65). Finally, costs for each treatment phase were calculated by multiplying the monthly cost for each treatment phase (shown in the last columns of Table 62 and Table 63) by the total months of therapy for each treatment phase. Total cost and overall budget impact results are presented in section 6.6.

6.5 Estimates of resource savings

Resource savings are expected to occur as a result of lower non-drug costs associated with use of midostaurin therapy compared with comparators (namely AE and indirect costs) expected after midostaurin introduction.

6.6 Estimated annual budget impact of introducing midostaurin

Budget impact estimates are shown in Table 66. Breakdowns of the specific costs in current practice (i.e. without midostaurin therapy) and in the base case (i.e. with the introduction of midostaurin therapy) are presented in Table 67 and Table 68, respectively. The eligible patient population has been estimated from ONS 2015-based population projections. Market share assumptions are defined in Table 61.

The total budget impact of introducing midostaurin is expected to be approximately £16 million over the 5-year period (2016 [baseline] and 2017–2022 for the scenario). It should be noted that the budget impact for the introduction of midostaurin is likely to be lower given that dose intensity has not be included.

Table 66 Overall budget impact results

Endpoint	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Estimated budget impact	0	£854,915	£1,995,303	£3,153,634	£4,329,908	£5,524,123	£15,857,883

[redacted]

Costs	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.7 Opportunities for resource savings not quantified in this analysis

Only direct drug and administration costs were included in the budget impact analysis. These estimates do not take into account any potential savings made as a result of reduced severity or number of AEs, or potential savings resulting from a reduced need for other medical care required after the introduction of midostaurin therapy. Dose intensity was also not included, and therefore the budget impact associated with the introduction of midostaurin is likely to be lower.

6.8 Limitations of the budget impact analysis

While this analysis provided accurate estimates for drug and administration costs, estimates for other costs not directly associated with drug utilisation were not included. Additionally, it should be noted that the results from this budget impact model may be optimistic, as UK clinical practice currently uses two cycles of consolidation therapy, while four cycles were used in the RATIFY trial and in this analysis. These additional cycles result in increased overall consolidation costs compared with current clinical practice, and may overstate our budget impact estimates.

7 References

1. Fathi AT, Chen YB. Treatment of FLT3-ITD acute myeloid leukemia. *Am J Blood Res* 2011;1:175-89.
2. Sekeres MA, Elson P, Kalaycio ME *et al.* Time from diagnosis to treatment initiation predicts survival in younger, but not older, acute myeloid leukemia patients. *Blood* 2009;113:28-36.
3. Cancer Research UK. Acute myeloid leukaemia (AML) survivalstatistics. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/survival. Accessed September 2016.
4. Maynadie M, De Angelis R, Marcos-Gragera R *et al.* Survival of European patients diagnosed with myeloid malignancies: a HAEMACARE study. *Haematologica* 2013;98:230-8.
5. Santos FP, Jones D, Qiao W *et al.* Prognostic value of FLT3 mutations among different cytogenetic subgroups in acute myeloid leukemia. *Cancer* 2011;117:2145-55.
6. Janke H, Pastore F, Schumacher D *et al.* Activating FLT3 mutants show distinct gain-of-function phenotypes in vitro and a characteristic signaling pathway profile associated with prognosis in acute myeloid leukemia. *PLoS One* 2014;9:e89560.
7. Gale RE, Green C, Allen C *et al.* The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. *Blood* 2008;111:2776-84.
8. Khan I, Altman JK, Licht JD. New strategies in acute myeloid leukemia: redefining prognostic markers to guide therapy. *Clin Cancer Res* 2012;18:5163-71.
9. British Committee for Standards in H, Milligan DW, Grimwade D *et al.* Guidelines on the management of acute myeloid leukaemia in adults. *Br J Haematol* 2006;135:450-74.
10. Milligan DW, Grimwade D, Cullis JO *et al.* British Committee for Standards in Haematology. Guidelines on the management of acute myeloid leukaemia in adults. *Br J Haematol* 2006;135:450-74.
11. Dohner H, Estey EH, Amadori S *et al.* Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood* 2010;115:453-74.
12. Fey MF, Buske C, on behalf of the ESMO Guidelines Working Group. Acute myeloblastic leukaemias in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6:vi138-43.
13. Stone RM, Mandrekar SJ, Sanford BL, *et al.* The multi-kinase inhibitor midostaurin prolongs survival compared with placebo in combination with daunorubicin/cytarabine induction, high-dose consolidation, and as maintenance therapy in newly diagnosed acute myeloid leukemia (AML) patients age 18-60 with FLT3 mutations: an international prospective randomized placebo-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]). *Blood* 2015;126:6.
14. Novartis. Midostaurin (Rydapt) Summary of Product Characteristics.
15. Gallogly MM, Lazarus HM. Midostaurin: an emerging treatment for acute myeloid leukemia patients. *J Blood Med* 2016;7:73-83.
16. Novartis. RATIFY CSR. Data on file.
17. Schlenk R, Döhner K, Salih H, *et al.* Midostaurin in combination with intensive induction and as single agent maintenance therapy after consolidation therapy with allogeneic hematopoietic stem cell transplantation or high-dose cytarabine. *Blood* 2015;126:322.
18. Schlenk RF, Fiedler W, Salih HR, *et al.* Impact of age and midostaurin-dose on response and outcome in acute myeloid leukemia with FLT3-ITD: interim-analyses of the AMLSG 16-10 trial. *Blood* 2016;128:449.
19. Novartis. Phase 2 study CSR (AMLSG16-10/CPKC412ADE02T) Data on file.
20. Novartis. Phase 2 study protocol (AMLSG16-10/CPKC412ADE02T) Data on file.
21. Kayser S, Levis MJ. FLT3 tyrosine kinase inhibitors in acute myeloid leukemia: clinical implications and limitations. *Leuk Lymphoma* 2014;55:243-55.
22. Kottaridis PD, Gale RE, Frew ME *et al.* The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. *Blood* 2001;98:1752-9.
23. Vardiman JW, Thiele J, Arber DA *et al.* The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood* 2009;114:937-51.

24. Meshinchi S, Appelbaum FR. Structural and functional alterations of FLT3 in acute myeloid leukemia. *Clin Cancer Res* 2009;15:4263-9.
25. Brandts CH, Sargin B, Rode M *et al.* Constitutive activation of Akt by Flt3 internal tandem duplications is necessary for increased survival, proliferation, and myeloid transformation. *Cancer Res* 2005;65:9643-50.
26. Smith CC, Wang Q, Chin CS *et al.* Validation of ITD mutations in FLT3 as a therapeutic target in human acute myeloid leukaemia. *Nature* 2012;485:260-3.
27. Weisberg E, Boulton C, Kelly LM *et al.* Inhibition of mutant FLT3 receptors in leukemia cells by the small molecule tyrosine kinase inhibitor PKC412. *Cancer Cell* 2002;1:433-43.
28. Williams AB, Nguyen B, Li L *et al.* Mutations of FLT3/ITD confer resistance to multiple tyrosine kinase inhibitors. *Leukemia* 2013;27:48-55.
29. Cools J, Mentens N, Furet P *et al.* Prediction of resistance to small molecule FLT3 inhibitors: implications for molecularly targeted therapy of acute leukemia. *Cancer Res* 2004;64:6385-9.
30. Novartis. Data on file.
31. Deschler B, Lubbert M. Acute myeloid leukemia: epidemiology and etiology. *Cancer* 2006;107:2099-107.
32. Arber DA, Orazi A, Hasserjian R *et al.* The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391-405.
33. Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. *Blood* 2012;119:34-43.
34. Howell DA, Smith AG, Jack A *et al.* Time-to-diagnosis and symptoms of myeloma, lymphomas and leukaemias: a report from the Haematological Malignancy Research Network. *BMC Hematol* 2013;13:9.
35. Majhail NS, Lichtin AE. Acute leukemia with a very high leukocytecount: confronting a medical emergency. *Cleve Clin J Med* 2004;71:633-7.
36. Appelbaum FR, Gundacker H, Head DR *et al.* Age and acute myeloid leukemia. *Blood* 2006;107:3481-5.
37. Kantarjian H, O'Brien S, Cortes J *et al.* Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer* 2006;106:1090-8.
38. Mohammadi M, Cao Y, Glimelius I *et al.* The impact of comorbid disease history on all-cause and cancer-specific mortality in myeloid leukemia and myeloma – a Swedish population-based study. *BMC Cancer* 2015;15:850.
39. Cannella L, Caocci G, Jacobs M *et al.* Health-related quality of life and symptom assessment in randomized controlled trials of patients with leukemia and myelodysplastic syndromes: What have we learned? *Crit Rev Oncol Hematol* 2015;96:542-54.
40. Redaelli A, Stephens JM, Brandt S, Botteman MF, Pashos CL. Short- and long-term effects of acute myeloid leukemia on patient health-related quality of life. *Cancer Treat Rev* 2004;30:103-17.
41. LeBlanc T, Wolf S, Davis D *et al.* Symptom burden, quality of life, and distress in acute myeloid leukemia patients receiving induction chemotherapy: A prospective electronic patient-reported outcomes study. *J Clin Oncol* 2015;33:e20702.
42. Schumacher A, Wewers D, Heinecke A *et al.* Fatigue as an important aspect of quality of life in patients with acute myeloid leukemia. *Leuk Res* 2002;26:355-62.
43. Sekeres MA, Stone RM, Zahrieh D *et al.* Decision-making and quality of life in older adults with acute myeloid leukemia or advanced myelodysplastic syndrome. *Leukemia* 2004;18:809-816.
44. Tamayo GJ, Broxson A, Munsell M, Cohen MZ. Caring for the caregiver. *Oncol Nurs Forum* 2010;37:E50-7.
45. Grimm PM, Zawacki KL, Mock V, Krumm S, Frink BB. Caregiver responses and needs. An ambulatory bone marrow transplant model. *Cancer Pract* 2000;8:120-8.
46. El-Jawahri AR, Traeger LN, Kuzmuk K *et al.* Quality of life and mood of patients and family caregivers during hospitalization for hematopoietic stem cell transplantation. *Cancer* 2015;121:951-9.
47. O'Donnell MR, Abboud CN, Altman J, Appelbaum FR, Coutre SE. Acute myeloid leukemia. *J Natl Compr Canc Netw* 2011;9:280-317.
48. Burnett AK, Russell NH, Hills RK *et al.* Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. *J Clin Oncol* 2013;31:3360-8.
49. Visser O, Trama A, Maynadie M *et al.* Incidence, survival and prevalence of myeloid malignancies in Europe. *Eur J Cancer* 2012;48:3257-66.

50. HMRN. AML statistics. Available at: https://www.hmrn.org/statistics Accessed October 2016.
51. Cancer Research UK. Acute myeloid leukaemia (AML) incidence statistics. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/incidence, Accessed September 2016.
52. Kantar Health. Future trends and insights: Western Europe. Acute myeloid leukemia. August 2016.
53. SEER Stat Fact Sheets: Acute Myeloid Leukemia (AML) Available at:https://seer.cancer.gov/faststats/selections.php?series=cancer (Accessed January 2017), from: http://seer.cancer.gov/statfacts/html/amyl.html (Accessed April 7, 2016).
54. Byrd JC, Mrozek K, Dodge RK *et al.* Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). *Blood* 2002;100:4325-36.
55. Grimwade D, Walker H, Harrison G *et al.* The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. *Blood* 2001;98:1312-20.
56. Grimwade D, Walker H, Oliver F *et al.* The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. *Blood* 1998;92:2322-33.
57. Slovak ML, Kopecky KJ, Cassileth PA *et al.* Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood* 2000;96:4075-83.
58. National Institute for Health and Care Excellence. NICE Guidance 47: Clinical pathway blood and bone cancers overview – leukaemia. Available at: http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers/leukaemia Accessed September 2016.
59. National Institute for Health and Care Excellence. Technology assessment 218. Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia. 2011 Available at: https://www.nice.org.uk/guidance/ta218/resources/azacitidine-for-the-treatment-of-myelodysplastic-syndromes-chronic-myelomonocytic-leukaemia-and-acute-myeloid-leukaemia-82600256379589 Accessed October 2016.
60. Brookmeyer R, Crowley J. A K-sample median test for censored data. *J Am Stat Assoc* 1982;77:433-40.
61. Stone RM, Fischer T, Paquette R *et al.* Phase IB study of the FLT3 kinase inhibitor midostaurin with chemotherapy in younger newly diagnosed adult patients with acute myeloid leukemia. *Leukemia* 2012;26:2061-8.
62. Cheson BD, Bennett JM, Kopecky KJ *et al.* Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol* 2003;21:4642-9.
63. Crespo C, Moreno E, Sierra J, Serip S, Rubio M. Cost-effectiveness analysis of azacitidine in the treatment of high-risk myelodysplastic syndromes in Spain. *Health Econ Rev* 2013;3:28.
64. Levy AR, Zou D, Risebrough N *et al.* Cost-effectiveness in Canada of azacitidine for the treatment of higher-risk myelodysplastic syndromes. *Curr Oncol* 2014;21:e29-40.
65. Batty N, Yin Y, Wetzler M. Decitabine is more cost effective than cytarabine and daunorubicin in elderly acute myeloid leukemia patients. *J Cancer Res Ther* 2014;2:68-73.
66. Pan F, Peng S, Fleurence R *et al.* Economic analysis of decitabine versus best supportive care in the treatment of intermediate- and high-risk myelodysplastic syndromes from a US payer perspective. *Clin Ther* 2010;32:2444-56.
67. Ramos C, Montano E, Reyes Lopez A *et al.* Economic evaluation of lenalidomide in the treatment of lower risk myelodysplastic syndromes with DEL5q (MDS DEL5q) in Mexico. *Value in Health* 2016;19:A248.
68. Cogle CR, Mukherjee S, Lawrence ME *et al.* Cost effectiveness of treatments after failure of a first-line hypomethylating agent in Myelodysplastic Syndromes (MDS). Available at: http://www.bloodjournal.org/content/124/21/1928. *Blood* 2014;124:1928.
69. Van de Velde AL, Beutels P, Smits EL *et al.* Medical costs of treatment and survival of patients with acute myeloid leukemia in Belgium. *Leuk Res* 2016;46:26-9.
70. Edlin R, Connock M, Tubeuf S *et al.* Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia. *Health Technol Assess* 2010;14 Suppl 1:69-74.

71. Mujica MR, Varley-Campbell J, Tikhonova I *et al.* Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts: A Single Technology Appraisal. 2011 Available at: https://ore.exeter.ac.uk/repository/handle/10871/22268. 2016.
72. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013 Available at: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 Accessed February 2017.
73. Kurosawa S, Yamaguchi H, Yamaguchi T *et al.* Decision analysis of allogeneic hematopoietic stem cell transplantation versus chemotherapy in cytogenetically standard-risk acute myeloid leukemia in first complete remission: The impact of FLT3-ITD profile. Available at: http://www.bloodjournal.org/content/124/21/1221. *Blood* 2014;124:1221.
74. Gidwani R, Khan ZM, Fenaux P, Beach CL, Pashos CL. A cost-effectiveness analysis of using azacitidine vs. decitabine in treating patients with myelodysplastic syndromes. *J Med Econ* 2012;15:145-54.
75. Uyl-de Groot CA, Lowenberg B, Vellenga E *et al.* Cost-effectiveness and quality-of-life assessment of GM-CSF as an adjunct to intensive remission induction chemotherapy in elderly patients with acute myeloid leukemia. *Br J Haematol* 1998;100:629-36.
76. Leunis A, Redekop WK, Uyl-de Groot CA, Lowenberg B. Impaired health-related quality of life in acute myeloid leukemia survivors: a single-center study. *Eur J Haematol* 2014;93:198-206.
77. Slovacek L, Slovackova B, Jebavy L, Macingova Z. Psychosocial, health and demographic characteristics of quality of life among patients with acute myeloid leukemia and malignant lymphoma who underwent autologous hematopoietic stem cell transplantation. *Sao Paulo Med J* 2007;125:359-61.
78. Goss TF, Szende A, Schaefer C *et al.* Cost effectiveness of lenalidomide in the treatment of transfusion-dependent myelodysplastic syndromes in the United States. *Cancer Control* 2006;13 Suppl:17-25.
79. Grulke N, Albani C, Bailer H. Quality of life in patients before and after haematopoietic stem cell transplantation measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C30. *Bone Marrow Transplant* 2012;47:473-82.
80. Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. *Eur J Health Econ* 2010;11:427-34.
81. Personal Social Services Research Unit. Unit Costs of Health and Social Care. 2015. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2015/ Accessed February 2017.
82. NHS England. National Schedule of Reference Costs - Year 2014 - 15 NHS trusts and NHS foundation trusts. 2015.
83. National Institute for Health and Care Excellence. Technology assessment 399. July 2016. Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts. Available at: https://www.nice.org.uk/Guidance/TA399 Accessed February 2017.
84. National Institute for Health and Care Excellence. Technology assessment 399. Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts. Evidence Review Report. April 2016.Available at: https://www.nice.org.uk/guidance/TA399/documents/committee-papers Accessed February 2017.
85. Nuffield Trust. Exploring the cost of care at the end of life. 2014. Available at: https://www.nuffieldtrust.org.uk/research/exploring-the-cost-of-care-at-the-end-of-life Accessed February 2017.
86. Office for National Statistics. National Life Tables, United Kingdom, 2013-2015. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/20132015 Accessed February 2017.
87. Claxton K, Sculpher M, McCabe C *et al.* Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. *Health Econ* 2005;14:339-47.
88. Briggs AH, Weinstein MC, Fenwick EA *et al.* Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--6. *Value Health* 2012;15:835-42.
89. England population mid-year estimate. 2016 Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/timeseries/enpop/pop Acessed February 2017
90. Acute myeloid leukaemia (AML) incidence statistics. Available at URL: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/incidence#heading-Zero Acessed on 3 feb., 2017.

91. Putnam Quant Research. Data on file. Physicians express their willingness to prescribe Rydapt in their induction patients with FLT3+ mutation status, UK survey of 50 physicians. Sept-Nov 2016
92. British National Formulary. Available at: https://www.bnf.org/ Accessed February 2017. 2016.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Midostaurin for newly diagnosed acute myeloid leukaemia [ID894]

Dear Novartis,

The Evidence Review Group, CRD/CHE University of York, and the technical team at NICE have looked at the submission received on 2 March 2017 from Novartis. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Tuesday 25 April 2017**.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Kirsty Pitt, Technical Lead (kirsty.pitt@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (stephanie.yates@nice.org.uk).

Yours sincerely

Nicola Hay
Technical Adviser – Appraisals
Centre for Health Technology Evaluation
On behalf of:
Frances Sutcliffe

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Population

A1. **Priority question**: In the RATIFY trial the population is restricted to people aged 18-60 years. However, the submission reports that of the new cases of acute myeloid leukaemia (AML) in England and Wales in 2011-2013, approximately 55% of people were aged 70 years or older. Is the population in RATIFY representative of people who have AML in the UK?

A2. **Priority question**: Please clarify the expected marketing authorisation for midostaurin – is it expected to include just young, relatively well people (reflecting RATIFY) or the whole FLT3+ve AML population?

A3. Were only people eligible for stem cell transplantation (SCT) eligible for RATIFY? If so, how was eligibility determined?

A4. Pages 32-33 of the company submission discuss the size of the population eligible to receive midostaurin, but does not provide an estimate of the population size. Based on the information presented in the company submission, the population size can be estimated to be between 510-681 people. Does the company agree that this is an accurate estimation based on the information on pages 32-33? However, on page 175, the size of the eligible population is stated as 160 people. Please provide further details on how this estimation of the size of the population in England eligible for midostaurin was obtained.

Patient disposition

A5. **Priority question**: Patient disposition for RATIFY is presented in the submission (figure 8, page 52) and in the clinical study report (CSR) (figure 10-1, page 62). Please provide further details for the categories, 'alternative therapies' and 'other', presented in this figure, in a tabular format:

a. Alternative therapies – what are they and how many patients received them?

b. 'Other' reasons for discontinuation – 'other' category is given in the CSR version of this figure but has been omitted from the submission.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A6. **Priority question**: Please provide detailed information on when participants received SCT – perhaps a flow diagram for RATIFY like figure 18 (which is for the phase 2 trial) plus text describing patient disposition so it is clear how many participants received SCT and when they received it.

Definition of CR

A7. **Priority question**: Recent publications (e.g. Dohner et al 2017 Blood 129(4):424-7) indicate that there is a role for minimal residual disease negative (MRD-ve) (or similar measure of the quality of response) in AML. Please provide a summary of the evidence relating to the quality of complete remission (CR) with midostaurin and how this compares with the quality of CR with standard of care (SOC).

A8. **Priority question**: The term complete remission (CR) is used in various ways through the company submission. Please clarify the various definitions of remission used in the submission and when they are applied: CR within 60 days; CR at any time; CR following 1st or 2nd induction; 'first CR'; CR1.

Comparator

A9. **Priority question**: The only comparator considered in RATIFY and the model is daunorubcin+cytarabine at specified doses. A Cochrane review found that idarubicin+cytarabine might be more effective than daunorubcin+cytarabine. Are there any data relating to the use of midostaurin with idarubicin+cytarabine in untreated FLT3+ve AML (or all AML)?

A10. **Priority question**: Please provide a commentary on the use of midostaurin in combination with other chemotherapy regimens. Is the marketing authorisation likely to be restricted to the combination with daunorubcin+cytarabine?

Overall survival

A11. **Priority question**: The data cut analysed was taken on 01 April 2015, before the prespecified number of events had occurred. Has the European Medicines Agency (EMA) requested a later data cut? Please provide a later data cut for overall survival (OS) and event-free survival (EFS) (Kaplan–Meier plots and analysis) if available.

A12. **Priority question**: The very large difference between the median and mean OS suggests that the data have a very long tail. Please provide the individual patient data for OS or a waterfall plot of OS.

A13. **Priority question**: From the subgroup analyses reported in the CSR (figure 11-2, page 74) it can be seen that there is an OS benefit in men (hazard ratio [HR] 0.53 95% confidence interval [CI] 0.39-0.72) but not women (HR 1.01 95% CI 0.76-1.34). Please explain the difference in OS benefit between the 2 groups. Please provide the equivalent subgroup analyses censored for SCT.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Midostaurin maintenance therapy

A14. Although the company submission and CSR state that patients in RATIFY were not to receive midostaurin monotherapy after SCT, please confirm whether or not any patients in RATIFY did receive midostaurin monotherapy after SCT (as in the phase II trial). Please also confirm how many (if any) patients received midostaurin after SCT. Please provide a commentary on whether it is anticipated that midostaurin monotherapy will be used post-SCT in clinical practice?

A15. **Priority question**: With reference to table 11-14, page 82 of the CSR please:

a. Explain why a large proportion of patients were not in CR when they received SCT. This appears to contradict the statement on page 111 of the company submission that states that, "only patients in CR could receive SCT prior to relapse in the clinical trial, as per current clinical guidelines".

b. Clarify if first complete remission in table 11-14 is the same as CR1 in the company submission. Also, is it restricted to CR within 60 days?

c. Explain what 'occurred after relapse' means. Did these patients receive SCT not in CR having relapsed? Or did the patients relapse on study treatment, achieve CR on alternative therapy, and then receive SCT?

d. Tabulate the numbers of patients receiving SCT by the treatment phases (i.e. induction, consolidation and monotherapy) along with type of response to chemotherapy prior to SCT (e.g. complete remission, partial remission, or failure).

A16. **Priority question**: From the data provided (tables 11-8 and 11-15 of the CSR) the ERG calculated that [redacted] patients in the midostaurin group and [redacted] in the placebo group died after receiving SCT. Please confirm whether this is correct.

A17. **Priority question**: It is unclear from figure 11 (page 58 of the company submission) what 'first CR (those occurring within 30 days of the last treatment)' means.

a. Does it mean within 30 days of 1st induction or 1st or 2nd induction?

b. Does it exclude some patients who achieved CR and continued to consolidation/maintenance therapy? If so why and how many?

c. Please confirm that CR1 is 'first CR', i.e. that the figure and the text relates directly to figure 11 (page 58 of the submission). If so, please explain why the numbers at risk in figure 11 do not correspond to the ones stated in the text.

A18. **Priority question**: Please provide additional Kaplan–Meier plots including the numbers at risk, HR, 95% CIs, and median survival for :

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

a. OS for all patients who received SCT

b. OS for all patients who did not receive SCT

c. Disease-free survival (DFS) for all patients who received SCT

d. DFS for all patients who received SCT in CR1

e. DFS for all patients who received SCT in other CR

f. DFS for all patients who did not receive SCT

Baseline characteristics

A19. Regarding time since initial pathologic diagnosis, please comment on the baseline imbalance between the treatment groups and the much larger variability in the placebo group. Please also provide an explanation for the high maximum values recorded. If available, please provide these values for the per-protocol analysis set?

Table 11-4 Disease characteristics (FAS), page 69 of the CSR

Disease status	MIDOSTAURIN	PLACEBO	ALL
Time since initial pathologic diagnosis (days)			
n			
Mean (SD)			
Median (min, max)			

Section B: Clarification on cost-effectiveness data

Additional analysis and functionality to incorporate within the executable model:

B1. Priority question: The ERG has serious concerns regarding the model structure and treatment effectiveness inputs used to populate the model. These problems largely stem from the use of a partitioned survival model (PSM) which may not be appropriate to AML. The ERG considers the current model to lack face validity and in particular notes the following key issues:

- The model does not allow patients to achieve complete remission (CR) beyond 60 days – this forces many patients into the residual relapse state where they stay for a prolonged period which is not reflective of clinical practice where patients are able to achieve CR on subsequent lines of treatment.
- Patients cannot relapse following stem cell transplantation (SCT) despite significant clinical evidence to the contrary. See for example Wingard et al, Journal of Clinical Oncology, 2011. It is also inconsistent with patients achieving complete remission via drug therapy who are able to relapse.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

- Relapse patients in the post-cure cut off portion of the model appear to die very slowly and at near general population rates; the state of relapse is not compatible with this low mortality rate.
- CR patients in the post-cure cut off portion of the model appear to remain in the CR state as determined by the extrapolation of the event-free survival (EFS) curve. This is inconsistent with patients experiencing general population mortality as the EFS curve is censored for both death and relapse/loss of response.
- Patients who receive SCT are assumed to experience no post-transplant adverse effects.

To address these significant issues with the model, please make the following amendments to the model:

- Replace the CR time to event data currently used in the model, with data on the proportion of patients in CR during trial follow-up. The definition of CR for this input should not depend on how or when CR was achieved i.e. include clinical remissions as result of second and subsequent lines of therapy, but should be censored for SCT to avoid double counting of patients.
- Replace the SCT time to event curve by a SCT time to event curve that is censored for both OS and relapse.
- Add relevant adverse events related to SCT and incorporate their subsequent costs and disutilities into the executable model.
- Following the trial follow-up period, the model should not use a PSM approach and patients should move to a natural history model populated using appropriate data. This model should preferably allow for the following:
    - Patients in the both SCT and CR health states should be able to transition to both the relapse and death health states,
    - The mortality rate in the relapse health state should be higher than for the CR and SCT health states.
    - Patients in the relapse health state should be able to transition to the CR health state and/or the SCT health state.

B2. **Priority question:** Please implement the half-cycle correction in the economic model.

B3. **Priority question:** The economic model allows for the time at which patients are on primary therapy to be estimated from the treatment duration time to event data from the RATIFY trial. However this has not been correctly implemented. Firstly, when this scenario is selected using cell ‘E43’ on the ‘Model Parameters’ sheet, only the dosing schedule is adjusted. However, the corresponding outcomes such as costs must also be adjusted for the scenario to be correctly implemented. For example, some patients in month 2 will be receiving induction therapy, while others are receiving consolidation therapy resulting in patients in cycle 2 incurring different costs. The outcomes must therefore be weighted to account for patients being in different treatment phases at different time points in the model. Please adjust the outcomes with treatment duration time to event data and adjust the data using half-cycle correction.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

B4. **Priority question:** Please provide additional clinical evidence to support the assumption that the mortality rate following SCT will be same as the general mortality rate after the end of the trial. Several clinical studies have reported lower estimates of long-term survival after SCT for AML patients (e.g. Wingard et al, Journal of Clinical Oncology, 2011; Bhatia et al, Blood, 2007; Shimoni et al, Journal of Hematology & Oncology, 2016) compared to the general population. Please incorporate additional flexibility in the Excel model to allow a higher standardised mortality ratio (SMR) to be applied in the post-Kaplan–Meier period compared to the general population. Please provide additional scenario analyses based on assuming higher SMR rates and with reference to existing clinical literature.

B5. **Priority question:** The calculation of per cycle rates has been incorrectly implemented in the model. This affects per cycle discount, adverse event and mortality rates. A per cycle rate is calculated as follows:

Per cycle rate = 1- EXP(LN(1-Annual rate)/cycles per year)
Please implement per cycle rates correctly in the model.

Generalisability of the RATIFY trial I data

B6. **Priority question:** A significant proportion of people with AML in the UK are over 60 years old and it is plausible that some people over the age of 60 will be treated with midostaurin (conditional on the marketing authorisation and NICE recommendation). The population in the RATIFY trial, however, is restricted to people who are 18 to 60 years old and therefore the clinical data used to populate the economic model do not match with the likely eligible population.

- Please comment on the proportion of people over 60 who would be eligible to be treated with midostaurin should it be recommended.
- The ERG speculates that the incremental cost-effectiveness ratio (ICER) for patients over 60 will likely be higher than for a younger patient group as absolute benefits will be significantly reduced (because of a worse prognosis and lower life expectancy) while costs, which are mostly incurred upfront, will not fall as much. The phase 2 trial provides some limited data on the relative effectiveness of midostaurin in an older patient group. If possible, please use this data to implement a scenario analysis in the economic model to estimate the cost-effectiveness in a population more representative of the eligible population in the UK. If it is not possible to use the data from the phase 2 trail, please provide a commentary on what you expect the ICER would be for the older patient group.

Baseline characteristics and subgroup analysis

B7. The subgroup analyses presented in the CSR (figure 11-2, page 74), show that there is an overall survival benefit in males (HR 0.53 95% CI 0.39-0.72) but not in females (HR 1.01; 95% CI 0.76–1.34). Additionally in the RATIFY trial, the proportion of women and ‘’white’’ patients is different between the two treatment arms. Therefore, it could be possible that the baseline characteristics (covariates) have an impact on the overall

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

survival. However, it is not plausible to predict the impact without a statistical modelling approach i.e. covariate adjustment.

- Please provide justification as to why covariate-adjusted survival analysis was not considered while estimating the clinical effectiveness (OS) in the executable model?
- Please implement covariate-adjusted survival analysis including the covariates which have significant clinical and/or statistical impact on OS (considering proportional hazard assumption as well as full parametric assumption).
- Please present the results as a scenario analysis.

B8. **Priority question:** Please provide additional clarity on calculation of SCT costs. The ERG has identified an alternative source of evidence (NHS Blood and Transplant, 2014) which suggests that the SCT costs are underestimated in the model. Specifically, the SCT treatment costs used in the model are much lower than the values in alternative evidence. Please implement the alternative source of SCT costs in the economic model and present as a scenario analysis.

B9. **Priority question:** Currently the economic model assumes significant ongoing health state costs (intensive monitoring) for patients in relapse, remission and post-recovery health states. Would such intensive monitoring would be required indefinitely, particularly in people who have been in remission/post-recovery for a long time?

- Please provide evidence that supports the inclusion of these ongoing costs in the current model.
- Please incorporate a scenario analysis in which monitoring costs are reduced after an appropriate duration of time to reflect the reduced monitoring required for patients in sustained remission?

B10. **Priority question:** Drug wastage as a result of mortality is not implemented in the economic model: the model does not reflect the drug wastage if people on treatment die mid-way through using a pack of tablets or chemotherapy. Please incorporate drug wastage as a result of death - assuming death will occur halfway through the model cycle - and present the results as scenario analysis.

B11. Please provide justification for omitting costs of drug monitoring tests and outpatient procedures (including transfusions). The evidence suggests that people with AML need close monitoring and testing for disease progression while on treatment (please see NICE technology appraisal guidance 399). Please implement additional costs of drug monitoring tests and outpatient procedures (including transfusions) for both arms in the economic model and present the results as a scenario analysis.

B12. The costs of second-line therapy are not calculated using the individual patient level data from the RATIFY trial. Therefore, the costs of the second-line therapy is not representative of the actual agents and doses used in the two treatment arms within the RATIFY trail. Please provide a summary of the second-line therapies used in the

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

RATIFY trial and implement in the cost-effectiveness model a scenario analysis in which the second-line treatment costs accurately reflect the second-line therapies used in the RATIFY trial.

Cost of FLT3 mutation test:

B13. The cost of FLT3 testing is implemented in both the midostaurin and standard of care (SOC) arms in the model.

- To what extent is FLT3 mutation testing routine in clinical practice?
- Please provide justification for including the costs of FLT3 testing for patients receiving SOC.
- Please provide a scenario analysis where diagnostic test costs are included for people receiving midostaurin only. This should account for the fact that all people with AML would need to be tested for FLT3 mutation, but not all people with AML would have a positive test result. Please see NICE technology appraisal guidance 406 for an example of diagnostic test costs related to treatment.

Others:

B14. On page 161 of the company submission, distribution of the treatment has been presented (figure 38). Please clarify what the treatment duration implies in this figure. Please clarify whether the figure refers to treatment with midostaurin or standard care.

Section C: Textual clarifications and additional points

Literature searching

C1. Please provide the full details of the supplementary searches of conference abstracts (page 6, appendix 2): the date of the search, whether searched online or via paper copies, the method of the search – browsed or searched by keywords/search strings (please provide).

C2. Please provide the full details of the trial registries search, including the date of the search and the search strings used.

C3. Please provide a source for the study design search filters for randomised controlled trials (RCTs) and non-RCTs used in the search strategy on pages 8-10 of Appendix 2.

Midostaurin for newly diagnosed acute myeloid leukaemia [ID894]

Response to ERG clarification letter

16 May 2017

A1. Priority question: In the RATIFY trial the population is restricted to people aged 18-60 years. However, the submission reports that of the new cases of acute myeloid leukaemia (AML) in England and Wales in 2011-2013, approximately 55% of people were aged 70 years or older. Is the population in RATIFY representative of people who have AML in the UK?

Midostaurin will be restricted to patients who are able to tolerate intensive chemotherapy. Age alone is no longer considered the most critical factor in determining suitability to receive intensive chemotherapy.[1] Patient fitness for intensive chemotherapy is generally considered more important than age, and this is related to factors such as performance status, functional status and comorbid conditions as well as age.[1,2] This has been confirmed by UK expert clinical opinion. Thus although it is expected that the marketing authorisation for midostaurin will not be restricted to younger patients, in clinical practice patients who would receive midostaurin are likely to be typical of those included in RATIFY in that most will have a performance status of 0 or 1. Thus the patient population included in RATIFY is likely to be representative of patients who would receive midostaurin in England and Wales. (For further discussion, see response B6). Data for the efficacy and safety of midostaurin in older patients (aged up to 70 years of age) are available from the phase 2 Schlenk study (rather than RATIFY), as reported in the submission.

A2. Priority question: Please clarify the expected marketing authorisation for midostaurin – is it expected to include just young, relatively well people (reflecting RATIFY) or the whole FLT3+ve AML population?

The anticipated indication for midostaurin is "Rydapt is indicated in combination with standard induction and consolidation chemotherapy, followed by Rydapt single agent maintenance monotherapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are Fms-like tyrosine kinase receptor (FLT3) mutation-positive and suitable for intensive chemotherapy."

Thus the expected marketing authorisation is for patients who are "suitable for intensive chemotherapy", irrespective of age. The determining factor will be ability to tolerate intensive chemotherapy which in turn is dictated by level of fitness as opposed to age. (See response A1 for discussion of patients who are actually likely to receive midostaurin.)

A3. Were only people eligible for stem cell transplantation (SCT) eligible for RATIFY? If so, how was eligibility determined?

No, eligibility for SCT was not an inclusion criterion for entry into RATIFY. Newly diagnosed patients who were FLT3 +ve and able to undergo intensive chemotherapy were admitted regardless of eligibility for transplant.

A4. Pages 32-33 of the company submission discuss the size of the population eligible to receive midostaurin, but does not provide an estimate of the population size. Based on the information presented in the company submission, the population size can be estimated to be between 510-681 people. Does the company agree that this is an accurate estimation based on the information on pages 32-33? However, on page 175, the size of the eligible population is stated as 160 people. Please provide further details on how this estimation of the size of the population in England eligible for midostaurin was obtained.

The likely number of patients who would receive midostaurin in England and Wales takes into account the fact that approximately 50% of eligible patients are likely to receive midostaurin in clinical trials and are therefore excluded from the final estimate (Table 1), see calculation provided in Section 6.1 (page 175). Estimates of the proportion of patients who receive intensive chemotherapy and the proportion with FLT3 mutation-positive disease are based on expert opinion for England and Wales rather than from published literature.

Section 3.4 (pages 32-33) provides a description of the likely number of patients eligible to receive midostaurin based on values given in published literature but which are not necessarily the most relevant estimates for England and Wales. Furthermore, the proportion of patients who are likely to receive midostaurin as part of a clinical trial is not considered or discussed. These differences account for the differences in the estimated patient population as described in the two sections of the submission.

Table 1 Eligible patient population

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Population in England and Wales (0.78% growth rate) [3]	66,118,190	66,633,242	67,152,306	67,675,414	68,202,596	68,733,885
Incidence of AML in UK (all population, 0.0048%)[4]	3,174	3,198	3,223	3,248	3,274	3,299
AML patients between 15-75 years old (56.09%)[4]	1,781	1,794	1,808	1,822	1,837	1,851
AML patients fit for intensive chemotherapy (70%)[a]	1,247	1,256	1,266	1,276	1,286	1,296
FLT3 mutation-positive AML patients (25%)[a]	312	314	316	320	322	324
FLT3 mutation-positive AML patients not randomised to other FLT3 clinical trials (50%)[b]	156	157	158	160	161	162

[a]Clinical expert opinion

[b]Clinical expert opinion suggests that midostaurin therapy use will likely be as a comparator in National NCRI trials, with midostaurin therapy being considered the standard of care (SOC). This suggests that, depending on the randomization ratio for intervention vs SOC, 25–75% of patients eligible to receive midostaurin would do so as part of a clinical trial. This figure is assumed to be 50% for this estimate.

A5. Priority question: Patient disposition for RATIFY is presented in the submission (figure 8, page 52) and in the clinical study report (CSR) (figure 10-1, page 62). Please provide further details for the categories, 'alternative therapies' and 'other', presented in this figure, in a tabular format:

a) Alternative therapies – what are they and how many patients received them?

b) 'Other' reasons for discontinuation – 'other' category is given in the CSR version of this figure but has been omitted from the submission.

An amended version of the patient disposition figure is shown below (Figure 1) and Table 2 provides more details of reasons for discontinuation in patients who did so for "Alternative therapy" and "Other".

Figure 1 Patient disposition in RATIFY

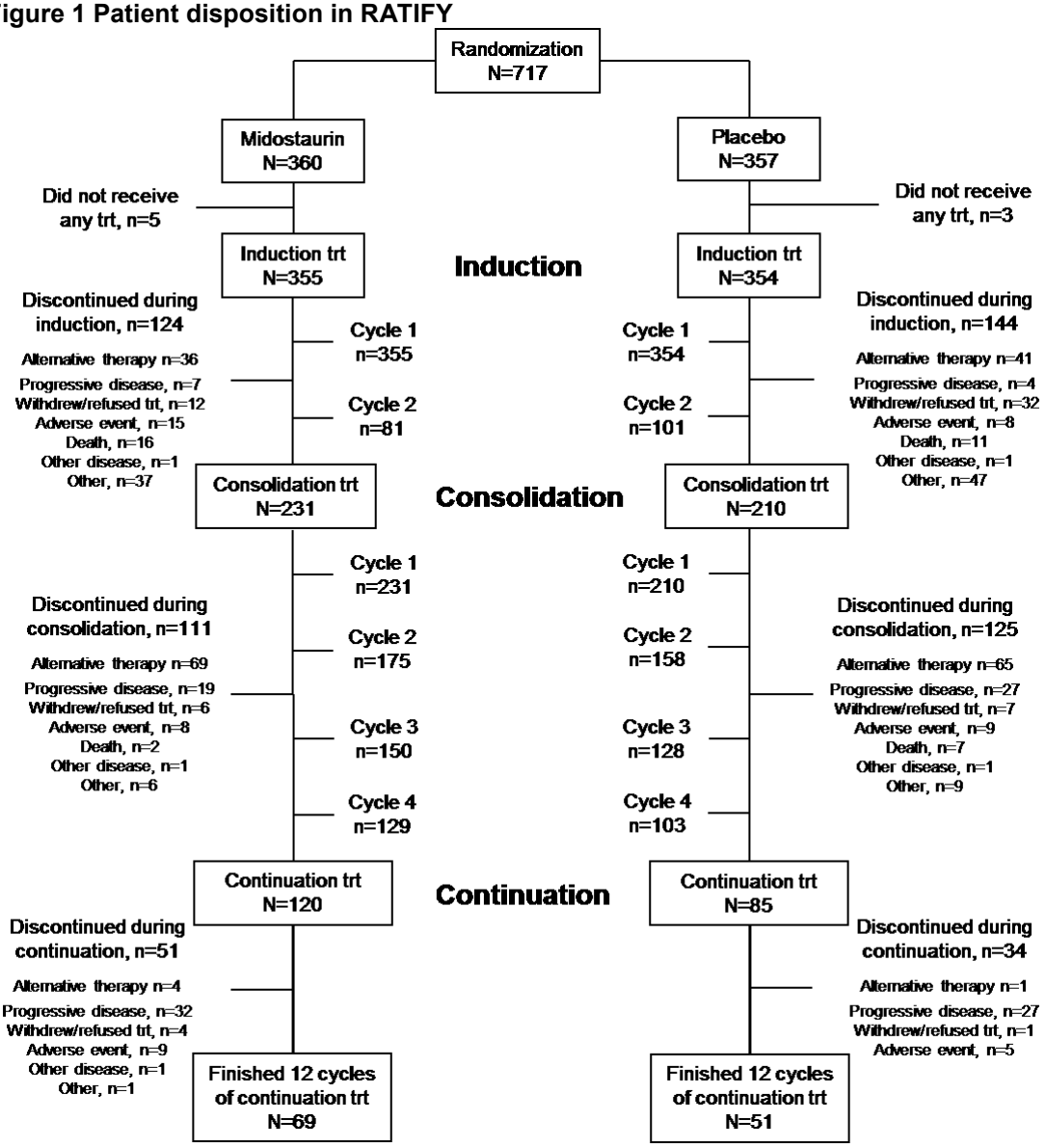


Table 2 Summary of reasons for discontinuation in patients doing so for alternative therapy or "other" reasons

Reason for discontinuation, n	Midostaurin	Placebo
Alternative therapy SCT Other	109 [redacted]	107 [redacted]
"Other" as reason for discontinuation Refractory disease Other	44 [redacted]	55 [redacted]

In total, 109 patients in the midostaurin group and 107 in the placebo group withdrew from the study because they received alternative therapies. For the midostaurin group, [redacted] patients who discontinued did so because they received SCT; [redacted] received other therapies but the details were not recorded. In the placebo group, [redacted] patients withdrew from the study because they received SCT and for [redacted] the alternative therapy was not recorded. (Note that patients recorded

as discontinuing for SCT are those in whom this was the reason for discontinuation, i.e. they received SCT in CR1. Other patients also received SCT – see response A6 – but this was not the reason for discontinuation. Such patients would have discontinued for other reasons and received SCT at some point after discontinuation from the study.)

In total 44 patients in the midostaurin group withdrew from the study due to "other" reasons. Reasons for discontinuation were refractory disease (n=[redacted]), non-compliant (n=[redacted]), shortage of cytarabine (n=[redacted]) and the following reasons were given for one patient each: ineligible, failed induction, leukaemia regrowth, stopped therapy, diagnosis of ALL, SAE prior to PR, patient taken off treatment, persistent disease, myelosuppression, patient removed from protocol, patient completed induction, no reason given, patient did not come for continuation and SCT.

In the placebo group 55 patients withdrew from the study due to "other" reasons. Reasons for discontinuation were refractory disease (n=[redacted]), and the following reasons were given for one patient each: non-compliant, AML-M3, progression, transplant, failed induction, SCT, treatment failure, treated with posacouazol, site error, sepsis in refractory leukaemia, couldn't swallow pill, medical decision, physician decision, insurance denied coverage, cytarabine not available and decision to discontinue.

A6. Priority question: Please provide detailed information on when participants received SCT – perhaps a flow diagram for RATIFY like figure 18 (which is for the phase 2 trial) plus text describing patient disposition so it is clear how many participants received SCT and when they received it.

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, or after CR1 (i.e. in relapse) or for patients who were treatment failures after they stopped treatment in 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 discontinued from the study for other reasons and then undergone SCT. Similarly patients undergoing SCT after relapse or after treatment failure would have received other therapies (off study) to achieve CR prior to SCT.

Details are provided in Table 3 regarding the proportion of patients who underwent SCT without CR, in CR1 and after relapse. For patients who underwent SCT in CR1, details are provided for the phase of treatment when patients discontinued from the study and whether the SCT occurred within 2 months of discontinuing from the study.

A slightly higher proportion of patients in the midostaurin group compared with the placebo group underwent SCT in CR1 (midostaurin, n = [redacted]; placebo, n = [redacted]). Of the patients who underwent SCT in CR1, in both treatment groups, most discontinued from the consolidation phase of the study (as would be expected) and the proportion of the total study population was slightly higher in the midostaurin group both overall (midostaurin, n = 68, [redacted]; placebo, n = [redacted]) and for those that underwent SCT ≤2 months after treatment discontinuation (midostaurin, n = [redacted]; placebo, n = [redacted]). In total, a further [redacted] (midostaurin) and [redacted] (placebo) patients discontinued treatment in the induction phase and [redacted] (midostaurin) and [redacted] (placebo) discontinued in the maintenance phase and then underwent SCT.

Although these data may suggest a possible benefit for midostaurin over placebo for enabling patients to receive SCT in CR1, the study was not designed to assess this and the results must necessarily be interpreted cautiously.

Table 3 Proportion of patients undergoing SCT according to remission status and stage of treatment

Patients undergoing SCT, n (%)	Midostaurin, n=360	Placebo, n=357
Overall	[redacted]	[redacted]
Following treatment failure	[redacted]	[redacted]
In first CR [a] Overall In induction ≤ 2 months from discontinuation In induction > 2 months from discontinuation In consolidation ≤ 2 months from discontinuation In consolidation > 2 months from discontinuation In maintenance ≤ 2 months from discontinuation In maintenance > 2 months from discontinuation Post maintenance ≤ 2 months from discontinuation Post maintenance > 2 months from discontinuation	[redacted]	[redacted]
After relapse	[redacted]	[redacted]

[a]CR defined as occurring during induction

A7. Priority question: Recent publications (e.g. Dohner et al 2017 Blood 129(4):424-7) indicate that there is a role for minimal residual disease negative (MRD-ve) (or similar measure of the quality of response) in AML. Please provide a summary of the evidence relating to the quality of complete remission (CR) with midostaurin and how this compares with the quality of CR with standard of care (SOC).

Response to therapy in RATIFY was assessed using the International Working Group for diagnosis, standardization of response criteria, treatment outcomes and reporting standards for therapeutic studies in AML.[5] The IWG criteria include definitions for CR, PR and treatment failure. Definitions for different types of CR and minimal residual disease are not included in the IWG criteria and were not assessed in RATIFY. At the time of designing the RATIFY trial, the IWG criteria were the current standard for assessing response to therapy in AML.

The 2017 ELN guidelines propose new response criteria, including CR without minimal residual disease (MRD).[1] However, these criteria are yet to be widely accepted and have only just been introduced.

A8. Priority question: The term complete remission (CR) is used in various ways through the company submission. Please clarify the various definitions of remission used in the submission and when they are applied: CR within 60 days; CR at any time; CR following 1st or 2nd induction; 'first CR'; CR1.

Rates of achieving complete remission (CR) are reported and in all cases these rates refer to the first CR (also described as CR1) achieved on study.

Three definitions for CR were used in the analysis of data from RATIFY (Table 4). In all cases the same criteria were used to define CR (following IWG criteria), the only difference being the time frame of the response. The protocol definition was CR defined as occurring within 60 days of treatment initiation. This definition however does not provide a clinically relevant summary of CRs since patients are excluded who achieved a CR in induction but after 60 days. For this reason analyses have also been performed using a revised definition that includes all CRs achieved during induction which is aligned with medical practice. A further definition – CR at any time (from randomisation up to 30 days after the end of treatment) – was also included as a sensitivity analysis but is considered to be less relevant as this includes responses occurring in later treatment phases.

For all endpoints which consider CR (i.e. EFS/DFS) the analyses are summarised in Table 5 for the protocol definition (as included in the submission) and for CR during induction.

Table 4 Definitions for complete remission used in RATIFY

CR	Definition
CR within 60 days	CR achieved within 60 days of start of study treatment. Per protocol definition.
CR during induction	CR achieved during induction phase (after one or two induction cycles)
CR at any time	CR achieved from randomization up to 30 days after the end of treatment.

Table 5 Summary of efficacy data for RATIFY relating to CR

Endpoint	CR achieved within 60 days of start of study treatment. Per protocol definition			CR achieved during induction phase		
	Midostaurin (N=360)	Placebo (N=357)	p-value or HR	Midostaurin (N=360)	Placebo (N=357)	p-value or HR
Complete remission, %	58.9	53.5	p=0.073	[redacted]	[redacted]	[redacted]
Median event-free survival, months	8.2	3.0	HR, 0.78 (0.662, 0.930), p=0.002	[redacted]	[redacted]	[redacted]
1-year, %	43	31		[redacted]	[redacted]	
5-year, %	28	19				
Median disease-free survival, months	26.7	15.5	HR, 0.709 (0.545,0.923), p=0.0051	[redacted]	[redacted]	[redacted]
1-year, %	71	57		[redacted]	[redacted]	
5-year, %	48	37				
Patients undergoing SCT All patients, % Patients with SCT in the 1st CR	59.4 [redacted]	55.2 [redacted]	p=0.250 [redacted]	[redacted]	[redacted]	[redacted]
Median event-free survival censored at SCT, months	8.3	2.8	HR, 0.81 (0.677, 0.975), p=0.0124	[redacted]	[redacted]	[redacted]
1-year, %	43	30		[redacted]	[redacted]	
5-year, %	25	21				
Median disease-free survival censored at SCT, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-year, %	[redacted]	[redacted]		[redacted]	[redacted]	
5-year, %						
Median duration of remission, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Median duration of remission censoring for SCT, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A9. Priority question: The only comparator considered in RATIFY and the model is daunorubcin+cytarabine at specified doses. A Cochrane review found that idarubicin+cytarabine might be more effective than daunorubcin+cytarabine. Are there any data relating to the use of midostaurin with idarubicin+cytarabine in untreated FLT3+ve AML (or all AML)?

No, the only data available are for midostaurin in conjunction with daunorubicin + cytarabine from RATIFY. (See response A10 for discussion of idarubicin as an alternative to daunorubicin.)

A10. Priority question: Please provide a commentary on the use of midostaurin in combination with other chemotherapy regimens. Is the marketing authorisation likely to be restricted to the combination with daunorubcin+cytarabine?

We do not expect the anticipated marketing authorisation (see response A2) to specify any particular chemotherapy regimen, rather that midostaurin can be given in conjunction with any standard regimen. Novartis are in discussion with various regulatory authorities regarding the possibility of specifying the chemotherapy regimen and will keep NICE updated on this. The FDA approved indication is specifically for midostaurin in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. The Swiss approved indication is for midostaurin in combination with standard induction and consolidation chemotherapy, followed by maintenance monotherapy.

As described below, the chemotherapy regimen used in RATIFY corresponds to current recommendations for management of newly diagnosed AML and recent guidelines suggest there is no advantage for idarubicin over daunorubicin.[1]

The recently updated 2017 ELN guidelines state that initial management of AML should involve induction therapy (one or two cycles) comprising three days of daunorubicin and seven days of continuous infusion cytarabine.[1] The daunorubicin dose ranges between 60 and 90 mg/m^2 per dose, and the clinical evidence indicates that the dose should not be less than 60 mg/m^2. The cytarabine should not exceed 1000 mg/m^2 daily during induction. In some centres daunorubicin is substituted with idarubicin at 12 mg/m^2 daily for three or four days. While one study has reported a higher CR for idarubicin compared with daunorubicin, no differences in relapse rates, event-free survival (EFS) or OS were noted.[6] The induction regimen used in RATIFY was daunorubicin (60 mg/m^2/day Days 1-3) plus cytarabine (200 mg/m^2/day Days 1-7) and thus corresponds to current recommendations for induction therapy. According to a survey of physicians in Western Europe who treat AML daunorubicin plus cytarabine was the most frequently used regimen; daunorubicin plus cytarabine (± etoposide) was used in approximately 50% of patients.[7] According to UK expert clinical opinion, cytarabine plus daunorubicin is the most frequently used regimen for newly-diagnosed AML although idarubicin is used in some patients <60 years; idarubicin is generally used in relapsed patients.

The 2017 ELN guidelines recommend 2–4 cycles of high-dose cytarabine or SCT as consolidation therapy. Thus the consolidation regimen used in RATIFY – high-dose cytarabine (3 g/m^2 iv every 12 hours on Days 1, 3 and 5) – corresponds to current ELN recommendations although the latter recommend use of a lower dose (1.0–1.5 g/m^2 iv every 12 hrs days 1–3 or once on days 1-5).

A11. Priority question: The data cut analysed was taken on 01 April 2015, before the prespecified number of events had occurred. Has the European Medicines Agency (EMA) requested a later data cut? Please provide a later data cut for overall survival (OS) and event-free survival (EFS) (Kaplan–Meier plots and analysis) if available.

The primary analysis of RATIFY (as reported in the submission) was conducted with a data cut-off date of 1st April 2015. A further update regarding OS has been performed with a cut-off date of 5th September 2016, representing an additional [redacted] months of follow-up compared to the primary analysis. During this time frame, [redacted] additional deaths occurred ([redacted] in the midostaurin

arm, and X in the placebo arm). The limited number of deaths confirms that in patients with newly-diagnosed AML few deaths occur after [redacted] years and hence there is a plateau effect.

The updated results for OS (non-censored for SCT) are provided in Table 6 and Figure 2. These data continue to demonstrate superiority of midostaurin over placebo. The KM survival estimates at specific time points demonstrate a consistent benefit for midostaurin over time, with the curves separating from [redacted] months onwards. The flattening of the KM curves around [redacted] years suggests that in this population there are a percentage of patients who are cured.

The data from the updated OS analysis are comparable to the earlier data-cut and would not impact on the cost-effectiveness evaluation.

Novartis has not performed a further analysis for EFS.

Table 6 Overall survival in RATIFY, non-censored at the time of SCT (FAS, data cut off, 5 September 2016)

	Midostaurin	**Placebo**
	N=360	N=357
Number of deaths (%)	[redacted]	[redacted]
Number of censored (%)	[redacted]	[redacted]
Alive at cut-off date	[redacted]	[redacted]
Last contact date within 6 months before cut-off date	[redacted]	[redacted]
Last contact date within 6 months - 1 year before cut-off date	[redacted]	[redacted]
Last contact date more than 1 year before cut-off date	[redacted]	[redacted]
KM estimates (95% CI)		
at 12 months	[redacted]	[redacted]
at 36 months	[redacted]	[redacted]
at 60 months	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]

Figure 2 Kaplan-Meier curve for OS in RATIFY, non-censored for SCT (FAS, data cut-off, 5th September 2016)

A12. Priority question: The very large difference between the median and mean OS suggests that the data have a very long tail. Please provide the individual patient data for OS or a waterfall plot of OS.

The large difference in the median OS between the two treatment groups is due to the plateau effect which occurred at [redacted] years – few deaths occurred after [redacted] years in either treatment group. In the placebo group [redacted] of patients died prior to [redacted] years. However in the midostaurin group [redacted] survival was not reached at [redacted] years and took much longer to be reached as few deaths occur after [redacted] years. The plateau effect does not affect mean values and hence the difference in mean OS for the two treatment groups is much less than for the median. The mean value is used in the economic model.

Figure 3 Waterfall plots of OS non-censored at the time of SCT for midostaurin and placebo

[redacted]

A13. Priority question: From the subgroup analyses reported in the CSR (figure 11-2, page 74) it can be seen that there is an OS benefit in men (hazard ratio [HR] 0.53 95% confidence interval [CI] 0.39-0.72) but not women (HR 1.01 95% CI 0.76-1.34). Please explain the difference in OS benefit between the 2 groups. Please provide the equivalent subgroup analyses censored for SCT.

Unexpectedly, the planned subgroup analyses by gender suggest a difference in treatment benefit in women and men regarding OS (Table 7). This gender difference has not previously been reported in the literature relating to the treatment of AML. However, women did benefit from the addition of midostaurin to the standard treatment of AML in terms of CR rate, EFS/DFS, and cumulative incidence of relapse (CIR). Furthermore, analysis of OS censored by SCT, in contrast, showed a benefit for midostaurin in both men and women, although the effect was greater in men (men: HR, 0.628, 95% CI 0.39, 1.02. women: HR, 0.899, 95% CI 0.59, 1.38). This suggests that differences in SCT or events occurring post-relapse and/or post treatment failure (as defined for EFS) could, at least in part, account for the difference in OS benefit observed for the men and women in the primary analysis of OS.

Post hoc data for NPM1 collected on a subset of patients confirmed that the results for OS within the subsets for the two genders are not due to an imbalance in NPM1 status across the two treatment arms. Novartis cannot exclude the possibility that it is just a random effect particular to the patients enrolled in this study. Overall, based on the improvements seen with midostaurin in terms of CR rate, EFS and CIR, midostaurin offers clinical benefit to female patients.

Table 7 Summary of evidence for a gender effects for the benefit of midostaurin, based on data from RATIFY

Endpoint	Overall	Males	Females	Gender effect
	95% CI	95% CI	95% CI	
OS (HR)	0.774 (0.629 – 0.953)	0.533 (0.392 – 0.725)	1.007 (0.757 – 1.338)	Yes
OS censored at SCT (HR)	[redacted]	[redacted]	[redacted]	[redacted]
CR induction (OR)	[redacted]	[redacted]	[redacted]	[redacted]
EFS (CR induction) (HR)	[redacted]	[redacted]	[redacted]	[redacted]
CIR (CR induction) (HR)	[redacted]	[redacted]	[redacted]	[redacted]

*Odds ratio calculated as (No complete remission in treatment/Complete remission in treatment) /(No complete remission in placebo/complete remission in placebo)

HR= Hazard ratio; OR=odds ratio

A14. Although the company submission and CSR state that patients in RATIFY were not to receive midostaurin monotherapy after SCT, please confirm whether or not any patients in RATIFY did receive midostaurin monotherapy after SCT (as in the phase II trial). Please also confirm how many (if any) patients received midostaurin after SCT. Please provide a commentary on whether it is anticipated that midostaurin monotherapy will be used post-SCT in clinical practice?

No patients in RATIFY received midostaurin following SCT. It is not anticipated that midostaurin monotherapy will be used post-SCT in clinical practice.

A15. Priority question: With reference to table 11-14, page 82 of the CSR please:

a) Explain why a large proportion of patients were not in CR when they received SCT. This appears to contradict the statement on page 111 of the company submission that states that, "only patients in CR could receive SCT prior to relapse in the clinical trial, as per current clinical guidelines".

The statement on p111 of the submission is incorrect i.e. the RATIFY protocol did not specify that patients would need to be in CR before undergoing SCT. Transplantation was not mandated in the protocol but was conducted at the discretion of the investigator. However, in the model it is assumed that only patients in CR would undergo SCT, as per current treatment guidelines.[1]

b) Clarify if first complete remission in table 11-14 is the same as CR1 in the company submission. Also, is it restricted to CR within 60 days?

First CR and CR1 both refer to the first complete remission achieved by the patient following initiation of therapy in the study. As per the footnotes to table 11-14, first CR in table 11-14 refers to CR achieved within 60 days of initiating therapy. (The equivalent data using the preferred definition for CR, i.e. occurring during induction, are summarised in Table 3 of this document.)

c) Explain what 'occurred after relapse' means. Did these patients receive SCT not in CR having relapsed? Or did the patients relapse on study treatment, achieve CR on alternative therapy, and then receive SCT?

"SCT after relapse" refers to patients who achieved a CR within 60 days of initiation of therapy, then relapsed and then underwent SCT (see footnote to table 11-14). Patients would probably have received further treatment (not study treatment) to achieve a CR before undergoing SCT but this information was not collected in the study. In the model it is assumed that patients with SCT post relapse, received second-line therapy and achieved CR before qualifying for SCT.

d) Tabulate the numbers of patients receiving SCT by the treatment phases (i.e. induction, consolidation and monotherapy) along with type of response to chemotherapy prior to SCT (e.g. complete remission, partial remission, or failure).

Responses to therapy were defined as complete response, partial response or treatment failure according to the IWG criteria. However, for the analyses, all patients not achieving a complete response were considered to be treatment failures.

The number of patients receiving SCT according to the treatment phase during which they discontinued from the study is given in Table 3 for patients who received SCT in CR1. As described in response A6, patients who received SCT other than in CR1 would first have discontinued from the study for another reason and hence their SCT would not have been related to any particular phase of treatment in the study.

A16. Priority question: From the data provided (tables 11-8 and 11-15 of the CSR) the ERG calculated that [redacted] patients in the midostaurin group and [redacted] in the placebo group died after receiving SCT. Please confirm whether this is correct.

This is correct. A total of [redacted] patients from the midostaurin group died and [redacted] of the deaths were in patients who did not undergo SCT. Similarly in the placebo group, [redacted] patients died and [redacted] of these deaths were in patients who did not undergo SCT. Thus [redacted] (midostaurin) and [redacted] (placebo) patients died following SCT. It is important to point out though that the deaths could have occurred a long time after receiving SCT. From a safety perspective deaths occurring post-SCT in patients who underwent SCT within X months of discontinuing study drug are considered to be relevant and are summarised in Table 8. There were more deaths in the placebo group.

Table 8 Summary of deaths in patients who underwent SCT within 2 months of discontinuing study drug and died within 100 days from SCT

Deaths	Midostaurin N=88	Placebo, N=86
No. of deaths, n (%)	[redacted]	[redacted]
Acute graft versus host disease	[redacted]	[redacted]
Cerebral haemorrhage	[redacted]	[redacted]
Graft versus host disease	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Transplantation complication	[redacted]	[redacted]
Venoocclusive disease	[redacted]	[redacted]
Acute graft versus host disease in intestine	[redacted]	[redacted]
Acute myeloid leukaemia	[redacted]	[redacted]
Cardiac failure acute	[redacted]	[redacted]
Mucormycosis	[redacted]	[redacted]
Multi-organ failure	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]

A17. Priority question: It is unclear from figure 11 (page 58 of the company submission) what 'first CR (those occurring within 30 days of the last treatment)' means.

a) Does it mean within 30 days of 1st induction or 1st or 2nd induction?

This means CR achieved anytime from randomization up to 30 days after the end of discontinuation of study treatment, see response to A8.

b) Does it exclude some patients who achieved CR and continued to consolidation/maintenance therapy? If so why and how many?

No, it includes all patients who achieved a CR during treatment.

c) Please confirm that CR1 is 'first CR', i.e. that the figure and the text relates directly to figure 11 (page 58 of the submission). If so, please explain why the numbers at risk in figure 11 do not correspond to the ones stated in the text.

CR1 is first CR.

Data from the RATIFY study have been analysed by Novartis using a data cut-off of April 2015 and have also been analysed by Alliance, the co-sponsor of the trial, with a data cut-off of March 2016. All data reported in the submission, except figure 11, relates to the Novartis analysis which included data activities to assure completeness of the data up to the data cut-off. The figure is taken from the Alliance analysis corresponding to a longer follow-up and hence includes greater number of patients.

A18. Priority question: Please provide additional Kaplan–Meier plots including the numbers at risk, HR, 95% CIs, and median survival for:

a) OS for all patients who received SCT

b) OS for all patients who did not receive SCT

c) Disease-free survival (DFS) for all patients who received SCT

d) DFS for all patients who received SCT in CR1

e) DFS for all patients who received SCT in other CR

f) DFS for all patients who did not receive SCT

The requested data are summarised in Table 9 and the KM plots are given below. We present DFS for all patients who received SCT after relapse. For DFS all patients who had a CR in induction were considered.

These data indicate that the improvement in OS seen with midostaurin therapy was broadly similar in patients who received and did not receive SCT. In addition, the improvement in DFS achieved with midostaurin therapy was comparable in patients who did or did not receive SCT. For patients who received SCT, the impact on DFS was greater in those who underwent SCT in CR1 compared with those who underwent SCT after relapse.

Table 9 Summary of OS and DFS data according to SCT status

Parameter	Midostaurin n/N	Placebo n/N	HR, 95% CI	Median OS/DFS, months (midostaurin vs placebo)
OS for all patients who received SCT	[redacted]	[redacted]	[redacted]	[redacted]
OS for all patients who did not receive SCT	[redacted]	[redacted]	[redacted]	[redacted]
DFS for all patients who received SCT (i.e. in CR1 and after relapse)	[redacted]	[redacted]	[redacted]	[redacted]
DFS for all patients who received SCT in CR1	[redacted]	[redacted]	[redacted]	[redacted]

Parameter	Midostaurin n/N	Placebo n/N	HR, 95% CI	Median OS/DFS, months (midostaurin vs placebo)
DFS for all patients who received SCT after relapse	[redacted]	[redacted]	[redacted]	[redacted]
DFS for all patients who did not receive SCT	[redacted]	[redacted]	[redacted]	[redacted]

Figure 4 OS for all patients who received SCT

[redacted]

Figure 5 OS for all patients who did not receive SCT

Figure 6 DFS for all patients who achieved CR during induction and received SCT

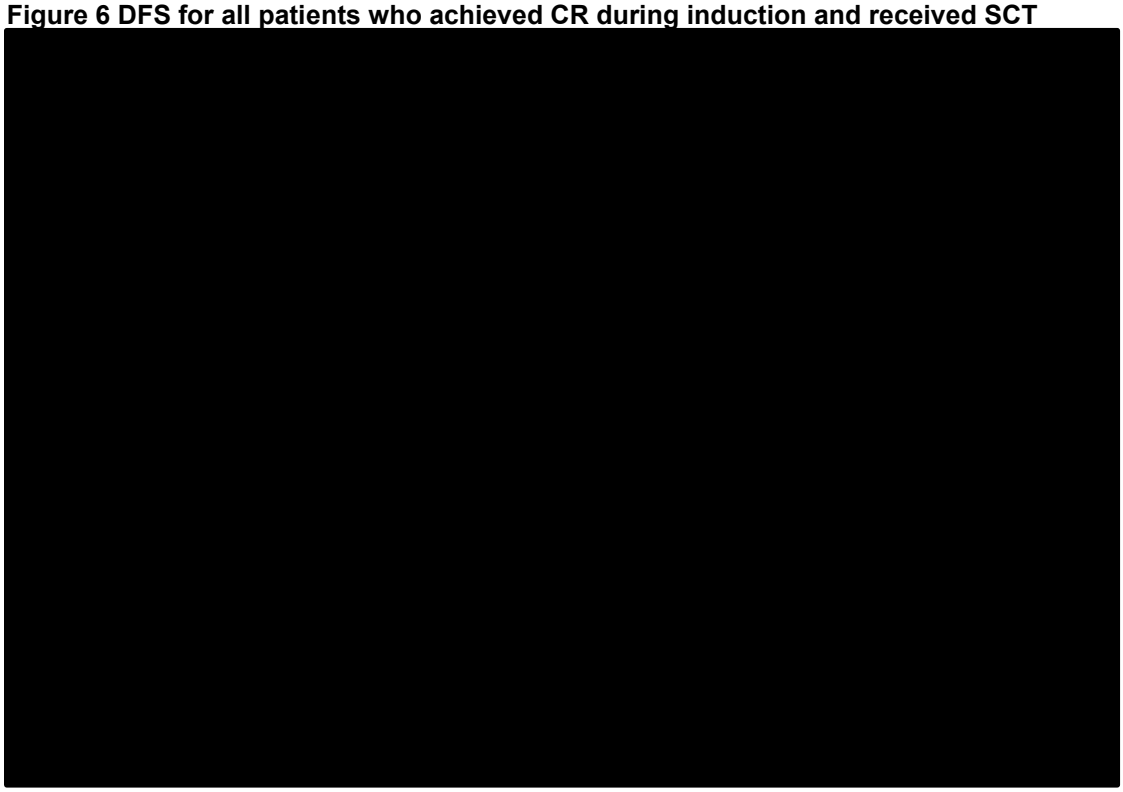


Figure 7 DFS for patients who achieved CR during induction and received SCT in CR1

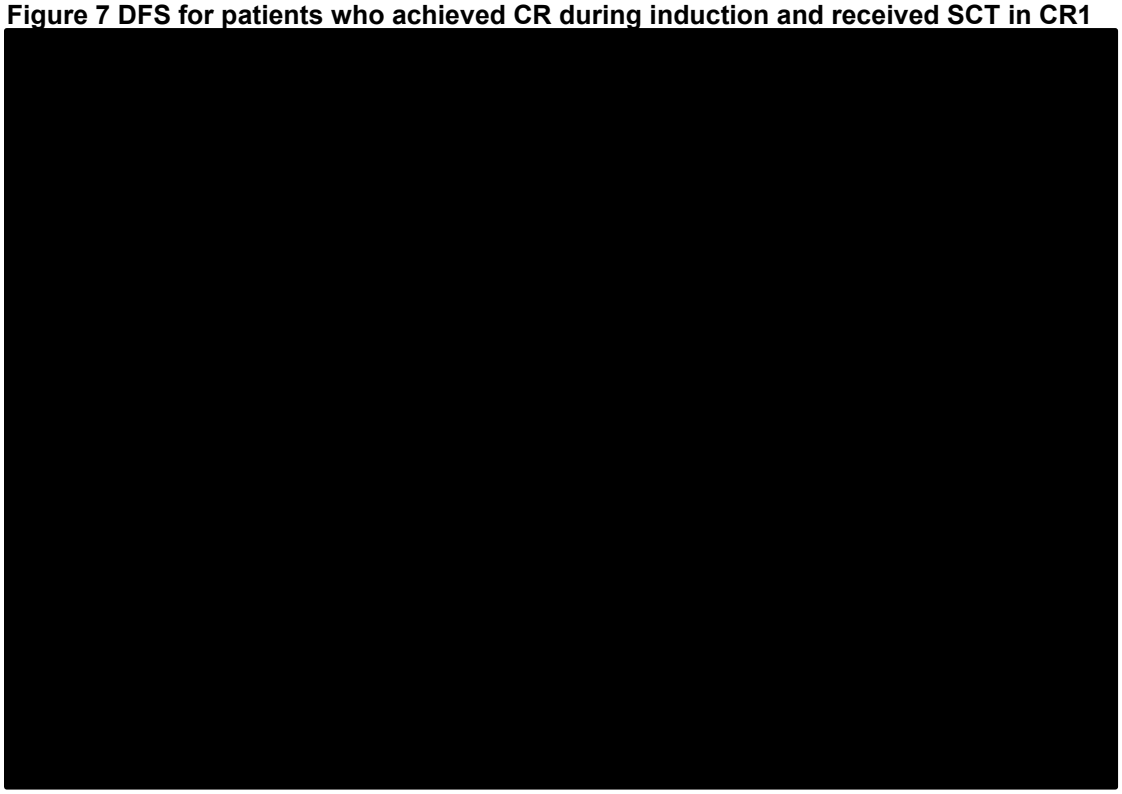


Figure 8 DFS for all patients who received SCT after relapse

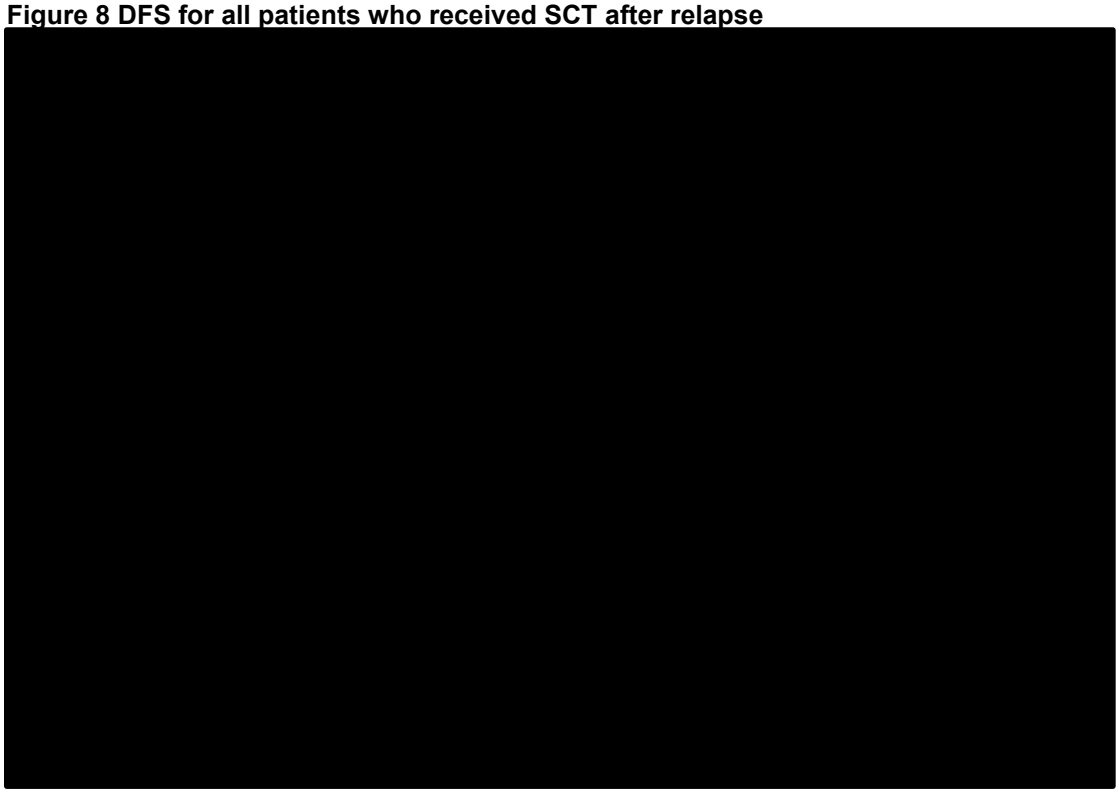
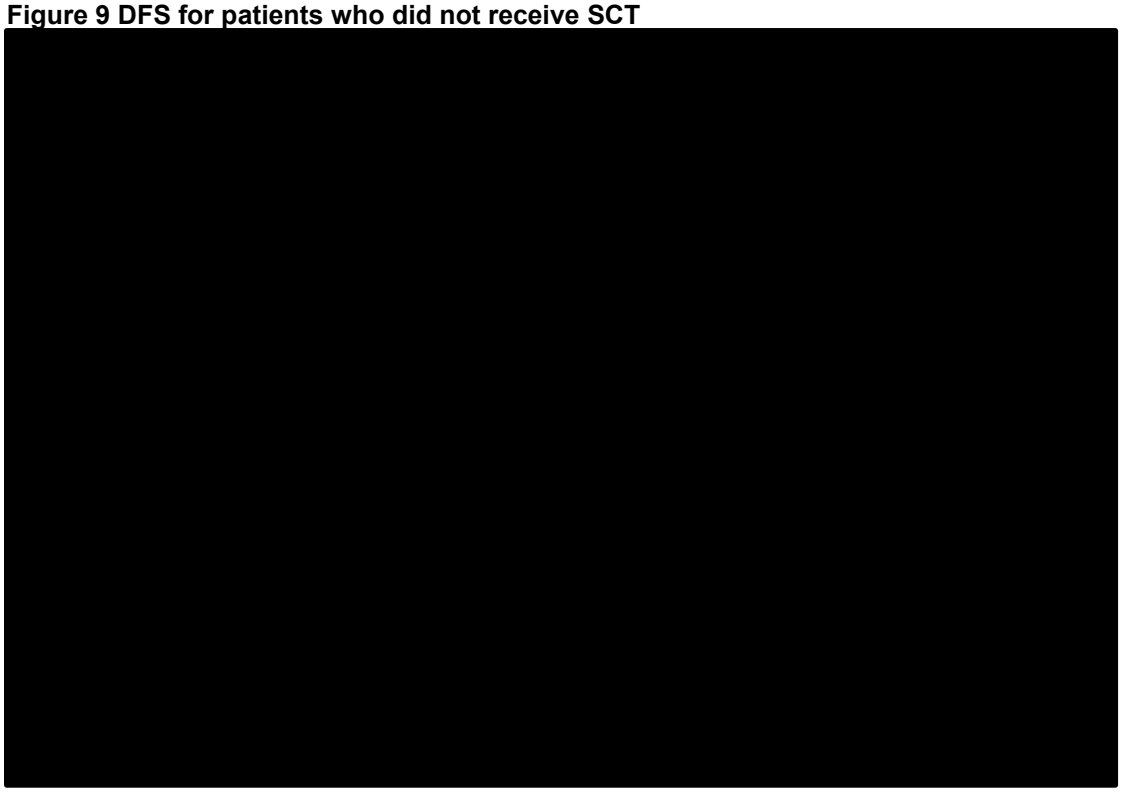


Figure 9 DFS for patients who did not receive SCT



A19. Regarding time since initial pathologic diagnosis, please comment on the baseline imbalance between the treatment groups and the much larger variability in the placebo group. Please also provide an explanation for the high maximum values recorded. If available, please provide these values for the per-protocol analysis set?

Table 10 Time since diagnosis for FAS and PPS

Time since initial pathologic diagnosis	Full analysis set			Per Protocol Set		
	Midostaurin	Placebo	All	Midostaurin	Placebo	All
N						
Mean (SD), days						
Median (range), days						

Median values are comparable for both treatment groups. Mean values only differ by [redacted] days (less than [redacted] week) between treatment groups and therefore the differences are unlikely to be clinically meaningful. The high maximum values recorded for both groups are outliers as evident from the low mean and median values.

B1. Priority question: The ERG has serious concerns regarding the model structure and treatment effectiveness inputs used to populate the model. These problems largely stem from the use of a partitioned survival model (PSM) which may not be appropriate to AML. The ERG considers the current model to lack face validity and in particular notes the following key issues:

- **The model does not allow patients to achieve complete remission (CR) beyond 60 days – this forces many patients into the residual relapse state where they stay for a prolonged period which is not reflective of clinical practice where patients are able to achieve CR on subsequent lines of treatment.**
- **Patients cannot relapse following stem cell transplantation (SCT) despite significant clinical evidence to the contrary. See for example Wingard et al, Journal of Clinical Oncology, 2011. It is also inconsistent with patients achieving complete remission via drug therapy who are able to relapse.**
- **Relapse patients in the post-cure cut off portion of the model appear to die very slowly and at near general population rates; the state of relapse is not compatible with this low mortality rate.**
- **CR patients in the post-cure cut off portion of the model appear to remain in the CR state as determined by the extrapolation of the event-free survival (EFS) curve. This is inconsistent with patients experiencing general population mortality as the EFS curve is censored for both death and relapse/loss of response.**
- **Patients who receive SCT are assumed to experience no post-transplant adverse effects.**

To address these significant issues with the model, please make the following amendments to the model:

- **Replace the CR time to event data currently used in the model, with data on the proportion of patients in CR during trial follow-up. The definition of CR for this input should not depend on how or when CR was achieved i.e. include clinical remissions as result of second and subsequent lines of therapy, but should be censored for SCT to avoid double counting of patients.**

Data on CR for second and subsequent lines of therapies (i.e. post-study treatment) were not collected during the trial. Only data on CR (whilst on midostaurin or placebo) were available and therefore used in the economic model.

In response to the ERG comment, we amended the model and replaced the CR time-to-event data used in the original submission with data on the proportion of patients in CR censored for SCT. Additionally, we added an option (E140 in model parameters) to modify the CR data to include CR in the trial follow-up (called the FAS). Whilst the uncensored CR partition could overestimate CR prevalence, the censored data could underestimate the CR prevalence by excluding patients that receive SCT several months after CR.

In our original submission the base case ICER was £34,327/QALY. Following changes requested by the ERG for B2, B3, B5 and B11, the ICER decreased from £34,327 to £33,672. These changes were implemented at this stage to correct for modelling inconsistencies identified by the ERG and raised in B2, B3, B5 and B11. The new base case includes CR censored for SCT (CR defined as occurring within 60 days). Following on from this, using CR at any time (instead of the first 60 days) and censoring the CR curve for SCT as requested by the ERG, changes the ICER from £33,672 to £26,507/QALY.

- **Replace the SCT time to event curve by a SCT time to event curve that is censored for both OS and relapse.**

The SCT time-to-event curve in the original submission was not censored for OS, but took into account the mortality of SCT patients (i.e., the patients who would be removed at time of death). Therefore, the data originally used was consistent with the SCT prevalence observed in the clinical trial and also accounted for mortality.

In the original model, the area under the curve would increase following a SCT flag in the trial and decrease when a mortality flag (after SCT) was reached. SCT relapse data were not collected directly in the clinical trial, i.e., only EFS events were recorded, and EFS events (without mortality) occurred after the SCT flag for 12 patients. If SCT relapse was censored for, some of the patients receiving SCT would be excluded from the analysis. Again, the prevalence of SCT would be significantly below the actual trial prevalence.

We believe the original approach of not censoring for OS to be more robust than censoring patient death which underestimates the prevalence and duration of SCT and leads to inconsistency with the patient level data from the Phase 3 study. The initial partition for SCT already excluded the patients who had a mortality event, rather than censoring them. As the censored data will never replicate the actual trial prevalence, the initial partition should be considered more accurate.

In our original submission, the base case ICER was £34,327/QALY. Following changes requested by the ERG for B2, B3, B5 and B11, the ICER decreased from £34,327 to £33,672. Following on from this, censoring the SCT time-to-event curve for OS as requested by the ERG, has limited impact on the ICER changing it from £33,672 to £33,306/QALY.

- **Add relevant adverse events related to SCT and incorporate their subsequent costs and disutilities into the executable model.**

We conducted a targeted literature search to identify Adverse Events (AEs) associated with SCT and disutilities resulting from these AEs. Graft Versus Host Disease (GVHD) was identified as the main AE leading to HRQoL decrements. According to Wingard, et al. (2011),[8] 39% of SCT patients experience GVHD, and a US-based electronic medical record study in 5240 patients with AML and SCT identified 2290 (43.7%) patients with GVHD (Novartis, DOF 2017). Peric, et al. (2016)[9] reported QLQ-C30 scores for patients undergoing SCT with and without GVHD. Using a previously published algorithm (Crott & Briggs, 2010),[10] we mapped the QLQ-C30 scores to the EQ-5D utilities and derived a disutility for GVHD (0.173).

The economic model was amended to include a 'GVHD complication' option for SCT patients. To incorporate the ERG's comment regarding use of an alternative source for cost of GVHD in order to represent the likely higher cost involved, we used a cost of £55,145, inflated from an estimate by Dignan F.L., et al.[11] Please note that routine care costs are excluded when this option is selected, as the routine care costs were included in the NHS calculation.

Some GVHD complication costs are likely to be included in the SCT costs, which could potentially result in double counting. As GVHD is a severe complication, an understanding of its potential impact is important and the inclusion of GVHD could be considered a conservative approach. It should be noted that a higher response in the midostaurin arm could represent lower GVHD prevalence or costs, although the model did not capture this.

In our original submission the base case ICER was £34,327/QALY. Following changes requested by the ERG for B2, B3, B5 and B11, the ICER decreased from £34,327 to £33,672. Following on from this, the addition of disutilities and costs associated with AEs relating to SCT as requested by the ERG, has limited impact on the ICER changing it from £33,672 to £36,339/QALY.

- **Following the trial follow-up period, the model should not use a PSM approach and patients should move to a natural history model populated using appropriate data. This model should preferably allow for the following:**
  - **Patients in the both SCT and CR health states should be able to transition to both the relapse and death health states,**
  - **The mortality rate in the relapse health state should be higher than for the CR and SCT health states.**

- **Patients in the relapse health state should be able to transition to the CR health state and/or the SCT health state.**

A partitioned survival model (PSM) approach was used to reflect the data available from the RATIFY trial. Whilst we acknowledge potential limitations with this approach as highlighted by the ERG (notably the lack of modelling of second-subsequent lines of therapies), we considered that the partitioned approach provided a more accurate estimate of OS compared with a state-transition model (STM) approach which would rely on a large number of assumptions that are not supported by the trial.

Whilst a state-transition approach could be considered 'in theory' more flexible, robust data are not available from the trial to populate such a model structure and therefore a large number of assumptions would be required which would deviate from the available trial data.

As previously mentioned, only data for CR following midostaurin or placebo were available from the trial. Data on CR following relapse were not collected. Whilst we agree that some patients may experience CR following subsequent lines of therapies, this information was not available and therefore, assumptions would be required. Furthermore, transitions between health states (CR, relapse, SCT and OS in second and subsequent lines are not available and therefore, assumptions would again be required.)

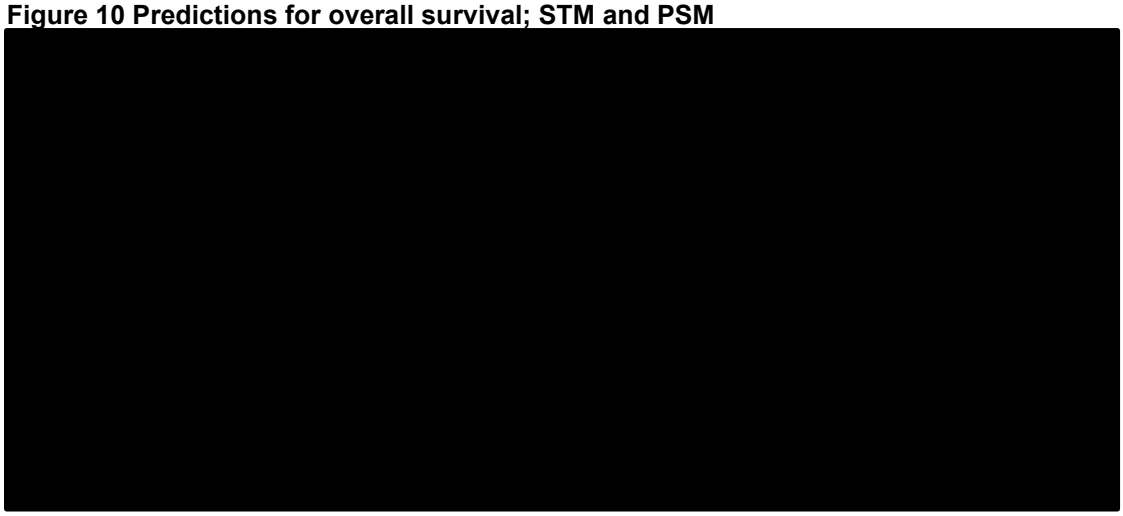
For transparency, in response to the ERG, we included an option where the extrapolated tail could be determined by a transition model, which could include transitions in any direction. The possibility of transition from both CR and SCT health states to relapse and death health states was included and were estimated from the RATIFY trial when possible. Notes on the transition model are included in the Appendix. It should be noted that the estimation of each of these transition probabilities are challenging. Relying on the literature to extrapolate the tail would create a model using a mix of various data, which can result in trend inconsistencies. Furthermore, very few relevant and robust long-term data exist for FLT3 patients, and the publications that do exist are often of inferior quality compared to the 717 patients within the RATIFY trial. Additionally, in the model, the CR health state corresponds to the CR whilst on midostaurin or placebo, and therefore, allowing patients to move from relapse to CR leads to inconsistencies as CR following relapse is unlikely to occur without further (non-trial) treatment.

In our original submission the base case ICER was £34,327/QALY. Following changes requested by the ERG for B2, B3, B5 and B11, the ICER decreased from £34,327 to £33,672. Following on from this, allowing patients to transition from relapse, SCT or CR to any of the other health states in the model as requested by the ERG, has a notable impact on the ICER changing it from £33,672 to £42,109/QALY.

However, this analysis should be considered exploratory and was presented to demonstrate the challenges associated with the STM. Despite some limitations, we consider that the PSM approach is more robust (when estimating OS) compared with the STM. The choice between PSM and STM is a trade-off between plausibility and detailed modelling of the pathway. We feel that the PSM provides a more accurate estimate of OS and therefore consider that the PSM represents the best estimate of the ICER.

Predictions for overall survival for placebo are compared below (Figure 10) using the PSM and STM approach. It can be seen that, using the STM, the OS curve drops quickly, in contrast with clinical opinion and expected OS in this population. As stated in the company submission, clinical experts considered that patients still alive by the time the trial ended would 'typically' experience the same rate of death as the general population.

Figure 10 Predictions for overall survival; STM and PSM



Additionally, discussion with clinical experts also lead to the conclusion that the PSM provides a more accurate estimate of OS for this population of patients.

In conclusion, whilst both approaches have strengths and limitations, we consider that the PSM, despite being simple, provides a more robust estimate of the ICER given the limited number of assumptions required and clinical validity of the OS prediction.

B2. Priority question: Please implement the half-cycle correction in the economic model.

As recommended by the ERG, a half-cycle correction was implemented in the amended PSM model. Additional modifications to the transition sheet, mainly in the QALY calculation and the % in each HCRU state, were needed to accommodate this option.

B3. Priority question: The economic model allows for the time at which patients are on primary therapy to be estimated from the treatment duration time to event data from the RATIFY trial. However this has not been correctly implemented. Firstly, when this scenario is selected using cell 'E43' on the 'Model Parameters' sheet, only the dosing schedule is adjusted. However, the corresponding outcomes such as costs must also be adjusted for the scenario to be correctly implemented. For example, some patients in month 2 will be receiving induction therapy, while others are receiving consolidation therapy resulting in patients in cycle 2 incurring different costs. The outcomes must therefore be weighted to account for patients being in different treatment phases at different time points in the model. Please adjust the outcomes with treatment duration time to event data and adjust the data using half-cycle correction.

The initially submitted PSM model was amended to include changes to the treatment duration partition as recommended by the ERG. The original model initiated each treatment phase according to schedule; the new treatment duration accounts for patients who start their treatment phases prior to schedule. This change did not lead to changes in the prevalence of treatment; however, the proportion of treatment at each cycle changed. The treatment usage/duration partition was weighted to account for patients in different treatment phases at different time points in the model. In this new model, patients can be in consolidation in cycle 2 and in the maintenance phase in cycle 6, to better fit the patient level data. See summary above.

While the available data was not designed to analyse the dosage this way and required a relatively complex method to render these data in such a way, we agree with your interpretation of the data and presented adjustments as close as possible to the request.

B4. Priority question: Please provide additional clinical evidence to support the assumption that the mortality rate following SCT will be same as the general mortality rate after the end of the trial. Several clinical studies have reported

lower estimates of long-term survival after SCT for AML patients (e.g. Wingard et al, Journal of Clinical Oncology, 2011; Bhatia et al, Blood, 2007; Shimoni et al, Journal of Hematology & Oncology, 2016) compared to the general population. Please incorporate additional flexibility in the Excel model to allow a higher standardised mortality ratio (SMR) to be applied in the post-Kaplan–Meier period compared to the general population. Please provide additional scenario analyses based on assuming higher SMR rates and with reference to existing clinical literature.

The ERG identified the Wingard and Shimoni studies that reported the probability of survival at 10 years after SCT to be approximately 84% for AML patients. Assuming an average age of 67 years old (UK average), the 10-year cumulative mortality rate of the general population in the UK would be 19.66%, which is close to the 16% reported in Shimoni and Wingard. Therefore we believe that using the rate of death from the general population to be a reasonable approximation of the rate for mortality post-SCT.

Given the modelling approach (PSM), it is not possible to only change the rate of death in patients receiving SCT, as OS is modelled directly from the overall trial population, and is not separated for patients receiving or not receiving a transplant.

However, for transparency, and in response to the ERG comment, an option was included in the model to vary the rate of death after the trial period (for the overall population). This is exploratory. In our original submission, a cure model was used after the end of the trial, using the rate of death from the general population. A scenario analysis is conducted varying the rate of death (after the end of the trial) by an arbitrary SMR of 2.00 to explore the impact on the ICER.

In our original submission the base case ICER was £34,327/QALY. Following changes requested by the ERG for B2, B3, B5 and B11, the ICER decreased from £34,327 to £33,672. Following on from this, using a higher SMR (RR of 2.00) for long term survival has limited impact on the ICER changing it from £33,672 to £34,102/QALY.

B5. Priority question: The calculation of per cycle rates has been incorrectly implemented in the model. This affects per cycle discount, adverse event and mortality rates. A per cycle rate is calculated as follows:

Per cycle rate = 1- EXP(LN(1-Annual rate)/cycles per year)

Please implement per cycle rates correctly in the model.

The model was amended to implement per cycle rates, except for the discounting rate where it is not normally applied. There is an option to apply the rate for adverse events, even if adverse event costs are applied linearly using a monthly rate in the model (cell E12).

The new formula is likely to over-estimate the AE rate for prevalent AEs (the total AE rate will be much higher than the trial rate for AEs with high prevalence using this formula). This option was tested in the summary above. As an example, the corrected rate for platelet count decrease in consolidation is [redacted] for 1 cycle, while the rate was [redacted] for the whole consolidation phase. The resulting calculation will be applied in the model.

- Cycle transition formula: [redacted] (affecting the cost proportionally)
- Linear calculation: [redacted]

The need to use the cycle transition formula for AEs and discounting is not clear to us. The method in which AEs are calculated in the transition model, as proposed by the ERG, might lead to a double counting of the AE costs if this assumption is used. However, for transparency, and in response to the ERG, we added an option to use the cycle transition formula for AEs and included the formula for mortality.

In our original submission, the base case ICER was £34,327/QALY. Following changes requested by the ERG for B2, B3, B5 and B11, the ICER decreased from £34,327 to £33,672. Following on from this, applying the cycle transition formula to the AE rates has limited impact on the ICER changing it from £33,672 to £33,905/QALY.

B6. Priority question: A significant proportion of people with AML in the UK are over 60 years old and it is plausible that some people over the age of 60 will be treated with midostaurin (conditional on the marketing authorisation and NICE recommendation). The population in the RATIFY trial, however, is restricted to people who are 18 to 60 years old and therefore the clinical data used to populate the economic model do not match with the likely eligible population.

- Please comment on the proportion of people over 60 who would be eligible to be treated with midostaurin should it be recommended.
- The ERG speculates that the incremental cost-effectiveness ratio (ICER) for patients over 60 will likely be higher than for a younger patient group as absolute benefits will be significantly reduced (because of a worse prognosis and lower life expectancy) while costs, which are mostly incurred upfront, will not fall as much. The phase 2 trial provides some limited data on the relative effectiveness of midostaurin in an older patient group. If possible, please use this data to implement a scenario analysis in the economic model to estimate the cost-effectiveness in a population more representative of the eligible population in the UK. If it is not possible to use the data from the phase 2 trail, please provide a commentary on what you expect the ICER would be for the older patient group.

As stated in question A1, whilst a proportion of patients with AML in the UK may be over 60 years old, midostaurin will be restricted to patients who are able to tolerate intensive chemotherapy. As previously stated, age alone is no longer considered the most critical factor in determining suitability to receive intensive chemotherapy. Patient fitness for intensive chemotherapy is generally considered more important than age, and this is related to factors such as performance status, functional status and comorbid conditions as well as age. Thus although it is expected that the marketing authorisation for midostaurin will not be restricted to younger patients, in clinical practice patients who would receive midostaurin are likely to be typical of those included in RATIFY in that most will have a performance status of 0 or 1. Thus we believe that the patient population included in RATIFY is likely to be representative of patients who would receive midostaurin in England and Wales.

Whilst we cannot rule out that a proportion of patients aged over 60 years will receive midostaurin, we believe this proportion to be relatively small.

Of note, data for the efficacy and safety of midostaurin in older patients (aged up to 70 years of age) are available from the phase 2 Schlenk study (rather than RATIFY), as reported in the submission. This more recent trial and registry data demonstrated reduced treatment-related morbidity and mortality and, indeed, significant survival gains compared to supportive care in fit patients ≥60 years.

Schlenk et al., 2016, reported that overall response after induction therapy was similar regardless of age (complete remission was observed in 76% of both younger patients [aged ≤59 years] and older patients [aged ≥60 years]), however, the risk of death was greater in the older population (10% versus 4%). Following SCT, the incidence of relapse and death was 13% and 16%, respectively, with no difference between older and younger patients (p=0.97 and p=0.41, respectively).

Whilst we believe that the population from the RATIFY trial is representative of people who would receive midostaurin in England and Wales, an exploratory scenario is presented for transparency in order to assess the potential impact on the ICER if a proportion of people were aged above 60 years.

It should be noted that this scenario is exploratory and presented for transparency. The proportion of people aged over 60 years old eligible for midostaurin is unclear, thus, we

arbitrarily assumed (for the sake of this exploratory scenario) that 50% of people eligible to receive midostaurin are aged above 60 years old. Whilst we expect this proportion to be significantly lower, this value was chosen to be conservative in the absence of robust evidence.

Within the PSM model, CR and SCT rate was assumed to be the same for people aged below and above 60 years old as demonstrated in Schlenk et al (2016). However, a SMR (of 2.5) was applied to OS to reflect the greater mortality rate in people aged over 60 years old. It should be noted for this exploratory analysis the SMR is only applied to the extrapolated tail beyond the trial period (within the cure model which assumes a mortality rate from the general population). This may be a limitation.

In our original submission the base case ICER was £34,327/QALY. Following changes requested by the ERG for B2, B3, B5 and B11, the ICER decreased from £34,327 to £33,672. Following on from this, including elderly patients has limited impact on the ICER changing it from £33,672 to £34,053/QALY.

B7. The subgroup analyses presented in the CSR (figure 11-2, page 74), show that there is an overall survival benefit in males (HR 0.53 95% CI 0.39-0.72) but not in females (HR 1.01; 95% CI 0.76–1.34). Additionally in the RATIFY trial, the proportion of women and ''white'' patients is different between the two treatment arms. Therefore, it could be possible that the baseline characteristics (covariates) have an impact on the overall survival. However, it is not plausible to predict the impact without a statistical modelling approach i.e. covariate adjustment.

- Please provide justification as to why covariate-adjusted survival analysis was not considered while estimating the clinical effectiveness (OS) in the executable model?
- Please implement covariate-adjusted survival analysis including the covariates which have significant clinical and/or statistical impact on OS (considering proportional hazard assumption as well as full parametric assumption).
- Please present the results as a scenario analysis.

As mentioned in question A13, the planned subgroup analyses by gender in the CSR suggested a difference in treatment benefit for women and men regarding OS, with men having a greater OS benefit than women. This gender difference has not been reported in the literature relating to the treatment of AML. However, women did benefit from the addition of midostaurin to the standard treatment of AML in terms of CR rate, EFS/DFS, and cumulative incidence of relapse (CIR). In contrast, analysis of SCT-censored OS showed a benefit for midostaurin in both men and women, although the effect was greater in men [redacted]. This suggests that differences in SCT or events occurring post-relapse and/or post treatment failure (as defined for EFS) account for the differences in OS benefit observed for men and women in the primary analysis of OS.

Gender was identified as a planned subgroup analysis rather than a stratification factor to be included in the ITT analysis. Whilst gender was a significant predictor of treatment effect, on its own (in the subgroup analysis), gender was no longer significant when included alongside age, ECOG and white blood cell in multivariate analysis in a Cox model.

Furthermore, the HR (for midostaurin vs. placebo) after adjustment is [redacted] versus [redacted] in the ITT analysis, which makes the two analyses identical in terms of results. Therefore, the resulting parametric extrapolations would be similar.

Consequently, given the absence of difference in the HR before and after adjustment for planned sub-groups including gender, no changes were made to the economic model.

B8. Priority question: Please provide additional clarity on calculation of SCT costs. The ERG has identified an alternative source of evidence (NHS Blood and Transplant, 2014) which suggests that the SCT costs are underestimated in the model. Specifically, the SCT treatment costs used in the model are much lower than the values in alternative evidence. Please implement the alternative source of SCT costs in the economic model and present as a scenario analysis.

The model was amended to incorporate new costs for SCT based on the ERG's suggestion. NHS Blood and Transplant (2014)[12] values were used and the results are presented in a scenario analysis. The cost in the NHS publication was £98,178 and we included a final cost of £110,930 to account for inflation. This cost includes personnel costs related to the surgery in addition to the follow-up routine care costs. Therefore, routine care costs are excluded when this option is selected (only physician visits were included for SCT), as these were included in the NHS calculation (for the first two years). See summary above.

The SCT process has evolved substantially since 2002 and is currently far more common. Therefore, inflating a 2002 cost to 2017 may overestimate the SCT cost. On the other hand, however, the NHS reference cost potentially excludes some of the SCT costs, though the more recent cost source is likely to be more accurate than the inflation of 2002 costs used in the NHS publication.

In our original submission the base case ICER was £34,327/QALY. Following changes requested by the ERG for B2, B3, B5 and B11, the ICER decreased from £34,327 to £33,672. Following on from this, using SCT cost based on NHS blood and transplant has limited impact on the ICER reducing it from £33,672 to £29,419/QALY.

B9. Priority question: Currently the economic model assumes significant ongoing health state costs (intensive monitoring) for patients in relapse, remission and post-recovery health states. Would such intensive monitoring would be required indefinitely, particularly in people who have been in remission/post-recovery for a long time?

- Please provide evidence that supports the inclusion of these ongoing costs in the current model.
- Please incorporate a scenario analysis in which monitoring costs are reduced after an appropriate duration of time to reflect the reduced monitoring required for patients in sustained remission?

As requested by the ERG, the model was amended to include an option to reduce monitoring costs. As per our interpretation of this question, we created an option reducing the routine care cost by a certain proportion, from a pre-specified threshold. Based on discussions with medical experts, the use of resources for AML survivors could be less, but evidence on the level of reduction is not available. We created an assumption that resource use would be reduced after 2 years, as KOL interviews indicated that the plateau observed after 2-3 years results from a population with better health status (lower mortality, lower relapse rate). The relapse rate and mortality were said to be lower in KOL interviews and the reduction would be 50%. The results are presented in a scenario analysis.

Reducing the routine care cost in the long run could create a realistic scenario when used with the cure model. For options with more aggressive OS curves (as in the transition option, for example) or short term routine care cost reductions, the reduction could lead to underestimation of the end of life curve.

In our original submission the base case ICER was £34,327/QALY. Following changes requested by the ERG for B2, B3, B5 and B11, the ICER decreased from £34,327 to £33,672. Following on from this, using a reduction in routine care costs in the long run (e.g. reduction of 50% after 26 cycles) has limited impact on the ICER changing it from £33,672 to £31,791/QALY.

B10. Priority question: Drug wastage as a result of mortality is not implemented in the economic model: the model does not reflect the drug wastage if people on treatment die mid-way through using a pack of tablets or chemotherapy. Please incorporate drug wastage as a result of death - assuming death will occur halfway through the model cycle - and present the results as scenario analysis.

The clinical data was not designed to easily evaluate the discontinuation caused by mortality or the treatment-free intervals. Most treatment discontinuation in the early days of the trial is caused by treatment-free intervals and switching to a subsequent treatment phase, rather than stopping treatment due to mortality (in the treatment arm only [redacted] patients died during their induction treatment and only [redacted] during consolidation, and in the placebo arm, [redacted] patients died in induction and [redacted] patients during consolidation). Furthermore, no patients in either treatment arm died during the maintenance phase. As a result, an adjustment for wastage based on the patient level data would potentially overestimate the proportion of patients dying during treatment. If such an option was properly applied, the adjustment would lead to a very small change in the results, since it is likely that the patient would be taken off their current treatment prior to mortality (i.e., relapse prior to mortality would be likely).

In the cohort model used, we track patients using their area under the curve and treatment duration. The cause of discontinuation, especially dose reduction, is difficult to evaluate. For example, if it is assumed that all patients who die waste 1/2 a pack, wastage will be overestimated, as only [redacted] patients out of 717 died during treatment, as presented in the data above. Indeed, if a patient dies during a treatment cycle, a portion of the pack could be wasted, but this fact applies to the comparator as well. The evidence suggests that the resulting changes would be very small and that wastage would potentially be overestimated.

Due to the potential bias of adopting this additional wastage approach, and the risk of overestimating wastage, the approach was not applied in the model.

B11. Please provide justification for omitting costs of drug monitoring tests and outpatient procedures (including transfusions). The evidence suggests that people with AML need close monitoring and testing for disease progression while on treatment (please see NICE technology appraisal guidance 399). Please implement additional costs of drug monitoring tests and outpatient procedures (including transfusions) for both arms in the economic model and present the results as a scenario analysis.

Specific additional drug monitoring is not required in relation to midostaurin therapy. Patients receiving midostaurin would require the same monitoring as that required for standard of care

therapy (i.e., laboratory tests performed before each cycle of therapy and every 3 months during maintenance therapy, based on clinical experts' interviews). The SmPC states that WBC should be monitored regularly, especially at treatment initiation; cardiac function should be monitored at baseline and during treatment; and patients should be monitored for pulmonary symptoms indicative of interstitial lung disease or pneumonitis.

Most patients in both treatment groups received platelet transfusions and red blood cell transfusions during each cycle of chemotherapy. The proportion of patients receiving transfusions was similar for the two treatment groups (see Table 11).

Table 11 Proportion of patients receiving platelet transfusions and red blood cell transfusions in RATIFY according to chemotherapy cycle

	Platelets		RBC	
	Midostaurin	Placebo	Midostaurin	Placebo
Induction cycle 1	[redacted]	[redacted]	[redacted]	[redacted]
Induction cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation cycle 1	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Consolidation cycle 4	[redacted]	[redacted]	[redacted]	[redacted]

Transfusions of red blood cells and platelets were added to the model as AEs for induction and consolidation. Transfusions were used as support during chemotherapy treatment and were not directly related to midostaurin, therefore the data were not collected during maintenance phase.

For the monitoring tests and the transfusions outside of induction/consolidation, the monitoring tests and transfusion utilization from ID829 was used as an option in the model. The midpoint between azacitidine and CCR from the Celgene HCRU questionnaire was used, as suggested by the ERG (Source: Celgene HCRU questionnaire; azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts [ID829]). The costs from ID829 were inflated to 2017. An option is available to include or exclude the monitoring costs. See summary above.

Total use of monitoring tests in the CCR arm

Unit costs

	Induction/pre-response	Remission	Stable disease	Progressive disease	Cost in 2013	Cost in 2017
Bone marrow aspirates	1.09	0.18	0.39	0.16	1.18	1.333
Bone marrow biopsies	0.46	0.00	0.06	0.02	1.18	1.333
Peripheral blood smears	1.05	0.68	0.80	0.76	3.00	3.390
Blood tests	11.26	2.69	7.18	7.78	3.00	3.390
DNA and RNA extractions for molecular testing	1.08	0.15	0.18	0.15	1.18	1.333
Extraction for cytogenetic testing	0.86	0.16	0.17	0.14	7.77	8.779
Serum blood chemistry	10.23	2.61	7.05	7.33	1.18	1.333
Red blood cell	0.00	0.44	3.03	4.67	121.85	137.677
Platelets	0.00	0.32	3.69	5.78	193.15	218.237

Source: Celgene HCRU questionnaire; Azacitidine for treating acute myeloid leukaemia with more than 30% bonemarrow blasts [ID829]

Final cycle cost of monitoring

	Induction/pre-response	Consoidation*	Remission	Stable disease	Progressive disease
Total	66.39	16.70	145.34	1,260.54	1,942.94

**Remission, excluding transfusion (already included in Aes)*

Additional drug monitoring was added to include additional potential costs, and to align with approaches used in the ID829 submissions.

In our original submission the base case ICER was £34,327/QALY. Following changes requested by the ERG for B2, B3, B5 and B11, the ICER decreased from £34,327 to £33,672 i.e. this ICER already includes the addition of drug monitoring tests and outpatient procedure costs.

B12. The costs of second-line therapy are not calculated using the individual patient level data from the RATIFY trial. Therefore, the costs of the second-line therapy is not representative of the actual agents and doses used in the two treatment arms within the RATIFY trial. Please provide a summary of the second-line therapies used in the RATIFY trial and implement in the cost-effectiveness model a scenario analysis in which the second-line treatment costs accurately reflect the second-line therapies used in the RATIFY trial.

Data on second-line therapies were not collected during the RATIFY study; hence it is difficult to suggest an accurate post-primary treatment market share. To obtain appropriate data for the UK setting, the Kantar Health data was used initially (physician survey), but it was determined during interviews with UK clinical experts that FLAG-Ida was the more suitable option for secondary therapy in the UK. Therefore, the average *duration* of FLAG-Ida was based on Kantar health data, and the use of FLAG-Ida was based on the clinical experts' interviews (Kantar Health. (2015). CancerMpact, AML report).[7]

B13. The cost of FLT3 testing is implemented in both the midostaurin and standard of care (SOC) arms in the model.

Based on clinical experts' interviews, all patients are already tested for FLT3 status in the UK regardless of midostaurin approval. FLT3 status is not only a disease progression predictor, but also an important prognostic factor for both the treatment effectiveness of chemotherapy and SCT. It is therefore needed for a proper diagnosis and an optimal treatment pathway selection.

Based on 50 UK physicians surveyed, the FLT3-ITD testing rate, as part of the standard molecular testing, is estimated at 98% (standard panel + separately) and FLT3-TKD testing rate at 75% (Source- Putnam Quant Research, Sep-Nov 2016; Q22-23. *Of the following biomarkers, which ones are included in standard molecular testing panel? Which specific ones do you typically order for AML (not as part of the standard testing panel)?*). Additionally, the analysis determined that in the UK: 64% of patients are tested at diagnosis, 8% before treatment, 4% during first treatment, 2% at failure, 8% at relapse, and 1% at another time point. Only 2% of the patients are not tested and 10% of the patients are tested multiple times (Source- Putnam Quant Research, Sep-Nov 2016; Q27. *In what percent of AML patients have you ordered these molecular tests?*)

Again, according to Putnam research performed on 230 physicians, fewer than 1% of patients would have unknown FLT3 status in the future (Source- Putnam Quant Research, Sep-Nov 2016; Q111. *What percent of your patients would you anticipate testing for FLT3 mutation in the future (when Product X becomes available) and at what point in treatment?*)

As presented above, the cost of FLT3 testing is already included in the treatment pathway, mainly to support decision making and risk assessment for chemotherapy course and SCT treatment. Additionally, based on the opinion of UK clinical experts and a UK physician survey, it was determined that since FLT3 testing is a part of routine practice, an option to include these tests only for patients on midostaurin would not be reflective of real life. Therefore, the approach proposed was not included in the model.

B14. On page 161 of the company submission, distribution of the treatment has been presented (figure 38). Please clarify what the treatment duration implies in this figure. Please clarify whether the figure refers to treatment with midostaurin or standard care.

The objective of this graph was to demonstrate the distribution of treatment duration for patients with a mortality event (i.e., its impact on the distribution of treatment duration) i.e. the graph presented in the original submission was for all patients, but with a mortality event. The graph was simply used to identify the proper distribution for the treatment duration in the PSA. The graph presents the treatment duration in days (x axis) and frequency, i.e. the number of patients (y axis). The duration of treatment is affected by relapse and mortality, so the distribution seems right-skewed

To provide an additional clarification on the distribution, the following graphs were included to show the same distribution but for all patients (dead or alive), regardless of their treatment.

It should be noted that the T-duration in days incorporates the treatment free-intervals: 7 days for each of the induction/consolidation cycles and spontaneous treatment-free intervals during maintenance therapy. Therefore, treatment duration (number of days in a treatment phase) is different from treatment exposure (number of days the patient received a dose).

All patients, any status

Patients receiving midostaurin, any status

Concluding Remarks

In summary, we consider that the Cure (PSM) model represents the most robust approach to evaluating cost-effectiveness. The initial base case submitted provided an ICER of £34,327. Taking into consideration the ERG's comments for B2, B3, B5 and B11, we agreed with these comments and made the necessary adaptations to give an ICER of £33,672/QALY. Further scenarios requested by the ERG have also been provided using the £33,672/QALY as a starting ICER. The below table (Table 12) summarises the adjustments made, and the resulting ICERs:

Table 12 Summary of ERG Revisions

Question #	Revision made	ICER result (per QALY)
Initially submitted base case	-	£34,327
New base case after ERG revisions (adjustment for B2, B3, B5 and B11)	-	£33,672
B-1a	Replace the CR time to event data currently used in the model with data on the proportion of patients in CR during trial follow-up	CR at any time and censored for SCT £26,507
B-1b	Replace the SCT time to event curve by a SCT time to event curve that is censored for both OS and relapse	£33,306
B-1c	Add relevant adverse events related to SCT and incorporate their subsequent	£36,339

Question #	Revision made	ICER result (per QALY)
	costs and disutilities into the executable model	
B-1d	Allow patients to transition from relapse, SCT or CR to any of the other health states in the model	£42,109
B-2	Implement the half-cycle correction in the economic model	Applied in new base case
B-3	Weight the outcomes to account for patients being in different treatment phases at different time points in the model	Applied in new base case
B-4	Use a higher SMR (RR of 2.00) for long term survival	£34,102
B-5	Apply the cycle transition formula to the AE rates	£33,905
B-6	Inclusion of elderly patients	£34,053
B-7	Covariate analysis and adjustment	Covariates were tested, and no notable difference between HR's before and after adjustment for important covariates were identified.
B-8	Use SCT costs based on NHS Blood and Transplant, 2014	£29,419
B-9	Reduce routine care costs in the long run (e.g. reduction of 50% after 26 cycles)	£31,791
B-10	Incorporate drug wastage as a result of death - assuming death will occur halfway through the model cycle	Due to the potential bias of adopting this additional wastage approach, and the risk of overestimating wastage, the approach was not applied in the model.
B-11	Include drug monitoring test and outpatient procedure costs	£33,672
B-12	Provide a summary of the second-line therapies used in the RATIFY trial and implement in the cost-effectiveness model a scenario analysis in which the second-line treatment costs accurately reflect the second-line therapies used in the RATIFY trial	Data on second-line therapies were not collected during the RATIFY study; hence it is difficult to suggest an accurate post-primary treatment market share. Based on interviews with clinical experts, FLAG-Ida was the more suitable for secondary therapy in the UK and was used in both the initially submitted base case and in the revised base case.
B-13	Justify using the cost of FLT3 testing in both the midostaurin and standard of care (SOC) arms	Based on clinical experts' interviews, all patients are already tested for FLT3 status in the UK regardless

Question #	Revision made	ICER result (per QALY)
		of midostaurin approval (part of routine practice).
B-14	Clarify the treatment duration figures	Addressed in the body of this document.

C1. Please provide the full details of the supplementary searches of conference abstracts (page 6, appendix 2): the date of the search, whether searched online or via paper copies, the method of the search – browsed or searched by keywords/search strings (please provide).

A conference search was conducted online on December 6th 2016 in order to identify all clinical evidence on interventional studies in acute myeloid leukaemia (AML). The purpose of the project was to include any relevant information from recent conferences. The search was conducted using the American Society of Hematology (ASH) and European Hematology Associations (EHA) websites. All abstract including the keyword AML or Acute Myeloid Leukaemia were screened. The relevance of each abstract identified from the website was based on the predefined selection criteria as follows:

- Population of interest: Patients with newly diagnosed FLT3-ITD-positive AML
- Interventions of interest: Cytarabine + daunorubicin; Cytarabine + idarubicin; Azacitibine; Mitoxantrone; Sorafinib; Quizartinib; Gemtuzumab ozogamicin/Mylotarg; Any intervention or comparator for economic and PRO review.
- Comparators of interest: Any active intervention of interest or placebo, or best supportive care.
- Outcomes of interest: Rates and mean duration of objective response (including overall partial, and complete response), rates and mean duration of overall survival (OS), progression-free survival (PFS), clinically-relevant PFS, disease-free survival, time to progression or treatment failure, HRQoL, rates and duration of adverse events (AEs), treatment discontinuations due to AEs or treatment-related AEs, treatment interruptions due to AEs, and dose modifications due to AEs for clinical review; economic model data, ICERs, QALYs, global health resource use, cost data of healthcare resource use for economic review; HRQoL data assessed by both generic and disease-specific instruments including the EQ-5D, FACT-Leu, EORTC QLQ-C30, EORTC QLQ-LEU, EORTC QLQ-CML, MDASI-CML, SF-12, and SF-36; utility scores; health state information, and patients satisfaction with treatment for PRO review
- Study design: Any RCT, non-randomized clinical trial, or observational study for clinical review; cost-effective evaluations and resource identification, measurement and valuation studies for economic review ;RCTs, utility, and a HRQoL studies for PRO review

Additional criteria: Conference abstracts were limited to 2014-2016.

C2. Please provide the full details of the trial registries search, including the date of the search and the search strings used.

A trial registry search was conducted on October 11th, 2016 in clinicaltrials.gov and the WHO International Clinical Trial Registry Portal search (WHO ICTRP) using the search term AML. 1246 records were identified in CT.gov and 2068 records were identified in WHO ICTRP (of which 883 were duplicates from the CT.gov search.

PICOS criteria were as follows: Population of interest:

- Patients with newly diagnosed FLT3-ITD-positive AML
- Interventions of interest: Cytarabine + daunorubicin; Cytarabine + idarubicin; Azacitibine; Mitoxantrone; Sorafinib; Quizartinib; Gemtuzumab ozogamicin/Mylotarg; Any intervention or comparator for economic and PRO review.

- Comparators of interest: Any active intervention of interest or placebo, or best supportive care.
- Outcomes of interest: Rates and mean duration of objective response (including overall partial, and complete response), rates and mean duration of overall survival (OS), progression-free survival (PFS), clinically-relevant PFS, disease-free survival, time to progression or treatment failure, HRQoL, rates and duration of adverse events (AEs), treatment discontinuations due to AEs or treatment-related AEs, treatment interruptions due to AEs, and dose modifications due to AEs for clinical review; economic model data, ICERs, QALYs, global health resource use, cost data of healthcare resource use for economic review; HRQoL data assessed by both generic and disease-specific instruments including the EQ-5D, FACT-Leu, EORTC QLQ-C30, EORTC QLQ-LEU, EORTC QLQ-CML, MDASI-CML, SF-12, and SF-36; utility scores; health state information, and patients satisfaction with treatment for PRO review
- Study design: Any RCT, non-randomized clinical trial, or observational study for clinical review; cost-effective evaluations and resource identification, measurement and valuation studies for economic review ;RCTs, utility, and a HRQoL studies for PRO review

A total of 2431 unique records were identified, of which 12 records were included in the review. Reasons for exclusion are as follows: Study design (148), Patient population (2072), Intervention (198), and Language (1).

C3. Please provide a source for the study design search filters for randomised controlled trials (RCTs) and non-RCTs used in the search strategy on pages 8-10 of Appendix 2.

OVID RCT study design filters were based on the BMJ OVID EMBASE and Medline combined randomised controlled trial strategies (http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html)

OVID RCT strategy:

25 "randomized controlled trial".pt.

26 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.

27 (retraction of publication or retracted publication).pt.

28 or/25-27

29 (animals not humans).sh.

30 ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.

31 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.

32 or/29-31

33 28 not 32

34 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.

35 RETRACTED ARTICLE/

36 34 or 35

37 (animal$ not human$).sh,hw.

38 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/

39 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/

40 or/37-39

41 36 not 40

42 33 or 41

- OVID non-RCT study design filters were based on BMJ RCT combination of the Medline and Embase Cohort study strategy (http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html)

OVID Non-RCT strategy:

54 exp cohort analysis/

55 exp cohort studies/

56 cohort$.tw.

57 exp longitudinal study/

58 exp prospective study/

59 exp follow up/

60 controlled clinical trial.pt.

61 exp case control study/

62 (case$ and control$).tw.

63 or/54-62

64 epidemiologic methods/

65 limit 64 to yr=1966-1989

66 63 or 65

References

1. Dohner H, Estey E, Grimwade D *et al.* Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017;129:424-447.
2. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidlines): Acute Myeloid Leukemia. National Comprehensive Cancer Network; 2016.
3. England population mid-year estimate. 2016 Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/timeseries/enpop/pop Acessed February 2017
4. Philippe P. Density incidence and cumulative incidence: a fundamental difference. *The Internet J of Internal Med* 2000;2:1-4.
5. Cheson BD, Bennett JM, Kopecky KJ *et al.* Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol* 2003;21:4642-9.
6. Gale RE, Green C, Allen C *et al.* The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. *Blood* 2008;111:2776-84.
7. Kantar Health. Future trends and insights: Western Europe. Acute myeloid leukemia. August 2016.
8. Wingard JR, Majhail NS, Brazauskas R *et al.* Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *J Clin Oncol* 2011;29:2230-9.
9. Peric Z, Desnica L, Durakovic N *et al.* Which questionnaires should we use to evaluate quality of life in patients with chronic graft-vs-host disease? *Croat Med J* 2016;57:6-15.
10. Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. *Eur J Health Econ* 2010;11:427-34.
11. Dignan FL, al. e. High Readmission Rates Are Associated with a Significant Economic Burden and Poor Outcome in Patients with Grade 3/4 Acute GvHD. *Blood* 2011;118:2061.
12. National Health Service Blood and Transplant. Unrelated donor stem cell transplantation in the UK. A Report from the UK Stem Cell Strategy Oversight Committee. November 2014, Available at: www.nhsbt.nhs.uk. Accessed May 2017.

Appendix: Important notes on the transition model

To include this option, many assumptions were required and some of these assumptions may conflict with patient level data. PSM have some limitations, for example, the health states are independent from the outcome, but transition models also have some severe limitations in this context. Mainly, a number of assumptions are required, which can lead to results that contrast with the trial results, or far greater or lower prevalence for SCT and CR can be generated. We believe that a PSM approach (using data from the trial) is more robust than an STM because it makes the best use of the available long term data and relies less on transitions based on assumptions. Data from RATIFY include CR1, relapse after CR1, SCT, and death but we have little information on patients with an EFS event, relapsing patients, and SCT patients.

The following cells should not be modified to avoid generating outcome results that oppose the patient level data:

- The transition model should be used only for tail extrapolation and not to replace the partition in the first 20 cycles.
- The threshold should be set at 40 cycles, as the transition rates were calculated based on this threshold.
- The cells C118 and J118 should be set at 0%, as patients should not be able to go to CR after SCT. CR or partial response is required prior to SCT.
- The proportion of patients going from SCT to CR (cells C117 and J117) should remain at 0%. The CR or partial remission rate after relapse is not available from the trial but, according to KOL interviews, the patients with sustainable CR2 will be transferred to SCT (available in the data). Forcing the inclusion of an assumption in C117 and J117 would indirectly increase the proportion of patients in SCT above the trial rate and potentially overestimate the proportion of relapsing patients with secondary response (double counting).

Please note that this option should only be used to extrapolate the model tail, i.e., optimally only after cycle 20, for 2 obvious reasons: (1) the patient level data is much more accurate for the early cycles (the actual uptake data is used instead of an assumption-based transition) and (2) technically speaking, the transition option only includes extrapolated health states, therefore, the treatment partitions, including the AML initiation health state, are not affected by this option.

Furthermore, since the uptake values for SCT and CR are driven by the partition, and if a threshold lower than 20 cycles is selected, the uptake/prevalence of SCT and CR could differ greatly from the trial data. Therefore, we recommend implementing this option at cycle 40 (we developed the transition data for this threshold). Cycle 40 was selected as the period-defining time point in the model because the trend seems to change between cycles 35 and 40. Therefore, we assumed that different transition rates were needed at that point, resulting in a transition model with 2 Markov matrices.

In summary, as patients transition to SCT and CR and then leave these health states, a standard approach should not be used to estimate the transition for the first 40 cycles. This option in the model should be used only for tail extrapolation and should be considered exploratory in nature. The following Markov matrices present the transition rates we used for the 2 periods featured in the model: prior to cycle 40 and after cycle 40 (based on patient transition data from cycle 40 to 69).

[redacted]

Additional data can be found in the model (transition and probabilities), but the formula for calculating the probabilities is the same as presented above: Per cycle rate = 1- EXP(LN(1-Annual rate)/cycles per year). The patients still in health states at cycle 40-69 were used to calculate the transition rate. However, it should be noted that the sample size is smaller as the transitions are smaller after cycle 40, i.e. [redacted]. The movement of patients in late stages is more accurate for extrapolation than the whole-time horizon, as the transition is better assessed after longer exposure to the health state and the disease.

Additional notes on the transition model:

- The model allows a transition from relapse to SCT and a transition from relapse to CR. The transition from relapse to CR was set at 0% for three reasons: (1) the data on secondary therapies and potential secondary CR were not collected during the trial, (2) according to clinical expert interviews, these relapsing patients would receive SCT and would not simply transition to CR, and (3) if we make assumptions on a proportion of patient transitioning to CR, we will be double-counting SCT patients, as the patients with CR after relapse most likely were the patients that received SCT (based on clinical expert interviews).
- The transition rates are based on actual patient level data; however, the sample size was relatively small for some health states. The Markov matrices for each arm were not developed and only one tail extrapolation matrix was developed for the following reasons: (1) as the patients are no longer treated at cycle 40, we avoided assuming a treatment effect, and (2) the sample size could be very small for some health states, so it would be technically difficult to estimate a robust transition for each arm. We included a matrix prior to cycle 40 for two reasons (1) to avoid generating errors in the model if cycle 30 or 35 was selected as a threshold (though we suggest that this option is not used), and (2) to show the evolution of the rates in time.
- An elderly population adjustment was also included in the transition matrix by increasing the risk of natural mortality 2.5 times.
- In the transition model, a standard Markov assumption was used, i.e., a fixed transition rate for the extrapolation tail and no adjustment for mortality, which leads to most of the patients dying within 10 years.
- The mortality rate is now differentiated per health state.
- The transition component is strictly exploratory and was not linked to the PSA (i.e., the transition rate will not be varied when the PSA is activated). This option was created to present an additional scenario.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Midostaurin for untreated acute myeloid leukaemia [ID894]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Leukaemia CARE

Your position in the organisation: [redacted]

Brief description of the organisation:

Leukaemia CARE is a national blood cancer support charity – founded in 1967 and first registered with the Charity Commission in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Our current membership database stands at approximately 18,500. This includes patients, carers, healthcare professionals etc.

Leukaemia CARE offers this care and support through our head office, based in Worcester and a network of volunteers all around the United Kingdom. Care and support is offered over eight key areas:

- 24-hour CARE Line
- Nurse Advisor Service
- Live chat (currently office hours only)
- Support groups
- Patient and carer conferences
- One-to-one phone buddy support
- Cancer campaigning and patient advocacy
- Information and booklets

Since its inception our CARE Line has taken many thousands of calls from patients, their carers, family and friends. Our website provides extensive information on all aspects of the blood cancer journey, running from diagnosis to what happens when treatment stops and includes emotional effects of a blood cancer and help for those caring for a patient. Our focus is providing

information and support for everyone affected by a diagnosis of blood cancer. See http://www.leukaemiacare.org.uk

Leukaemia CARE also works with other charities and policy/decision makers to campaign for the rights of all patients affected by a blood cancer to have access to and receive the best possible treatment and care when they need it.

Organisational Funding:

Over 85% of our total funding comes from our own fundraising activities and those of our volunteers. This includes a wide range of activities – such as legacies, community events, marathons, recycling campaigns etc.

Leukaemia CARE receives funding from a wide range of pharmaceutical companies, but in total those funds do not exceed 15% of our total income. Any funds received from the pharmaceutical industry are received and dispersed in accordance with the ABPI Code of Practice and the Leukaemia CARE code of practice. Our Code of Practice is a commitment undertaken voluntarily by Leukaemia CARE to adhere to specific policies that regulate our involvement with the pharmaceutical industry.

A copy of our code of practice is available at:

- http://www.leukaemiacare.org.uk/resources/code-of-practice

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: N/A

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Acute myeloid leukaemia (AML) is a rapidly progressing form of leukaemia. In 2014, there were 2,590 new cases diagnosed in England and 201 diagnosed in Wales. In 2014, there were 2,127 deaths in England and 130 in Wales.

This submission is informed by a patient survey of 373 adult AML patients (16+), carried out by Leukaemia CARE.

Symptoms experienced prior to diagnosis include fatigue (70%), feeling weak or breathless (56%), bruising or bleeding (31%), fever or night sweats (26%), bone or joint pain (24%) and frequent and repeated infections (21%).

The rapidly progressing nature of this condition means that 53% of AML patients are diagnosed via emergency presentation (NCIN/NCRAS routes to diagnosis report). This compares to a cancer average of 22%. Additionally, 79% of patients start treatment within a week of their diagnosis.

Being diagnosed with AML can also have a huge emotional impact, prompting patients (and their families) to experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation and depression. In our survey, 51% of AML patients reported that they have felt depressed or anxious more often since their diagnosis. The emotional impact does not affect the patient in isolation and is often also felt by carers and family members. This can place huge emotional strain on families and friends, many of whom may be affected by the diagnosis. As such, improvements in a patients' treatment and prognosis will also have a wider impact on the lives of their family and friends.

The most common symptoms encountered by AML patients since their diagnosis are fatigue (73%), feeling weak or breathless (51%), memory loss or loss of concentration (38%), bleeding and bruising (37%), itchy skin (35%), nausea or vomiting (35%), sleeping problems (34%), infections (32%), bone or joint pain (31%), weight loss (28%) and muscle pain (23%).

AML also has a wider practical impact, with 52% of patients experiencing pain as a direct result of their condition (31% occasionally, 17% regularly and 4% constantly). Additionally, 51% of patients have difficulty moving around (sometimes 27%, often 15% and always 9%) and 69% of AML patients have difficulty performing some of their daily routines, such as cooking or cleaning. Another 38% reported that they have problems taking care of themselves. Of those in work or education before their diagnosis, 77% have been impacted (32% reduced hours, 45% no longer able to work or continue education). Consequently, 53% of AML patients reported a negative financial impact as a result of having cancer (increased costs or reduced income).

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

When asked what they considered to be important features of a new treatment, AML patients listed: improved or longer survival (86%), improved quality of life (70%), a remission or response (61%), tolerable side effects (56%), improved blood counts or test results (50%), a reduced impact on carers or family members (42%) and certainty of available treatment data (31%).

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Current treatment for newly diagnosed AML patients is induction with daunorubicin and cytarabine, followed by high-dose cytarabine in the consolidation phase.

The most common side effects reported by AML patients were fatigue (76%), hair loss (54%), neutropenia (44%), diarrhoea (41%), sore mouth (40%), nausea or vomiting (39%), muscle or joint pain (34%), loss of concentration or memory (33%), constipation (29%), bone and joint pain (28%), sleeping problems (28%), anaemia (26%), weight loss (25%), fever (25%), bruising (22%), breathing difficulties (20%) and dizziness (20%).

Midostaurin would be used in addition to these treatments, as maintenance for patients who have achieved a complete remission, a new concept in AML.

AML patients have an extremely poor prognosis, with AML accounting for over half of all leukaemia deaths. Around a third of AML patients have the FLT3 mutation, which is a predictor of poor prognosis, with shorter survival than those without the mutation. There have been no significant treatment advances since the 1990s. As such, any improvements would be strongly welcomed by patients.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Midostaurin appears to offer the following benefits:

- Improved survival - OS (74.74 months v 25.59 months); EFS (8 months v 3 months) and reduced mortality risk
- Improved remission/response rates – complete remission rate (27 v 22)
- Higher transplant rate (58% v 54%)
- Oral treatment

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

See above

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

N/A

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

- Side effects – fatigue (76%), hair loss (54%), neutropenia (44%), diarrhoea (41%), sore mouth (40%), nausea or vomiting (39%), muscle or joint pain (34%), loss of concentration or memory (33%), constipation (29%), bone and joint pain (28%), sleeping problems (28%), anaemia (26%), weight loss (25%), fever (25%), bruising (22%), breathing difficulties (20%) and dizziness (20%).

Please list any concerns patients or carers have about the treatment being appraised.

The use of midostaurin as a maintenance treatment means that patients will have an elongated treatment period. However, this would be easily offset by the survival benefit it offers.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

N/A

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

X Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

We would question the overall survival data for the placebo arm of the RATIFY trial (25.59 months), which did not include any UK sites. We think this is an overestimate of the survival of patients in UK clinical practice.

This is echoed by the EUROCARE 5 data (http://www.eurocare.it/) which shows that AML survival in the UK is below the European Average. In England, five-year survival for males is approximately 93% of the European Average and for females it is approximately 89%. In Wales, five-year survival is 80% of the European Average for males, but data is not available for females.

On the available data, AML survival in the UK is approximately 90% of the European Average. As such, the likely survival for the placebo arm would be approximately 23.2 months for the three groups combined (and below 24 months for each group individually).

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☒ Yes ☐ No

If yes, please provide references to the relevant studies.

Leukaemia CARE patient experience survey of 373 acute myeloid leukaemia patients, unpublished. This was part of a wider survey of 2,519 blood cancer patients undertaken between September and December 2016.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being

or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

N/A

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

N/A

9. Other issues

Do you consider the treatment to be innovative?

X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Midostaurin is the first targeted treatment to show an improvement in overall survival for AML patients and the FLT3 mutation. Midostaurin also introduces the concept of maintenance treatment to AML.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- AML is a rapidly progressing form of leukaemia, with 53% of patients diagnosed via emergency presentation and 79% of patients starting treatment within a week of their diagnosis.
- AML patients have an extremely poor prognosis, with AML accounting for over half of all leukaemia deaths. There has been no progress in the treatment of AML since the 1990s. The FLT3 mutation is associated with aggressive disease and shorter survival.
- It also has a significant symptom burden (fatigue, feeling weak or breathless, memory loss or loss of concentration, bleeding and bruising, itchy skin, nausea or vomiting, sleeping problems, infections, bone or joint pain, weight loss and muscle pain), as well as a financial and emotional impact.
- The RATIFY trial did not have any UK sites. As such, the OS data for the placebo arm is not representative for UK patients, as UK survival for AML is lower than the European Average. Applying EUROCARE 5 data to the RATIFY comparator arm survival figure, we expect overall survival in this setting (for patients who do not receive midostaurin) to be approximately 23.2 months.
- Midostaurin is an oral treatment which offers improved survival (OS and EFS), complete remission rates and transplant rates.

NHS England submission on midostaurin in newly diagnosed FMS-like tyrosine kinase 3 (FLT3) acute myeloid leukaemia (AML)

1. NHS England notes that the median duration of survival for the control (placebo) group was over 2 years at 25.6 months and that there was no cross over allowed in the RATIFY trial. It also notes that in the economic model in the original company's submission the life years in the control group was 8.93 years. The ERG's preferred base case results do not state the life years but judging from the QALY figure, the number of life years must be greatly in excess of 2 years for the control group. The final company ICER results do not state the figures for life years. Whatever the survival for the whole population with FLT3 AML in England, the survival was in excess of 2 years for those fit for intensive chemotherapy in the trial. This figure would therefore apply to the type of patients that would receive such treatment in England.
2. NHS England welcomes the modest benefit associated with treatment with midostaurin and the fact that such benefit is seen at the expense of little in the way of additional toxicity. NHS England urges the company to price midostaurin to reflect the modest size of the survival benefit in FLT3 AML.
3. NHS England notes that the maximum of 12 months of maintenance midostaurin comes according to the company at 'no additional cost'. This is incorrect as for each month of midostaurin treatment, hospital Trusts would charge NHS England the monthly oral chemotherapy HRG tariff (£120) whereas no such payment currently occurs as there is no active maintenance therapy.
4. The costs of cytotoxic chemotherapy in the economic modelling were taken from the BNF. These costs should have been taken using eMit (electronic market information tool) although NHS England acknowledges that this will have made little difference to the ICERs.
5. NHS England notes that there were no UK patients in the RATIFY trial and thus the issue arises of generalisability. One (good) reason for the absence of UK patients is the very high recruitment rate to national AML studies in England which thus might have precluded English centres from wishing to enter patients.

[redacted]

NHS England [redacted]

November 2017

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Midostaurin for untreated acute myeloid leukaemia [ID894]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: NCRI-ACP-RCP

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

Not applicable

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Midostaurin for untreated acute myeloid leukaemia [ID894]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?

The standard therapy for younger AML patients (less than 60 years old), and fitter older patients (aged 60+) is an initial combination of induction chemotherapy consisting of Daunorubicin (60mg/m^2 -3 doses) with Cytarabine Arabinoside (ara-C) (100mg/m^2- 20 doses) given as a 10 day schedule- often referred to as DA eg. DA3+10. Upon achievement of remission patients receive a further course of DA therapy and then consolidation therapy in the form of 1/2 further courses of High Dose Cytarabine Arabinoside (HDAC) or allogeneic stem cell transplant. The decision to transplant is based upon a number of factors (age, cytogenetic findings, molecular profile, presenting WBC count, de-novo/secondary disease, response to initial therapy and the availability of a donor).

This technology is specifically targeted at the population of AML patients with a *FLT3* mutation – either an internal tandem duplication (ITD) mutation or a mutation within the FLT3 tyrosine kinase domain (TKD). Although the presence of *FLT3* mutations is routinely evaluated at diagnosis, the mutational status results are rarely available at the time of initiating therapy.

The combination of *FLT3* and *NPM1* (nucleophosmin) gene mutation status at diagnosis frequently influences the decision whether to offer allogeneic stem cell transplant as part of consolidation therapy in patients achieving a first complete remission. Approximately 50% of FLT3-ITD positive patients will be *NPM1* negative; this is considered a 'high risk' genotype (high relapse risk) and such patients will generally be transplanted in first remission. Most 'dual positive' (FLT3-ITD positive / NPM1 positive) patients will be treated with chemotherapy consolidation alone although practice may vary and is starting to be influenced by the monitoring of 'minimal residual disease' (such as NPM1 Q-PCR assays).

In the UK, a large proportion of these patients are currently recruited into the NCRN front line AML studies – currently AML19 for patients aged 18-60, AML18 for patients over 60 who are considered suitable for intensive therapy. Within the studies, choice of chemotherapy regimens will be determined by the trial protocol, including randomised treatment allocations. There is currently no inclusion of FLT3-targeted therapy with induction chemotherapy at the time of diagnosis for *FLT3* positive patient within in the NCRN protocols.

Is there significant geographical variation in current practice?

Not within England.

Are there differences of opinion between professionals as to what current practice should be?

Not in terms of initial induction chemotherapy, variation exists on the application of allogeneic transplant as the optimal consolidation (as above).

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

A number of other FLT3-targeted agents have been evaluated in clinical trials, including lestaurtinib (CEP701) and sorafenib but, so far, none have demonstrated a significant benefit in a randomised controlled study and none are currently licensed for this indication. Other 'second generation' FLT3 inhibitors, including quizartinib (AC220), crenolabib and gilteritinib, are currently undergoing phase III clinical trials in combination with chemotherapy in patients with newly-diagnosed *FLT3*-mutated AML.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

The technology is applicable to a specific sub-group of AML patients with a *FLT3* mutation. It is worth emphasising that the 2 main types of *FLT3* mutations (ITD and TKD) carry different prognostic associations. Approximately 20-25% of AML patients have *FLT3*-ITD at diagnosis; this is associated with increased relapse rate and poorer overall survival (partially offset if *NPM1* mutation also present). 5-8% of patients have a *FLT3*-TKD point mutation at diagnosis; TKD mutations are not generally felt to be associated with poor prognosis, but the pathogenetic effects of these mutations may also be potentially modulated by FLT3-inhibitory therapy.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

The technology is applicable to a specific sub-group of AML patients with a *FLT3* mutation.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

This would be used only in specialist secondary services- designated centres providing high-Intensity chemotherapy (NICE guideline 47- 2016).

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Midostaurin for untreated acute myeloid leukaemia [ID894]

Midostaurin is not currently available as a standard approach - Novartis do have a compassionate access programme for newly-diagnosed patients who are known to be *FLT3*-mutated; it is currently unclear if any UK sites have utilised this.

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

The current UK based AML treatment guidelines have not been updated in time to evaluate this technology. The European Leukaemia Network (ELN) guidelines were updated in 2017 and state that 'patients with FLT3 mutated AML may be considered to receive intensive chemotherapy with midostaurin'. This was based upon the RATIFY study (increased CR rate 66% vs 59% [p= 0.045] and OS [HR 0.77, p=0.0074].

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK.

Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The practical challenge for the NHS is in the timely evaluation of *FLT3* mutational status. Patients with newly-diagnosed AML need to commence induction chemotherapy on an urgent basis following diagnosis and, if being stratified for the applicability of FLT3-inhibitor treatment with induction, would need a mutation result to be available within 7 days. At present the UK is set up to deliver FLT3 mutation results within 2-3 weeks, the current purpose of the test being to give prognostic information that influences the planning of post-cycle 1 consolidation strategies. If midostaurin therapy were to become standard for FLT3-mutated patients, analysis would need to become more streamlined – whereas many labs currently 'batch' samples, PCR runs would need to be performed more frequently, often for single patient samples which would potentially drive up laboratory costs.

Midostaurin itself is a relatively well-tolerated, oral therapy which clinicians should be able to manage effectively. Although gastrointestinal toxicity was seen, especially in combination with chemotherapy at 100mg bd dosing, the recommended dose (50mg bd) has been well-tolerated in published clinical studies.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements

for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

As above - delay in mutational analysis turn-around times. Laboratory costs are likely to rise in order to achieve the necessary reduction in turn-around times for the timely implementation of midostaurin therapy.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

The principal clinical trial evidence supporting the efficacy of midostaurin in combination with chemotherapy in *FLT3*-mutated AML comes from the RATIFY study. At present this has still only been presented in abstract form (at the American Society of Hematology Annual meeting 2015) and not yet published in a peer-reviewed journal.

There were some differences in clinical practice in the RATIFY trial in comparison to standard UK practice (as described in question 1). In RATIFY, patients received up to 6 cycles of chemotherapy (2 induction and 4 consolidation) in comparison to 4 total cycles (or 3 in >60yrs) in standard UK practice. Many of the RATIFY patients only received a single induction therapy to induce remission, whereas 'double induction' is always standard in UK practice. Additionally the duration of cytarabine induction was only 7 days in RATIFY compared to 10 in the UK. Extrapolating from similar clinical trial populations in the UK, however (eg AML15, 17 study), overall remission rates and survival of *FLT3*-mutated patients and proportions of patients receiving allogeneic SCT in first complete remission were broadly similar. A small proportion of patients in the RATIFY study received maintenance treatment with midostaurin following completion of chemotherapy; it is not currently standard practice in the UK for AML patients to receive maintenance therapy following completion of chemotherapy treatment.

What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The endpoints within the RATIFY seem appropriate- primary endpoint being overall survival and secondary endpoints of complete remission, event and disease free survival.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

As outlined above, Midostaurin at the proposed dosing is well tolerated with a spectrum of side effects that are comparable to all the Tyrosine kinase inhibitors - a class of drug which clinicians are very familiar with managing. The reported gastrointestinal toxicity is manageable in the context of patients undergoing intensive chemotherapy.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Outside the RATIFY study, the published clinical evidence relating to the use of Midostaurin in AML is largely limited to phase I and II studies, either as monotherapy or in combination with hypomethylating agents, so less relevant to the question being considered here. We are not aware of relevant registry or nationally-coordinated clinical audits, certainly not in the UK population where there has been minimal Midostaurin use in AML to date.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

A high proportion of NHS staff (clinicians and nursing staff) are already familiar with 'Midostaurin like' therapy being combined with standard intensive chemotherapy through previous experience of oral FLT3-directed therapy (Lestaurtinib / CEP701) being added to chemotherapy for *FLT3*-mutated patients in the AML15 and 17 studies. Limited additional education would be required, comparable to the introduction of any new drug therapy into clinical practice,

The significant challenge to introduction is the impact on timely molecular diagnostic evaluation as outlined above.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. *Please let us know if you think that this appraisal:*

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

We do not believe there would be any such impact.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report

Midostaurin for untreated acute myeloid leukaemia

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD Name of TAR Centre
Authors	Robert Hodgson, Lead Health Economist, CRD
	Mousumi Biswas, Research Fellow, CRD
	Teumzghi Mebrahtu, Research Fellow, CRD
	Philip Morgan, Research Fellow, CRD
	Melissa Harden, Information Specialist, CRD
	Nerys Woolacott, Senior Research Fellow, CRD
Correspondence to	Nerys Woolacott, Senior Research Fellow, CRD, University of York, York YO10 5DD s
Date completed	30/06/2017

Source of funding

This report was commissioned by the NIHR HTA Programme as project number 16/108/05.

Declared competing interests of the authors

None.

Acknowledgements

We would like to thank Dr Eleni Tholouli, Consultant Haematologist and Director of the Adult Stem Cell Transplant Unit, Department of Haematology, Manchester Royal Infirmary for her expert clinical advice throughout the project.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

This report should be referenced as follows:

Hodgson R, Biswas M, Morgan P, Mebrahtu T, Harden M, Woolacott N. Midostaurin for untreated acute myeloid leukaemia: A Single Technology Appraisal. CRD and CHE, University of York, Technology Assessment Group, 2017.

Contributions of authors

Robert Hodgson, Mousumi Biswas, and Philip Morgan, wrote the cost effectiveness sections of the report. Mousumi Biswas conducted the economic analyses. Teumzghi Mebrahtu and Nerys Woolacott wrote the clinical effectiveness sections of the report. Melissa Harden wrote the sections on the search strategies. Nerys Woolacott and Rob Hodgson commented on drafts of the report and took overall responsibility for the clinical and cost-effectiveness effectiveness sections of the report respectively.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined

Copyright statement

Table of Contents

Table of Tables

Table of Figures

List of abbreviations

AEs	Adverse events
ALL	Acute Lymphocytic Leukaemia
AML	Acute myeloblastic leukaemia ()
ASH	American Society of Hematology
BID	Bis In Die (twice daily)
BNF	British national formulary
CEA	Cost-effectiveness analysis
CR	Complete remission
CR 1L	Complete remission after discontinuation of primary therapy
CS	Company submission
CSR	Clinical study report
DFS	Disease-free survival
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
ERG	Evidence review group
FGFr 1-3	Fibroblast growth factor receptor 1-3
FLT3	FMS-like tyrosine kinase 3
HRQoL	Health related quality of Life
HTA	Health Technology Assessment
SCT	Stem cell transplantation
ICER	Incremental cost-effectiveness ratio
ITD	Internal tandem duplication
LYS	Life Years
MDS	Myelodysplastic syndromes
MRD	Minimal residual disease
MOS	Median overall survival
NICE	National Institute for Health and Care Excellence
OS	Overall survival
ONS	Office of national statistics
PR	Partial remission
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSM	Partition survival model
RTK	Receptor tyrosine kinases
RBC	Red blood cells

RFS	Relapse-free survival
SAEs	Serious adverse events
SOC	Standard of care
SMR	Standardised mortality ratio
TKI	Tyrosine kinase inhibitor
TKD	Tyrosine kinase domain
TTO	Time trade off
VEGFR2	Vascular endothelial growth factor receptor
WTP	Willingness-to-pay
WBCs	White blood cells

1 Summary

Acute myeloblastic leukaemia (AML) is an aggressive haematological malignancy and is usually considered as a clinical emergency; without treatment, patients would die within 11–20 weeks of diagnosis, with mortality being due to complications such as serious infection and haemorrhage.

The signs and symptoms of AML are fever, fatigue, pain, shortness of breath, cough, bleeding and bruising, pallor and persistent or frequent infections.

In 2013, there were 2,467 new cases of AML in England and 196 in Wales. The age-standardised incidence for the UK was 5.0 per 100,000 population, and around 30% of them were FMS-like tyrosine kinase 3 (FLT3) mutant patients. There are two types of genomic alterations in FLT3 gene; FLT3/ITD and FLT3/TKD. People with FLT3+ve AML are considered at intermediate or high risk (mostly high risk) and standard treatment comprises intensive chemotherapy: induction with cytarabine plus daunorubicin, followed by consolidation with high-dose cytarabine and if appropriate (usually if complete remission is achieved) and possible, stem cell transplant (SCT) (usually allogenic).

Midostaurin is an oral, type III, multi-target receptor tyrosine kinase inhibitor (TKI) that acts on FLT3 and multiple other receptor tyrosine kinases (RTKs), including fibroblast growth factor receptor 1-3 (FGFr 1-3), KIT and vascular endothelial growth factor receptor (VEGFR2).

1.1 Critique of the decision problem in the company's submission

The population considered in the company submission (CS) are people with newly diagnosed, FLT3 mutation-positive AML, which exactly matches that of NICE scope. However, the anticipated product licence for midostaurin restricts the population to those suitable for intensive chemotherapy. Furthermore, the ERG notes that the RCT evidence submitted by the company, is restricted to people aged 18-60 years, which is a sub-group of the patient population described in the final NICE scope. Older patients are not well reflected in the clinical evidence submitted.

The intervention identified by the NICE scope and CS is midostaurin. The dosing and treatment schedule is not described in the NICE scope as the drug has not yet been licensed in the UK. However, the CS indicates that midostaurin is an oral therapy to be given in addition to standard chemotherapy. The anticipated recommended dose is 50 mg twice daily, with each 50 mg dose administered as 2 x 25 mg soft gel capsules. In the treatment of adult patients with newly diagnosed AML who are FLT3 mutation-positive, midostaurin is to be given on days 8–21 of induction and consolidation chemotherapy cycles, and is then taken twice daily as single-agent therapy for up to 12 months.

The comparator specified in the NICE final scope and in the CS is "Established clinical management without midostaurin". Although, the NICE final scope lists the most commonly used induction chemotherapies (cytarabine, daunorubicin, mitoxantrone, etoposide, idarubicin, and fludarabine), and consolidation chemotherapies (cytarabine, etoposide, amsacrine, and mitoxantrone), as comparator therapies, the clinical evidence in the CS included only cytarabine plus daunorubicin and high-dose cytarabine during induction and consolidation phases, respectively as a comparator. This comparator as well as being in line with NICE scope, is the standard intensive chemotherapy regimen used in NHS clinical practice.

The CS statement of the decision problem adheres to the clinical outcome measures specified in the NICE scope (overall survival, event-free survival, disease-free survival, health-related quality of life, and adverse effects of treatment).

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS included data from two non-randomised trials and one double-blind RCT (RATIFY). The trials investigated midostaurin in combination with an induction regimen of daunorubicin plus cytarabine followed by high-dose cytarabine.

The two non-randomised, non-comparative open label trials are inherently prone to bias, and can only be interpreted as supporting evidence. The phase Ib trial was largely about pharmacokinetics and dose determination of midostaurin. It is the only midostaurin trial to include both FLT3 mutant and FLT3 wild-type AML patients. The data indicate that midostaurin has some activity in FLT3 wild-type, as well as mutant positive AML. The phase II trial was a single-arm study that evaluated the midostaurin regimen that was later investigated in the phase III double-blind RCT (the licensed regimen). It provides the only data for the use of the licensed regimen in patients aged over 60 years (up to age 70 years). The results of this Phase II trial indicate that midostaurin treatment response is better in younger patients (< 60 versus > 60 years of age).

The RATIFY trial, a double-blind, multi-centre, RCT, compared the clinical effectiveness of the licensed regimen of midostaurin with placebo (in addition to standard intensive chemotherapy).

Based on the double-blind RCT, the median overall survival (primary outcome) was significantly longer in the midostaurin than placebo (74.7 months vs 25.6 months; HR: 0.77 (95% CI 0.63–0.95), p=0.0078), giving a median OS improvement of 49 months. The mean OS improvement was [redacted]. Results of analyses exploring the interaction of midostaurin with SCT, found that this benefit of midostaurin [redacted]

[redacted] the chance of a successful SCT. However, the quality of remission was not studied in the RATIFY trial.

A higher proportion of the midostaurin patients achieved complete remission (CR) than placebo although the difference was not statistically significant (58.9% vs. 53.5% ; one-sided p value = 0.073). Overall, a slightly higher proportion of patients in the midostaurin group, compared with the placebo group, underwent SCT (midostaurin=59.4% and placebo=55.2%), but the trial was not designed to assess this outcome. Median event free survival was significantly longer for those randomised to midostaurin (8.2 months (95% CI 5.4–10.7 months)) than the placebo than placebo (3.0 months (95% CI 1.9–5.9 months)). The median DFS was also longer in the midostaurin than the placebo group (26.7 months vs. 15.5 months, respectively).

The RATIFY trial results show that the safety profile of midostaurin is similar to placebo. Results from the phase II trial also show that midostaurin appears to have better safety profile in the younger patients than the older patients.

No other trials that assessed the clinical effectiveness of midostaurin or standard chemotherapy in the FLT3 mutant AML patient population were identified. Hence, no meta-analysis or indirect comparison was carried out.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic review presented in the CS used adequate methods to identify relevant studies of pharmacological treatments for newly diagnosed FLT3-positive AML. The CS search did not include all chemotherapy agents, but no relevant trial will have been missed due to the absence completed/published trials in the relevant patient group.

Of the trials identified, the phase Ib trial was largely about midostaurin dosing schedule determination (concomitant or sequential) and pharmacokinetics, and the phase II trial was also non-comparative study. Hence, the CS's evidence for clinical effectiveness is based largely on the double-blind RCT (RATIFY trial).

RATIFY is a good quality study but, due to the lack of strict specification of SCT and subsequent therapies and the necessary long follow-up in the RATIFY trial, there is some uncertainty around the size of the treatment effect of midostaurin. However, there is nothing to indicate that patients in the trial were not treated according to standard guidelines.

The RATIFY trial's methods and results may not be entirely generalisable to the NHS patients who would be eligible for midostaurin. The trial's population is adults 18-60 years of age whilst a large proportion (>60%) of AML patients to be treated in the UK are over 60 years. Therefore, the trial's

results may not be generalizable to the whole eligible population, or those over 60 years of age. Given that the only available data on older patients (up to age 70 years of age, the Phase II trial) found that treatment response was better in those under 60 years of age compared with those over 60 years, there is uncertainty about the size of the treatment benefit to be achieved with midostaurin in older eligible patients, who may be older than 70 years. This means that there is also uncertainty about the size of the effect for the whole eligible population (including all ages).

Patients in the RATIFY trial who did not achieve complete remission after first induction cycle underwent a second induction cycle with the same treatment whilst a different chemotherapy for the second cycle may be used in UK practice. Hence, the treatment scheduling may not represent practice in the UK. Consequently, the effect size seen in the trial may not be achieved in clinical practice.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's economic submission included a systematic review of published evidence on the cost-effectiveness, health-related quality of life, resource use and costs associated with midostaurin in the treatment of AML. The review identified a number of economic evaluations of other therapies for AML, including UK based economic evaluations, but did not identify any relevant economic assessments of midostaurin.

The cost effectiveness of midostaurin was informed by an economic evaluation conducted by the company. The company's model uses a partition survival model approach or "area under the curve" analysis. This type of model directly uses the time-to-event data from a clinical trial to determine the distribution of patients between the health states. The model structure consisted of five health states: (i) AML diagnosis/induction; (ii) complete response/remission (CR); (iii) relapse, (iv) stem cell transplant (SCT), and (v) death. The CR health state is split into three further sub-states, indicating the phase of treatment a patients is in: consolidation, monotherapy, and CR post discontinuation of first line treatment (CR 1L). The SCT health state is similarly split into series of tunnels states, these states consisted of SCT treatment, SCT recovery, and post-SCT recovery. The efficacy data, treatment and comparator dosage, duration of primary therapy, adverse event rates and patient characteristics (age, weight, body surface area) used in the economic model were sourced from the RATIFY trial, with the remaining inputs informed by studies identified in the cost-effectiveness review and other sources Overall survival, within the first 80 cycles (~6.2 years) of the model, was estimated using Kaplan-Meier data from the RATIFY clinical trial. Thereafter, patients were assumed to be cured and experienced general population mortality.

The company found midostaurin to be more costly (cost difference of ££[redacted]) and more effective ([redacted] QALY gain) compared with standard of care. The deterministic base case ICER was £33,672 per QALY, and the mean probabilistic ICER was £33,273 per QALY. The predicted probability that

midostaurin was cost-effective compared with standard care was 42.7% at cost-effectiveness threshold of £30,000 per QALY and 86.3% at a cost-effectiveness threshold of £50,000. The majority of the QALYs gained were generated as a result of additional life years. The company reported that the most influential parameters in the one way sensitivity analysis included the rate of SCT, variations in the midostaurin overall survival hazard ratio, differences in CR rate, and discount rates.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The economic analysis presented by the company was inadequate to fully address the decision problem specified in NICE's scope. The structure of the model, although accommodating key elements of the treatment of AML, contained a number of significant structural flaws meaning that the model lacks face validity. These issues stem primarily from assumptions made regarding the modelling of patients with refractory and relapsed AML. These patients are assumed to remain within a health state, defined with respect to the acute treatment of these patients, and does not accommodate response to subsequent treatment. The impact of these structural failures in the model is significant and is likely to underestimate the ICER.

The ERG is also concerned about the cure assumption used in the model, which assumes that after 80 cycles (~ 6.2 years) all patients are cured and will experience general population mortality rates. The ERG acknowledges that this is a common assumption applied within existing models in the general area but considers that this assumption is subject to significant uncertainty. The ERG's specific concerns relate both to the timing of the cure point, and the assumption that patient experience general population mortality after this point. The choice of cure point is a key driver of cost-effectiveness as survival gains observed at the cure point are extrapolated over an entire lifetime. The cure point selected, however, was based arbitrarily on the end of the trial, and alternative cure points were not explored in the scenario analysis carried out by the company. The ERG considers this a key area of uncertainty, with potentially significant implications for the estimated ICER. With respect to the assumption that patients revert to general population mortality the ERG notes that several clinical studies have formally assessed the long-term survival of AML patients and have consistently reported higher long-term morality rates amongst survivors compared to the general population. This assumption is likely to lead to an overestimation the benefits of cure and as a consequence, the cost-effectiveness of midostaurin.

The ERG raised concerns about the representativeness of the patient population modelled which was based on patients enrolled in the RATIFY trial. The population recruited to the RATIFY trial excluded patients over the age of 60 and therefore excluded a significant proportion of patients potentially eligible for treatment with midostaurin. Exclusion of this high-risk group of patients is likely to have created a more favourable treatment effect for midostaurin in the primary efficacy analysis, with a commensurate effect on cost-effectiveness. Further, given the potential for cure, the

benefit of treatment with midostaurain will be lower in an older population compared with a younger population due to the fact that older patients on average have fewer years to live than younger patients. Extrapolation of the cost-effectiveness results for younger patients to an older population is therefore not appropriate and the ERG consider it is likely that midostaurain will be less cost-effective (higher ICER) in older patients.

The ERG identified several areas of uncertainty regarding the utilities assigned to some of the health states used in the model. It also had concerns regarding the choice of utility values applied to long-term survivors as they implied that the HRQoL of survivors would, in time, exceed that of the general population.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Clinical effectiveness

The main clinical effectiveness was derived from a directly relevant, good quality RCT, the RATIFY trial. The results of this trial provide reliable evidence of a clinically and statistically benefit of midostaurin in overall survival; the median survival benefit is 49 months and the mean benefit is 6 months

Cost-effectiveness

The company's economic submission met the requirements of the NICE reference case. The company submission was informed by data from a high quality RCT which had an extensive follow up period. The economic model accommodated a number of key clinical elements of the treatment of AML and incorporated a range of scenario analyses that allowed the impact of alternative assumptions to be explored.

1.6.2 Weaknesses and areas of uncertainty

Clinical effectiveness

As stated in Section 1.3, due to the lack of strict specification of SCT and subsequent therapies and the necessary long follow-up in the RATIFY trial, there is some uncertainty around the size of the treatment effect of midostaurin.

Whilst both median and mean benefits in overall survival are clinically significant, they are discrepant: 49 months and [redacted] months respectively. This is because of the plateauing of the curves and, in part, the impact of SCT on survival.

There is uncertainty around the treatment effect of midostaurin in older, yet fit FLT3-positive patients, suitable for intensive chemotherapy.

It is also uncertain that the effect size seen in RATIFY would be replicated a trial that included the full age range of eligible patients, i.e. those suitable for intensive chemotherapy but not restricted to no older than 60 years of age.

It is also uncertain that the effect size seen in RATIFY would be replicated in a trial in which patients who did not achieve complete remission after first induction cycle, underwent a second induction cycle with a different chemotherapy as may happen in UK practices.

Cost-effectiveness

The principle weakness of the economic evidence submitted by the company relates to the model structure adopted and, in particular, a failure to appropriately model patients with refractory and relapsed AML. The ERG also had substantive concerns relating to the health state costs used for patients who have achieved remission and discontinued therapy/received SCT.

There are three significant areas of uncertainty in the cost-effectiveness analysis. The first relates to the additional survival gains in patients who have achieved cure for which there is limited, weak evidence to inform assumptions. The second relates to uncertainty regarding long-term health-related quality of life of patients who achieve long-term remission, both with and without SCT. The third concerns the age of the population eligible for treatment with midostaurin.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a series of exploratory analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. The most of important these scenarios related to changes made by the ERG to the model structure; the ERG analysis explored a number of iterations of the model in which alternative assumptions regarding the model structure were made. The results of this analysis demonstrated that these structural issues have a significant impact on the ICER, see Table 1. The ERG also presented an alternative base-case based on a combination of a number of these scenario analyses. The ERG's base-case makes the following amendments to the company's revised base-case:

1. Corrections for calculation errors;
2. Addition of new OS data;
3. Addition of original CR data;
4. ERG's preferred model structure;
5. Applies a four-fold risk ratio to post cure mortality;
6. Applies age adjusted utility decrement into the model;
7. Increases the maximum number of cycles of monotherapy to 18;
8. Assumes total number of units of therapy matches the original company model;

9. Incorporates adverse events resulting from SCT.

The results of these scenario analyses including the ERG's base-case are summarised in Table 1 Summary the relevant amendments to the company's revised base-case and impact of those amendments on the ICER

Table 1 Summary the relevant amendments to the company's revised base-case and impact of those amendments on the ICER

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	***Midostaurin therapy***	[redacted]	[redacted]	[redacted]	[redacted]	***£28,465***	*n/a*
	SOC	[redacted]	[redacted]	[redacted]	[redacted]	-	-
ERG's preferred model structure	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£39,720	£11,255
	SOC	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Four-fold increase in risk of mortality	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,899	+£434
	SOC	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Up to 18 cycle of monotherapy	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,569	+£104
	SOC	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Discrepancy in total units of treatment corrected	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£30,904	+£2,438
	SOC	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Age adjusted utility decrement	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£30,354	+£1,889
	SOC	[redacted]	[redacted]	[redacted]	[redacted]	-	-
SCT related AE's	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£30,869	+£2,404
	SOC	[redacted]	[redacted]	[redacted]	[redacted]	-	
ERG's preferred base case	***Midostaurin therapy***	[redacted]	[redacted]	[redacted]	[redacted]	***£62,810***	***+£34,344***
	SOC	[redacted]	[redacted]	[redacted]	[redacted]	-	-
$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care							

The ERG base-case analysis estimated midostaurin to be more costly (cost difference £[redacted]) and more effective ([redacted] QALY gain) compared with standard of care and suggests that the ICER for Midostaurin compared with SOC is around £62,810 per QALY.

The ERG also carried out a further series of exploratory analyses to explore the impact of alternative assumptions regarding the selected cure point, long-term health-related quality of life of patients who achieve long-term remission, and the average age of patients eligible for treatment with midostaurin. These analyses indicate that the ERG's base-case ICER is likely to represent a lower bound with the majority of analysis's resulting in increases in the ICER; range £53,718 and £92,619 per QALY, assuming the ERG's base-case assumptions.

2 Background

2.1 Description of the technology under appraisal

The company submission (CS) states that midostaurin is an oral, type III, multi-target receptor tyrosine kinase inhibitor (TKI) that acts on FMS-like tyrosine kinase 3 (FLT3) and multiple other receptor tyrosine kinases (RTKs), including fibroblast growth factor receptor 1-3 (FGFr 1-3), KIT and vascular endothelial growth factor receptor (VEGFR2). Midostaurin inhibits the FLT3-receptor signalling in leukaemic cells that express FLT3 internal tandem duplication (ITD) or tyrosine kinase domain (TKD) mutant receptors, leading to cell cycle arrest and apoptosis.

The CS also states that midostaurin is taken orally twice daily on days 8–21 of the 28-day induction and consolidation chemotherapy cycles, and twice daily as single-agent therapy for up to 12 months following combination treatment.

Midostaurin does not currently have UK marketing authorisation and does not have regulatory approval in the EU; however, it has been approved by the US FDA and in Switzerland. Midostaurin was granted orphan status for the treatment of acute AML by the European Medicines Agency (EMA) in 2004 and by the US Food and Drug Administration in 2009. A marketing authorisation application for midostaurin, in combination with chemotherapy followed by midostaurin monotherapy as treatment for adult patients with newly diagnosed AML who are FLT3 mutation-positive, was submitted to the EMA in July 2016. The CS states that an opinion from the EMA is expected in October 2017.

2.2 Critique of company's description of underlying health problem.

The manufacturer presented a brief definition, epidemiology, diagnosis and prognosis of the health problem.

2.2.1 Definition and pathophysiology of AML

The CS states that AML is an aggressive haematological malignancy and is usually considered as a clinical emergency.[1, 2] Without treatment, patients would die within 11–20 weeks of diagnosis; treatment should therefore be initiated as soon as possible, ideally within a matter of days of diagnosis.[3]

The CS also states that AML develops as a consequence of a series of genetic changes in haematopoietic precursor cells. In AML, immature monocytes and granulocytes are overproduced by the bone marrow and do not develop into leukocytes. Normal white blood cells (WBCs) are therefore replaced by leukaemic cells that have a diminished ability to defend against infection. The production of normal blood cells is decreased – resulting in anaemia, thrombocytopenia and neutropenia – and

the overproduction of abnormal, immature cells, leads to an accumulation of leukaemic blood cells in the bone marrow, peripheral blood, spleen and liver.

The CS states that research into understanding the role of FLT3 and factors that may cause its overexpression have identified that genetic alterations to the FLT3 gene (FLT3 ITD and FLT3 TKD mutations) are common in a number of haematological malignancies, implicating this RTK in AML pathogenesis. Indeed FLT3 mutations are noted in around 30% of all AMLs. [4, 5] Patients with FLT3 mutations (e.g., FLT3-ITD) have an aggressive disease phenotype with inferior outcomes. The expected 5-year survival for younger patients with AML is lower among those with FLT3 mutation-positive AML than among those without such mutations (wild-type FLT3 AML).[6] The same is probably true of older patients, although the ERG did not find any specific data to support this.

After a brief review of the literature and the CS's references, the ERG agrees with the definition and characterisation of the disease.

2.2.2 Epidemiology

The CS states that in 2013, there were 2,467 new cases of AML in England and 196 in Wales, and the age-standardised incidence for the UK was 5.0 per 100,000 population.[7, 8] Approximately 55% of patients were aged 70 years or older.[7] Based on literature, [4, 5] the CS estimates 30% of AML patients in the UK, harbour FLT3 mutations; the clinical advisor to the ERG agreed with this estimate, suggesting a range of 20% to 34%.

The CS suggests (section 2.1, page 20 of the CS) that there are two types of genomic alterations in the FLT3 gene: internal tandem duplication of the juxtamembrane domain coding sequence in FLT3 (FLT3-ITD) and activation loop mutation, also referred to as FLT3 tyrosine kinase domain mutations (FLT3-TKD), which is supported by the literature. [9, 10] The ERG understands that the FLT3-TKD is largely rare (5–10% of AML patients) whilst the FLT3/ITD is more prevalent, albeit age dependent (5 to10% in children, 5% to 10% in age 5 to 10 years, 20% in young adults, and >35% in AML patients older than 55 years).[9]

2.2.3 Diagnosis of AML

The CS states that the early signs and symptoms of AML can be vague and non-specific and may include fever, fatigue, pain, shortness of breath, cough, bleeding and bruising, pallor and persistent or frequent infections, which is supported by the literature. [11, 12] The CS also states that many patients are asymptomatic and are discovered through routine blood tests. However, the CS acknowledges that some patients present with signs and symptoms of serious illness, accompanied by a very high or low white blood cells (WBC) level, during routine blood counting, which warrants further investigation.

Based on current guidelines, [13] the CS indicates that a definitive diagnosis of AML requires examination of peripheral blood and bone marrow specimens to assess cell morphology. It involves cytochemistry, immunophenotyping, cytogenetics and molecular genetics to describe the features of AML.

FLT3 mutation testing

The CS assumes that testing for FLT3 mutations is recommended and is often performed routinely in the prognostication of patients with AML; thus, no additional tests over those required for initiating standard chemotherapy will be associated with midostaurin in the UK. The CS also states that no additional tests or investigations are needed for the selection of FLT3-mutant AML patients However, the clinical advisor to the ERG stated that FLT3 testing up-take may vary across different practices in the UK: whilst the up-take of the test is considered standard practice it still may not be routinely performed on all patients although this is (rapidly) changing.

2.2.4 Prognosis of AML patients

The CS suggests that AML usually develops fast and is a fatal disease; without treatment, patients would die within 11–20 weeks of diagnosis, with mortality being due to complications (such as serious infection or haemorrhage) that are associated with the fundamental bone marrow failure. [14] The clinical advisor to the ERG agrees with this characterisation of the disease.

The CS states that FLT3 mutations are a particularly aggressive form of AML, with inferior overall survival (OS) and duration of remission. The expected 5-year survival for younger patients with AML is lower among those with FLT3 mutation-positive AML than among those without such mutations (wild-type FLT3 AML).[6] An analysis of data for a young UK cohort (median age, 43 years) reported a 5-year OS of 15–31% among patients with FLT3 mutations compared with 42% among those without such mutations.[6]

The CS also indicates that the most important factors predicting treatment outcomes in AML patients are: age, karyotype, and molecular genetics. [15, 16] Age or fitness has an influence on survival and prognosis, in part related to the fact that initial treatment with intensive chemotherapy may not be tolerated by many older and less healthy patients.[17]This is important given that the majority of AML patients are aged over 75.[7]

The CS reports estimates of 5-year OS for patients with newly diagnosed AML in the UK that range from 12–27% overall, and may be as low as 5% in individuals aged 65 years or older, and only 3% in patients aged 70 or older.[18, 19] The CS reports estimates of median OS for newly diagnosed AML patients as less than 12 months[18, 20] However, when analysed by age, the SEER (Surveillance, Epidemiology, and End Results) data for 1988–2012 found a median OS of 2-4 years in those under

50 years of age.[20] The ERG identified some additional estimates from the literature: RCTs of younger patients published in 2009, 2011 and 2014. They reported median overall OS of 1.5, 3.5 and 4 years, respectively. [21-23] An RCT that included only elderly AML patients (≥65 years), with intermediate- or poor-risk cytogenetics, who were not eligible for hematopoietic stem - cell transplantation, reported that the median OS for conventional care and azacitidine were approximately 7 and 12 months, respectively. [24] The ERG suggests that, these studies taken together, indicate that the median OS for younger AML patients may be higher than that stated in the CS, although it may not be so in older AML patients.

Mutations in the genes for FLT3 have been identified as an important adverse prognostic factor, with FLT3 alterations presenting as a single molecular abnormality, or with a high allelic ratio, predicting a high and early relapse rate. [13, 16] The CS reported data for a UK cohort (median age, 43 years) suggesting that the expected 5-year survival for younger patients with AML is lower among those with FLT3 mutations than among those without such mutations (wild-type AML) (15–31% vs. 42%).[6] A further UK study has reported a 5-year survival of 32% for FLT3-ITD versus 44% for FLT3 wild type disease. [25]

In summary, the ERG considers that the company's description of the underlying health problem is appropriate and sufficient.

2.3 Critique of company's overview of current service provision

The CS states that technology appraisal 218 [26] recommends azacitidine as a therapy for myelodysplastic syndromes and as a treatment option for adults AML patients not eligible for stem-cell transplantation (SCT).

The ERG found another AML-related appraisal (NICE TA399) that states that azacitidine is not recommended, within its marketing authorisation, for treating acute myeloid leukaemia (AML), with more than 30% bone marrow blasts, in people of 65 years or older who are not eligible for a haematopoietic stem-cell transplant. [27]

The CS indicates that there is no NICE guidance specific to FLT3 mutation positive AML patients and assumes that the treatment pathways for the care of AML patients in the UK typically follow current UK or European guidelines.[15, 16] The clinical advisor to the ERG agrees with this assumption.

2.3.1 Management of AML in current practice

The CS, presented a treatment pathway for the management of AML (figure 3, page 31 of the CS), based on the UK and European guidelines.[15, 16]The CS's treatment pathway indicates that newly diagnosed AML patients are assessed for fitness; fit and less fit patients would receive intensive and non-intensive induction chemotherapy, respectively. Those who respond to intensive induction

chemotherapy are then risk classified in order to receive consolidation chemotherapy or SCT. FLT3-positive patients are intermediate or high risk. Based on advice from the clinical advisor to the ERG, this pathway appears to be largely similar to the current practice in the UK.

Induction therapy

The CS states that AML patients eligible for intensive induction chemotherapy usually receive a combination of 3 days of anthracycline drug and 7 days of cytarabine. [13, 16]The clinical advisor to the ERG also confirmed that anthracycline and cytarabine is the standard induction intensive chemotherapy regimen in the UK.

The CS did not present or discuss the conventional regimen for those who are not eligible for intensive chemotherapy (less-fit AML patients) although in figure 3 of page 31, it mentions a low-dose of cytarabine as an example regimen. However, the ERG notes that current guidelines recommend that azacitidine, decitabine, and low-dose cytarabine should be considered. [15, 16] The clinical advisor to the ERG also stated that the treatment option for the less fit AML patients in the UK, are azacitidine [until progression], low dose of cytarabine and palliative therapy.

Consolidation therapy

The CS states that for patients who achieve complete remission after intensive induction therapy, consolidation chemotherapy is usually considered based on patient's fitness. In general, cytarabine alone is the most widely used conventional consolidation regimen if they are of favourable-risk genetics patients. However, if the patients are intermediate-risk genetics, a high dose of cytarabine therapy followed by SCT (usually allogenic), or SCT alone is used. Further, if patients are high-risk, SCT is used. The CS assumptions are in line with the current guidelines; [16] and reflect the expert opinion of the clinical advisor to the ERG.

The CS did not discuss the role of complete remission (CR) in the success of SCT. The ERG points out a recent report of a case series of SCT in FLT3-positive AML patients.[28] This study found that relapse following SCT was numerically lower in patients whose CR was minimal residual disease (MRD) negative (23%) than in those whose was not (39%). On multivariate analysis MRD status was an independent factor influencing the risk of relapse.

Relapsed and refractory patients

The CS states that in most patients who achieve a CR following induction chemotherapy, the disease will recur within 3 years. Thus, the CS cites cytarabine (intermediate or high dose) or anthracyclines as second-line treatment options for relapsed patients. These treatment options are supported by current guidelines, [13, 15, 16] and the clinical advisor to the ERG. However, the ERG notes that SCT is also considered as another option for the treatment of relapsed patients.[16]The clinical advise to the ERG was that, if fit enough patients would always receive chemotherapy as described here, and then

if CR is achieved, the patient would go into SCT. Some patients are not fit for SCT and would benefit from a maintenance treatment to keep them in remission longer.

Furthermore, the ERG notes that the CS did not discuss or consider patients who fail to respond to induction treatment or *primary refractory* patients. Based on current guidelines,[13, 15, 16] the ERG understands that the most widely used salvage regimens are: intermediate-dose cytarabine with or without anthracycline, FLAG-IDA (a combination of fludarabine, cytarabine, idarubicin, and G-CSF), fitoxantrone plus etoposide plus cytarabine, and allogenic SCT. [16] According to the clinical advisor to the ERG, idarubicin is used in combination with cytarabine and fludarabine in second line (after relapse or in refractory disease) treatment in UK practice which is in line with the guidelines' recommendation.

Maintenance therapy

The CS did not discuss maintenance therapy in current practice. The ERG, however, notes that there is no evidence to suggest that maintenance chemotherapy is of benefit in the treatment of AML. [15, 16]

2.4 Expected role of midostaurin in UK practice

The CS states that midostaurin fits within current clinical pathways as an addition to first-line chemotherapy, followed by its use as monotherapy for about 12 months as a bridge to SCT. The anticipated licensed indication for midostaurin is for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3-mutation-positive and suitable for intensive chemotherapy. [29]This assumption is based on a phase III randomised double-blind trial that showed midostaurin in combination with chemotherapy, followed by midostaurin monotherapy for up to 12 months, significantly extended OS, even-free survival (EFS), disease-free survival (DFS), duration of remission and treatment-free interval, as well as increasing the proportion of patients achieving CR after one induction cycle versus standard-of-care treatment.

The ERG notes that there is no NICE guidance specific to FLT3 mutant AML patients.

The CS states midostaurin is administered as an oral therapy and that there are no additional administration costs over and above those incurred during the current standard treatment of newly diagnosed AML. Use of midostaurin in the management of newly diagnosed AML will not adversely impact or alter current infrastructure and service provision requirements. There are no concomitant therapies specified in the Summary of Product Characteristics or used in the pivotal phase 3 trial that differ from those used with standard therapy in the relevant setting. Based on the available information, the ERG believes that the CS's assumptions are reasonable.

In the CS and in the company's clarification response the company provided an estimate of the number of patients who would be eligible for midostaurin in the NHS. This was based on expert

opinion rather than the literature, which did not reflect the NHS. The number of FLT3 mutation-positive AML patients who would be suitable for intensive chemotherapy, was estimated as between 312 and 324 per year. It was estimated that 50% of these patients would be entered into clinical trials and therefore, the number requiring treatment on the NHS would be 156 to 162 patients per year.

3 Critique of company's definition of decision problem

3.1 Population

The company provided a statement of the decision problem (page 13-14 of the CS). The CS states that the patient population is people with newly diagnosed, FLT3 mutation-positive acute myeloid leukaemia which exactly matches that of the NICE scope.

However, the ERG notes that the RCT evidence submitted by the company is restricted to people aged 18 to 60 years, which is a sub-group of the patient population described in the final NICE scope. The ERG understands that older patients (> 60 years of age) comprise a significant proportion of the population who will be eligible for midostaurin. This group is not well reflected in the clinical evidence submitted.

The RCT population is also restricted to patients who can receive daunorubicin plus cytarabine induction therapy. This is standard intensive chemotherapy, and reflects the anticipated product licence.

3.2 Intervention

The NICE final scope states that the intervention treatment is Midostaurin in combination with standard induction and consolidation chemotherapy followed by single agent maintenance therapy. The CS states that the intervention treatment is Midostaurin in combination with established chemotherapy followed by midostaurin monotherapy. The ERG believes despite that the slight difference in the wording between the two statements the CS meets the NICE scope.

The CS states that midostaurin is an oral therapy and the anticipated recommended dose of midostaurin is detailed as 50 mg twice daily, with each 50 mg dose administered as 2 x 25 mg soft gel capsules. In the treatment of adult patients with newly diagnosed AML, who are FLT3 mutation-positive, midostaurin is given on days 8–21 of induction and consolidation chemotherapy cycles, and is then taken twice daily as single-agent therapy for up to 12 months. The ERG confirms that this dosing regimen reflects the anticipated licensed indication for midostaurin, and that the chemotherapy regimen reflects standard intensive chemotherapy.

3.3 Comparators

The comparator specified in the NICE final scope and in the CS is "established clinical management without midostaurin". The NICE final scope lists the most commonly used induction chemotherapies (cytarabine, daunorubicin, mitoxantrone, etoposide, idarubicin, and fludarabine) and consolidation chemotherapies (cytarabine, etoposide, amsacrine, and mitoxantrone). The clinical evidence in the CS relates to daunorubicin plus cytarabine and high-dose cytarabine, during the induction and consolidation phases, respectively, which is appropriate given that it is the standard intensive

chemotherapy regimen used, and midostaurin's anticipated licence is only for patients suitable for intensive chemotherapy.

3.4 Outcomes

The outcome measures considered by the CS were:

- overall survival
- event-free survival
- disease-free survival
- adverse effects of treatment
- health-related quality of life

These outcomes match those of the NICE's final scope. The CS states health-related quality of life was not assessed in the clinical trials.

4 Clinical Effectiveness

This section contains a critique of the methods of the review of clinical effectiveness data, followed by a description and critique of the trials included in the review, including a summary of their quality and results and the results of any synthesis of studies.

4.1 Critique of the methods of review(s)

The company conducted a systematic literature review designed to identify all published RCTs and non-RCTs concerning the efficacy and safety of midostaurin for the treatment of patients with newly diagnosed FLT3-positive AML.

4.1.1 Searches

The CS described the search strategies used to identify relevant studies of clinical data related to newly diagnosed FLT3-positive AML. The search strategies were briefly described in the main body of the submission in Section 4.1 and full details were provided in Appendix 8.2.

The searches were performed on 12 October 2016. The following electronic databases were searched: MEDLINE, MEDLINE in Process, EMBASE, and EBM Reviews - Cochrane Central Register of Controlled Trials (CENTRAL). Supplementary searches were undertaken for the following conference abstracts from 2014 to 2016 and from trial registries: American Society of Hematology (ASH), http://www.hematology.org/, and European Hematology Association (EHA), http://www.ehaweb.org/. The search for conference abstracts was limited to 2014 to 2016. In addition, searches of the following trials registers were carried out on 11 October 2016: National Institute of Health (NIH) ClinicalTrials.gov, http://www.clinicaltrials.gov/, WHO International Clinical Trials Registry Platform (ICTRP), and http://www.who.int/ictrp/en/.

ERG comments

There were some discrepancies in the reporting of the searches in Section 4.1 and Appendix 8.2. In Section 4.1 the searches are described as "devised to identify studies relating to any pharmacological therapy for this patient population". However the search strategies presented in Appendix 8.2 (p. 8) show that the searches were limited to those drugs included at line 23 of the search strategy: midostaurin, azacitidine, cytarabine, daunorubincin, idarubicin, mitoxantrone, quizartinib, sorafenib, gemtuzumab ozogamicin, and mylotarg. The search strategy did not include etoposide, fludarabine, etoposide and amsacrine which are mentioned in the NICE scope document. In addition, the description of the searches in Section 4.1 states that published studies were sought for the systematic review, however the searches provided in Appendix 8.2, and in the company responses to the points for clarification, demonstrate that unpublished as well as published studies were sought.

MEDLINE, MEDLINE in process, EMBASE and CENTRAL were searched simultaneously via the Ovid platform. Due to differences in the indexing systems between MEDLINE and EMBASE it is preferable when producing sensitive search strategies to search each database separately to ensure all of the correct indexing terms have been included. In addition, as the search strategy included a search filter to limit the results to RCTs and non-RCTs this limit would have been applied to the records from CENTRAL. This limit is unnecessary in CENTRAL as this database is pre-filtered to include only controlled clinical trials.

No date limits were applied to the database searches, however a limit to English language studies was applied. Study design search filters were applied to the search strategy to limit retrieval to RCTs or non-RCTs. The company clarified that the source of the search filters was BMJ Clinical Evidence. The BMJ Clinical Evidence filters are developed in-house rather than undergoing more formal development and validation. As the purpose of the search was to retrieve randomised as well as non-randomised studies, the sensitivity of the search could have been improved by removal of the BMJ Clinical Evidence study design search filters. An alternative approach would have been to use study design search filters that have undergone more thorough development and testing and that have published performance data available.

Searches of databases containing systematic reviews were not included in the CS and the searches of MEDLINE, EMBASE and CENTRAL would not have identified the relevant systematic reviews as the results from these databases were limited to RCTs or non-RCTs. Therefore any relevant systematic reviews would not have been identified by the searches presented in the submission.

4.1.2 Inclusion criteria

Inclusion criteria for the systematic literature review were presented in Table 4, pages 35-36 of the CS. An initial screening included studies (RCTs, non-RCTs, and observational studies) of any pharmacological intervention, for patients with newly diagnosed FLT3 mutation-positive AML. However, after a second screening, the final review included only midostaurin studies. The clinical effectiveness outcomes considered were: rates and mean duration of objective response (including overall, partial, and complete response), OS, progression-free survival (PFS), clinically relevant PFS, disease-free survival, time to progression or treatment failure, and health related quality (HRQoL). Safety outcomes considered were: rate and duration of adverse events (AEs), treatment discontinuations due to AEs or treatment-related AEs, treatment interruptions due to AEs, and dose modifications due to AEs.

The methods used to screen and select the relevant literature were generally of a good standard, with two reviewers independently screening titles and abstracts for inclusion. Full-text screening according

to the inclusion/exclusion criteria, was then performed on those publications identified as being potentially relevant, with disagreements resolved by a third reviewer.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was presented in Figure 5, page 37 of the CS. A total of 6,794 unique records were identified for screening, of which 84 underwent full-text assessment for eligibility for inclusion, yielding a total of three trials to be included in the review. Two of the trials were non-randomised (phase Ib and phase II) and were published in peer-reviewed journals, with the third being an RCT yet to be published.

4.1.3 Critique of data extraction

There was no data extraction plan presented in the CS. The submitted evidence is mainly based on the unpublished RCT, which was conducted by the company. In addition, the ERG noted that the data reported in the clinical effectiveness section of the CS match the NICE scope and study protocols.

4.1.4 Quality assessment

The CS presented a quality assessment of the three trials. The Centre for Reviews and Dissemination (CRD) risk of bias assessment tool was used for the randomised double-blind trial. However, it was not clear what risk of bias assessment tool was used for the two non-randomised trials.

4.1.5 Evidence synthesis

The company did not perform a meta-analysis of the three trials of midostaurin because only one was an RCT, one non-RCT was an early stage dose tolerance trial, and the other was a single-arm non-comparative trial. The ERG agrees with the company's decision not to combine the results from these three trials.

The ERG notes that trials between comparators listed in the NICE scope, were not included in the systematic review. The ERG considers that this was appropriate, because the RATIFY trial provides a direct, randomised comparison of midostaurin with the standard of care.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 List of available randomised controlled trials

The company identified one relevant RCT through its systematic search, see Table 2 below. The results of the RCT, known as RATIFY, have been published as an abstract. However, the detailed results are yet to be published in a peer-reviewed journal.

Table 2 List of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator
CALGB 10603/ CPKC412A2301 (RATIFY) Phase-3 randomised, double-blind, placebo-controlled study (NCT00651261)	Adults (18–60 years) newly diagnosed with FLT3-mutation-positive AML	Cytarabine Daunorubicin Midostaurin N=360	Cytarabine Daunorubicin Placebo N=357

Key: AML, acute myeloid leukaemia; FLT3, FMS-like tyrosine kinase receptor-3; RCT, randomised controlled trial

4.2.2 The RATIFY trial

A summary of the RATIFY trial was presented in Table 6 of the CS, page 38-40. In brief, the trial was an international multicentre (225 sites in 17 countries), phase 3 randomised double-blind study, that assessed the clinical effectiveness of midostaurin in combination with standard intensive chemotherapy (daunorubicin plus cytarabine, followed by midostaurin monotherapy (N=360) versus standard chemotherapy alone (N=357), in newly diagnosed FLT3 mutation-positive AML (ITD or TKD) patients. To be eligible for inclusion, patients had to be ≥18 and <60 years old with >20% blasts in the bone marrow based on the WHO classification (excluding acute promyelocytic leukaemia) and have had no previous chemotherapy for leukaemia or myelodysplasia. Patients were excluded if at least one of the following was present: AML blasts were found in the cerebrospinal fluid suggestive of central nervous system leukaemia, the AML was as a result of chemotherapy or radiotherapy for another cancer, congestive heart failure, a total bilirubin ≥2.5 xULN, pregnant/nursing patient, history of antecedent myelodysplastic syndromes with prior cytotoxic therapy (azacitidine or decitabine), and pregnant or nursing patients.

The ERG notes that the age range of the RATIFY population does not encompass the full range to be seen in clinical practice: a large proportion (>60%) of AML patients to be treated in the UK are over 60 years.[7] This was queried by the ERG. The company in their clarification response, stated that midostaurin will be restricted to patients who are able to tolerate intensive chemotherapy. The response stated that, patient fitness for intensive chemotherapy is generally considered more important than age, and this is related to factors such as performance status, functional status and comorbid conditions, as well as age. Thus, the company stated, the patient population included in RATIFY is likely to be representative of patients who would receive midostaurin in England and Wales. The clinical advisor to the ERG agreed that patient fitness for intensive chemotherapy is generally considered more important than age, but believed that there are older, fit patients who would also benefit from

midostaurin in clinical practice. The ERG has concerns that these patients were not represented in the RATIFY trial.

In their clarification response the company confirmed that eligibility for SCT was not an inclusion criterion for entry into RATIFY: newly diagnosed patients who were FLT3 positive and able to undergo intensive chemotherapy were admitted regardless of eligibility for transplant.

Combination chemotherapies used

The trial consisted of three treatment phases:

- Induction (1–2 cycles): cytarabine plus daunorubicin plus midostaurin OR placebo
- Consolidation (1–4 cycles) – high-dose cytarabine plus midostaurin OR placebo
- Monotherapy maintenance (up to 12 cycles) – midostaurin OR placebo

Further detail is given in the 'Trial treatment phase' sections below (also see Figure 6 page 41 of the CS).

Although there is no NICE guidance specific to FLT3 mutant AML patients, the clinical advisor to the ERG stated that the chemotherapy regimen in the trial reflected clinical practice.

The ERG identified that, in a meta-analysis of randomised trials, AML patients treated with idarubicin plus cytarabine as induction therapy appeared to achieve better complete remission, event free survival, disease free survival and overall survival than those treated with daunorubicin pluscytarabine, although the risk of disease and the incidence of grade 3/4 mucositis was higher. [30] The ERG, in its points for clarification letter, requested that the company comment on the use of this alternative treatment. Based on a recent guideline, [16] the company suggested that daunorubicin+cytarabine is the recommended regimen. The clinical advisor to the ERG also indicated that daunorubicin + cytarabine (DA) remains the standard induction therapy in the UK.

The midostaurin regimen is the (anticipated) licensed one. [29]

Therefore, the ERG considers the treatment phases of the trial to be similar to the expected clinical practice in the UK.

Treatment response/progress assessment

The CS (page 41) states that no crossover between study groups was permitted. Progression from one phase to the next was based on the patient achieving CR at the end of each phase. CR was defined as all of the following criteria by 60 days after the initial induction therapy was started, unless otherwise specified:

- **Peripheral blood counts**: ANC ≥1000/μL, platelet count ≥100,000/μL, no leukaemic blasts in the peripheral blood, and adequate erythroid recovery so that red blood cells (RBC) transfusions were not necessary
- **Bone marrow**: adequate cellularity, no Auer rods, <5% blast cells, and no extramedullary leukaemia (such as central nervous system or soft tissue involvement).

Based on the current guidelines the ERG considers the trial's definition of CR to be appropriate. However, the clinical advisor to the ERG stated that in clinical practice a less stringent definition of CR is used (<15% blast cells).

Trial's treatment phases

Induction therapy

The company (page 42 of the CS) presented the induction treatment schedule as the following:

- Cytarabine 200 mg/m^2/day by continuous intravenous (IV) infusion on days 1–7
- Daunorubicin 60 mg/m^2/day by IV (push or short infusion) on days 1–3.
- Either midostaurin 50 mg OR placebo twice daily (BID), orally on days 8–21.

The ERG notes that the treatment schedule and dosing of cytarabine and daunorubicin are in line with the recommendation of the current guideline. [16]

The CS (page 42) states that patients not achieving CR after the first induction cycle underwent a second induction cycle with the same treatment. However, the clinical advisor to the ERG stated that in clinical practice, patients who don't respond to the first cycle are given a different chemotherapy for the second cycle.

Patients who did not achieve CR after the second induction cycle were discontinued from the study treatment, but were followed-up for OS at least every 2 months for years 1 and 2, every 3 months for years 3 and 4 and then annually for a maximum of 10 years from study entry. Patients achieving CR after one or two induction cycles, proceeded to consolidation therapy.

Although it was not clearly stated in either the CS or clinical study report (CSR) documents, in the letter of response to ERG points for clarification, the company stated that SCT was not mandated in the RATIFY trial protocol, nor did the protocol specify that patients would need to be in CR before undergoing SCT, but it was conducted at the discretion of the investigator. The company did state that current guidelines recommend that only patients in CR undergo SCT. [16]

Consolidation therapy

The CS (page 42) presented the consolidation treatment schedule as follows:

- High-dose cytarabine 3 g/m^2 IV every 12 hours on days 1, 3, and 5 of each cycle
- Midostaurin 50 mg OR placebo BID on days 8–21.

The ERG notes that the cytarabine dosing was in line with the current guideline for intermediate-risk genetics AML patients.

Each consolidation cycle was a minimum of four weeks in duration and was to begin within two weeks following haematological recovery (ANC ≥1000/μL and platelet count ≥100,000/μL), but not sooner than four weeks from the beginning of the previous cycle (page 42 of the CS). Patients, who remained in CR after up to four cycles of consolidation therapy, proceeded to midostaurin monotherapy. Patients unable to complete four courses of high-dose cytarabine consolidation therapy because of toxicity, could still be eligible for monotherapy, but this required discussion with the Study Chair.

The ERG notes, based on the current guidelines and the opinion of their clinical advisor, that SCT is in reality a form of consolidation treatment. SCT was not mandated in the RATIFY trial, but was left to clinical judgement. The current guideline recommends that SCT be used after high-dose chemotherapy in the intermediate/high-risk genetics AML patients.[16] This is reflected in the treatment pathway for the management of AML presented in the CS text (pages 31 and 32, and figure 3, page 31 of the CS). Although the CSR states that information on SCT, including type of SCT and date was captured on the follow-up form (page 29 of the CSR) and that in the event a patient received SCT directed against their leukaemia, midostaurin/placebo therapy was not to be resumed, the trial protocol was not explicit about SCT. Despite this, there is no indication that fewer patients received SCT in the trial than would in clinical practice.

Midostaurin monotherapy

Patients received midostaurin 50 mg OR placebo BID given continuously on days 1–28 of each 28 day cycle for up to 12 cycles or until leukaemia relapse.

Follow-up

The CS states that patients continued with study treatment until one of the following occurred:

- Completion of all protocol-specified treatments
- Failure to achieve CR after two courses of induction therapy
- Presence of leukaemic cells in cerebrospinal fluid
- Leukaemic regrowth: absolute peripheral leukaemic cells that were previously absent and then reappeared to a level of 1000/μL
- Relapse during post-remission therapy, with relapse defined as any of the following, occurring after either CR or partial remission (PR):

- The reappearance of circulating blast cells not attributable to "overshoot" following recovery from myelosuppressive therapy
- >5% blasts in the marrow, not attributable to another cause (e.g., bone marrow regeneration)
- Development of extramedullary leukaemia.

Outcomes considered

The outcomes considered by the RATIFY trial are listed below in Table 3.

The ERG noted that the term complete remission (CR) was used in various ways throughout the company submission. The company, in its points for clarification, elaborated that three definitions of CR were used in the analysis of data from the RATIFY trial: CR within 60 days (CR achieved within 60 days of the start of study treatment; per protocol definition), CR during induction (CR achieved during the induction phase; after one or two induction cycles) and CR at any time (CR achieved from randomisation up to 30 days after the end of treatment). Overall, the ERG believes that outcomes considered by the trial were in line with the current guidelines.

Table 3 List of outcomes considered in the RATIFY trial

Type of outcome	Definition given in the CS
Effectiveness outcome	
Overall survival [a]	"All deaths up to and including the cut-off date of 01 April 2015 were considered as OS events. Patients known to be alive at their last contact and whose vital status was not updated during the data sweep were censored at their date of last contact before 01 April 2015. The remaining patients were considered as alive on 01 April 2015 and were censored for the OS analysis on this date"
Complete remission [b]	"Two definitions of CR rate were employed. The primary measure was the proportion of patients achieving a CR within 60 days of treatment initiation. A secondary measure was the proportion of patients achieving a CR at any time"
Event free survival [b]	"An EFS event was defined as a failure to obtain a CR within 60 days of initiation of protocol therapy, or relapse from CR, or death from any cause, whichever occurred first, and was measured as the time from randomisation plus 1 day to the event. All patients were followed up for this endpoint irrespective of when they stopped study treatment."
Disease-free survival [b]	"This included patients who achieved CR by day 60 after study treatment initiation; patients were not censored at the time of SCT. DFS was measured from the date of the first CR to relapse or death from any cause, whichever occurred first"
Remission duration [b]	"The duration of remission was measured for patients who achieved CR in 60 days and was defined as the time between the first CR and relapse or death due to AML, whichever occurred first. Two analyses were performed, one non-censored for SCT and the other censored at the time of SCT. Patients who died due to other reasons were censored at their date of death with the duration measured as the time between the first CR plus 1 day and the event"
Safety outcome	
AEs and SAEs	Any AEs and SAEs related to study treatment both for overall treatment and for each phase of treatment.

Key: [a] primary outcome; [b] secondary outcome; AEs, adverse events; AML, acute myeloblastic leukaemia; CR, complete remission; DFS, disease free survival; EFS, event free survival; OS, overall survival ;SAEs, serious adverse events; SCT, stem cell transplant.

Summary of comments on RATIFY trial design and conduct

In summary, the ERG is satisfied with the clarity and relevance of the trial's methodology although concerned about the generalisability, particularly regarding the age of the trial population, which does not encompass fitter patients aged over 60 years who would be eligible for midostaurin in clinical practice.

Patients were followed up for OS and other outcomes after treatment discontinuation. The ERG understands that patients received either second-line treatment (for primary refractory or relapse) or SCT after treatment discontinuation. Therefore patient outcomes will be influenced by these subsequent therapies. The ERG has some concerns over how well differences between the treatment arms were accounted for in the analysis. This is discussed further in section 4.2.2.2.

4.2.2.2 Participant flow in RATIFY trial

The CS presented a patient disposition flow chart (figure 8 page 52 of the CS). The flow diagram shows that both treatment arms (midostaurin and placebo) had three treatment phases (induction, consolidation and monotherapy), a cycle of treatments, and the number of patients progressed from

one treatment phase to the next. The ERG believes that the flow diagram provides sufficient information on the flow of participants except there was insufficient information on 'other' reasons for withdrawal and that it was not clear what alternative treatments were received when patients discontinued midostaurin/placebo during the three treatment phases. The ERG, in its points for clarification, requested that the company provide information about these points. Table 2 and associated text in the company's response clarified the 'other' reasons. The ERG notes that of the 44 patients who withdrew from midostaurin for other reasons, 26 did so due to 'refractory disease'; the corresponding figure for the placebo arm was 39/55. It is not clear to the ERG whether these withdrawals due to refractory disease were counted as events in the EFS analysis, but it assumes so, as the number of events is close to the total number of discontinuations (Figure 8 in CS), excluding withdrawals due to adverse events or other disease..

The company explained that SCT was one of the alternative treatments (received by 61 midostaurin and 47 placebo patients, and provided further information about when patients received SCT. The company confirmed that no patient received midostaurin after SCT. The company response did not provide information on other subsequent treatments, stating they were not recorded as part of the trial. Due to the lack of strict specification of SCT and subsequent therapies and the necessary long follow-up in the RATIFY trial, the ERG suggests there is some uncertainty around the size of the treatment effect from this trial. However, there is nothing to indicate that patients in the trial were not treated according to standard guidelines.

4.2.2.3 Baseline patients' characteristics

The baseline characteristics of participants were presented in Table 9 of the CS (page 53) based on age, sex, body surface area, Eastern Cooperative Oncology Group (ECOG) performance status, race, region, and FLT3-mutations status. The baseline characteristics were balanced between the treatment groups although the proportion of men was higher for midostaurin (174/360) than for placebo (145/357). The ERG agrees with the CS's conclusion that the treatment groups were largely balanced.

The baseline characteristics indicate that there are questions regarding the generalisability of the trial to NHS clinical practice. In particular, the mean age of 45.2 years is low. In addition, non-white patients appear to be under-represented, however, there was a very high proportion recorded as 'unknown' (56.5%).

4.2.2.4 Quality assessment of the RATIFY trial

The CS presented a quality assessment of the RATIFY trial (Table 10, page 54 of the CS) and concluded that the trial had a low risk of bias. The ERG conducted its own risk of bias assessment using the Cochrane risk of bias tool (see Table 4 below). The ERG agrees with the CS's conclusion

that the risk of bias is largely low; however, the effect of missing data on the results remains unknown, as no information about missing data methods was presented in the CS and the CSR.

Table 4 Quality assessment of the RATIFY trial using the Cochrane risk of bias tool

Assessment criterion	Risk of bias judgement	Support for judgement
Sequence generation	Low	Patient identification numbers were generated via the Alliance web based patient registration system.
Allocation concealment	Low	Alliance web-based patient registration system was used
Baseline comparability	Low	Baseline characteristics appear to be balanced except sex
Blinding of participants and personnel	Low	"patients and all site study personnel including Investigators, Pharmacists remained blinded to the identity of the treatment from the time of randomization until after database lock (DBL)"
Blinding of outcome assessment	Low	"people performing the study assessments remained blinded to the identity of the treatment from the time of randomization until after database lock (DBL)"
Incomplete outcome data	Unclear	No information was presented in the CS on how missing data were handled.
Selective reporting	Low	Outcomes reported in the CS match outcomes reported in the trial's protocol (https://www.clinicaltrials.gov/ct2/show/NCT00651261)

4.2.2.5 Effectiveness results of the RATIFY trial

Overall survival

Figure 1 Overall survival – non-censored at the time of SCT (Figure 10, page 57 of the CS)

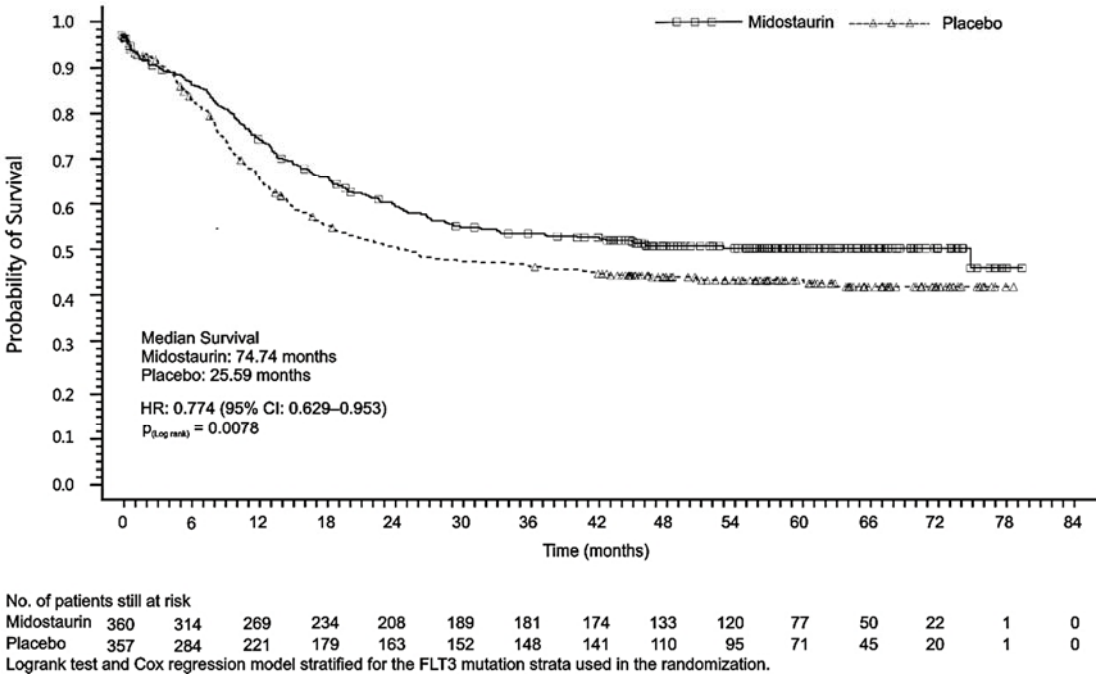


Table 5 Summary of the overall survival data for the RATIFY trial (adapted from CS Table 11, page 55 and text)

Outcome	Midostaurin (N=360)	Placebo (N=357)	Hazard Ratio and/or p-value
Patients undergoing SCT			
All patients, %	59.4	55.2	
Patients with SCT in the 1st CR	[redacted]	[redacted]	
Median OS, months	74.7	25.6	HR= 0.77 (95% CI 0.63-0.95); p=0.0078
3-year, %	54 (95% CI 0.49–0.59)	47 (95% CI 0.41–0.52)	
5-year, %	51 (95% CI 0.45–0.56)	43 (95% CI 0.38–0.49)	
Mean overall survival, months	[redacted]	[redacted]	
Median OS censored at SCT, months (sensitivity analysis)	NE	NE	HR=0.745 (95% CI 0.54-1.03), p=0.0373
3-year, %	65	58	
5-year, %	64 (95% CI 0.56–0.71)	56 (95% CI 0.47–0.63)	
Median OS SCT only in first CR	[redacted]	[redacted]	HR=0.63 (95% CI:0.38-1.05)
Mean OS SCT only in first CR	[redacted]	[redacted]	
Median OS censoring for SCT, months	[redacted]	[redacted]	[redacted]
Mean OS censoring for SCT, months [c]	[redacted]	[redacted]	
Median OS only received SCT, months	[redacted]	[redacted]	[redacted]
Mean OS only received SCT, months [c]	[redacted]	[redacted]	
Median OS not received SCT, months	[redacted]	[redacted]	[redacted]
Mean OS not received SCT, months [c]	[redacted]	[redacted]	

Key: [a] CRs within 60 days of therapy initiation; [b] All CRs during protocol treatment and those in the 30 days following treatment discontinuation; [c] Reconstructed from respective Kaplan-Meier graphs; CR, complete remission; NE, not estimable (or not reached)

As can be seen from the results presented in Table 5and **Figure 1**, OS was significantly longer for midostaurin than placebo and both the three-year and five-year survival rates were higher for midostaurin than placebo. The company also provided OS results for the most recent data cut (5th September 2016): median OS and the hazard ratio results remained similar to those from the original data cut [redacted]. In order to calculate the mean OS from this latest data cut, the ERG reconstructed individual patient data (IPD) using the Kaplan-Meier graphs included in the company's clarification response. The ERG adapted the Guyot et al.[31] method of reconstructing data from published Kaplan-Meier survival curves, and used WebPlotDigitizer (http://arohatgi.info/WebPlotDigitizer/app/) to generate plot points and Excel

to calculate the mean OS. The calculated mean OS for the most recent data cut is [redacted] for midostaurin and [redacted] for placebo. These are similar to those from the original data cut [redacted] respectively).

Analysis of data censored for SCT, generated results similar to the main analysis (the hazard ratio remained similar), although the three-year and five-year survival rates are higher for midostaurin and placebo than the main analysis. The median was not reached for either of the two arms; however, the means were higher than the main analysis ([redacted] months and [redacted] months for midostaurin and placebo arms, respectively).

Four further analyses of OS explored the interaction between midostaurin and SCT. Two were included in the CS (only patients who received SCT during first CR, and those who received SCT not in first CR) (Figure 11 of the CS) and the ERG requested the other two: only patients who had received SCT, and only patients who had not received SCT "(see figures 4 and 5 in company response).

The analysis that included only patients who received SCT during first CR (this CR could be at any time during the study up to 30 days after the last treatment) again found a benefit of midostaurin: HR 0.63 (95% CI 0.38–1.05, and the mean OS benefit was [redacted] months. This suggests that the CR achieved with midostaurin is 'better' than that achieved with daunorubicin plus cytarabine or cytarabine alone, and hence increases the chance of a successful SCT in patients who achieved CR and undergo SCT. However, the quality of remission was not studied in the RATIFY trial. No benefit for midostaurin over placebo was observed for patients who received SCT outside of the first CR (i.e as primary refractory or post first relapse): both treatment groups did equally poorly (figure 11, page 58 of the CS).

The two further OS survival analyses of patients who received SCT and those who did not, again find a treatment benefit of midostaurin. The benefit of midostaurin is maintained in those who received SCT ([redacted]) and those who did not (mean [redacted]). These findings confirm that the benefit of midostaurin is not entirely as a bridge to transplant.

Complete remission, Event-free survival, disease free-survival and duration of remission

A summary of the other key effectiveness results is presented in Table 5 below (based on Table 11, page 55 of the CS and results reported in the CS text).

Table 6 Summary of the key effectiveness data for the RATIFY trial (adapted from Table 11, pages 55 of the CS and CS text)

Outcome	Midostaurin (N=360)	Placebo (N=357)	Hazard Ratio and/or p-value
Complete remission, %			
Protocol defined [a]	58.9	53.5	p=0.073
Expanded definition [b]	65.0	58.0	p=0.027
After 1st induction only	[redacted]	[redacted]	[redacted]
Median event-free survival, months	8.2 (95% CI 5.4–10.7)	3.0 (95% CI 1.9–5.9)	HR=0.78 (95% CI 0.66-0.93), p=0.002
1-year, %	43 (95% CI 0.38–0.49)	31 (95% CI 0.27–0.36)	
5-year, %	28 (95% CI 0.23–0.33)	19 (95% CI 0.15–0.24)	
Median event-free survival censored at SCT, months (sensitivity analysis)	8.3	2.8	HR=0.81 (95% CI 0.68–0.98), p=0.0124
1-year, %	43 (95% CI 0.38-0.49)	30 (95% CI 0.25-0.35)	
5-year, %	25 (95% CI 0.20-0.31)	21 (95% CI 0.16-0.27)	
Median disease-free survival [a], months	26.7 (95% CI 19.4-NE)	15.5 (95% CI 11.3 -23.5)	HR=0.714 (95% CI 0.55-0.92), p=0.0051
1-year, %	71 (95% CI 0.64-0.76)	57 (95% CI 0.49-0.64)	
5-year, %	48 (95% CI 0.41-0.54)	37 (95% CI 0.29-0.44)	
Median disease-free survival [a] censored at SCT, months	[redacted]	[redacted]	[redacted]
3-year, %	[redacted]	[redacted]	
5-year, %	[redacted]	[redacted]	
Median duration of remission, months	[redacted]	[redacted]	[redacted]
Median duration of remission censoring for SCT, months	[redacted]	[redacted]	[redacted]

Key: [a] CRs within 60 days of therapy initiation

Rates of complete remission

As can be seen from the results presented in Table 6, a higher proportion of the midostaurin patients achieved CR within 60 days of treatment initiation (protocol-defined CR), than did placebo patients, although the difference was not statistically significant (one-sided p value = 0.073). The proportion of patients achieving CR after one cycle of induction therapy was also higher in the midostaurin group

compared with placebo. When the CRs that occurred any time during treatment (and up to 30 days following treatment discontinuation) were analysed, the treatment difference in favour of midostaurin was statistically significant (one-sided p value = 0.027).

Event-free survival

Using the protocol definition of CR (occurring with 60 days of treatment initiation), the median event free survival was significantly longer for those randomised to midostaurin and higher proportions of those randomised to midostaurin than to placebo achieved one- and five-year event- free survival (**Error! Reference source not found.**). Analysis of data censored for SCT also indicate that midostaurin group had longer median EFS, and higher one-year and five-year survival rates than placebo.

Sensitivity analyses using different definitions of CRs, rather than just the protocol specified one (those occurring with 60 days of treatment initiation) generated hazard ratios in favour of midostaurin similar to those of the main analysis (see Table 12, page 60 of the CS).

Disease-free survival and remission duration

DFS was defined as the period from CR to relapse or *death from any cause*. Remission duration was defined as the period from CR to relapse or *death due to AML*. For both outcomes the protocol definition of CR was used.

As can be seen from the results presented in Table 5, the median DFS was longer in the midostaurin than the placebo group and the proportions of patient achieving one-year and five-years DFS were higher for midostaurin than placebo. Analysis of data censored for SCT also indicated that the midostaurin group had longer median DFS, and higher three-year and five-year survival rates than placebo.

Those who were randomised to midostaurin also had a statistically significant longer median duration of remission than the placebo group ([redacted] vs [redacted] months). Analysis of the data censored for SCT indicated that the median duration of remission for midostaurin was greatly reduced, indicating that SCT accounts for much of the remission duration in the midostaurin arm.

Subgroup analyses

Subgroup analysis results for overall survival were presented in the CSR (Figure 11-2, page 74 of the CSR), and are summarised below in Table 7. The results show that subgroups in the midostaurin arm appeared to have longer overall survival than in the placebo arm, although the reverse was true if patients were female, had a history of myelodysplastic syndrome (MDS), were Black or African American, had an ECOG performance score ≥2, or had AML with inv(16) (p13; q22) or t(16;16)

(p13; q22). However, most of the subgroup results did not reach statistical significance, probably due to a lack of power in the tests.

In response to a query on the issue of the apparent lack of a treatment benefit in women, the company admitted that unexpectedly, the planned subgroup analyses by gender did suggest a difference in treatment benefit in women and men regarding OS (**Error! Reference source not found.**). The company pointed out that women did benefit from the addition of midostaurin to the standard treatment of AML, in terms of CR rate, EFS/DFS, and cumulative incidence of relapse (CIR). Furthermore, analysis of OS censored by SCT, in contrast, showed a benefit for midostaurin in both men and women, although the effect was greater in men (men: HR, 0.628, 95% CI 0.39, 1.02. women: HR, 0.899, 95% CI 0.59, 1.38). the company suggested that differences in SCT or events occurring post-relapse and/or post treatment failure (as defined for EFS) could, at least in part, account for the difference in OS benefit observed for the men and women in the primary analysis of OS.

The company also stated that, post hoc data for NPM1 collected on a subset of patients confirmed that the results for OS within the subsets for the two genders are not due to an imbalance in NPM1 status

across the two treatment arms. The company could not exclude the possibility that it is just a random effect particular to the patients enrolled in this study.

Table 7 Subgroup analyses of overall survival (adapted from Figure 11-2, page 74 of the CSR)

Grouping characteristics		Midostaurin: Placebo Hazard Ratio and 95% CI
FLT3 mutation status	TKD	0.77 (0.44 to 1.24)
	ITD<0.5 allelic ratio	0.80 (0.54 to 1.20)
	ITD≥0.5 allelic ratio	0.76 (0.57 to 1.00)
FLT3 subtype	TKD	0.74 (0.44 to 1.24)
	ITD	0.77 (0.62 to 0.97)
Gender	Male	0.53 (0.39 to 0.72)
	Female	1.01 (0.76 to 1.34)
Prior MDS	Yes	1.91 (0.78 to 4.71)
	No	0.74 (0.60 to 0.92)
Cytogenics	AML with t(8;21) (q22; q22)	0.33 (0.05 to 2.15)
	AML with inv(16) (p13; q22) or t(16;16) (p13; q22),	2.51 (0.62 to 10.09)
	AML with 11q23 (MLL) abnormalities	<0.001
	Other	0.79 (0.63 to 0.98)
White Blood Cell count	$<50x10^9/L$	0.80 (0.60 to 1.06)
	$\geq 50x10^9/L$	0.72 (0.53 to 0.99)
Race	Black or Africa American	1.06 (0.30 to 3.71)
	White	0.87 (0.64 to 1.20)
	Other	0.66 (0.49 to 0.89)
ECOG performance status	0-1	0.74 (0.59 to 0.93)
	≥2	1.04 (0.59 to 1.85)

Use of Stem Cell transplant

The CS did not provide detailed information about when patients received SCT in the RATIFY trial, although the company provided information in response to points for clarification to the ERG, which is summarised below.

The company states that 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, or in relapse, or for patients who were refractory to induction. The data on SCT in the RATIFY study are summarised in Table 7.

Table 8 Proportion of patients undergoing SCT according to remission status and stage of treatment (adapted from Table 3, page 6, and text page 5 of points for clarification response)

Patients undergoing SCT, n (%)	Midostaurin, n=360	Placebo, n=357
Overall in study	214 (59.4)	197 (55.2), p=0.250
[redacted]	[redacted]	[redacted]

Overall, a slightly higher proportion of patients in the midostaurin group, compared with the placebo group, underwent SCT (midostaurin=59.4% and placebo=55.2%). The proportions of patients who underwent SCT in CR1, after relapse or following treatment failure were approximately similar (**Table 8**).

Although these data may suggest a possible benefit for midostaurin over placebo for enabling patients to receive SCT in CR1, the treatment difference is not large. Furthermore, the trial was not designed to assess this.

As stated earlier, due to the lack of strict specification of SCT, and subsequent therapies, and the necessary long follow-up in the RATIFY trial, there is some uncertainty around the size of the treatment effect of midostaurin. However, there is nothing to indicate that patients in the trial were not treated according to standard guidelines, or that this introduced bias into the comparison.

4.2.3 List of available non-randomised trials

The company presented two relevant non-randomised trials for midostaurin in patients with newly diagnosed AML as part of the evidence. The first trial was a phase 1b study that assessed the efficacy, safety and pharmacokinetics of several dosing schedules for midostaurin in addition to standard chemotherapy. The second trial was a phase II open-label single-arm assessment of the efficacy and

safety of midostaurin in addition to standard chemotherapy followed by midostaurin monotherapy in patients with newly diagnosed FLT3-ITD-positive AML.

4.2.4 The Phase Ib trial

The Phase Ib trial was conducted in newly diagnosed patients, both FLT3 wild-type and mutation-positive AML. Participants were 18–60 years old with AML (as defined by WHO criteria) and Karnofsky Performance Status score of ≥70. Further details are given in the CS (page 69). This trial included a total of 69 patients in six centres (four in the USA and two in Germany).

The aim of the trial was to assess the safety, efficacy, and pharmacokinetics of combining midostaurin with an induction regimen of daunorubicin plus cytarabine followed by high-dose cytarabine consolidation.

Induction therapy consisted of midostaurin either concomitant or sequential to conventional chemotherapy (daunorubicin 60 mg/m^2 [days 1–3] and cytarabine 200 mg/m^2 [days 1–7]) according to the following three schedules:

- Dosing schedule 1: midostaurin 100 mg BID days 1–28 days (concomitant) or days 8–28 days (sequential)
- Dosing schedule 2: midostaurin 100 mg BID for 14 days (concomitant [days 1–7 and 14–21] or sequential [days 8–21])
- Dosing schedule 3: midostaurin 50 mg BID for 14 days (concomitant [days 1–7 and 14–21] or sequential [days 8–21]).

Consolidation therapy was administered to patients achieving CR at the end of induction cycles 1 or 2. Consolidation therapy consisted of three cycles of high-dose cytarabine and midostaurin. After completion of planned chemotherapy, patients could receive midostaurin monotherapy for 14 days in each 28-day cycle according to the patient's original assignment.

Three outcomes were considered in the trial: complete remission rate, overall survival, and disease free survival.

4.2.4.1 Participant disposition of the Phase Ib trial

There was no participant flowchart presented although the CS reports that there were 69 patients in two treatment groups: 29 patients in the midostaurin 100 mg BID group; and 40 patients in the midostaurin 50 mg BID group (page 71 of the CS). The ERG however has found a CONSORT flow diagram from the published version of the trial, [32] and is largely satisfied.

4.2.4.2 Baseline patients' characteristics of the Phase Ib trial

No detailed baseline characteristics of the participants were presented although the CS stated that "of those who received midostaurin 50 mg BID, mean (median) age was 39 (48.5) years, 60% were males, over half (55%) had a Karnofsky Performance Status score of ≥90 (equivalent to ECOG score=0 or fully active, able to carry on all pre-disease performance without restriction) , and 52% had a cytogenetic profile that was either favourable or normal. There were 13 and 27 patients in the FLT3 mutation-positive and FLT3 wild-type groups, respectively".

4.2.4.3 Effectiveness results of Phase Ib trial

The company presented the effectiveness results of one arm of the Phase Ib trial: for midostaurin 50 mg, based on 40 patients (page 71 of the CS). The overall CR rate was 80%, and there was no difference between the concomitant and sequential dosing schedules. Most patients (92%) in the FLT3 mutation-positive group achieved a CR, whilst 74% of patients in the FLT3 wild-type group achieved a CR. The overall and disease free survival rates were similar among FLT3 mutation positive and FLT3 wild-type groups.

OS probabilities for the FLT3 mutation-positive and FLT3 wild-type groups were similar at one year (0.85 (95% CI 0.65–1.0) and 0.78 (95% CI 0.62–0.93), respectively) and two years (0.62 (95% CI 0.35–0.88) and 0.52 (96% CI 0.33–0.71), respectively)

The ERG notes that, although not conclusive, due to being a small sample study with no placebo control, the results indicate that midostaurin is effective in FLT3 wild-type and mutation-positive AML subpopulations.

4.2.5 The Phase II trial

The phase II trial included patients aged 18-70 years, with newly diagnosed FLT3-positive AML. It was a multicentre (five Austrian and 45 German sites), single-arm study that evaluated the efficacy and safety of midostaurin added to chemotherapy (induction followed by consolidation) followed by midostaurin monotherapy. The CS stated that the primary objective of the trial was to compare outcomes for patients aged 18–60 years with those aged 61–70 years. The trial included 145 participants (≤60 year olds=99 and >60 year old=46).

Treatment consisted of induction and consolidation followed by midostaurin monotherapy given for up to one year. Induction therapy consisted of daunorubicin (days 1–3), cytarabine (days 1–7) and midostaurin 50 mg BID (from day 8 to 48 hours before start of the next treatment cycle). Patients achieving a PR could receive an optional second induction cycle. Those achieving a CR after either induction cycle could receive a single cycle of consolidation therapy consisting of high-dose cytarabine and midostaurin. Further consolidation therapy consisted of allogeneic SCT from a matched donor. Patients ineligible for allogeneic SCT, or those with no compatible donor or not giving consent, received

consolidation therapy consisting of three cycles of high-dose cytarabine plus midostaurin. Monotherapy of midostaurin could be given after SCT.

Event free survival (EFS) was the primary outcome. The rate of complete remission (CR), relapse-free survival (RFS), overall survival (OS), cumulative incidence of relapse, and cumulative incidence of death were secondary outcomes.

As a single arm non-comparative trial, this can provide only supporting results for comparability. It does, however, provide data relating to people with AML aged over 60 years of age, although none for patients aged over 70 years.

4.2.5.1 Participant disposition of the Phase II trial

The CS presented the patient disposition flow chart (figure 18 page 77 of the CS). The flow diagram included three treatment phases (induction, consolidation and monotherapy), and the number of patients who progressed from one treatment phase to the next.

The CS states that a total of 149 patients received induction therapy; of these, six proceeded straight to allogeneic SCT, 69 proceeded to consolidation cycle 1, 35 received a second induction cycle and the rest withdrew from the study. Of the 35 patients receiving a second induction cycle, 14 progressed to allogeneic SCT and 11 progressed to consolidation cycle 1 (in total 80 patients received consolidation cycle 1). A total of 41 patients who received consolidation cycle 1, and 10 who received consolidation cycle 2, progressed to allogeneic SCT (in total 71 patients received allogeneic SCT). A total of [redacted]

The ERG believes that the flow diagram and accompanying text provides sufficient information on the flow of participants during the follow-up period.

4.2.5.2 Baseline patients' characteristics of the Phase II trial

The baseline characteristics based on sex, age, ECOG performance status, and FLT3 mutation status were presented in the CS (Table 17, page 78 of the CS). [redacted].

4.2.5.3 Effectiveness results of Phase the II trial

A summary of the key effectiveness results is presented in Table 8 (Table 18, page 79 of the CS).

Table 9 Summary of the efficacy results for the phase II trial (Table 18, page 79 of the CS)

Endpoint	All patients (N=145)	Aged ≤60 years (N=99)	Aged >60 years (N=46)
CR, n (%)	[redacted]	[redacted]	[redacted]
EFS	[redacted]	[redacted]	[redacted]
Median EFS, months	[redacted]	[redacted]	[redacted]
2-year EFS, %	[redacted]	[redacted]	[redacted]
OS	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]
2-year OS, %	[redacted]	[redacted]	[redacted]
RFS	[redacted]	[redacted]	[redacted]
Median RFS, months	[redacted]	[redacted]	[redacted]
2-year RFS, %	[redacted]	[redacted]	[redacted]
Cumulative incidence of relapse, %	[redacted]	[redacted]	[redacted]
Cumulative incidence of death, %	[redacted]	[redacted]	[redacted]

Key: CR, complete remission; CSR, clinical study report; EFS, event-free survival; OS, overall survival; RFS, relapse-free survival.

The results show that younger FLT3positive AML patients (≤60 years old) appeared to have better median overall survival [redacted] than those who were older (>60 year old).

The company also conducted an exploratory analysis of relapse free survival, comparing trial data with historical controls, and the presented results appear to indicate that for both age groups, patients treated with midostaurin achieved better outcomes than controls.

4.2.6 Adverse events of midostaurin

Adverse events from the RATIFY trial

Adverse events of the RATIFY trial were presented in the CS (Tables 20-22, pages 84-89 of the CS). The key reported adverse events are summarised below in Table 10. The results show that the safety profile of midostaurin is similar to that of placebo.

Table 10 Key adverse events reported from the RATIFY trial

	Grade 3/4 AEs suspected be related to treatment	SAEs	Grade 3/4 infections	Withdrawal due to Grade 3/4 AEs	Death within 30 days of starting treatment	Deaths at anytime
Placebo (N=335)	[redacted]	163 (48.7%)	[redacted]	15 (4.5%)	21 (6.3%)	[redacted]
Midostaurin (N=345)	[redacted]	162 (47%)	[redacted]	21 (6.1%)	15 (4.3%)	[redacted]

Key: AEs, adverse events; SAEs, serious adverse events; SCT, stem cell transplant

Adverse events from the phase II trial

Safety results of the phase II trial were reported in Table 19, page 81 of the CS. Midostaurin appear to have a better safety profile in the younger patients than the older patients (see Table 11 below).

Table 11 Key adverse events reported from the phase II trial

	Treatment related AEs	SAEs	Withdrawal due to AEs	Death during treatment 30-day follow-up period
Aged ≤60 years (N=98)	[redacted]	[redacted]	[redacted]	[redacted]
Aged >60 years (N=46)	[redacted]	[redacted]	[redacted]	[redacted]

Key: AEs, adverse events; SAEs, serious adverse events

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No trials were identified by the company's searches.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The company did not carry out indirect comparison and/or multiple treatment comparison analyses, due to the absence of data on the comparators that targeted the FLT3 mutant AML population. The ERG did a preliminary search and agrees with the company that no trials or data were available for the analyses.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work was carried out by the ERG.

4.6 Conclusions of the clinical effectiveness section

The CS included data from one double-blind RCT (RATIFY) and two non-randomised trials. All the trials investigated midostaurin in combination with an induction regimen of daunorubicin plus cytarabine, followed by high-dose cytarabine, in newly diagnosed FLT3-positive AML patients.

The two non-randomised, non-comparative open-label trials are inherently prone to bias, and can only be interpreted as supporting evidence. The phase Ib trial was largely about pharmacokinetics and dose determination of midostaurin. It is the only midostaurin trial to include both FLT3-mutant and FLT3 wild-type AML patients. The data indicate that midostaurin also has some activity in FLT3 wild-type AML. The phase II trial was a single-arm study that evaluated the same midostaurin regimen that was later investigated in the phase III double-blind RCT (the licensed regimen). It provides the only data for the use of the licensed regimen in patients aged over 60 years (up to age 70 years). The results of this Phase II trial indicate that midostaurin treatment response is better in younger patients (< 60 versus > 60 years of age).

The RATIFY trial, a double-blind, multi-centre, RCT, compared the clinical effectiveness of the licensed regimen of midostaurin with placebo (in addition to standard intensive chemotherapy). It found that patients who were randomised to midostaurin achieved better overall survival (primary outcome), complete remission rate, event free survival, disease free survival and remission duration than those randomised to placebo. Overall, a slightly higher proportion of patients in the midostaurin group, compared with the placebo group, underwent SCT but the trial was not designed to assess this outcome. Median OS was increased by 49 months and mean OS by [redacted] months. Results of analyses exploring the interaction of midostaurin with SCT, found that this benefit of midostaurin was apparent across all analyses, except where patients received SCT post-relapse. These results demonstrate the same relative benefit of midostaurin in the patients who do, and do not, undergo SCT as part of first line therapy for AML. In addition, the results suggest that in first line treatment of AML, the CR achieved with midostaurin is 'better' than that achieved with daunorubicin plus cytarabine/cytarabine alone, and hence increases the chance of a successful SCT. However, the quality of remission was not studied in the RATIFY trial. When added to standard intensive chemotherapy, midostaurin appears to have a safety profile similar to that of placebo.

Due to the lack of strict specification of SCT and subsequent therapies and the necessary long follow-up in the RATIFY trial, there is some uncertainty around the size of the treatment effect of midostaurin. However, there is nothing to indicate that patients in the trial were not treated according to standard guidelines.

The RATIFY trial lacks generalisability to FLT3-positive AML patients in the UK, due to the age of the included population (restricted to 60 years, with a mean age of 45 years. Given that the only

available data on older patients (up to age 70 years of age, the Phase II trial) found that the treatment response was better in those under 60 years of age compared with those over 60 years, there is uncertainty about the size of the treatment benefit to be achieved with midostaurin in eligible patients who may be older than 70 years. This means that there is also uncertainty about the size of the effect for the whole eligible population (including all ages).

Patients in the RATIFY trial who did not achieve complete remission after first induction cycle underwent a second induction cycle with the same treatment whilst a different chemotherapy for the second cycle may be used in UK practices. Hence, the treatment scheduling may not represent practice in the UK. Consequently, the effect size seen in the trial may not be achieved in clinical practice.

5 Cost-Effectiveness

This section focuses on the economic evidence, submitted by the company, and the additional information provided in response to the ERG's points for clarification. The submission was subject to a critical review, on the basis of the company's report, and by direct examination of the electronic version of the economic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of the economic evaluation and a narrative review to highlight key assumptions and areas of uncertainty. Section 6 presents additional analyses and scenarios, requested from the company, or independently undertaken by the ERG, to further explore these uncertainties.

The company's economic submission included:

- A description of each systematic review conducted to identify published evidence on the cost-effectiveness, health-related quality of life (HRQoL)/utilities and resource usage/costs (CS, Sections 5.1, 5.4, 5.5), with further details presented in separate appendices (CS, Appendices 11, 13, 14).
- A report on the de novo economic evaluation, conducted by the company. This report includes a description of the patient population and the model structure (CS, Section 5.2); the clinical parameters used in the economic model (CS, Section 5.3); the measurement and valuation of health effects and quality-of-life data used in the cost-effectiveness analysis (CS, Section 5.4); the cost and healthcare resource use identification, measurement, and valuation (CS, Section 5.5); a summary of the inputs and assumptions used in the model (CS, Section 5.6); the cost-effectiveness results for the base-case (CS, Section 5.7) and sensitivity analyses (CS, Section 5.8); an overview of any subgroup analyses (CS, Section 5.9); the methods of validation (CS, Section 5.10); and the final interpretation and conclusion of the economic evidence (CS, Section 5.11).
- An electronic copy of the company's economic model developed in Microsoft Excel®.

In response to a number of points for clarification raised by the ERG, the company further submitted:

- A descriptive reply to the ERG's points for clarification, alongside additional data and analyses requested by the ERG.
- An updated Excel-based model correcting minor errors and incorporating the additional scenario analyses requested by the ERG.

5.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review to identify relevant published cost-effectiveness studies associated with AML. The ERG's critique of the systematic review presented by company is given below.

5.1.1 Searches

The CS described the search strategies used to identify relevant studies related to the cost-effectiveness of systemic therapies in AML. The company also searched for economic analyses in myelodysplastic syndromes (MDS), due to the lack of economic data in AML. The search strategies were described in Section 8.11, Appendix 11.

MEDLINE, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and EMBASE were searched via the Ovid platform, covering the period January 1st, 2006 to November 20th, 2016. The bibliographies of relevant systematic reviews and meta-analyses, found through the database searches, were checked to identify further relevant studies. Unpublished literature was sought from searches of conference proceedings from: the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), and the American Society of Hematology (ASH). In addition, information from Health Technology Assessment (HTA) publications and guidance on AML was identified by searching relevant websites..

The sources searched by the company were appropriate for a systematic review of cost-effectiveness studies. They made efforts to identify studies from both the published and unpublished literature and sought further relevant information from guidance agencies in the UK, Canada and Australia.

The ERG was unable to assess the appropriateness of the search strategies, for the systematic review of cost-effectiveness, as they were not provided in the original submission and were not requested in the points for clarification. However, the ERG is not aware of any missing studies from the systematic review carried out by the company.

5.1.2 Inclusion/exclusion criteria used for study selection

Details of the inclusion and exclusion criteria, in the selection of cost-effectiveness studies, are listed in **Error! Reference source not found.**.

Table 12: Eligibility criteria used in the search strategy

Cost-effectiveness	Inclusion criteria	Exclusion criteria
Population	• Patients with AML • Patients with high-risk MDS	Non-human
Intervention and comparators	All, including no intervention	None

Cost-effectiveness	Inclusion criteria	Exclusion criteria
Outcomes	• Cost-effectiveness • Incremental cost-effectiveness ratio (ICER) • Cost per life-year saved (LYS) • Cost per QALY	Studies not including at least one of the outcomes of interest
Study design	Cost-effectiveness analysis (CEA)	• Studies not reporting CEA • Editorials • Notes • Comments • Letters • Reviews
Language restrictions	English	Non-English
Time restriction	Published January 2006 to present	Published prior to 2006

The inclusion/exclusion criteria, used by the company for study selection, followed the usual PICOS framework. Studies were independently assessed by two reviewers against each eligibility criterion. Any discrepancies, regarding the inclusion of studies, were checked and a decision made by the lead reviewer.

The ERG considers that the inclusion/exclusion criteria were largely reasonable. The exclusion of non-English language studies may have led to some studies being missed, although the ERG considers this unlikely.

5.1.3 Studies included and excluded in the cost-effectiveness review

In total, nine studies were identified in the company's cost-effectiveness review; none was of midostaurin. Two of the nine evaluations were UK economic evaluations, both carried out as part of previous NICE technology appraisals; TA218 and TA399. TA218 assessed the effectiveness of azacitidine for AML patients with >30% bone marrow blasts, in people >=65 years who were not eligible for SCT, and TA399 assessed azacitidine for adult patients who were not eligible for SCT with Int-2/HR MDS, myelomonocytic leukaemia or AML with 20–30% blasts. Reflecting the different decision problems, the economic evaluation adopted very different model structures, see Table 13. Full details of all nine economic evaluations are presented in section 5.1.2 of the CS's main submission (pages 96 to 101) and Appendix 11 (pages 28 to 35)

Table 13 Summary of published UK cost-effectiveness studies

Study	Population	Interventions	Model description	Estimated ICER
NICE Azacitidine HTA 2011 (TA218)[26]	Adult patients who are not eligible for SCT with Int-2/HR MDS, CMML or AML with 20–30% blasts	Azacitidine vs conventional care (BSC), low-dose chemotherapy (LDC) or standard dose chemotherapy (SDC)	Two-arm health state transition model with 2 health states: MDS and death. Lifetime horizon was used	BSC: £63,177 per QALY, LDC: £49,030 per QALY, SDC: £51,252 per QALY
NICE Azacitidine 2016 (TA399)[27]	AML with >30% bone marrow blasts in people >=65 years who are not eligible for SCT t	Azacitidine vs conventional care	Semi-Markov model based on 4 health states: remission, non-remission, relapsed or progressive disease, and death. A 10-year time horizon was used	£20,648 per QALY
ICER: Incremental cost-effectiveness ratio; LYS: Life-years saved; QALY: Quality-adjusted life-year				

The company did not attempt a synthesis of the identified cost-effectiveness studies, nor did they provide any details of how they were used in the development of the *de novo* model.

5.1.4 Conclusions of the cost-effectiveness review

The company's cost-effectiveness review did not identify any relevant economic assessments of midostaurin. The company's review, however, identified a number of economic evaluations of other therapies for AML, including the UK-based economic evaluations. These economic evaluations provide a useful insight into the assumptions made in previous economic models, and provide an external validity check on the results of the de novo model presented by the company.

5.2 ERG's summary and critique of the company's submitted economic evaluation

An overall summary of the company's approach, and signposts to the relevant sections in the company's submission, are reported in Table 14.

Table 14 Summary of the company's economic evaluation (and signposts to CS)

	Approach	Source / Justification	Signpost (location in company submission)
Model	A decision model based on a partitioned survival approach. Separate health states were used based on AML diagnosis/induction, CR, relapse and SCT outcomes. 700 cycles (28-day cycles) or approximately 54 years, which is equivalent to a life-time horizon.	A partitioned survival approach was used, due to its intuitive implementation, with the patient-level data available, as the model did not deviate from the trial data, and because the patient data were relatively mature (in the sense that most short- and medium-term events occurred during the trial period) and was considered reflective of real clinical practice.	Section 5.2.2 pages 102-106
States and events	The model consisted of five main mutually exclusive health states: (i) AML diagnosis/induction, (ii) CR, (iii) SCT (iv) relapse and (v) death. Additional tunnel states were used, within the SCT state, to reflect variation in costs	These health states were selected based on the clinical pathway and current guidelines for treatment of newly diagnosed FLT3-mutation-positive AML. Additional tunnel states for SCT were justified as the costs and patient utilities	Section 5.2.2 pages 102-106

	and utilities within this health state (i.e. SCT treatment, SCT recovery and post-SCT recovery).	vary over the course of SCT (i.e. SCT treatment, SCT recovery and post-SCT recovery).	
Comparators	The comparators used in the CS model were: cytarabine plus daunorubicin in the induction phase, followed by high-dose cytarabine in the consolidation phase.	The comparators were in line with the NICE scope and reflected the established clinical management without midostaurin.	Section 5.2.4 pages 107-108
Subgroups	No subgroup analysis was undertaken.	This was justified as the FLT3-mutation-positive AML population was a specific subgroup of the AML population. Additionally, survival was similar across the FLT3-mutation stratification subgroups and further stratification would have significantly reduced the precision of the estimates.	Section 5.2.1 page 102 Section 5.9 page 171
Treatment effectiveness	CR and SCT outcomes were derived from the RATIFY trials. For CR, time-to-CR patient-level data from the RATIFY trial were used for the trial period. Extrapolated data, based on EFS data, were used following trial cut-off. For SCT, uptake of SCT (censored for mortality) data were used for the trial period. No further SCT was assumed in the model after the end of the trial. Only patients in CR could receive SCT prior to relapse, in the clinical trial. SCT and CR were independent in the model. The relapse outcome was assumed to absorb any patients still alive and not in any other health state.	The assumption of "only patients in CR could receive SCT prior to relapse" was justified by referencing current clinical guidelines. It was reported that the dependency between CR and SCT was embedded in the patient's treatment pathway data. The assumption of no further SCT after the end of the trial was reported to be validated by clinical advisors.	Section 5.3 pages 109-116
Mortality	The OS Kaplan-Meier-curve from the RATIFY trial was used to estimate mortality within the trial period (approx. 6.2 years). A cure model, assuming the rate of death from the general population after the end of the trial, was implemented. The mortality rate was the same between the two arms, after the end of the trial. General population, all-cause mortality rates for England and Wales (ONS 2013-2015) were applied after the cure point. The cure model was fitted from the last event. All-cause mortality was adjusted for the baseline age and gender of the trial population.	The provided justifications for the cure assumption were: • following the first 2 years, patients are likely to become more stable depending on their disease status, with relapse and mortality becoming less frequent, • after 5 years, patients are likely to follow a natural mortality curve as most of the leukaemia relapse occurred prior to this stage, • 10-year survival is likely to be approximately 10% lower than at the end of the trial (about 6.7 years prior), so the mortality trend should not be too aggressively extrapolated after the end of the trial, • the aggressive mortality/relapse rate of the first 2–3 years of the trial is not a good base for the long-term extrapolation, • the plateau seen at the end of the trial is likely to be relatively constant over time, which is consistent with the natural	Section 5.3 pages 109-116

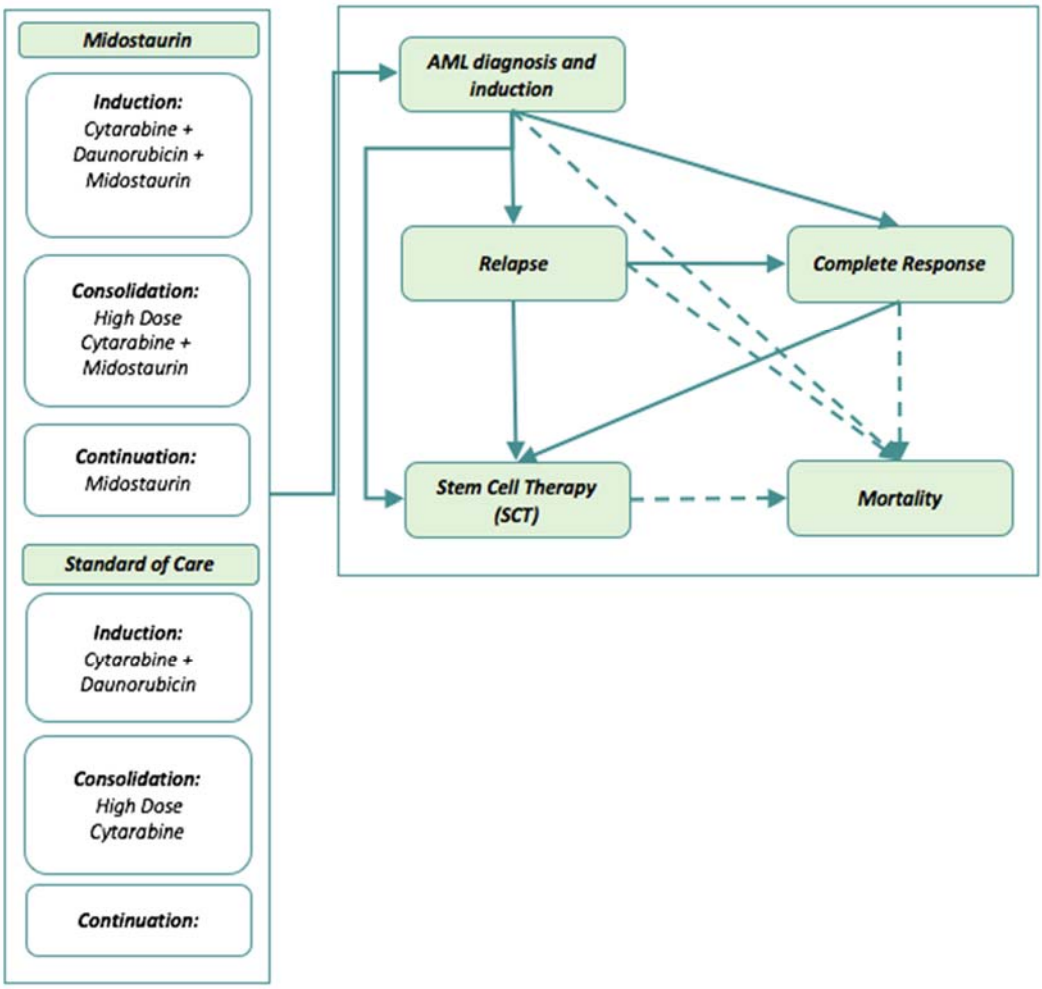
		mortality of the patients and should consider continuation of the plateau effect The cure assumption, and same mortality etween the two arms, were reported to be validated by clinical advisors. The use of the last event in the trial was considered most appropriate, based on clinical judgement. All-cause mortality was obtained from UK life tables (ONS 2013-2015). The distribution of age and gender were obtained from the RATIFY trial, at baseline, to adjust the all-cause mortality.	
Adverse events	In the CE model, grade 3/4 AEs with a prevalence of ≥5% in any of the three treatment phases (induction, consolidation, and monotherapy) were included to estimate the adverse-event-related costs. Specific utility values for AEs were not utilised in the model.	The inclusion of higher grade AEs was justified as these were likely to bear substantial costs. AE prevalence, for each phase, was derived from the clinical trial results and used to estimate the prevalence per 28-day treatment cycle for each AE. The per-cycle prevalence of AEs was used to estimate per-cycle costs of AEs in each treatment group and treatment phase. Costs for each AE were based on NHS Healthcare Resource Group (HRG) estimates. The CS model used utility values specific to each phase (induction, consolidation, CR, etc.) and was assumed to include the disutilities for toxicities during treatment.	Section 5.5.4 pages 139-144 Section 5.4 page 123
Health-related quality of life	Health-state utilities were assigned to each health state and the separate sub-states, and were derived from published evidence.	The RATIFY trial did not collect HRQoL evidence from the trial, therefore published evidence was used. The utility values were from the published literature for the health states of complete remission post-first line (no relapse) and relapse, and the sub-states of treatment (induction, consolidation and monotherapy). The utility values for the three sub-states of SCT (treatment, recovery and post recovery) were mapped from published QLQ-C30 data[33] onto EQ-5D values, using an algorithm developed by Crott et al. (2010).[34]	Section 5.4 pages 116-124
Resource utilisation and costs	The resource use and costs included: drug acquisition costs, drug administration costs, SCT costs, costs related to the health states, mortality costs, and costs associated with adverse events.	The resource use and costs, associated with drug acquisition, were based on the dosing in the RATIFY trial. The resource use and costs, associated with additional lines of therapy (secondary therapy), were based on the literature. The costs associated with SCT were derived from average utilisation of different types of SCT in the NHS. The resource use and costs associated with routine care (i.e. non-medication costs), in	Section 5.5 pages 124-144

		different health states, were derived from a previous NICE appraisal in AML TA 399. Mortality-related costs were obtained from the Nuffield Trust (2014), which reported the healthcare utilisation costs in the final three months of life. The costs associated with AEs were derived from the RATIFY trial. The unit costs were based on the literature, NHS Reference costs 2015-16, PSSRU 2015, Where appropriate, the unit costs were inflated to 2016/2017 prices. The FLT3-ITD testing cost was obtained from clinical expert interviews.	
Discount rates	The costs and benefits were discounted at 3.5% per annum	In accordance with the NICE reference case.	Section 5.2.2 page 106
Sensitivity analysis	Probabilistic sensitivity analysis was performed. Deterministic analysis was performed on a series of model parameters. A series of scenario analyses was also performed.	In accordance with the NICE reference case.	Section 5.8 pages 156-171

5.2.1 Model structure

The *de novo* analysis, presented by the company, compares the cost-effectiveness of daunorubicin/cytarabine chemotherapy (Standard of Care (SOC)), with adjunctive midostaurin i.e. midostaurin plus chemotherapy. The company model uses a partition survival model (PSM) approach or "area under the curve" analysis. This type of model directly uses the time-to-event data from a clinical trial to determine the distribution of patients between the health states. The model structure is depicted in Figure 2 and consists of five health states: (i) AML diagnosis/induction; (ii) complete response/remission (CR); (iii) relapse, (iv) stem cell transplant (SCT) and (v) death, which is the absorbing state. The CR health state is split into three further sub-states, indicating the phase of treatment that a patients is in consolidation, monotherapy, and CR post discontinuation of primary treatment (CR 1L). The SCT health state is similarly split into a series of tunnel states, these states consist of SCT treatment, SCT recovery, and post-SCT recovery.

Figure 2 Model Structure (CS, figure 20 pg. 105)



The use of a partition survival model means that transitions between health states are not explicitly incorporated into the analysis using probabilities, however, transitions between health states are implied by the model structure and the clinical data used to populate the model. Table 15 describes the transitions possible for each health state.

Table 15 Transitions between health states

Health state	Description	Possible transitions
AML diagnosis/induction	Patients enter the model in the AML diagnosis/induction state in which initial induction therapy is received for a maximum of two cycles.	Patients who respond to induction therapy, and achieve complete remission, transition to one of the Complete response sub-states (consolidation, monotherapy or CR 1L). Patients who fail to achieve complete remission within two cycles, transition to the Relapse health state.
Complete response	Consists of patients who are responders to primary therapy, and is separated into three sub-states indicating the phase of treatment: consolidation, monotherapy or CR 1L.	Patients in the CR health states following induction treatment can either stay there or can transition to the Relapse, SCT or Death health states.
Relapse	Patients can enter the Relapse health state from either the Induction health state or from any of the CR health states. Patients in the Relapse health state therefore consist of both refractory and relapsed patients.	Patients in the Relapse health state are assumed to remain there until SCT or death.
Stem cell transplant	Stem cell transplant is for patients receiving a SCT, and consists of three tunnel states: SCT treatment, SCT recovery, and post-SCT recovery. Patients enter SCT from either the CR or Relapse health states; response is therefore not a perquisite for receiving SCT.	Once a patient reaches the final tunnel state (post-SCT recovery) they are assumed to remain there until death.
Death	Patients can enter the death state at any time in the model	Absorbing state.

The cycle length used in the model was 28 days, chosen to coincide with the length of a treatment cycle, and the model used a 700-cycle time horizon, equivalent to a life-time time horizon. The efficacy data, treatment and comparator dosage, duration of primary therapy, AE rates and patient characteristics (age, weight, and body surface area), used in the economic model, were sourced from the RATIFY trial, with the remaining inputs informed by studies identified in the cost-effectiveness review and other sources.

Overall survival, within the first 80 cycles (~6.2 years) of the model, was estimated using Kaplan-Meier data from the RATIFY clinical trial. Thereafter, patients were assumed to be functionally cured and to follow similar characteristics to those of the general population (same mortality risk), while still accounting for potential morbidities affecting quality of life and resource use among AML survivors.

ERG Comment

The structure of the model, although accommodating a number of key clinical elements of the treatment of AML patients, has a number of significant weaknesses. In particular, there are a number of issues relating to how patients progress through the model; these mostly result from the clinical data used to populate the model. These issues result in several inconsistencies in the model and mean that the model exhibits a lack of face validity. These issues are discussed in turn below.

Possibility of response to subsequent therapy, for refractory or relapsed patient

As described above, patients who fail or relapse following first-line therapy, move to the relapse health state. On entering the relapse health state, patients cannot return to the CR health state and can only move to the SCT or death states. Patients in the relapse health state therefore have two treatment pathways. The first is to receive subsequent therapy followed by SCT, which is allowed for in the model. The second is receive subsequent therapy, but no SCT. This latter pathway is not full accounted for in the model. Within the model patients, as in RATIFY patients could and did receive subsequent therapies (as they would in clinical practice). The model, however does not accommodate response to this subsequent therapy and these patients are assumed to remain in the relapse health state with their mortality determined by observed by OS in the RATIFY trial. As consequence of this patients tend to stay in the relapse health state for a long time. This is evidenced by the fact that, at cycle 130 (~10 years), 15% of the patients initiating midostaurin are in the relapse health state. The consequence of this failure to accommodate response to subsequent therapies is very significant: the relapse heath state is defined, with low utility (0.53 QALYs per year) and very high health state costs (~60,000 per annum). The model therefore assumes that all patients who enter the relapse state and do not subsequently receive SCT, even those that subsequently respond to secondary therapy will continue to stay the relapse health state experiencing the morality benefits of subsequent therapy but also very low HRQoL and incurring very high care costs. The ERG considers it implausible that patients would continue to experience such low HRQoL and such high health care costs over such an extended period.

This issue has a significant impact on the model, leading it to underestimate the ICER, and it results in the model making logically inconsistent predictions. Firstly, it implies that patients who are responders to first-line therapy experience much higher HRQoL and much lower care costs than patients who are responders to subsequent therapy. Secondly, it means that the model reacts to inputs in odd ways. One of the clearest examples of this can be observed in a scenario analysis, carried out by the company, in which an alternative extrapolation point for OS data was chosen. In this scenario, the OS benefits of midostaurin were reduced and, in such a scenario, we would expect the ICER to increase to reflect these reduced benefits, yet it results in a significant drop in the ICER (£34,327 vs £21,552 per QALY). This reduction in the ICER is observed because, in this scenario, fewer

midostaurin patients are in the relapse health state and, therefore, this avoids the significant costs associated with this state.

This issue was raised with the company, at the clarification stage, and the ERG requested that the model allow patients who have relapsed, to be able to transition to the CR health state after the induction period. The company's response stated that the RATIFY trial did not collect data on CR for second and subsequent lines of therapy and, therefore, the company's revised model was not able to address this issue given the data available.

The company, however, did modify the model to include new Kaplan-Meier data for CR, to partially respond to points raised by the ERG. These new CR data, however, lack face validity and are very different to the CR data used in the original model. The company also expressed doubts regarding the validity of using this data and suggested that they may underestimate the prevalence of CR. The ERG, therefore, questions whether these new data are correct, and considers the original data to be the most accurate reflection of CR observed in the RATIFY trial. The ERG, therefore, reincorporated the original CR data in the model, as part of the exploratory analysis carried out by the ERG. Further, the ERG presents a scenario analysis, in Section 6, which attempts to address the identified issues with the relapse health state, by amending the model structure, so that patients do not remain in the relapsed health state in perpetuity.

Health state costs for the CR 1l and post-SCT recovery health states

The health states CR 1L (Complete remission post discontinuation of first-line treatment) and post-SCT recovery represent the terminal alive health states for patients who have successfully been treated and who have discontinued therapy. The company's model, however, assumes that both these health states are associated with significant ongoing health state costs, equivalent to approximately £8,000 per annum. This means that even decades after diagnosis patients are still accruing significant costs. The ERG considers that these ongoing health state costs are unjustified and are inconsistent with previous economic evaluations, in similar therapeutic areas. For example, in NICE TA [ID893], which evaluated inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia (ALL), no ongoing health state costs were assumed after discontinuation of treatment.[35] The impact of this assumption significantly overestimates the ICER, because patients in midostaurin have a greater chance of achieving a CR on primary therapy and a greater chance of receiving SCT.

At the clarification stage, the ERG requested that the company comment on the ongoing health costs associated with the CR 1L and SCT post-recovery health states. The company's response to this question outlined an additional scenario, in which the routine care costs for patients after 26 cycles were 50% reduced for all surviving patients. This scenario was justified on the basis that after 2 years the rates of relapse and mortality begin to plateau and, therefore, monitoring costs will fall after this

period. The ERG does not consider that this scenario fully addresses the issue, as it still implies that patients accrue significant ongoing health care costs and, therefore, the ERG considered further scenarios as part of their exploratory analysis, see Section 6 for details and results.

Relapse following SCT

As depicted in the model diagram, patients who enter the SCT health state can only transition into the death health state. The model, therefore, makes the implicit assumption that patients who receive SCT cannot relapse. The ERG is concerned about the validity of this assumption, as the literature suggests that relapse following SCT is not uncommon, with between 25% and 40% [36-38] of patients experiencing relapse following SCT. This is also inconsistent with the patients who achieve remission on drug therapy, who are able to relapse. The mortality impact of these relapsing patients is accounted for in the model, because the SCT Kaplan-Meier curve, used to determine the proportion of patients in the SCT health state, is censored for OS. The model, however, does not take into account the fact that patients who relapse following SCT will experience lower HRQoL, at least for a period of time, and will accrue significant health care and drug acquisition costs, relating to salvage therapy received by these patients. The impact of this omission is difficult to determine as the number of patients who relapse on SCT will be determined by the number of patients who receive SCT, in each arm, and the likelihood of relapse following SCT.

At the clarification stage, the ERG requested that the company modify the economic model to allow patients who receive SCT to relapse, by censoring the SCT Kaplan-Meier curve of relapse as well as OS. The company's response outlined that this was not possible due to a lack of available data on relapse after discontinuation of primary treatment. Because of this lack of data the ERG also unable to explore this issue any further.

Rate of SCT

The majority of the additional QALYs, generated by midostaurin treatment, result from the increased OS. The OS benefits generated by midostaurin treatment result from three factors:

- Improving the survival of patients who do not receive SCT;
- Improving survival post SCT; and
- Increasing the rate of SCT.

The last of these benefits occurs because patients who receive SCT have significantly improved prognosis, compared with patients who do not receive SCT. Within the RATIFY trial 59.4% of patients, in the midostaurin arm, received SCT, compared with 55.2%, in the standard care arm. Within the economic model, this difference in the rate of SCT, and the OS benefits that go with this, are entirely attributed to primary therapy. It, however, is not clear that midostaurin increases the rate

of SCT as this difference is not statistically significant (p value 0.25). It is, therefore, highly uncertain whether the predicted increase in OS benefits, attributed to midostaurin, will be realised in practice as a proportion of the observed gain is due to the fact that more patients in the midostaurin arm received SCT. Because of the way in which the company's model is set up and the fact that response to primary therapy and SCT are not linked it is very difficult to explore the impact of this issue without completely changing the structure. The ERG are therefore unable to explore this issue further in Section 6.

5.2.1.2 Additional scenario analysis carried out as part of the clarification response

As described above, the ERG has serious concerns about the model structure adopted by the company. These issues were raised with the company, at the clarification stage, to give the company the opportunity to modify their model. As part of the clarification questions, the ERG suggested that following the trial follow-up period, the model should not use a PSM approach and instead patients should move to a natural history model, populated using appropriate data. This change would address a number of issues with the model and would mean that it better reflect the long-term costs and benefits of midostaurin. In response to this request, the company included a scenario analysis, in which patients move to a transition model after cycle 80. Transitions in the scenario were determined using data from the RATIFY trial after cycle 40. This scenario has a notable impact on the ICER changing it from £33,672 to £42,109 per QALY. The ERG has two criticisms of this scenario. Firstly the ERG questions whether the RATIFY trial was an appropriate source of data. A central assumption of the company's model was the cure point and it does not seem consistent with this assumption to use data from before the cure point to determine transitions after this period. External data, therefore, might have been a more appropriate choice, given this assumption. Secondly, these changes, while accommodating some of the ERG concerns raised above in section 5.2.1, do not fully address these issues and, in particular, they do nothing to address the failure to properly accommodate the response to subsequent therapy.

5.2.2 The company's economic evaluation compared with the NICE reference case checklist

Table 16 summarises the economic submission and the ERG's assessment of whether the *de novo* evaluation meets NICE's reference case and other methodological recommendations.

Table 16 Features of de novo analysis

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Comparator(s)	The comparator specified in the NICE final scope and CS is "Established clinical management without midostaurin". The NICE final scope lists the most commonly used induction chemotherapies (cytarabine, daunorubicin, mitoxantrone, etoposide, idarubicin, and fludarabine) and consolidation chemotherapies (cytarabine, etoposide, amsacrine, and mitoxantrone).	Yes	The comparators used in the CS model were: cytarabine plus daunorubicin, in the induction phase, followed by high-dose cytarabine, in the consolidation phase. Therefore, the CS's comparators are in line with the NICE scope and reflect the established clinical management without midostaurin.
Type of economic evaluation	Cost-effectiveness analysis.	Yes	
Perspective on costs	NHS and personal and social services	Yes	NHS and PSS costs have been taken into account.
Perspective on outcomes	All health effects on individuals.	Yes	QALY benefits to treated individuals were considered.
Time horizon	Sufficient to reflect any differences in costs or outcomes between the technologies being compared.	Yes	The time horizon used in the economic model was 700 cycles or approximately 54 years equivalent to a life-time horizon.
Synthesis of evidence on outcomes	Systematic review.	Yes	
Measure of health effects	QALYs.	Yes	Utility values were used directly from the published literature for states of complete remission post-1L (no relapse) and relapse, and sub-states of treatment (induction, consolidation and monotherapy). Utility values for the three sub-states of SCT (treatment, recovery and post recovery) were mapped from published QLQ-C30 data[33] into EQ-5D values, using an algorithm developed by Crott et al. (2010).[34]
Source of data for measurement of HRQoL	Reported directly by patients and/or caregivers.	Yes	
Source of preference data for valuation of changes in HRQoL	Representative sample of the public.	Yes	
Discount rate	Annual rate of 3.5% on both costs and health effects.	Yes	Costs and benefits were discounted at 3.5% per annum.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	No special weighting undertaken.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was undertaken.

5.2.3 Population

The population included in the economic evaluation corresponded to the population recruited to the RATIFY trial. As discussed in Section 4, the trial population was broadly in line with the NICE scope and was in line with the expected licenced population. However, as stated in Section 4, the ERG

considers that the population recruited to the RATIFY trial represents a more restricted population than is likely to be treated in practice, because the RAFTIFY trial excluded patients over the age of 60. The exclusion of such patients is important, as a significant proportion of patients with AML are over the age of 60[7], and the prognosis of AML is strongly associated with age.[17]

Reflecting these concerns, at the clarification stage, the ERG asked the company comment on the representativeness of the RATIFY trial, and to speculate on how the exclusion of patients over the age of 60 would impact upon the estimated ICER. The company's response made it clear that they expected the licence for midostaurin to reflect a broader population than that included in the RATIFY trial and to include patients over the age of 60, it also stated that it expected that the number of patients over the age of 60, who will be eligible for midostaurin, will be small. Further to the above, the company also cited evidence from a Phase II study, and suggested that the benefits of midostaurin treatment are independent of age, noting that older and younger patients in this study experienced similar responses, relapses and post-SCT mortality. However, as discussed in Section 4, this trial did demonstrate a better response to treatment in younger patients, and the company's exploratory analysis of relapse free survival, comparing trial data with historical controls, may not be reliable.

To accommodate the ERG's concerns, the company included a scenario in their model to reflect the possibility that the eligible population may be older. In this scenario patients were assumed to have an elevated mortality in the post-trial phase of the model (post cycle 80). This was included by applying a standardised mortality ratio (SMR), of two, to the office of national statistics (ONS) mortality data used in the post-cure period of the model. This scenario did not make any change to the rates of CR, SCT and survival pre cycle 80 and, therefore, assumed that these would not change for older patients. These assumptions were justified on the basis of data from a phase II study that included patients up to the age of 70 years.

ERG Comment

The ERG acknowledges that some older patients will not be eligible for midostaurin treatment due to the requirement that patients should be able to tolerate intensive chemotherapy, but disagrees with the company that few patients over the age of 60 years will be eligible for treatment with midostaurin. Examination of the literature on the treatment of patients with AML, suggests that patients over 60 are commonly treated with intensive chemotherapy.[39-41] This was also confirmed by the clinical advisor to the ERG.

With regards to the scenario analysis presented by the company, the ERG does not consider this scenario analysis to adequately account for the differences between older and younger patients. The assumption that CR, SCT and OS prior to cycle 80 would be the same for both younger and older patients is overly simplistic and not justified by the data. Furthermore, the application of the SMR in

the post-cure period does not make sense. If the company was aiming to account for the lower life expectancy of older people, then it would have been more appropriate to use the age distribution in the phase II study to calculate mortality using ONS general population statistics.

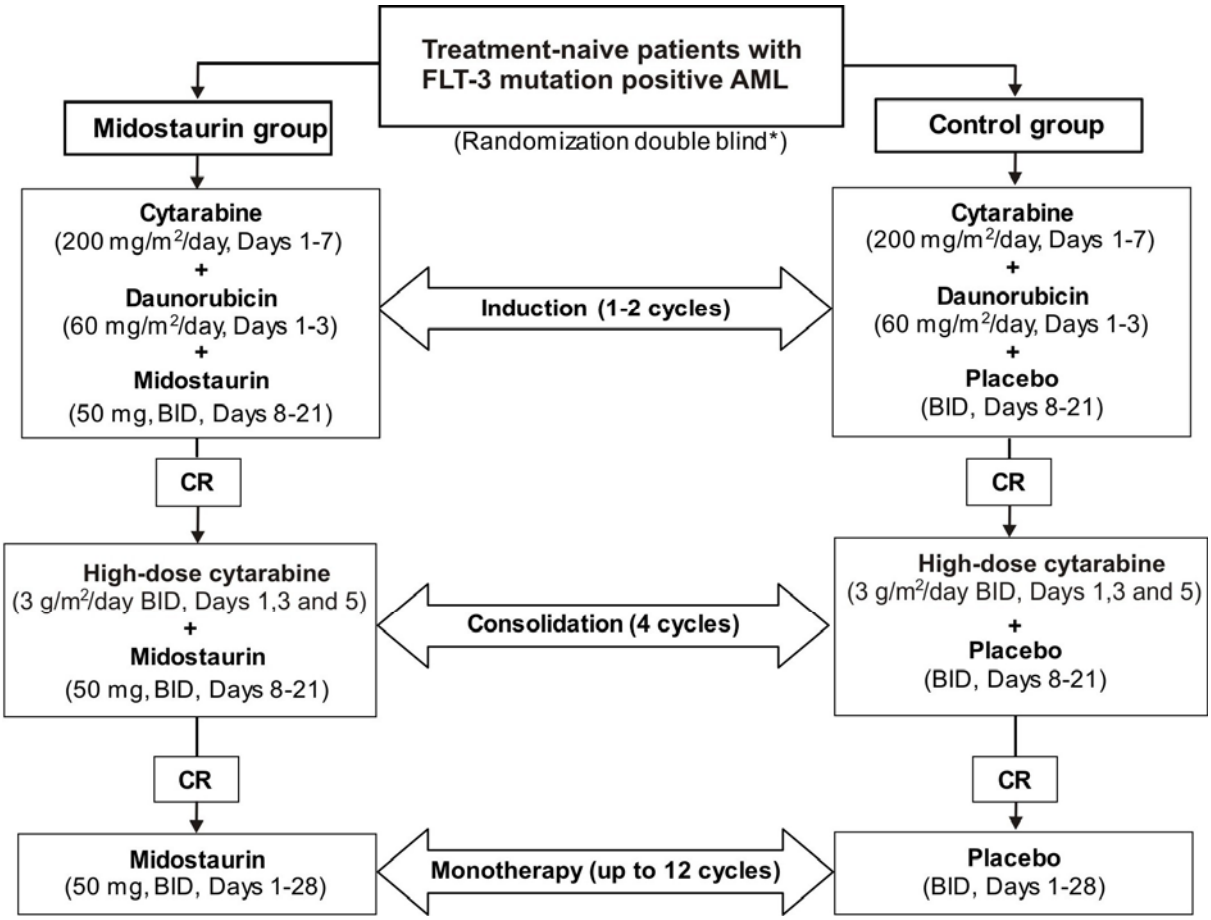
Fully assessing the impact of increasing the age of the eligible population on the cost-effectiveness of midostaurin is difficult, due to the lack of appropriate data, but the ERG considers that the exclusion of this high-risk group of patients is likely to have created a more favourable treatment effect for midostaurin in the primary efficacy analysis, with a commensurate effect on cost-effectiveness. Further, even if the relative benefits of midostaurin treatment are the same across both younger and older patients, the absolute benefits of treatment in older people are likely to be much lower than in younger people, in part because the prognosis of older patients is worse, but also because older patients on average have fewer years to live than younger patients and, therefore, the benefits of cure are lower in older patients. The ERG presents an additional scenario analysis, in Section 6, to explore the impact of age on the ICER.

5.2.4 Interventions and comparators

The intervention and comparator implemented within the model were in accordance with the administration schedule used in the RATIFY trial. The RATIFY trial evaluated the addition of midostaurin (oral therapy) to conventional care, which consisted of up to two cycles of daunorubicin plus cytarabine (SOC), in the induction phase, followed by four cycles of high-dose cytarabine, in the consolidation phase, and for patients who achieved full remission, continued treatment with midostaurin as a single agent for up to one year (12 cycles) after that.

The anticipated recommended dose of midostaurin is detailed as 50 mg twice daily, with each 50 mg dose administered as 2 x 25 mg soft gel capsules. Midostaurin is administered on days 8–21 of induction and consolidation chemotherapy cycles, and is then taken twice daily as single-agent therapy for up to 12 months. Dosage in the executable model was based directly on the therapy received in the RATIFY trial. The dosing of midostaurin, in the model, was therefore in line with the (anticipated) recommended dose of midostaurin outlined above. The dosing of chemotherapy agents in both the midostaurin and SOC arms was as follows: during the induction phase, cytarabine (200mg/m^2/day; days 1-7) plus daunorubicin (60mg/m^2/day; days 1-3); followed by cytarabine (3g/m^2/day; days 1, 3, and 5), during the consolidation phase. See Figure 3 for a schematic of the detailed dosing schedule that was used in the RATIFY trial. Dose reductions, due to adverse events, were accounted for in the executable model, using data on the within-trial distribution of doses of midostaurin and chemotherapy agents.

Figure 3 Dosing used in the RATIFY clinical trial (CS, Figure 21, page 108)



RATIFY CSR.[16]
AML, acute myeloid leukaemia; BID, twice daily; CR, complete remission; CSR, clinical study report; FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; TKD, tyrosine kinase domain.
* Central randomization within 3 strata: FLT3-TKD, FLT3-ITD with allelic ratio ≥ 0.7; FLT3-ITD with allelic ratio <0.7.
** Up to 12 cycles.

For costs purposes only, patients within the economic model, are permitted to receive secondary therapy after the failure of primary treatment. Failure of treatment occurs if patients experience a non-mortality-related EFS event (relapse or failure to achieve CR). The RATIFY trial did not record therapies received following the discontinuation of primary therapy and, therefore, external evidence was used to inform the costs of additional lines of therapy. The composition of secondary therapy was informed by expert opinion and was assumed to consist solely of FLAG-Ida. The duration and frequency, with which patients received secondary therapy, was sourced from the Kantar CancerMPact report,[42] which elicited information from 75 physicians on the proportion of AML patients receiving second, third and fourth lines of therapy.

ERG Comment

The ERG considers the intervention and comparator therapies, used in the model, to be appropriate and in line with the NICE scope.

The ERG also considers the assumptions made regarding secondary therapies to be reasonable and consistent with care in the UK. The ERG, however, does note that there is some potential for bias within the cost-effectiveness evaluation as a consequence of the use of external data to populate the model. This is because, without knowing what secondary therapy patients received in the RATIFY trial, there is uncertainty as to whether there were any systematic differences in the secondary therapies received, by each treatment arm, and, therefore, whether the observed OS gains were in part be due to differences in secondary therapies received. Further, if the secondary therapies, received by patients enrolled in the RATIFY trial, differed significantly from UK practice, there is the possibility that observed OS gains in the RATIFY trial may differ substantively from OS gains that would be realised in UK practice.

5.2.5 Duration of treatment

The duration of treatment within the economic model was based on the entire treatment pathway reported in the clinical trial data. The duration of primary treatment, therefore, includes treatment received during induction, consolidation, and monotherapy. The proportion of patients receiving treatment in each cycle was based on patient-level data from the RATIFY trial, but with the assumption that the maximum number of cycles of monotherapy was 12. This is consistent with the draft summary of product characteristics for midostaurin, but inconsistent with the RATIFY trial, in which a small number of patients received monotherapy for longer than 12 cycles. The company presented a scenario analysis, in which the maximum number of cycles of monotherapy was increased to 18 cycles, after which all patients in the RATIFY trial had discontinued therapy. The company justified the use of patient-level data, rather than using time-to-event data, on discontinuation, on the basis that the time-to-event data would not have accounted for the fact that some patients in the RATIFY trial had treatment-free periods and, therefore, did not receive therapy. A scenario analysis was, however, included, in which time-to-event data were used to model the effects of time on treatment.

ERG Comment

The ERG accepts that the use of the patient-level data, in place of time to discontinuation, was a reasonable base-case, but notes that there is some uncertainty as to whether treatment breaks would result in fewer packets of midostaurin being administered. The ERG, however, considers it unreasonable to cap the number of cycles of monotherapy at 12, as this means that the cost data being used in the model are inconsistent with the clinical data. The ERG therefore considers that the

scenario, in which the maximum number of cycles of monotherapy is increased to 18, is the more plausible.

The ERG also noted that the scenario, in which time-to-event data are used in place of patient-level data, did not correctly calculate the proportion of patients in the induction, consolidation and monotherapy treatment phases. At the clarification stage, the ERG therefore requested that the company fix this calculation error. The response and revised model provided by the company, unfortunately, did not address this issue and instead reconfigured the calculation of the base-case scenario. These changes addressed a simplifying assumption, made in the original model, to avoid complications arising from the fact that some patients received one cycle of induction therapy and others two. These changes, however, also unfortunately completely removed the time-to-event scenario. Further, the ERG noted discrepancies in the total units of treatment received, between the original company model and the revised model provided at the clarification stage. In the original model, in total, 6.19 cycle-units of midostaurin treatment were administered, compared with 6.02 in the updated model. Similarly, a total of 2.84 cycle-units of SOC was implemented in the original model, compared with 2.89 cycle-units in the updated model. These differences act to reduce the ICER, because they reduce the difference in drug acquisition costs. The ERG is very concerned about the amendments made by the company at the clarification stage, and can see no reason why the total units of therapy received should change. The ERG is not able to discern which of these sets of values is correct and, therefore, presents exploratory analysis, in section 6, in which the time-to event scenario is added back into the model, and in which the impact of the revisions made by the company at the clarification stage is explored.

5.2.6 Perspective and time horizon

The economic model adopted a National Health Service (NHS) perspective in accordance with the NICE reference case.

The time horizon used in the economic model was 700 cycles or approximately 54 years. The NICE reference case indicates that the time horizon used for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs and benefits between the technologies being compared. The ERG considers that the 700 cycle was an appropriate time horizon, as very few patients are predicted to remain alive beyond 700 cycles.

5.2.7 Discounting

The costs and benefits in the model were discounted at an annual rate of 3.5%, as per the NICE reference case.

5.2.8 Treatment effectiveness and extrapolation

As stated previously, to establish the cost-effectiveness of Midostaurin, the company used a partition survival approach, which used the RATIFY trial to provide a direct comparison of the timing and rates of complete remission, relapse, SCT, and death. For details of the RATIFY trial, see section 4. The company used the data cut-off 01 April 2015 for the primary efficacy analyses to inform the base-case. As noted in section 4, a further data cut for the RATIFY trial is now available and this was requested by the ERG, at the points for clarification stage. These data were not included in the company's revised economic model as part the company's clarification response; but are explored as part of the additional analysis, carried out by the ERG, see Section 6 for details.

Within the first 80 cycles (~ 6.2 years), the model calculated the proportion of patients in each health state, by treatment, at 28-day intervals, using Kaplan-Meier data on OS, CR, SCT and time on primary therapy. The calculation of the proportion of patients in each of the five health states was as follows:

- **AML diagnosis/induction –** All patients enter the model in the AML diagnosis health state and is calculated as the proportion of patients on treatment, but not in CR. Note all patients who do not achieve CR by cycle two discontinue therapy and, therefore, patients can only stay in the AML diagnosis health state for a maximum of two cycles.
- **Complete Response/remission (CR) –** Time-to-event data on CR and time on treatment.
- **Relapse –** This a residual health state and calculated as one minus the AML diagnosis, CR, SCT and death health states.
- **Stem cell transplant (SCT) –** Time-to-event data on SCT censored for OS.
- **Death –** The proportion of dead patients is calculated as one minus the OS curve.

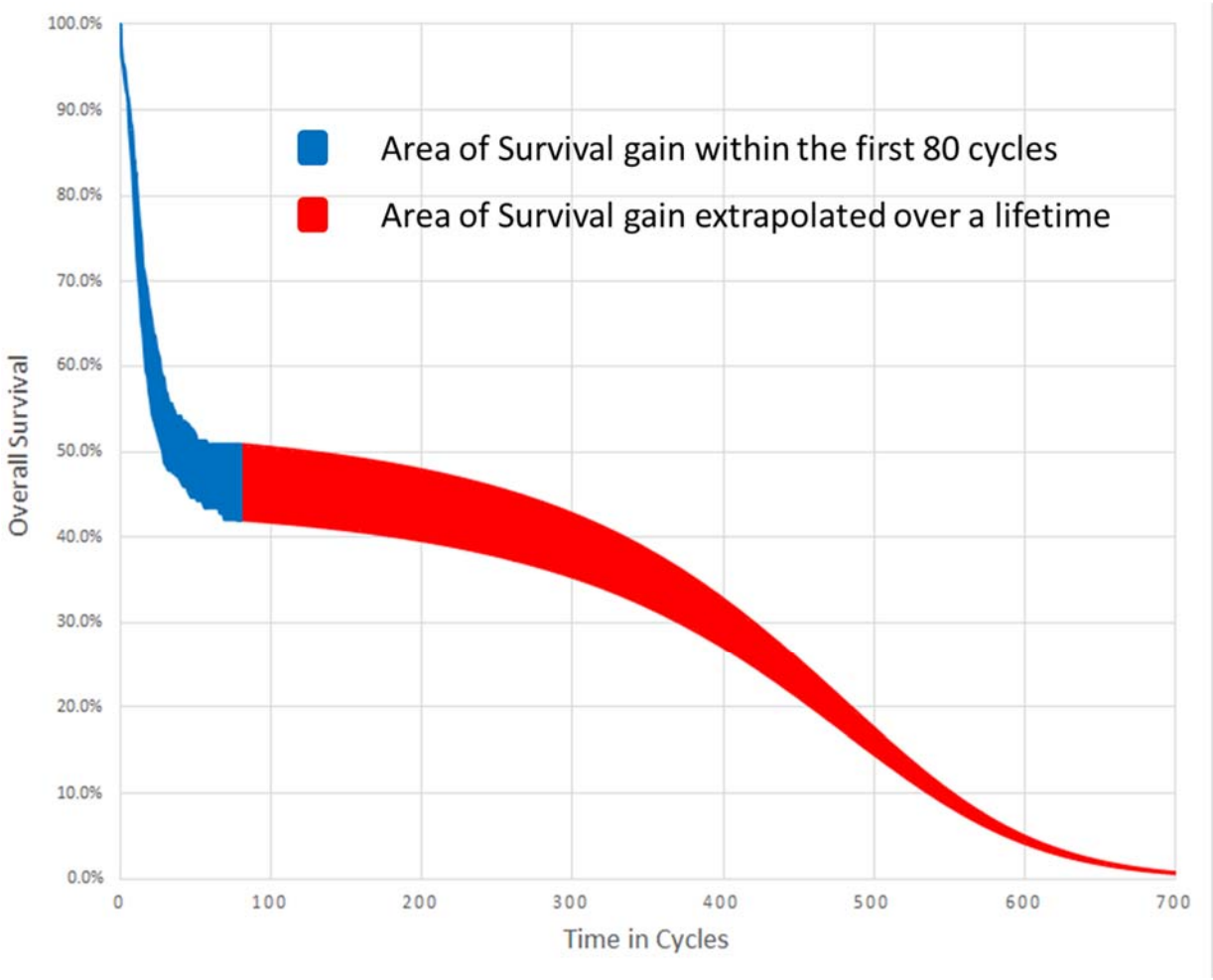
After cycle 80, surviving patients in all health states are assumed to be cured and are considered to be survivors, who experience a low risk of relapse. Therefore, after cycle 80 of the model, the company assumed that surviving patients entered a phase where they followed similar characteristics to that of the general population (same mortality risk). The specific choice of cure point, selected by the company, was determined by the availability of Kaplan-Meier data from the RATIFY trial, and was when the final event was observed in the chemotherapy arm. The company also put forward a series of arguments justifying the cure assumption, based on clinical opinion which noted the following: *"(1) following the first 2 years, patients are likely to become more stable depending on their disease status, with relapse and mortality becoming less frequent …; (2) after 5 years, patients are likely to follow a natural mortality curve as most of the leukaemia relapse occurred prior to this stage; (3) 10-year survival is likely to be approximately 10% lower than at the end of the trial (about 6.7 years prior), so the mortality trend should not be too aggressively extrapolated after the end of the trial; (4)*

the aggressive mortality/relapse rate of the first 2–3 years of the trial is not a good base for the long-term extrapolation…" (CS, page 113).

ERG Comment

The choice of cure point is very important to the outcomes of the model, because the survival gains observed at that chosen time point are extrapolated over an entire lifetime. This is illustrated in Figure 4, which shows the area of survival gain within the observed time period of 80 cycles (represented by the blue area between the treatment curves) and the area of survival gain extrapolated over a life-time (represented by the red area between the curves), with patients assumed to follow similar characteristics to those of the general population, after cycle 80.

Figure 4 Area of survival gain within observed and extrapolated time periods



The company's justification for the chosen cure point of 80 cycles was driven, in part, by this being the final observation and, in part, by clinical arguments suggesting that patients beyond this point will

experience general population mortality. With regards to the latter clinical arguments, advice from the clinical advisor to the ERG, suggests that the clinical justification put forward by the company with regards to the timing of the cure point is reasonable and the ERG further notes that the selected cure point aligns with the cure point used in economic models of other therapies in similar therapeutic areas.[35]

The selection of the cure point at 80 cycles is, however, somewhat arbitrary and while the ERG consider it a reasonable base-case, due to the fact it maximises the observable data available, the ERG is concerned by the fact that the sensitivity analysis did not explore the impact of selecting alternative cure points. The exploration of this uncertainty is important for two reasons. Firstly, as stated above, survival gains observed at the cure point are extrapolated over an entire lifetime and, therefore, the cure point is an important driver of cost-effectiveness. Secondly, because, there are relatively few patients observed in the later part of the Kaplan-Meier curve, the observed differences in OS in the tail of the Kaplan-Meier curve is subject to considerable uncertainty.

The updated model sent at the clarification stage did not incorporate the updated data from RATIFY as this was not requested by the ERG. However, the updated data were used in the ERG model, which reduces the uncertainty in the estimated OS differences at the base-case cure point of 80 cycles, as there are nearly four times the number of patients being observed.

5.2.8.2 Extrapolation beyond the trial follow-up

Overall survival

As stated above, the company directly incorporates the Kaplan-Meier data available on OS into the model and extrapolates these data, assuming that patients beyond cycle 80 experience general population mortality. The company's approach, therefore, did not fit parametric curves typically used in the extrapolation of time-to event data. The company justified this approach to extrapolation by having explored a range of parametric approaches, including using piecewise extrapolation of the Kaplan-Meier data and fitting parametric functions for the whole model duration. These approaches to extrapolation were, however, considered implausible on the basis of the clinical opinion cited above, which suggested that, after 5 years, patients were likely to follow a natural mortality curve. These alternative (parametric) models, were, however, explored in the scenario analysis for completeness.

The ERG considers that the approach taken by the company was the most appropriate, given the available data, because it avoids the need to make any assumptions about the data, e.g. proportional hazards, and it reflects the actual treatment effect observed in the trial.

Complete remission and EFS

As described above, in the trial follow-up period, the proportion of patients in the CR health state was determined using the Kaplan-Meier data from the RATIFY trial. To extrapolate beyond the trial follow-up period of 80 cycles, the company explored a range of parametric approaches, in which parametric functions were fitted to EFS Kaplan-Meier data. As with OS, the company's approach to extrapolation considered both using piecewise extrapolation of the Kaplan-Meier data and fitting parametric functions for the whole model duration. The selection of the most appropriate distribution considered (i) the visual fit to the observed Kaplan–Meier, (ii) statistical goodness of fit (measured using the AIC and BIC, and (iii) the plausibility of the long-term extrapolation.

The company noted that this process did not result in the identification of a distribution that both resulted in a smooth extrapolation of the EFS and was consistent with the extrapolation of OS. The company, therefore, opted to use a piecewise approach, in which a Weibull distribution was fitted to the tail of the Kaplan-Meier curve. This approach did not provide a smooth extrapolation after the end of the trial, but led to EFS extrapolation consistent with OS.

The ERG considers the company's approach to the extrapolation of CR to be extremely problematic. This is because it implies that some patients will not maintain their remission in the post-trial period and results in patients moving from the CR health state to the relapse health state after the cure point. This is inconsistent with the cure assumption for two reasons. Firstly, because it implies that cured patients are experiencing relapse, and secondly, because EFS includes mortality as an event, which means that patients in the CR health state are dying at a different rate to patients in the SCT and relapse health states. These problems largely result from issues with the model structure adopted and how patients are assumed to transition through the model, see section 5.2.1 for details.

With regards to the selection of the appropriate distribution, the ERG considers that it is unnecessary to extrapolate CR if you are assuming cure after 80 cycles. The selection of the most appropriate curve is therefore largely irrelevant and not discussed further.

5.2.8.3 Mortality beyond the trial follow-up

As stated above, after cycle 80, surviving patients in all health states are assumed to be cured and are considered survivors. After the cure point, general population mortality rates were applied to both treatment arms, using gender- and age-adjusted mortality data from the ONS. These adjustments for gender and age were based on the gender and age distribution of the patients in the RATIFY trial.

ERG Comment

The ERG has significant concerns with regards to the cure assumption and specifically the assumption that patients revert back to general population mortality rates. The ERG acknowledges that this is a common assumption, applied within existing models, in the general area, but considers that this assumption is subject to significant uncertainty. The ERG notes that several clinical studies have

formally assessed the long-term survival of AML patients, and have consistently reported higher long-term morality rates amongst survivors, compared with the general population.[43-46]

During the clarification stage, the ERG requested that the company provide additional clinical evidence to support the cure assumptions and to discuss the generalisability of the findings from existing studies, which suggest ongoing mortality differences, compared with the general population. In their response, the company acknowledged the potential for an elevated mortlaity risk amongst survivors and modified mortality, after the cure point, to include a standardised mortality risk of 2.0. A justification for using the value of 2.0 was not given and was not based on any of the cited literature on the long-term survival of AML patients.

The ERG considers that there remains significant uncertainty surrounding the longer-term survival of AML patients. For example, the study by Martin et al. (2011),[45] which considers post-SCT patients, concluded that, while mortality improves dramatically during the first five years after SCT the rates "remain four to nine-fold higher than the general population for at least 25 years thereafter".[45] The ERG acknowledges that many of the studies are derived from historic cohorts and hence may over-estimate mortality, compared with current practice. The ERG also acknowledges that these studies focus on the long-term survival of AML patients, following SCT, and that the long-term survival of patients achieving remission with drug therapy alone may be different. However, the vast majority of survivors in the RATIFY trial received SCT, and it is clear, from the literature, that concerns persist regarding the long-term effects of SCT.[47] The ERG, therefore, includes further scenarios applying alternative SMRs, based on the literature, to explore this uncertainty, in Section 6.

5.2.9 Health-related quality of life (HRQoL)

5.2.9.1 Health State utilities

The pivotal clinical RATIFY trial did not collect HRQoL evidence from the trial participants. The company therefore undertook a systematic literature review of utility studies that reported relevant health-state values.

The CS described the search strategies used to identify relevant studies of utility values/HRQoL associated with AML. The search strategies were briefly described, in the main body of the submission, and full details were provided in Appendix 13. MEDLINE, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and EMBASE were searched, via the Ovid platform, covering the period January 1st, 2006 to November 20th, 2016. The bibliographies of relevant systematic reviews and meta-analyses, found through the database searches, were checked to identify further relevant studies.

The sources, searched by the company, were appropriate for a systematic review of HRQoL studies. The ERG was unable to assess the appropriateness of the search strategies for the systematic review of HRQoL studies, as they were not provided in the original submission and were not requested in the points for clarification. However, the ERG is not aware of any missing studies from the systematic review carried out by the company.

The systematic search identified ten studies that reported health-state-specific values. In the base-case model, the identified utility values were used directly for the CR 1L (complete response emission following discontinuation of therapy), relapse and on treatment (induction, consolidation, and monotherapy) health states. The utility values for the three SCT sub-states (treatment, recovery, and post recovery) were mapped from published EORTC Quality of Life Core Questionnaire (QLQ-C30) data[33] onto EQ-5D values, using an algorithm developed by Crott et al. (2010).[34]

The company also conducted a separate time trade-off study (TTO), which recruited 212 participants from the general population. Each participant had a face-to-face interview and was asked to value a range of health state descriptions, by choosing between living in the given state, for 10 years, or living in perfect health, for a set amount of time. The study followed the NICE guidance by complying with the York measurement and valuation of health protocol. However, the company chose not to use the resulting values from this study in their base-case analysis, citing inconsistencies in the study. Sensitivity analysis, conducted by the company, found that using the values estimated from the TTO study in the executable model resulted in the ICER increasing, though not markedly.

Table 17 provides a summary of the utility values used within the model for the base-case and scenario analyses, including the source.

Table 17 Summary of utility values applied in the model (CS, table 29, page 123)

Utility state	Utility values used in base case (literature)	Values used in scenario analysis (TTO)	Source (literature values)
Induction treatment*	0.648	[redacted]	Uyl-de Groot _Br J Haematol_1998[48]
Consolidation treatment*	0.710	[redacted]	Batty et al. 2014[49]
Monotherapy treatment*	0.810	[redacted]	Batty et al. 2014[49]
Complete remission post-1L (No relapse)	0.830	[redacted]	Leunis et al. 2014[50]
Relapse	0.530	[redacted]	Pan et al 2010[51]
SCT Treatment *	0.613	[redacted]	Source for Algorithm - Crott et al. 2010;[34] Source of QLQC30 data – Grulke et al. 2012[33]
SCT Recovery	0.810	[redacted]	Source for Algorithm - Crott et al. 2010;[34] Source of QLQC30 data – Grulke et al. 2012[33]
Post-SCT Recovery	0.826	[redacted]	Source for Algorithm - Crott et al. 2010;[34] Source of QLQC30 data – Grulke et al. 2012[33]
*Includes treatment disutility Post-1L, post-first line; SCT, stem cell transplantation			

ERG Comment

The ERG agrees with the company that the values from the literature are superior to those generated by the TTO analysis. The values generated by the TTO analysis do appear to lack face validity, when compared with the values from the literature presented in the company's systematic review, and are also inconsistent with a TTO analysis of 125 members of the UK general public[52] published during the appraisal.

The, ERG, however, does have some concerns about the utility values used in the model. For several health states, there were multiple values published in the literature, and the company did not clearly justify how these values were selected from the multiple sources. For the SCT, SCT recovery and Post-SCT recovery states, the company used values from Grulke et al.,[33] but values were also available from two other sources Uyl de Groot et al. [48] and Kurosawa et al.[53] No justification was given for why the values from Grulke et al.[33] were used. The value used in the Post-SCT recovery health state was particularly important as a substantial number of patients spend an extended period of time in this health state, and the use of the lower values in Uyl de Groot, 1998[48] and Kurosawa et al.[53] increases the ICER. Further, the ERG notes that the values reported in Uyl de Groot et al. [48] and Kurosawa et al.[53] are more consistent with the values estimated in the new TTO analysis[52] mentioned above.

Further to the above, the ERG notes that the utility values, applied to the CR 1L and Post-SCT recovery health values, refer to specific time points. Evidence suggests that utility declines with age[54] and, therefore, while the utilities applied to the CR1L and Post-SCT recovery health states are lower than those typically reported for the general population at age 45 (the mean age in the model) these

values would eventually exceed general population utility estimates, when accounting for age-related decline in HRQoL. The ERG therefore considers that the utilities used in the CR 1L and Post-SCT recovery health states should be further adjusted for age to account for age-related decline in HRQoL. This is explored further in section 6.

5.2.9.2 Adverse event disutilities

The company's model did not incorporate disutilities for adverse events, relating to primary treatment, SCT or secondary therapy. The company's justification for this approach was that the disutilities associated with treatment toxicity were accounted for by using utility values specific to each phase of treatment and recovery.

ERG Comment

With respect to primary treatment and secondary therapy, the ERG considers that the company's justification is not unreasonable, due to the fact that the model distinguishes between patient's phase of therapy (induction, consolidation, monotherapy) and patients in relapse. The ERG, however, notes that this approach does not account for any additional toxicity associated with midostaurin treatment in the induction and consolidation phases. The overall impact of this assumption is, however, likely to be minimal, given the AE profile of midostaurin. With respect to SCT, though, the ERG does have some concerns. Stem-cell transplant is associated with a range of complications, the most serious of these is Graft Versus Host Disease (GVHD), a life-threatening adverse event, which affects approximately 40% of SCT recipients.[46] The base-case model, however, does not distinguish between patients who experience GVHD and those who do not, and, therefore, does not account for the quality-of-life reductions associated with this AE. This issue was raised with the company, during the clarification process. In the company's clarification response, they stated that they conducted a targeted literature search to identify any AEs associated with SCT and concluded that GVHD was the main AE leading to HRQoL decrements. The company therefore presented a scenario analysis including a disutility of 0.173 for GVHD. This disutility was derived from a study by Peric, et al. (2016),[55] which reported QLQ-C30 scores for patients undergoing SCT with and without GVHD. These QLQ-C30 scores were then mapped to EQ-5D utilities, using the Crott et al.[34] algorithm. The incidence of GVHD was assumed to be 39%, based on Wingard et al. 2011.[46] Additional costs associated with GVHD were added to the model in this scenario, see section 5.2.10 for details.

5.2.10 Resources and costs

The CS gave a detailed description of the resource use and costs incurred over time. These included: drug acquisition costs, drug administration costs, SCT costs, costs related to the health states, mortality costs, and costs associated with adverse events. To identify the cost and resource use data to inform the assessment of cost-effectiveness, the company performed a systematic review of the

literature to identify relevant studies containing cost and resource use information associated with the treatment of patients with AML (CS, Section 8.14, Appendix 14).

Nineteen studies met the inclusion criteria of this review, reporting a variety of cost valuations or health resource use consumption, and these are presented in Section 8.14, Appendix 14 of the CS.

5.2.10.1 Drug acquisition costs

Primary therapy costs

The CS noted that the drug acquisition cost for midostaurin was not yet available in the British National Formulary (BNF). Pack size, and price of each pack, of midostaurin were therefore based on Novartis data on file. For the AML indication, midostaurin is taken as 25 mg soft capsules and is provided as four packs of 28-day capsules, giving 112 capsules at a cost of [redacted]. The CS assumed no additional administration cost for midostaurin, as it is administered orally. The drug acquisition cost for SOC was taken from the BNF. Administration costs were assumed to be included within the health state costs.

The distribution of dosage, given in the trial, was used to calculate the drug acquisition cost per cycle. Tables 32, 33, and 34 of the CS (pages 126-128) present the distribution of dosage for the primary therapies (midostaurin, cytarabine, and daunorubicin, respectively), at each treatment phase. To estimate the cost per cycle, it was assumed that the average patient had a body surface area of 1.9 m^2 and a weight of 70 kg. This was based on the average body surface area and weight in the RATIFY trial. To obtain total costs per cycle of each therapy, the total dose (mg) of treatment per cycle (including wastage and dose reduction) was divided by the size of pack/vial before being multiplied by the price per pack/vial. The costs of primary therapy are presented in Table 18.

Table 18 Per-cycle costs of primary therapies (CS, response to clarification, updated executable model)

Phase	Arm	Regimen	Dose	mg per cycle	Vial size mg (or tablet)	Price per vial/tablet	Cost per cycle as per indication	Cost with wastage and dose reduction
Induction	Midostaurin therapy arm	Cytarabine	200 mg/m^2/day (1-7)	2660	500	[redacted]	[redacted]	[redacted]
		Daunorubicin	60 mg/m^2/day (1-3)	342	20	[redacted]	[redacted]	[redacted]
		Midostaurin	50 mg (2 x 25) twice per day (8-21)	1400	25	[redacted]	[redacted]	[redacted]
		Total cost per cycle					[redacted]	[redacted]
	Standard of care (SOC)	Cytarabine	200 mg/m^2/day (1-7)	2660	500	£19.50	£103.74	£112.68
		Daunorubicin	60 mg/m^2/day (1-3)	342	20	£65.00	£1,111.50	£1,216.16
		Total cost per cycle					***£1,215.24***	***£1,328.84***
Consolidation	Midostaurin therapy arm	High-dose cytarabine	3000 mg/m^2/day (1, 3, 5) twice per day	34200	500	[redacted]	[redacted]	[redacted]
		Midostaurin	50 mg (2 x 25) twice per day (8-21)	1400	25	[redacted]	[redacted]	[redacted]
		Total cost per cycle					[redacted]	[redacted]
	Standard of care (SOC)	High-dose cytarabine	3000 mg/m^2/day (1, 3, 5) twice per day	34200	500	£19.50	£1,333.80	£1,585.32
		Total cost per cycle					***£1,333.80***	***£1,585.32***
Monotherapy	Midostaurin therapy arm	Midostaurin	50 mg (2 x 25) twice per day (1-28)	2800	25	[redacted]	[redacted]	[redacted]
		Total cost per cycle					[redacted]	[redacted]
Cost source: British National Formulary								

Within the economic model, dose reduction was accounted for in the drug costs of all primary therapies (midostaurin, daunorubicin, and cytarabine) by using patient-level data, on the proportion of patients receiving therapy, from the RATIFY trial (See Section 5.2.5 for more details).

ERG comment

The ERG is largely satisfied with the sources and methods used to calculate the drug acquisition costs. The ERG is, however, concerned that drug wastage attributable to discontinuation of treatment was not accounted for in the model. For example, where patients die mid-way through using a pack of tablets. This issue was raised during the clarification process, with specific reference to mortality related discontinuation. In response, the CS stated that the clinical data were not designed to evaluate the discontinuation caused by mortality and they noted that very few patients died while on treatment.

The ERG accepts that drug wastage resulting from mortality related discontinuation is likely to be minimal, but notes that discontinuation occurs for reasons other than death, including AEs, relapse, or receipt of SCT. Further, inspection of the time-to-event data on treatment discontinuation, shows that many patients do not complete each phase of treatment, suggesting that abrupt discontinuation of treatment is common. The ERG does not explore this issue further in the exploratory analysis, however, because the use of patient-level data to model time on treatment makes the calculation of drug wastage very difficult to incorporate in to the economic model.

Subsequent (second-line) therapy costs

Within the model, it was assumed for costs purpose only that patients would go on to receive additional therapy if they experienced a non-morality related EFS event (e.g., relapse or failure to achieve CR). The RATIFY trial did not record therapies received following the discontinuation of primary therapy. Therefore, external evidence was used to inform the costs of additional lines of therapy. The duration and frequency with which patients received additional lines of therapy were from the Kantar CancerMPact report (2015),[42] which elicited information from 75 physicians on the proportion of AML patients receiving second, third and fourth lines of therapy. The Kantar report[42]also presented the most common regimen utilised for AML patients. The composition of subsequent therapy implemented in the model, however, was informed by expert opinion and assumed to consist solely of FLAG-Ida.

The duration of subsequent therapy was based on data from the Kantar report (2015),[42] which estimated that patients received 2.2 cycles of secondary therapy, on average. Based on these data, the company estimated that the average relapsed or refractory patient would receive 0.95 additional cycles of subsequent therapy, which was rounded up to 1 cycle in the base-case analysis.

The cost per cycle of subsequent therapy (i.e. therapies received following the first relapse) was calculated in the same way as for primary therapy costs, using data from the RATIFY trial on body surface area and weight, but it did not include the effect of dose reduction due to AEs. The average cost per cycle of subsequent therapy is presented in Table 19.

Table 19 Secondary therapy costs (CS, table 37, page 132)

Combination	Regimen	Dose	Body surface area/mass, m^2/kg	Dose	Number of days	mg per cycle	Vial size mg (or µg)	Price per vial, £	Price per cycle, £	Average number of cycles[a]
FLAG-Ida	Fludarabine	30 mg/m^2 IV CI, days 1-5	1.900	30	5	285.00	50.00	£155	£883.50	
	Cytarabine	2000mg/m^2/day (1-7)	1.900	2000	7	26600	500.00	£19.5	£1,037.40	
	Idarubicin	10 mg/m^2/d IV, days 1-3	1.900	10	3	57	10.00	£174.72	£995.90	
	Filgrastim (G-CSF)	5 mcg/kg, days 6-9	70.000	5	3	1050	300.00	£52.70	£184.46	
	Total cost per cycle								£3,101.27	2.2

aSource: Kantar Health. (2015)[42], Table 17 Utilization and number of cycles of systemic therapy at first relapse and second relapse, acute myeloid leukemia, Western Europe, 2015

ERG comment

Given the limited trial data, the ERG agrees that the choice of subsequent therapy was appropriate for UK practice, and for the general approach to implementing this, in the model. As, discussed in Section 5.2.4, the use of external data on secondary therapies does, however, mean that the clinical data, used in the model, do not match with the cost data. There is, therefore, some potential for bias in the estimated cost-effectiveness, if subsequent therapies have a substantial impact on outcomes.

5.2.10.2 SCT costs

The costs of SCT were drawn from NHS reference costs and calculated as a weighted average (weighting for the frequency of each type of SCT) of the cost of different types of SCT listed in NHS reference costs. This SCT cost was applied to all patients who received SCT as a "one-off" cost applied on entry to the SCT treatment health state. The additional costs associated with routine care during SCT treatment and SCT recovery were also implemented within the model (see details in section 5.2.10.3). The costs of long-term SCT post-recovery were assumed to be identical to the costs during CR 1L (see details in section 5.2.10.3).

ERG comment

The ERG is satisfied with the source of SCT costs used in the company's base-case, but notes that alternative sources suggest much higher costs for SCT. For example, the values identified by the ERG from NHS blood and transplant (2014)[56] suggest that the average cost of SCT is £98,178 (£110,930 accounting for inflation).

At the clarification stage, the ERG cited the alternative costs identified in NHS blood and transplant and requested further clarification about the alternative source of the SCT costs. In response to clarification, the CS provided a scenario analysis implementing the values from the NHS Blood and Transplant (2014).[56] The company, however, noted that the costs cited in the NHS blood and transplant report were from 2002, and that the SCT process had changed substantially in the intervening period, and that inflating 2002 costs to 2017 may not accurately reflect the current costs of SCT. The ERG considers the points raised, with regards to the cited costs from NHS blood and transplant, to be reasonable, but, given the significant differences between estimates, suggests that there is uncertainty regarding the costs of SCT. Examination of the results of the new scenario presented in the clarification response, however, suggests that the costs of SCT are not a significant driver of cost-effectiveness and, therefore, the ERG does not explore this uncertainty further.

5.2.10.3 Routine care costs

As described above, a systematic review of the literature was conducted to identify studies that reported resource utilisation. The assessment of these studies, by the company, to obtain appropriate resource data, however, noted that the identified studies were often lacking details on how the costs were estimated. Further, the health states used were different to those used in the company's model. See Section 5.5.2; and CS, Section 8.13, Appendix 13, for details of the identified studies.

Given the above lack of literature, the company opted to base their health state costs, in the model, on a previous NICE appraisal of AML, TA399:[27] Azacitidine for the treatment of AML in people aged 65 years or older with more than 30% bone marrow blasts who are not eligible for haematopoietic SCT. The company noted that the population considered in TA399 was somewhat different to the population considered in the current appraisal. The company, however, consulted with clinical experts about how these differences might impact on the resource use, in the population considered in this appraisal, and they considered that the resource use would be broadly the same between the two populations.

In NICE TA399,[27] the healthcare resource use was estimated from a clinician survey, conducted to quantify the resource use in terms of medical staff contacts (doctor, nurse, pharmacist, senior nurse, and consultant), monitoring and outpatient procedures, and hospital-related costs (e.g., inpatient stays). The healthcare resources used were estimated for four health states: (1) induction/pre-response, (2) in remission, (3) not in remission (which could include partial response, stable disease, or not in remission without progressive disease), and (4) progressive disease. Healthcare resource use was estimated separately by treatment arm for people initiating azacitidine and people initiating conventional chemotherapy regimens.

The mapping between the health state definitions from NICE TA399[27] and the health states used for the resource use is summarized in Table 20.

Table 20 Health states applied from NICE TA399 (CS, table 40, page 136)

Health states used in the model	Health states applied from NICE TA399	Rationale
Induction	'Induction/pre-response'	Identical health states
Second induction and secondary therapy	'Induction/pre-response'	Similar health states
Consolidation	'Remission'	Complete remission is required for reaching consolidation.
Maintenance/complete remission	'Remission'	Similar health states
Relapse	'Progressive disease' and 'not in remission' (midpoint)	Relapse in our model include both patients not in remission with and without progressive disease'.
SCT treatment	'Progressive disease' (doctor visit only)	SCT and recovery require active treatment and monitoring
SCT recovery	'Progressive disease' (doctor visit only)	
NICE TA399[27]		

The details of resource use items for the calculation of health state costs were presented in Table 41 of the CS (page 137). The unit costs of the different resources used were mostly obtained from the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care (2015) [with the exception of inpatient day care (obtained from NHS reference costs)]. Table 21 presents the routine care costs (per cycle) for the different health states implemented in the economic model.

Table 21 Routine care cost (per cycle) (CS, table 42, page 138; and CS, response to clarification, updated executable model)

Health states	Initiation costs	Induction	Secondary therapy	Consolidation	Monotherapy/Complete remission	Relapse	SCT treatment *	SCT recovery
Clinical nurse specialist Haematologist		£88.68	£88.68	£44.15	£44.15	£109.59	£0.00	£0.00
Consultant		£108.51	£108.51	£29.22	£29.22	£62.56	£0.00	£0.00
Day care nurse		£85.14	£85.14	£9.30	£9.30	£100.98	£0.00	£0.00
Day care specialist registrar		£46.18	£46.18	£19.33	£19.33	£36.87	£0.00	£0.00
District Nurse		£45.15	£45.15	£13.66	£13.66	£37.50	£0.00	£0.00
Doctor		£63.46	£63.46	£28.35	£28.35	£32.97	£170.62	£170.62
Jnr doctor		£69.40	£69.40	£5.26	£5.26	£32.78	£0.00	£0.00
Pharmacist		£78.88	£78.88	£1.70	£1.70	£24.90	£0.00	£0.00
Oncology nurse		£22.00	£22.00	£0.00	£0.00	£4.17	£0.00	£0.00
Inpatient day		£5385.59	£5385.59	£362.83	£362.83	£2498.76	£0.00	£0.00
ITD FLT3 testing	£150.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00	£0.00
Total cost	**£150.00**	**£5992.99**	**£5992.99**	**£513.78**	**£513.78**	**£2941.04**	**£170.62**	**£170.62**
Monitoring costs[$]		£66.39	£66.39	£16.70	£145.34	£1,942.94	£0.00	£0.00
Total cost^	**£150.00**	**£6,059.39**	**£6,059.39**	**£530.49**	**£659.12**	**£4,883.98**	**£170.62**	**£170.62**

*Follow-up included in the SCT unit costs
$ In response to clarification, monitoring costs were included
^ Total cost implemented in the updated executable model

ERG comment

The first and most important issue concerning the routine care costs, used in the model, relates to the model structure. Within this structure, these costs impact upon the health state costs used in the relapse, CR 1L, and post-SCT recovery health states. This issue is discussed in detail in Section 5.2.1, but is briefly repeated here, with emphasis on the cost values selected.

Relapse health state costs

As stated in the section 5.2.1, the company's model does not explicitly model the remission achieved on s subsequent therapy, therefore, once patients enter the relapse health state they cannot move back to the CR health state. This means that patients who are successfully treated with secondary therapies reside within the relapse health state for a very long time. The health states costs from TA399,

however, do not match with the mix of patients included in the relapse health state, because in TA399 this health state is for patients either receiving intensive second line therapy or, where subsequent therapy is inappropriate, palliative care. Patients, therefore, should not remain within this health state for an extended period of time. As stated in section 5.2.1, this issue has significant consequences and undermines the face validity of the model.

CR 1L, and post-SCT recovery health state

Both the CR 1L, and post SCT recovery health states are associated with ongoing health state costs, based on the health state costs assigned to the remission health state in TA399. As stated in Section 5.2.1, the ERG considers the application of the health state costs to the CR 1L, and post-SCT recovery health states to be inappropriate, as it is unreasonable to assume that patients will continue to utilise NHS resources in perpetuity, it is also inconsistent with other economic evaluations in similar therapeutic areas. The reason why the health state costs are applied in TA399 is because the population considered in TA399 had more severe disease and the patients were certain to relapse within in a relatively short time. The health state costs used in the remission health state in TA399 are therefore inconsistent with the current appraisal, where many patients survive for decades after diagnosis.

Monitoring and testing costs

In addition to the model structure-related issue identified, the ERG notes that the company's model was selective in incorporating all components of resource utilisation from NICE TA399.[27] The CS did not include the costs for drug monitoring tests and outpatient procedures (including transfusions) from NICE TA399.[27] Consideration of the literature, however, supports the inclusion of these resource items.[27] During the clarification process, this issue was raised with the company and the ERG requested further clarification on why the resource items were omitted. The company acknowledged the omission of these costs and included a scenario analysis, in which monitoring tests and transfusion costs were included. Drug monitoring tests were incorporated using the values used in TA399, inflated to 2017 prices, while transfusions of red blood cells and platelets were added to the model as AEs for induction and consolidation treatments phases. The incidence of these events was derived from the RATIFY trial results, and the costs were sourced from TA399.[27]

5.2.10.4 Mortality costs

Within the economic model, mortality-related costs were applied on death to represent the acute costs of care towards the end of life. These costs were obtained from Nuffield Trust (2014)[57] data, which included acute hospital care (all hospital contacts, emergency inpatient admissions, non-emergency inpatient admissions, outpatient visits, and accident and emergency visits), local authority-funded social care, district nursing care, and general practitioner visit costs in the final three months of life. The cost per mortality event was reported to be £13,176 in 2013[57] and then adjusted for inflation to

2017 values, based on PSSRU inflation rates. The economic model used a cost of £14,887 (inflation-adjusted) per mortality event.

ERG comment

The ERG considers the sources and assumptions made with respect to mortality costs to be reasonable.

5.2.10.5 Costs associated with adverse events

Within the economic model, grade 3/4 AEs with a prevalence of ≥5% in any of the three treatment phases (induction, consolidation, and monotherapy) were included. AE prevalence for the treatment phases was derived from the RATIFY trial results.[58] The AE prevalence per 28-day treatment cycle, for each AE, was calculated using the trial AE prevalence and the average duration of exposure to treatment in the trial (in cycle numbers) [RATIFY[58], CSR CPKC412A2301 - Table 12-2 Duration of exposure to study drug (Safety set)]. The unit costs for each AE were based on NHS Healthcare Resource Group (HRG) estimates (CS, Table 44, pages 141-142). The cost and prevalence of each AE (adjusted per 28-day cycle duration) are presented in Table 22. The final costs for AEs in each treatment group and treatment phase were calculated using weighted average costs of AEs and the proportion of people in the EFS in each cycle.

Table 22 AE cost and prevalence (adjusted per 28-day cycle duration) (CS, response to clarification, updated executable model)

AEs	Unit cost	Induction		Consolidation		Monotherapy	
		Midostaurin therapy	SOC	Midostaurin therapy	SOC	Midostaurin therapy	SOC
Platelet count decreased	£2,470	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count	£1,076	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemoglobin	£1,143	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	£3,579	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia NOS	£1,076	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphopenia	£1,957	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea NOS	£818	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	£1,320	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	£2,421	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dermatitis exfoliative NOS	£1,057	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	£664	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia NOS	£1,054	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis NOS	£892	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	£664	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	£959	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood bilirubin increased	£959	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infection	£3,630	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphataemia	£959	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma-glutamyltransferase increased	£959	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	£959	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Radiation mucositis	£664	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoalbuminaemia	£959	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	£664	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet transfusion[$]	£138	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Red blood cell transfusion[$]	£218	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost, £		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[$] added to the model during the clarification process							

As described previously, the subsequent therapies received by patients in the RATIFY trial were not recorded and, therefore, were not included in the economic model. Further, no adverse events relating to SCT were included in the economic model.

ERG comment

The ERG is largely satisfied with the approach used to implement the AE-related costs for primary therapy, although it notes some discrepancies in the input data, see Section 5.12 for details.

With respect to the AEs relating to subsequent therapy, the ERG considers this omission to be unfortunate, but not likely to have a significant impact on the ICER. This omission will also favour SOC, due to the fact that a higher proportion of SOC patients receive subsequent therapy.

The ERG considers the omission of AE's related to SCT to be more problematic and, as described in Section 5.2.9, asked the company to include AEs resulting from SCT. As described previously, the company carried out a targeted literature search to identify any AEs associated with SCT and concluded that GVHD was the main AE leading to a HRQoL decrement. The company therefore presented a scenario analysis that included a cost of treating GVHD of £55,145 sourced from Dignan et al.[59] The incidence of GVHD was assumed to be 39% based on Wingard et al. 2011.[46] An additional disutility, associated with GVHD, was added to the model in this scenario, see section 5.2.9 for details.

5.2.11 Cost effectiveness results

The executable model, developed by the company, was updated, at the clarification stage, to address a number of issues raised by the ERG. The revised model made the following changes to the executable model:

- Altered the calculation of time on treatment, to remove a simplifying assumption made in the original model, to avoid complications arising from the fact that some patients receive one cycle of induction therapy and others two (see section 5.2.5 for details)
- Implemented half-cycle correction
- Applied a corrected cycle transition formula to the AE rates
- Applied a corrected cycle transition formula to the discount rates
- Applied a corrected cycle transition formula to the mortality rates
- Included drug monitoring test and outpatient procedure costs (see section 5.2.10 for details).

The results presented in this section are extracted from the company's updated executable model and, therefore, differ from those presented in the CS. In this section, the results are presented for the deterministic base-case analysis; probabilistic sensitivity analysis; deterministic sensitivity analysis; and scenario analyses.

5.2.11.1 Base-case incremental cost-effectiveness analysis results

The base-case results are presented in Table 23. The company's base-case found midostaurin to be more costly (cost difference of £[redacted]), but also more effective (gain of [redacted] QALYs), compared

with SOC. The resulting deterministic ICER was £34,327 per QALY gained. The updates to the model, during the clarification process, had minimal impact on the model, reducing both the incremental costs and the incremental QALYS slightly, with a net effect of reducing the ICER to £33,672 per QALY.

Table 23 Base-case incremental cost-effectiveness ratios for midostaurin therapy vs SOC

Technology (and comparators)	Total costs	Total life-years	Total QALYs	Incremental costs	Incremental life-years	Incremental QALYs	ICER
Base-case in original executable model (CS main submission)							
SOC (Chemotherapy)	[redacted]	[redacted]	[redacted]				
Midostaurin therapy (midostaurin plus chemotherapy followed by midostaurin monotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,327
Base-case in updated executable model (CS response to clarification)							
SOC (Chemotherapy)	[redacted]	[redacted]	[redacted]				
Midostaurin therapy (midostaurin plus chemotherapy followed by midostaurin monotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,672

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; SOC, standard of care

5.2.11.2 Results of sensitivity analysis and scenario analysis

Probabilistic sensitivity analysis results

The company performed a probabilistic sensitivity analysis (PSA), where the parameters were sampled probabilistically from distributions based on 1,000 simulations. The PSA parameters and statistical distributions were presented in the CS main submission, Table 53 pages 156-157. The ICER results from the PSA were lower than from those of the deterministic analysis, as shown in Table 24.

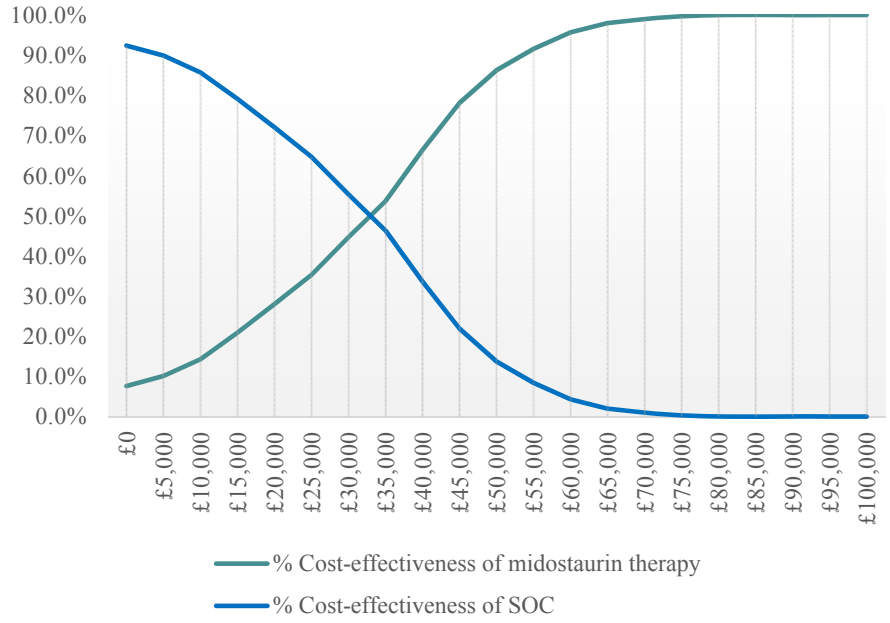
Table 24 Probabilistic sensitivity analysis results (CS, response to clarification, updated executable model)

Technology (and comparators)	Total costs	Total QALYs	Incremental costs (95% CI)	Incremental QALYs (95% CI)	ICER (95% CI)
SOC (Chemotherapy)	[redacted]	[redacted]			
Midostaurin therapy (midostaurin plus chemotherapy followed by midostaurin monotherapy)	[redacted]	[redacted]	[redacted]	[redacted]	£33,273 (-£5,780 to £58,254)
CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; SOC, standard of care					

The average QALYs gained with midostaurin therapy, compared with SOC, were [redacted] The average incremental cost was £[redacted]), resulting in an average ICER of £33,273 (95% CI, -£5,780 to £58,254) per QALY gained. The results of the PSA were different to those of the deterministic analysis (compare Table 23 and Table 24). Comparing the PSA results with the deterministic analysis results, there are significant increases in total costs and small decreases in total QALYs, for both treatments. Although, the differences in resulting incremental costs and QALYs are less in the PSA, than in the deterministic analysis, resulting in a lower ICER. This suggests that the model is non-linear in its inputs and, therefore, the deterministic results should not be relied upon.

A cost-effectiveness acceptability curve (CEAC) is presented in Figure 5. The results indicate that midostaurin therapy has 42.7% chance of being the cost-effective treatment, at the £30,000 willingness-to-pay (WTP) threshold, and 86.3% chance at the £50,000 WTP threshold.

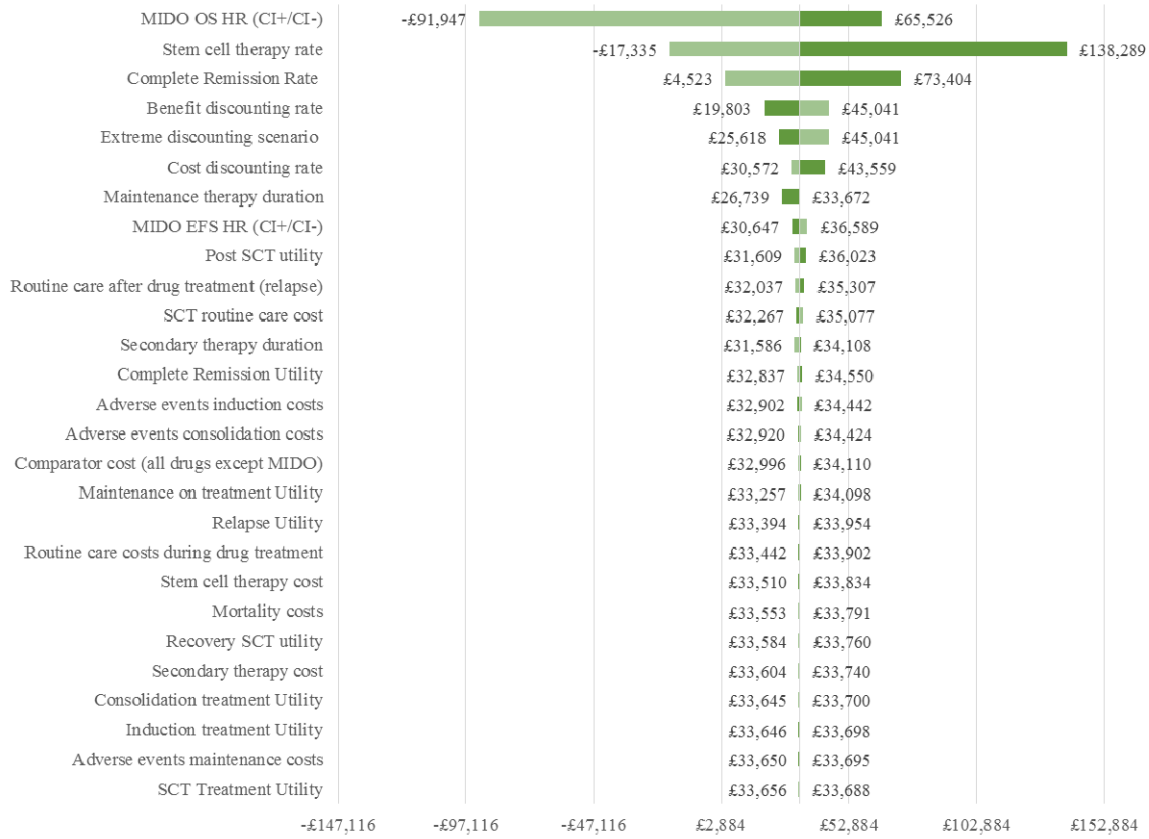
Figure 5 Cost-effectiveness acceptability curve (CS, response to clarification, updated executable model)



Deterministic sensitivity analysis results

The company presented a series of deterministic sensitivity analyses, to assess the impact of varying key model input parameters, on the ICER. Figure 6 shows a tornado diagram, summarising the influential parameters reported by the company. The results indicate that varying midostaurin's overall survival hazard ratio, the stem cell transplant rate, complete remission rate, and benefit discounting rate, have large effects on the ICER.

Figure 6 Deterministic sensitivity analysis results (cost per QALY) (CS, response to clarification, updated executable model)



Scenario analysis results

The submission also included an extensive series of scenario analyses to check the robustness of the model results to uncertainty relating to survival data, the parameters, and the structural assumptions. The results of the scenarios explored are presented in

Table 25. The results were notably most sensitive to variations in the time horizon and the point at which cure was assumed. The majority of the company's scenario analyses showed the cost-effectiveness of midostaurin therapy, compared with standard therapy, and a few scenarios showed midostaurin therapy as dominant. The scenario analyses, assuming a shorter time horizon, showed that midostaurin therapy was not cost-effective at the £30,000 WTP threshold, and the analyses incorporating the transition model (Markov state transition model) showed that midostaurin therapy was not cost-effective at the £30,000 WTP threshold.

Table 25 Scenario analysis results (CS, response to clarification, updated executable model)

	Technique	**Midostaurin therapy vs SOC**		
Scenarios		**Δ costs**	**Δ Benefit**	**ICER**
Base-case		[redacted]	[redacted]	**£33,672**
Cure model	Individual parametric curves with Gompertz distribution	[redacted]	[redacted]	£22,042
	Piecewise model with last observation as extrapolation cut-off	[redacted]	[redacted]	Dominant
	Cure model including adjustment for elderly	[redacted]	[redacted]	£26,225
Transition model	Using transition model after month 40 (transition based on patient level data)	[redacted]	[redacted]	£33,321
	Transition model with elderly adjustment	[redacted]	[redacted]	£38,599
Natural mortality rate	SMR at 200% of the general population	[redacted]	[redacted]	£26,167
Utility	Utility values from the TTO study	[redacted]	[redacted]	£23,547
Time horizon	Trial horizon	[redacted]	[redacted]	£68,198
	10 years	[redacted]	[redacted]	£44,146
Health care resource use	Chemotherapy instead of midpoint	[redacted]	[redacted]	£25,454
	Reducing HCRU by 50% after two years	[redacted]	[redacted]	£27,651
Overall Survival - Piecewise (Kaplan-Meier + tail)	Weibull	[redacted]	[redacted]	£28,557
	Exponential	[redacted]	[redacted]	£28,616
	Log-normal	[redacted]	[redacted]	£27,055
	Log-logistic	[redacted]	[redacted]	£26,579
	Gamma	[redacted]	[redacted]	£26,417
	Gompertz	[redacted]	[redacted]	£27,556
Overall Survival - Parametric with treatment covariate	Weibull	[redacted]	[redacted]	£24,637
	Exponential	[redacted]	[redacted]	£38,994
	Log-normal	[redacted]	[redacted]	£15,343
	Log-logistic	[redacted]	[redacted]	£21,049
	Gamma	[redacted]	[redacted]	£54,514
	Gompertz	[redacted]	[redacted]	£24,976
Overall Survival - Individual models	Weibull	[redacted]	[redacted]	£27,020
	Exponential	[redacted]	[redacted]	£39,087
	Log-normal	[redacted]	[redacted]	£28,820
	Log-logistic	[redacted]	[redacted]	£29,668
	Gamma	[redacted]	[redacted]	£22,322
	Gompertz	[redacted]	[redacted]	£21,560
Event Free Survival - Piecewise (Kaplan-Meier + tail)	Weibull	[redacted]	[redacted]	£26,507
	Exponential	[redacted]	[redacted]	£39,261
	Log-normal	[redacted]	[redacted]	£19,567
	Log-logistic	[redacted]	[redacted]	£17,119
	Gamma	[redacted]	[redacted]	£9,057
	Gompertz	[redacted]	[redacted]	Dominant
Event Free Survival - Parametric with treatment covariate	Weibull	[redacted]	[redacted]	£26,507
	Exponential	[redacted]	[redacted]	£39,261
	Log-normal	[redacted]	[redacted]	£19,567
	Log-logistic	[redacted]	[redacted]	£17,119
	Gamma	[redacted]	[redacted]	£9,057
	Gompertz	[redacted]	[redacted]	Dominant
Event Free Survival - Individual models	Weibull	[redacted]	[redacted]	£25,608
	Exponential	[redacted]	[redacted]	£39,260
	Log Normal	[redacted]	[redacted]	£17,955
	Log Logistic	[redacted]	[redacted]	£15,890
	Gamma	[redacted]	[redacted]	£9,510
	Gompertz	[redacted]	[redacted]	Dominant
Additional scenarios presented in response to clarification				

	Technique	Midostaurin therapy vs SOC		
Scenarios		**Δ costs**	**Δ Benefit**	**ICER**
Response to clarification question: B-1a	The CR time to event data currently used in the model with data on the proportion of patients in CR during trial follow-up was replaced	[redacted]	[redacted]	£26,507
Response to clarification question: B-1b	The SCT time to event curve by a SCT time to event curve that is censored for both OS and relapse was replaced	[redacted]	[redacted]	£33,306
Response to clarification question: B-1c	Relevant adverse events were added	[redacted]	[redacted]	£36,339
Response to clarification question: B-1d	Patients to transition from relapse, SCT or CR to any of the other health states in the model were allowed	[redacted]	[redacted]	£42,109
Response to clarification question: B-4	A higher SMR (RR of 2.00) for long-term survival was used	[redacted]	[redacted]	£34,102
Response to clarification question: B-5	The cycle transition formula to the AE rates was applied	[redacted]	[redacted]	£33,905
Response to clarification question: B-6	Inclusion of elderly patients	[redacted]	[redacted]	£33,994
Response to clarification question: B-8	SCT costs based on NHS Blood and Transplant, 2014 was used	[redacted]	[redacted]	£29,419
Response to clarification question: B-9	Reduce routine care costs in the long run (e.g., reduction of 50% after 26 cycles)	[redacted]	[redacted]	£31,791
Response to clarification question: B-11	Drug monitoring test and outpatient procedure costs were included	[redacted]	[redacted]	£33,672

5.2.11.3 Conclusions

The analyses show that midostaurin therapy is not cost-effective at the £30,000 WTP threshold with deterministic ICER of £33,672 per QALY. The probabilistic analysis -case found that midostaurin therapy has a 42.7% chance of being the cost-effective treatment at the £30,000 WTP threshold and an 86.3% chance at the £50,000 WTP threshold. Additionally, the probabilistic and deterministic sensitivity analyses results, and pre-defined scenario testing, demonstrate that there is significant uncertainty relating to the survival data and extrapolation, parameters, and structural assumptions. The ICERs were most sensitive to variations in the time horizon and the point at which a cure was assumed.

5.2.12 Model validation and face validity check

Validation carried out by the company

The CS reports that several levels of model validation were undertaken as part of the model development process. These included assessment by clinical experts of key assumptions, and quality

assessment of the model, carried out by an external health economist and internal Health economists form Novartis.

Internal validation carried out by the ERG

The ERG undertook a review of the company's base-case and sensitivity analyses. This included the use of a checklist to carry out a series of black-box tests, to evaluate the internal validity of the model. These black-box tests examined the internal logic of the model, as well checking the predictive validity of the parameter inputs (e.g., that increasing the effectiveness of the treatment lowers cost-effectiveness). Further to this, the code of the model was examined for potential errors, this included tracking how the parameters fed into the model and an examination of the main calculation sheets, with a view to understanding how the QALYs and costs were accumulated in the model. This review identified a number of relatively minor calculation errors and inconsistencies. These were corrected by the ERG and the results for the corrected model are presented in Section 6. A full list of corrections made by the ERG is given below:

- Corrected calculation of the proportion of patients on induction therapy;
- Corrected calculation of proportion of patients in the relapse health state;
- Corrected input value used in the calculation of AE rates;
- Partially corrected calculation of proportion of patients initiating secondary therapy (data unavailable to fully correct);
- Corrected half-cycle correction calculations;
- Improved presentation of calculations pages to improve transparency (not a correction, but helped the ERG validate the model).

5.3 Conclusions of the cost effectiveness section

The cost-effectiveness review carried out by the company did not identify any published evidence on the cost-effectiveness of midostaurin in FLT3-mutation-positive AML in the UK. Consequently, the company's model represents the most relevant source of existing evidence. The ICER presented in the CS's original submission was £34,327 per QALY; and in the CS's response to clarification (using the updated model) was £33,672 per QALY.

In addition to the base-case analysis, the company presented a series of one-way sensitivity analyses and scenario analyses, to assess the impact of uncertainty around the key input variables and assumptions, on the ICER estimates. The results of these indicated that the base-case cost-effectiveness estimates were most sensitive to: (i) the overall survival hazard ratio, (ii) the SCT rate, (iii) the complete remission rate, and (iv) the benefit discounting rate.

The ERG considers that the company's economic submission meets the requirements of the NICE reference case but, is subject to a number of issues, which limit the credibility of the company's results. The principal issues identified by the ERG are outlined in brief below.

1. *Model structure*

   The ERG has significant concerns regarding the model structure, and notes a number of significant structural flaws, meaning that the model lacks face validity. Most importantly, the model does not fully accommodate h subsequent therapies and implies that responders to subsequent therapy remain the relapse health state while experience the OS benefits of subsequent therapy. The ERG is also concerned about the health costs assigned to the CR 1L (patients in remission post discontinuation of treatment) and post-SCT recovery health states lack validity and have a large impact on the ICER.

2. *The cure assumption*

   The model includes a point beyond which all surviving patients have general population mortality but, there is uncertainty surrounding this. Existing epidemiological evidence suggests that patients remain at a higher mortality risk for up to 30 years after SCT. Although this risk declines with time, the risk for patients surviving at least five years after SCT, without relapse, remains considerably higher than that for the general population (between 4 to 9 times higher, irrespective of age).

3. *The choice of the cure time point*

   The ERG is concerned about the lack of any real justification for the 80-cycle end point assumed in the base-case, which is largely determined on the basis that this was the last event in the RATIFY trial. The ERG considers this to be a reasonable base-case, as it is clinically justifiable and maximises the use of the available data, but noted the available OS data at these time points is subject to significant uncertainty as and consider that the impact of selecting alternative (clinically justified) cure points should have been explored in scenario analysis.

4. *Representativeness of the modelled population*

   The patient population modelled was based on patients enrolled in the RATIFY trial, which excluded patients over the age of 60 years. Epidemiological evidence suggests that the over 60's represent a significant proportion of the patients who are potentially eligible for treatment with midostaurin. Exclusion of this high-risk group of patients is likely to significantly underestimate the ICER, and there remains significant uncertainty as to the cost-effectiveness of midostaurin in older populations.

5. *The need to age-adjust utility estimates*

   When utility values are considered over a 60-year lifetime horizon, it is evident that the utility values assigned to the CR 1L and post-SCT recovery states may eventually exceed general population utility estimates, which naturally decline with age. The ERG thus considers that utilities in the CR 1L and post-SCT recovery state should be further adjusted for declining HRQoL with age.

6. *Adverse events related to SCT*

   The company's model did not included any AE's associated with SCT. Stem-cell transplant is associated with a range of complications, the most serious of these is GVHD, a life-threatening adverse event, which affects approximately 40% of SCT recipients.[46] The ERG consider unreasonable to omit SCT related AEs, particular given the fact that the rates of SCT are higher in patients who receive midostaurin.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.1 Overview

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the company's cost-effectiveness analysis presented in Section 5. This section is organised in five parts. Section 6.2 details the impact of errors identified in ERG's validation of the executable model and the impact of new OS and CR data provided by the company at the clarification stage. Section 6.3 details a series of exploratory analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. The analyses presented in Section 6.3 focus on exploring the following issues and uncertainties:

- Alternative assumptions regarding the model structure and ongoing differences in costs and QALYs.
- Alternative assumptions regarding post cure mortality rates;
- Increasing the maximum number of cycles of monotherapy.
- Discrepancies in the total units of therapy received in the original and revised company model.
- Adjusting utilities for the age of the cohort.
- Additional of SCT related AE's

In Section 6.4, based on a combination of the exploratory analyses presented in Section 6.3, the ERG presents an alternative ERG base-case that the ERG's considers to be more reflective of the cost-effectiveness of midostaurin. Section 6.5 then goes on to presented a series of further exploratory analyses using the ERG's preferred base-case model to explore remaining uncertainties regarding the cure point adopted, utility values used in the CR1L and post-SCT recovery health states, and the mean age of eligible patients. Section 6.6 presents a brief conclusion summarising the ERG's additional analyses.

6.2 ERG corrections and adjustments to the company's base case model

6.2.1 Calculation correction

As described in Section 5.2.12, the revised model provided by the company at the clarification stage contained a number calculation errors and inconstancies, which the ERG corrected. All changes made by the ERG were validated by members of the team working on this appraisal and by an ERG health economists external to this appraisal. A full list of all changes made by the ERG to the revised company model is included in Appendix 2. These corrections to the company's model reduce the deterministic ICER from £34,327 per QALY to £28,270 per QALY (See Table 26). This reduction

occurs due primarily to changes made by the ERG in the proportion of patients in the relapse health state, which reduces the incremental costs associated with the provision of midostaurin.

Table 26 ERG corrections to company's revised model

	Costs	QALYs	Incremental cost	Incremental QALY	ICER	Change in ICER
Company's base case results - original model (CS main submission)						
Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£34,327	n/a
SOC	[redacted]	[redacted]	-	-	-	-
Company's base case results - updated model (CS response to clarification)						
Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£33,672	- £655
SOC	[redacted]	[redacted]	-	-	-	-
Company's base case results - ERG's additional calculation correction implemented to CS updated model						
Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,270	-£6,057
SOC	[redacted]	[redacted]	-	-	-	-
ICER, incremental cost effectiveness ratio ; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care						

6.2.2 New OS data

As noted in Section 4.2.1, a further data cut for the RATIFY trial is now available and this was made available to the ERG as part of the company's clarification response. Table 27**Error! Reference source not found.** presents the results when this new OS data are used in the company's revised model: the deterministic ICER is reduced from £33,672 per QALY to £25,137 per QALY.

Table 27 Impact of the new OS data on ICER

Scenarios	**Treatments**	**Costs**	**QALYs**	**Inc. cost**	**Inc. QALY**	**ICER**	**Change in ICER**
CS base case[$]	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£33,672	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
New OS data	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£25,137	-£8,535
	SOC	[redacted]	[redacted]	-	-	-	-
$, CS base case results - updated model (CS response to clarification); ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care							

6.2.3 Original CR data

The revised model provided by the company at the clarification stage included new CR data, which censored the CR data for SCT events. These new data however, did not appear to be consistent with the uptake of SCT and lacked face validity. The ERG therefore considers the original uncensored CR data provided in the original company model, to be more representative of CR in the RATIFY trial. Table 28 presents the impact of reincorporating the original CR data into the company's revised model. This results in a reduction in the ICER from £33,672 per QALY to £31,531 per QALY.

Table 28 Impact of original CR data on ICER

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$]	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£33,672	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
CR data from original submission	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£31,531	-£2,141
	SOC	[redacted]	[redacted]	-	-	-	-
$, CS base case results - updated model (CS response to clarification); ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care							

6.2.4 All ERG corrections and adjustments implemented to the company's base case model

Table 29 presents the results of implementing the new OS and original CR data into the ERG's corrected model: the ICER reduces from £33,672 per QALY to £28,465 per QALY.

Table 29 Incremental cost-effectiveness ratio incorporating all corrections and adjustments to the company's base-case model

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$]	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£33,672	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
ERG's corrections and adjustments to the company's base case model	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	-£5,207
	SOC	[redacted]	[redacted]	-	-	-	-
$, CS base case results - updated model (CS response to clarification); ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care							

6.3 Exploratory ERG analyses

All analyses in this section are presented using the model presented in Section 6.2.4 which incorporates the new OS data, original CR data and calculation corrections made by the ERG.

6.3.1 Alternative assumptions regarding the model structure and ongoing differences in costs and QALYs

As outlined in Section 5, the ERG has substantial concerns about the model structure adopted by the company. The two primary concerns relate to (i) the failure to incorporate response to subsequent therapy, and (ii) the assumption that patients experience ongoing health state costs in the CR1L *(Complete remission following discontinuation of first lien therapy) and post-SCT recovery health states. It is not possible within the context of this critique for the ERG to compete rebuild the company's model. In this section the ERG therefore explores a number of assumptions, which remove some of the inconsistencies in the company's model structure and provided an indication of the results to be expected from a model structure that fully captures the costs and benefits of midostaurin treatment. .

6.3.1.1 Implementing response to secondary therapy

One of the clearest problems that arises from the failure to incorporate response to subsequent therapy in the model. To explore this issue the ERG made a number of changes to the company model implementing a new cured health state in which patients all alive patients experience CR1L costs and QALYs. In the first scenario it is assumed that patients enter the new cured health state at the cure point of 80 cycles (~6.2 years). The results of this first scenario are present in Table 30. The impact of implementing the cured health state in the model is to increase the ICER from ICER from £28,465per QALY to £30,821 per QALY.

Table 30 Additional of cured health state

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Cured health state	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£30,821	£2,355
	SOC	[redacted]	[redacted]	-	-	-	-

$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care

The model described above, while logically more consistent that the company's base-case does not fully address the issues relating to the relapse health state and the failure to model subsequent therapy.

Specifically, it still means that patients who achieve response to subsequent therapy can spend up to 78 cycles accruing significant health state costs and experiencing far lower HRQoL than responders to first-line therapy. The ERG therefore considers two further scenarios in which patients enter the cure health state earlier.

In scenario two, the model assumes that patients enter the new cured health state after three years. Three years is selected because after this point there is a clear plateauing of the OS curve and, as outlined in the CS, the rate of relapse drops significantly. In this new scenario patients continue to experience mortality events in line with the OS data from the RATIFY trial up until cycle 80, and therefore the cure health state does not imply that patient are fully cured, just that they are in remission. To account for the small number of relapses that occur after three years, this model also introduces a one off cost and disutility applied on relapse. This is assumed to be the equivalent to patients spending one cycle in the relapse health state. The model also keeps the cost of subsequent therapy which is also incurred on relapse.

In the third scenario the point at which patients enter the cured health state is pushed back even further to the point where patients discontinue first-line therapy. This version of the model all but removes the relapse health state from the model: patients can spend only a single cycle in the relapse health state. As in scenario two, patients continue to experience mortality events in line with the OS data from the RATIFY trial up until cycle 80 and one off costs and disutility of relapse are similarly included.

The results of these analyses are presented in Table 31. In scenario two where patients enter the cured health state after three years, the ICER increases from £28,465 per QALY to £36,555 per QALY. In scenario three where patients enter the cured health state after first-line treatment, the ICER increase from £28,465per QALY to £49,720 per QALY.

Table 31 Exploring timing of entering new cured health state

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Cure health state after 3 years	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,555	£8,090
	SOC	[redacted]	[redacted]	-	-	-	-
Cure health state after primary treatment	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£49,720	£21,255
	SOC	[redacted]	[redacted]	-	-	-	-

$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care

6.3.1.2 Ongoing health state in CR 1L and post-SCT recovery

As outlined in Section 5.2.1, the ERG consider the ongoing health state costs associated with the CR 1L and post-SCT recovery health states to be unjustified and it unreasonable to assume that patients will continue to accrue significant costs even after cure. To explore the impact of this assumption the ERG presents three scenario's mirroring those presented in Section 6.3.1.1 above. In the first scenario, zero health state costs are assumed in the CR 1L and post-SCT recovery health states after the cure point. In scenario two zero health state costs are assumed in the CR 1L and post-SCT recovery health states after 3 years and in scenario three zero health state costs are assumed in the CR 1L and post-SCT recovery health states after discontinuation of treatment. The results of these three scenario are present in Table 32 below. In scenario one the ICER is reduced to £21,201 per QALY , in scenario two it is reduced £19,263 per QALY and in scenario three it is reduced to £16,772 per QALY.

Table 32 Alternative CR 1L and post-SCT recovery health state costs

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Scenario 1 zero costs after cure point	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£21,201	-£7,265
	SOC	[redacted]	[redacted]	-	-	-	-
Scenario 2 zero costs after 3 years	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£19,263	-£9,203
	SOC	[redacted]	[redacted]	-	-	-	-
Scenario 3 zero costs after treatment	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£16,772	-£11,694
	SOC	[redacted]	[redacted]	-	-	-	-

$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care

6.3.1.3 ERG's preferred model structure

Section 6.3.1.1 and 6.3.1.2 presented scenario analyses in which the ERG modified the company's model in an attempt to address the identified flaws in the model structure. These scenarios, are not corrections and do not fully address all the issues with model. Selection of the most appropriate model structure given the limitations of the data available is somewhat subjective, but the ERG considers that a combination of both scenarios 3s (only a single cycle of relapse) from sections 6.3.1.1 and 6.3.1.2 gives the nearest approximation to an appropriate model structure. This scenario is the most different from the company's model and potentially represents the least conservative option, but there are several good reasons to consider this the most realistic version of the model. Firstly, with respect to ongoing health state costs it is consistent with previous models in other therapeutic areas which assume no further care costs after discontinuation of treatment. Secondly, this model implies consistency between the assumed subsequent therapy costs used, which are applied for one cycle, and the care costs associated with delivering subsequent therapy will are also only applied for one cycle. Thirdly, for those patients who do not receive subsequent therapy and instead receive palliative care, the model already incorporated end of life costs, and therefore additional costs of caring for these patients are not needed. Despite these strengths this version of the model also has some weaknesses. The most significant of these it that it does not properly account for QALY losses resulting from patients with refractory or relapsed disease. Table 33 presents the results of combing scenario 3 from both sections 6.3.1.1 and 6.3.1.2. The impact of these changes to the model is to increase the ICER form £28,465 per QALY to £39,720 per QALY.

Table 33 ERG's preferred model structure

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
ERG's preferred model structure	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£39,720	£11,255
	SOC	[redacted]	[redacted]	-	-	-	-
$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care							

6.3.2 Cure assumption

To explore the uncertainty surrounding the longer-term survival of patients beyond the cure point the ERG considers two scenarios is in which four-fold and nine-fold SMR are respectively applied to the general population mortality data used after the cure point. These represent the range of mortality risks reported in a study by Martin et al.(2010).[45] The results are presented in Table 34. Applying a four-fold mortality risk increases the ICER from £28,465 per QALY to £28,899 per QALY. Applying a nine-fold mortality risk increases the ICER from £28,465 per QALY to £29,205 per QALY.

The ERG's preferred base case is to use a four-fold higher mortality rate, in line with the lower bound estimated in Martin et al. (2010).[45] The use of the lower bound is more conservative, but could mitigate concerns about the historic nature of the cohort required for this type of long-term outcome analysis.

Table 34 Impact of increase in risk of mortality compared to general population after cure point

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected) [no adjustment assuming increased mortality after cure point]	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Four-fold increase in risk of mortality	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,899	+£434
	SOC	[redacted]	[redacted]	-	-	-	-
Nine-fold increase in risk of mortality	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£29,205	+£740
	SOC	[redacted]	[redacted]	-	-	-	-
$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care							

6.3.3 Duration of treatment

6.3.3.1 Alternative assumption of maximum cycle of monotherapy

As described in Section 5.2.5, the company's model assumed that the maximum number of cycles of monotherapy was 12. This is consistent with the draft SPC for midostaurin, but inconsistent with the RATIFY trial. Table 35 presents the results of scenario analysis in which the maximum number of cycles of monotherapy is increased to 18, after which all patients in the RATIFY trial had discontinued therapy. The impact of this scenario is to increase the ICER from £28,465 per QALY to £28,569 per QALY.

Table 35 Impact of alternative assumption of maximum cycle (up to 18 cycles) of monotherapy

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected) - [up to 12 cycle of monotherapy]	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
up to 18 cycle of monotherapy	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,569	£104
	SOC	[redacted]	[redacted]	-	-	-	-

$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care

6.3.3.2 Correct for discrepancy on total unit of treatment

As part of the revisions made by the company at the clarification stage the company modified the way in which time on treatment is calculated. These changes had the effect of reducing the total number of units of midostaurin that patients receive and increasing the total units of SOC. The ERG is not able to discern which of these sets of values is correct and can see no reason why they should differ. The ERG therefore, implemented a scenario analysis in which adjustments to the total units of treatment are applied to bring the time on treatment data into line with old model. This adjustment is carried out by applying a multiplier to the proportion of patients receiving consolidation and monotherapy, such that the total number of units of therapy now matches the total units received in the company's original model. The impact of this adjustment is to increase the ICER from £28,465 per QALY to £30,904 per QALY (see Table 11).

Table 36 Impact of correction for discrepancy on total unit of treatment

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Discrepancy in total units of treatment corrected	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£30,904	£2,438
	SOC	[redacted]	[redacted]	-	-	-	-
$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care							

6.3.4 Age adjusted disutility

The ERG believes it is appropriate to apply age adjusted utilities, to account for that fact that the benefits of cure are accrued over an extended period (see Table 37). The resulting ICER increases by £1,889 per QALY compared to CS base case.

Table 37 Impact of age adjusted utility decrement

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Age adjusted utility decrement	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£30,354	+£1,889
	SOC	[redacted]	[redacted]	-	-	-	-
$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care							

6.3.5 Addition of adverse events related to SCT

Table 38 presents the results of incorporating adverse events associated with SCT into the model: the ICER increased from £28,465 per QALY to £30,869 per QALY.

Table 38 Impact of SCT related AE's

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
SCT related AE's	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£30,869	+£2,404
	SOC	[redacted]	[redacted]	-	-	-	-
$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care							

6.4 ERG's preferred base case

Table 39 presents the ERG's preferred base-case which combines a number of the changes to the company base-case explored in Section 6.3. Specifically, the ERG base-case makes the following amendments to the company's revised base-case:

10. Corrections for calculation errors;
11. Addition of new OS data;
12. Addition of original CR data;
13. ERG's preferred model structure;
14. Applies a four-fold risk ratio to post cure mortality;
15. Applies age adjusted utility decrement into the model;
16. Increases the maximum number of cycles of monotherapy to 18;
17. Assumes total number of units of therapy matches the original company model;
18. Incorporates adverse events resulting from SCT.

The ERG considers this alternative base-case to be superior to the company's revised base-case and that the resultant estimate of the cost-effectiveness of midostaurin more plausible, notwithstanding the remaining issues with the model structure. The impact of combining these modifications to the company model is substantial, increasing the ICER from £34,327 in the revised company model to £62,810 in the ERG's preferred base-case.

Table 39 ERG's preferred base case

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
ERG's preferred base case	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£62,810	+£34,344
	SOC	[redacted]	[redacted]	-	-	-	-

$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care

6.5 Further exploratory analysis of uncertainties

This section presents additional scenario analyses considering uncertainty surrounding three assumptions/ inputs used in the model. These concern the cure point selected, the utility values for the CR 1L and post-SCT recovery health states, and the mean age of the population eligible for treatment with midostaurin. These additional analyses are performed using the ERG's preferred base case model.

6.5.1 Alternative cure point

As noted in Section 5.2.8, the choice of cure point is very important to the outcomes of the model because the survival gains observed at that chosen time point are extrapolated over an entire lifetime. Given the influence of the cure point, the ERG considers that further exploration of alternative cure points is warranted. The ERG explores this issue by assuming the following alternative cure points 4 years, 5 years and 7 years. The results of the analysis are presented in Table 40. The alternative cure points have significant influence on resulting ICER, with all three alternatives increasing the ICER. This is because the observed difference in OS is larger at cycle 80 (~6.2 years) than at any of the alternative cure points considered.

Table 40 Impact of alternative cure points assumption

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
ERG's preferred base case [cure point ~6.2 yrs]	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£62,810	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Cure point at 4 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£70,160	+£7,351
	SOC	[redacted]	[redacted]	-	-	-	-
Cure point at 5 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£64,207	+£1,397
	SOC	[redacted]	[redacted]	-	-	-	-
Cure point at 7 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£84,161	+£21,351
	SOC	[redacted]	[redacted]	-	-	-	-

ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care; yrs, years

6.5.2 Alternative assumption of utility values for CR 1L and SCT post-recovery health states

As outlined in Section 5.2.8, there were multiple sources of utility values for several health states in the model. The company, however, presented only limited scenario analysis exploring the impact of alternative utility values. The ERG therefore presents additional scenario analyses considering alternative sources for the CR 1L and post-SCT recovery states. The ERG focus on these two health states as the model is most sensitivity to the utility values for these states. In the scenarios carried out by the ERG it is assumed that the utility values for both health states will be the same on the basis these two states represent the "remission/potentially cured" health states in the model. To explore the uncertainty in the utility values for these health states, the ERG presents three scenarios representing the range of values reported in the literature. Table 41 presents the results of this analysis. The impact of using alternative utility values for these two health states is quite significant, with the ICERs ranging from £53,718 per QALY to £66,429 per QALY.

Table 41 Impact of alternative assumption of utility values for CR and SCT post-recovery health states

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
ERG's preferred base case	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£62,810	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Pessimistic assumption (Kurosawa-2014)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£66,429	+£3,619
	SOC	[redacted]	[redacted]	-	-	-	-
Optimistic assumption (Novartis-TTO)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£53,718	-£9,092
	SOC	[redacted]	[redacted]	-	-	-	-

$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care

6.5.3 Alternative assumptions of mean age of the AML population

One of the key issues raised in Section 4 and Section 5.2.3 concerning the trial was that it excluded patients over the age of 60. It is not possible to fully correct for the fact that the RATIFY trial excluded older patients, as there no other comparative efficacy data for midostaurin. It is however, possible to modify the model to take into account the fact that the benefit of cure will be lower in older patients due to reduced life expectancy. Table 42 presents the results of scenario analysis in which the mean age of patients is changed from 45 to 50, 55, and 60 years of age. The impact of increasing mean age is very significant, increasing the ICER substantially. This is because increasing the age of patients dramatically reduces the benefits of cure.

Table 42 Impact of alternative assumptions of mean age of the AML population

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
ERG's preferred base case [mean age – 45 yrs]	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£62,810	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Mean age – 50 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£70,513	+£7,704
	SOC	[redacted]	[redacted]	-	-	-	-
Mean age – 55 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£80,325	+£17,515
	SOC	[redacted]	[redacted]	-	-	-	-
Mean age – 60 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£92,619	+£29,809
	SOC	[redacted]	[redacted]	-	-	-	-

ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care; yrs, years

6.6 Conclusions from ERG analyses

The ERG has presented a number of additional analyses. These analyses were carried in a number of stages. The first stage addressed a number of minor calculation errors in the company's revised model and incorporated new OS data the original CR data into the revised company model. The impact of these changes was reduce the ICER from £33,672 per QALY to £28,569 per QALY.

Using the corrected and updated model the ERG then presented a number of analysis considering a range of issues raised in Section 5. These scenario analyses addressed the following issues:

- The model structure and ongoing differences in costs and QALYs.
- Assumptions regarding post cure mortality rates;
- The maximum number of cycles of monotherapy.
- Discrepancies in total units of therapy received in the original and revised company model.
- Adjusting utilities for the age of the cohort.
- Additional of SCT related AE's

The most of important these scenarios related to changes made by the ERG to the model structure and the ERG analysis explored a number of iterations of the model in which alternative assumptions regarding the model structure were made. These analysis explored two distinct issues with the company's model structure, firstly that it does not accommodate response to subsequent therapy and secondly that it assumes ongoing care costs for patients who are "cured". The results of this analysis

demonstrated that these structural issues have a significant impact on the ICER. This exploration of alternative model structures was concluded with the ERG presenting a preferred model structure. The ERG, while considering this model a more appropriate vehicle through which to assess the cost-effectiveness of midostaurin, do emphasise that this model does not represent a fully appropriate model: it still has significant limitations and weaknesses.

The ERG base-case analysis estimated midostaurin to be more costly (cost difference £[redacted]) and more effective ([redacted] QALY gain) compared with standard of care and suggests that the ICER for Midostaurin compared with SOC is around £62,810 per QALY.

A further series of exploratory analyses explored the impact of alternative assumptions regarding the selected cure point, utility values used in the CR 1L and post-SCT recovery health state and mean age of eligible patients indicate that the ERG's base-case ICER is likely to represent a lower bound with the majority of analysis's resulting in increases in the ICER; range £53,718 and £92,619 per QALY, assuming the ERG's base case assumptions.

Based on the ERG's base case analysis midostaurin is unlikely to represent good value to the NHS considering typical WTP thresholds.

7 End of life

NICE end of life supplementary advice should be applied in the following circumstances and when both the criteria below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

Regarding the criterion on normal life expectancy, the CS states that median OS for patients with AML in Europe is estimated to be less than 12 months. This is based on a report by Maynadie et al.[18] From the published Kaplan-Meier curves the ERG calculated a mean overall survival of 18 months. These two estimates of 'normal life expectancy might suggest one of less than 24 months. However, the relevance of these estimates of median and mean OS is questionable as they are derived from 1995-2002 cancer registry data and do not identify patients' age or treatment.

After a brief search of the literature, the ERG identified estimates of OS for AML patients that were more relevant to the current appraisal, in that they are for patients who had received the standard intensive chemotherapy that patients would receive were midostaurin not available (daunorubicin plus cytarabine). These are presented in Table 43 below.

This range of estimates reveals that the median OS for younger AML patients (15-64 years) on standard treatment appears to be significantly higher than that of reported by Maynadie et al., and improving over time: only the oldest estimates (from 2009) is of a median OS of less than 24 months. In addition, all the estimates of mean OS (calculated by the ERG) are over 40 months. Importantly, none of the studies provide a relevant estimate for OS in older AML patients

Table 43 mean and median overall survival estimates

Study	Country	Indication	Age group(yrs)	Treatment [Induction]	Median OS (months)	Mean OS (months)
Maynadie et al, 2013	Europe	AML	15-70+	NR	9.1 [a]	18 [a]
Recher et al, 2014 [23]	France	AML	15-60	Daunorubicin (60mg/m^2/day for 3 days) +cytarabine (200mg/m2/day for 7 days)	33 [a]	45 [a]
Ohtake et al, 2011 [22]	Japan	AML	15-64	Daunorubicin (50mg/m^2/day for 5 days) +cytarabine (100mg/m2/day for 7 days)	53 [a]	46 [a]
Mandelli et al, 2009 [21]	Europe	AML	15-60	Daunorubicin (50mg/m^2)+ cytarabine (25mg/m^2)+etoposide (100mg/m^2)	17 [a]	41 [a]
Stone et al, 2015 [60] RATIFY trial April 2015 cut-off data	worldwide	FLT3+ve AML	18-60	Daunorubicin (60mg/m^2 for 3 days)+Cytarabine (200mg/m^2 for 7 days)	26	[redacted]
CS-RATIFY trial September 2016 cut-off data	worldwide	FLT3+ve AML	18-60	Daunorubicin (60mg/m^2 for 3 days)+Cytarabine (200mg/m^2 for 7 days)	[redacted]	[redacted]
Key: [a], IPD data were reconstructed using respective Kaplan-Meier graphs so figures may not be entirely correct; NR, not reported.						

The current appraisal is, however, in the higher risk FLT3 mutant sub-group of the AML population. There is a paucity of RCT data on overall survival in this specific sub-group. The ERG agrees with the CS statements that FLT3 mutant AML patients, especially those with high mutant/wild type allelic ratio, have lower median OS than the more general AML population. However, whilst the cited estimate of OS for FLT3 mutant AML patients of less than 12 months (page 94 of the CS) is based on a cohort that did include older patients, it is relatively old data (1998-2002), and does not identify treatment regimens.[6]

The RATIFY study provides directly relevant, recent data on overall survival in the young FLT3 mutant AML population, on standard chemotherapy without midostaurin: median OS was 26 months and mean OS was 41 months.[60] See Table 43 above.

This estimate may lack generalisability to the FLT3+ve AML population in clinical practice eligible to receive midostaurin, because no patients aged over 60 years were included in the trial. It is unclear whether older patients, fit enough to receive intensive chemotherapy (and hence eligible to receive midostaurin) would have the same life expectancy as younger eligible patients. In the company's

clarification response, they argued that the RATIY population were representative of clinical practice. If this is true, then this population does not meet the first of NICE's End of Life criteria.

The data presented in the CS demonstrates clearly that addition of midostaurin increases OS by more than a normal 3 months, with a median increase of 49 months, and a mean increase of [redacted]. However, again it is not clear how generalisable this treatment benefit is to the population treated in practice; in practice where older (albeit fit enough for intensive chemotherapy) patients are treated, will the treatment benefit be as great?

8 Overall conclusions

Clinical effectiveness

Although the results of the RATIFY trial demonstrate a clear beneficial effect of midostaurin, with a median OS benefit of 49 months (and mean OS benefit of [redacted] months), in patients who do, and do not, undergo SCT as part of first line therapy for AML, there is significant uncertainty regarding the effect size.

This uncertainty relates mainly to the age of the RATIFY trial population, which was restricted to 60 years, with a mean age of 45 years. Given that the only available data on older patients (up to age 70 years of age, the Phase II trial) found that the treatment response was better in those under 60 years of age compared with those over 60 years, there is uncertainty about the size of the treatment benefit to be achieved with midostaurin in eligible patients who may be older than 70 years. This means that there is also uncertainty about the size of the effect for the whole eligible population (including all ages).

Cost effectiveness

The economic evidence presented by the company primarily consisted of a *de novo* model. The company's model used a partition survival model approach which directly used the time-to-event data from the RATIFY trial to determine the distribution of patients between the health states. The company found midostaurin to be more costly (cost difference of £[redacted]) and more effective ([redacted] QALY gain) compared with standard of care. The deterministic base-case ICER was £33,672 per QALY.

The ERG considers that the economic analysis presented by the company was inadequate to fully address the decision problem specified in NICE's scope. The ERG's principal concerns related to the structure of the model, which contained a number of significant structural flaws meaning that the model lacks face validity. The ERG was unable to fully rectify all the identified issues with the company's model, but was able to carry out a number of analyses using assumptions and data inputs it believes are more plausible than those used in the company's base-case analysis. The ERG base-case analysis estimated midostaurin to be more costly (cost difference £[redacted]) and more effective ([redacted] QALY gain) compared with standard of care and suggests that the ICER for Midostaurin compared with SOC is around £62,810 per QALY.

8.1 Implications for research

Further RCT evidence in of older (aged > 60 years) FLT3-positive patients, who are suitable for intensive chemotherapy, is required.

9 References

1. Fathi AT, Chen Y-B. Treatment of FLT3-ITD acute myeloid leukemia. *Am J Blood Res* 2011;1:175-89. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3301423/

2. Sekeres MA, Elson P, Kalaycio ME, Advani AS, Copelan EA, Faderl S, et al. Time from diagnosis to treatment initiation predicts survival in younger, but not older, acute myeloid leukemia patients. *Blood* 2009;113:28-36. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2614639/

3. Dohner H, Estey EH, Amadori S, Appelbaum FR, Buchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood* 2010;115:453-74. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19880497

4. Janke H, Pastore F, Schumacher D, Herold T, Hopfner KP, Schneider S, et al. Activating FLT3 mutants show distinct gain-of-function phenotypes in vitro and a characteristic signaling pathway profile associated with prognosis in acute myeloid leukemia. *PLoS One* 2014;9:e89560. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24608088

5. Santos FP, Jones D, Qiao W, Cortes JE, Ravandi F, Estey EE, et al. Prognostic value of FLT3 mutations among different cytogenetic subgroups in acute myeloid leukemia. *Cancer* 2011;117:2145-55. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21523727

6. Gale RE, Green C, Allen C, Mead AJ, Burnett AK, Hills RK, et al. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. *Blood* 2008;111:2776-84. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17957027

7. Cancer Research UK. *Acute myeloid leukaemia (AML) incidence statistics*. 2016. [cited April 07, 2017 Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-aml/incidence#heading-Zero.

8. Haematological Malignancy Research Network (HMRN). *Acute Myeloid Leukaemia (AML) incidence statistics*. 2016. [cited October 2016 Available from: https://hmrn.org/statistics/incidence.

9. Meshinchi S, Appelbaum FR. Structural and functional alterations of FLT3 in acute myeloid leukemia. *Clin Cancer Res* 2009;15:4263-9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19549778

10. Small D. FLT3 mutations: biology and treatment. *ASH Education Program Book* 2006;2006:178-84. Available from: http://asheducationbook.hematologylibrary.org/content/2006/1/178.abstract

http://asheducationbook.hematologylibrary.org/content/2006/1/178.full.pdf

11. Cancer Research UK. *Acute myeloid leukaemia (AML): symptoms*. 2016. [cited April 07, 2017 Available from: http://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/symptoms.

12. Howell DA, Smith AG, Jack A, Patmore R, Macleod U, Mironska E, et al. Time-to-diagnosis and symptoms of myeloma, lymphomas and leukaemias: a report from the Haematological Malignancy Research Network. *BMC Hematology* 2013;13:1-9. Available from: http://biomedcentral.com/2052-1839/13/9

13. Fey MF, Buske C, ESMO Guidelines Working Group. Acute myeloblastic leukaemias in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24(Suppl. 6):vi138-43. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23970018

14. Deschler B, Lubbert M. Acute myeloid leukemia: epidemiology and etiology. *Cancer* 2006;107:2099-107. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17019734

15. Milligan DW, Grimwade D, Cullis JO, Bond L, Swirsky D, Craddock C, et al. Guidelines on the management of acute myeloid leukaemia in adults. *Br J Haematol* 2006;135:450-74.

16. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017;129:424-47. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5291965/

17. Appelbaum FR, Gundacker H, Head DR, Slovak ML, Willman CL, Godwin JE, et al. Age and acute myeloid leukemia. *Blood* 2006;107:3481-5. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16455952

18. Maynadie M, De Angelis R, Marcos-Gragera R, Visser O, Allemani C, Tereanu C, et al. Survival of European patients diagnosed with myeloid malignancies: a HAEMACARE study. *Haematologica* 2013;98:230-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22983589

19. Cancer Research UK. *Acute Myeloid Leukemia (AML): Survival*. 2016. [cited 2017 April 07]. Available from: http://www.cancerresearchuk.org/about-cancer/acute-myeloid-leukaemia-aml/survival.

20. National Institute for Health (NIH). *National Cancer Institute: SEER-Surveilance, Epidemiology, and End Results program: Cancer Stat Facts: Acute Myeloid Leukemia (AML)*. National Cancer Institute 2017. [cited 2017 June]. Available from: https://seer.cancer.gov/statfacts/html/amyl.html.

21. Mandelli F, Vignetti M, Suciu S, Stasi R, Petti MC, Meloni G, et al. Daunorubicin versus mitoxantrone versus idarubicin as induction and consolidation chemotherapy for adults with acute myeloid leukemia: the EORTC and GIMEMA groups study AML-10. *J Clin Oncol* 2009;27:5397-403. Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2008.20.6490

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2773224/pdf/zlj5397.pdf

22. Ohtake S, Miyawaki S, Fujita H, Kiyoi H, Shinagawa K, Usui N, et al. Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 Study. *Blood* 2011;117:2358. Available from: http://www.bloodjournal.org/content/117/8/2358.abstract

http://www.bloodjournal.org/content/bloodjournal/117/8/2358.full.pdf

23. Recher C, Bene MC, Lioure B, Pigneux A, Vey N, Delaunay J, et al. Long-term results of a randomized phase 3 trial comparing idarubicin and daunorubicin in younger patients with acute myeloid leukaemia. *Leukemia* 2014;28:440-43. Available from: http://dx.doi.org/10.1038/leu.2013.290

http://www.nature.com/leu/journal/v28/n2/pdf/leu2013290a.pdf

24. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood* 2015;126:291. Available from: http://www.bloodjournal.org/content/126/3/291.abstract

http://www.bloodjournal.org/content/bloodjournal/126/3/291.full.pdf

25. Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, Belton AA, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle ofchemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML10 and 12 trials. *Blood* 2001;98:1753-59.

26. National Institute for Health and Care Excellence (NICE). *TA 218: Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia*: NICE; 2011. Available from: nice.org.uk/guidance/ta218

27. National Institute for health and Care Excellence (NICE). *TA 399: Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts*: NICE; 2016. Available from: nice.org.uk/guidance/ta399

28. Gaballa S, Saliba R, Oran B, Brammer JE, Chen J, Rondon G, et al. Relapse risk and survival in patients with FLT3 mutated acute myeloid leukemia undergoing stem cell transplantation. *Am J Hematol* 2017;92:331-37.

29. Novartis. *Summary of Product Characteristics: Rydapt*: Novartis; 2016.

30. Li X, Xu S, Tan Y, Chen J. The effects of idarubicin versus other anthracyclines for induction therapy of patients with newly diagnosed leukaemia. *Cochrane Database Syst Rev* 2015:CD010432. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26037486

31. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;12:9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22297116

32. Stone RM, Fischer T, Paquette R, Schiller G, Schiffer CA, Ehninger G, et al. Phase IB study of the FLT3 kinase inhibitor midostaurin with chemotherapy in younger newly diagnosed adult patients with acute myeloid leukemia. *Leukemia* 2012;26:2061-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22627678

33. Grulke N, Albani C, Bailer H. Quality of life in patients before and after haematopoietic stem cell transplantation measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C30. *Bone Marrow Transplant* 2012;47:473-82. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21602898

34. Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. *Eur J Health Econ* 2010;11:427-34. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20473703

35. National Institute for Health and Care Excellence (NICE). *[ID893] Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia. In development [GID-TA10091]*. NICE; 2017. [cited 2017 June]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10091/documents.

36. Barrett AJ, Battiwalla M. Relapse after allogeneic stem cell transplantation. *Expert Rev Hematol* 2010;3:429-41. Available from: <Go to ISI>://WOS:000284801700014

37. Bhatia S. Long-term health impacts of hematopoietic stem cell transplantation inform recommendations for follow-up. *Expert Rev Hematol* 2011;4:437-52.

38. Fathi AT, Chen YB. Treatment of relapse of acute myeloid leukemia after allogeneic hematopoietic stem cell transplantation. *Curr Hematol Malig R* 2014;9:186-92. Available from: <Go to ISI>://WOS:000336975400013

39. Eleni LD, Nicholas ZC, Alexandros S. Challenges in treating older patients with acute myeloid leukemia. *J Oncol* 2010;2010:943823. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20628485

40. Juliusson G, Antunovic P, Derolf A, Lehmann S, Mollgard L, Stockelberg D, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood* 2009;113:4179-87. Available from: <Go to ISI>://WOS:000265846300013

41. Schiffer CA. "I Am Older, Not Elderly," Said the Patient With Acute Myeloid Leukemia. *J Clin Oncol* 2010;28:521-23. Available from: <Go to ISI>://WOS:000274138800002

42. Kantar Health. *Treatment architecture: Western Europe leukemia, acute myeloid*. New York: Kantar Health; 2016.

43. Socié G, Stone JV, Wingard JR, Weisdorf D, Henslee-Downey PJ, Bredeson C, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. *N Engl J Med* 1999;341:14-21.

44. Bhatia S, Francisco L, Carter A, Sun C-L, Baker KS, Gurney JG, et al. Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the BMT survivor study. *Blood* 2007.

45. Martin PJ, Counts GW, Appelbaum FR, Lee SJ, Sanders JE, Deeg HJ, et al. Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. *J Clin Oncol* 2010;28:1011-16. Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2009.25.6693

46. Wingard JR, Majhail NS, Brazauskas R, Wang Z, Sobocinski KA, Jacobsohn D, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *J Clin Oncol* 2011;29:2230-39.

47. Battiwalla M, Hashmi S, Majhail N, Pavletic S, Savani BN, Shelburne N. National Institutes of Health hematopoietic cell transplantation late effects initiative: developing recommendations to improve survivorship and long-term outcomes. *Biol Blood Marrow Transplant* 2017;23:6-9.

48. Uyl-De Groot CA, Lowenberg B, Vellenga E, Suciu S, Willemze R, Rutten FFH. Cost-effectiveness and quality-of-life assessment of GM-CSF as an adjunct to intensive remission induction chemotherapy in elderly patients with acute myeloid leukaemia. *Br J Haematol* 1998;100:629–36.

49. Batty N, Wiles S, Kabalan M, Sharma R, Shatzel J, Pang J, et al. Decitabine is more cost effective than standard conventional induction therapy in elderly acute myeloid leukemia patients. *Blood* 2013;122.

50. Leunis A, Redekop WK, Uyl-de Groot CA, Lowenberg B. Impaired health-related quality of life in acute myeloid leukemia survivors: a single-center study. *Eur J Haematol* 2014;93:198-206.

51. Pan F, Peng S, Fleurence R, Linnehan JE, Knopf K, Kim E. Economic analysis of decitabine versus best supportive care in the treatment of intermediate- and high-risk myelodysplastic syndromes from a US payer perspective. *Clin Ther* 2010;32:2444-56. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21353113

52. Castejon N, J. C, Cuervo J, K. L, Mehta P, Mokgokong R, et al. Estimating health state utilities for patients with acute myeloid leukemia. *Value Health* 2017;222:A179.

53. Kurosawa S, Yamaguchi H, Yamaguchi T, Fukunaga K, Yui S, Kanamori H, et al. Decision analysis of allogeneic hematopoietic stem cell transplantation versus chemotherapy in cytogenetically standard-risk acute myeloid leukemia in first complete remission: The impact of FLT3-ITD profile. *Blood* 2014;124.

54. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. *Value Health* 2011;14:539-45.

55. Peric Z, Desnica L, Durakovic N, Ostojic A, Pulanic D, Serventi-Seiwerth R, et al. Which questionnaires should we use to evaluate quality of life in patients with chronic graft-vs-host disease? *Croat Med J* 2016;57:6-15. Available from: <Go to ISI>://WOS:000371916000003

56. National Health Service Blood and Transplant. *Unrelated donor stem cell transplantation in the UK. A report from the UK stem cell strategy oversight committee*; 2014. Available from: nhsbt.nhs.uk

57. Nuffield Trust. *Exploring the cost of care at the end of life*. London: Nuffield Trust; 2014. Available from: https://www.nuffieldtrust.org.uk/files/2017-01/end-of-life-care-web-final.pdf

58. Novartis. *Interim Clinical Study Report: Phase-II study evaluating midostaurin in induction, consolidation and maintenance therapy also after allogeneic blood stem cell transplantation in patients with newly diagnosed acute myeloid leukemia exhibiting a FLT3 internal tandem duplication*; 2012.

59. Dignan FL, Potter MN, Ethell ME, Brennan J, McNamara L, Evans SO, et al. High readmission rates are associated with a significant economic burden and poor outcome in patients with grade 3/4 acute GvHD. *Blood* 2011;118:904-05.

60. Stone RM, Mandrekar S, Sanford BL, Geyer S, Bloomfield CD, Dohner K, et al. The multi-kinase inhibitor Midostaurin (M) prolongs survival compared with Placebo (P) in combination with Daunorubicin (D)/Cytarabine (C) induction (ind), high-dose c consolidation (consol), and as

maintenance (maint) therapy in newly diagnosed Acute Myeloid Leukemia (AML) patients (pts) age 18-60 with *FLT3* mutations (muts): an international prospective randomized (rand) P-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]). *Blood* 2015;126:6. Available from: http://www.bloodjournal.org/content/126/23/6.abstract

10 Appendix Description of changes to the revised executable model

Table 44 Description of changes to the revised executable model

Description of change	Original calculation/coding	New calculation/coding
Calculation error corrected – 'Appendix Adverse events'!P8	=(13+13.9)/(28/2)	=(13+13.8)/(28/2)
Error in the code corrected which estimated "Switching to secondary therapy" in SOC arm - 'Appendix Transition'!I735 to I1434	=IF(SC_inclusio="Excluded",0,IF(((G734-G735)-('Appendix Extrapolation'!DV736-'Appendix Extrapolation'!DV735)-(R735-R734)-(Q735-Q734)-(O735-O734))<0,0,(G734-G735)-('Appendix Extrapolation'!DV736-'Appendix Extrapolation'!DV735)-(R735-R734)-(Q735-Q734)-(O735-O734)))	=IF(SC_inclusio="Excluded",0,IF(((G738-G739)-('Appendix Extrapolation'!EJ20-'Appendix Extrapolation'!EJ19)-(R739-R738)-(Q739-Q738)-(O739-O738))<0,0,(G738-G739)-('Appendix Extrapolation'!EJ20-'Appendix Extrapolation'!EJ19)-(R739-R738)-(Q739-Q738)-(O739-O738)))
AML diagnosis and induction replaced with on treatment 'Appendix Transitions' - Col N	=IF((H18-O18)<0,0,(H18-O18))	On treatment =SUM(C21:F21)
Replaced CR health state with CR1L 'Appendix Transitions' - Col O	=L18	CR 1L =IF((L20-CO20-CN20-CM20)<0,0,(L20-CO20-CN20-CM20))
Relapse calculation changed 'Appendix Transitions' - Col P	=IF((1-N19-O19-Q19-R19)<0,0,1-N19-O19-Q19-R19)	Cycle 1 hard codded to =0 Cycle 1+ =1-N21-O21-Q21-R21
Secondary therapy moved and calculation changed 'Appendix Transitions' - Col U	=IF((P19-J19)<0,J19+(P19-J19),J19)	Cycle 1 and 2: Hard coded to 0 Cycle 3 = relapse (assumption) Cycle 3+ =L23-L24
Half cycle correction calculation changed 'Appendix Transitions' - Col AA to AO	NA	Half cycle applied to health states and inserted in Col AA to AO
Induction state calculation changed and scenario analysis added. 'Appendix Transitions' - Col D	=IF((D19*$H19-BW19-BV19)<0,0,(D19*$H19-BW19-BV19))	=IF('Model Parameters'!$M$47>='Appendix Transition'!$B21,'Appendix Extrapolation'!DI20,0)

Description of change	Original calculation/coding	New calculation/coding
Consolidation state calculation changed and scenario analysis added 'Appendix Transitions' -Col E	=E19*$H19	=IF(AND(B21<=('Model Parameters'!$M$48+'Model Parameters'!$M$47)),'Appendix Extrapolation'!DJ20,0)
Monotherapy state calculation changed and scenario analysis added 'Appendix Transitions' - Col F	=F19*$H19	=IF(AND(B21<=('Model Parameters'!$M$48+'Model Parameters'!$M$47)),'Appendix Extrapolation'!DJ20,0)
AE's linked to new induction, consolidation and monotherapy states 'Appendix Transitions' - Col AX, Ay and AZ	NA	=AB20*$H20*AEC
Routine care costs after treatment calculation changed "Appendix Transition" - Col BA (~Col AJ, CS response to clarification)	=(BS19*RC_SI+BU19*RC_Relapse+BT19 *RC_Maintenance+IF('Appendix Sensitivity Analysis'!$U$47="Excluded",BV19* RC_Relapse,0))*IF($B19>Threshold_routine,(1-Threshold_reduction),1)	=(AK20*RC_SI)+AF20* IF(AND('Model Parameters'!$I$149="Yes",'Model Parameters'!$L$22<$B20),RC_Maintenance,IF(AND('Model Parameters'!$I$153="Yes",40<$B20),RC_Maintenance,RC_Relapse))+(AE20*RC_Maintenance)*IF($B20>Threshold_routine,(1-Threshold_reduction),1)* IF(AND('Model Parameters'!$I$155="Yes",'Model Parameters'!$L$22<$B20),0,1)*IF(AND('Model Parameters'!$I$157="Yes",40<$B20),0,1)
SCT care costs calculation changed "Appendix Transition" - Col BB (~Col AK, CS response to clarification)	=U19*IF('Appendix Sensitivity Analysis'!$U$47="Excluded",0,SCT_cost)+(V19*IF('Appendix Sensitivity Analysis'!$U$47="Excluded",0,RC_SCT_treatment)+IF('Appendix Sensitivity Analysis'!$U$47="Excluded",0,W19*RC_SCT_recovery)+IF('Appendix Sensitivity Analysis'!$U$47="Excluded",0,IF('Model Parameters'!$L$36="NHS HRG 2015 codes",X19*RC_Maintenance,0)))*IF($B19>Threshold_routine,(1-Threshold_reduction),1)	=((AL20*SCT_cost)+(AM20*RC_SCT_treatment)+((AN20*RC_SCT_recovery)+(AO20*RC_Maintenance))*IF($B20>Threshold_routine,(1-Threshold_reduction),1)*IF(AND('Model Parameters'!$I$155="Yes",'Model Parameters'!$L$22<$B20),0,1))*IF(AND('Model Parameters'!$I$157="Yes",40<$B20),0,1)*IF('Appendix Sensitivity Analysis'!$U$47="Excluded",0,1)
Mortality costs linked to new half cycle corrected costs 'Appendix Transitions' - Col BC	NA	NA
Discounted and half-cycle corrected costs linked to new half cycle corrected costs (applies to all cost	NA	NA

Description of change	Original calculation/coding	New calculation/coding
categories) 'Appendix Transitions' - Col BG to BS		
Life years calculation changed 'Appendix Transitions' - Col BU	=M19/cycle_in_year	=(1-AH21)/cycle_in_year
QALYs calculation changed and linked to new half cycle corrected health states "Appendix Transition" - Col BV	=((BO19)*UTI_induction+(BP19)*UTI_induction+(BQ19)* UTI_conso+(BR19)*UTI_maintenance+(BT19)*UTI_CR+(BU19)* UTI_relapse+(BS19)*UTI_induction+(V19)* UTI_SCT_treat+(W19)*UTI_SCT_reco+UTI_SCTpost_reco*(X19))/ cycle_in_year	=IF(AND('Model Parameters'!$I$147="Yes",'Model Parameters'!$L$22<$B20),((1-AH20)*UTI_CR)/cycle_in_year,(AB20*UTI_induction+AC20*UTI_conso+AD20*UTI_maintenance+AE20*UTI_CR+AF20*IF(AND('Model Parameters'!$I$151="Yes",40<$B20),UTI_CR,UTI_relapse)+AM20*UTI_SCT_treat+AN20*UTI_SCT_reco+AO20*UTI_SCTpost_reco+(AK20*(UTI_CR-'Appendix Costs'!$R$124)*IF('Model Parameters'!$I$161="Excluded",0,1)))/cycle_in_year)*VLOOKUP('Appendix Life table'!P12,age.adjust.table,4)
Discounted and half-cycle corrected Life years QALYs calculation changed linked to new half cycle corrected life years and QALYs 'Appendix Transitions' - Col BX and BY	NA	NA
Selection of trial duration changed "'Model Parameters'!N10:O10"	87	=IF(P22="New",91,87)
Selection of cut-off point – MIDO changed "'Model Parameters'!L22"	=IF(Maintenance="No maintenance sub-group",81,IF($L$20="Last observation",87,81))	Cell formatted to "Any values"
Selection of cut-off point – MIDO changed "'Model Parameters'!M22"	=IF(Maintenance="No maintenance sub-group",83,IF($L$20="Last observation",87,IF($P$20="Same cut-off",L22,69)))	Cell formatted to "Any values"
Selection of relapse health state utility changed "Utility!D13"	='Appendix Costs'!R124	=IF('Model Parameters'!I161="Excluded",'Appendix Costs'!R124,UTI_CR)
Consolidation dosing schedule corrected "Appendix Transition" - Col E	=IF(AND(B19<=('Model Parameters'!$M$48+'Model Parameters'!$M$47)),'Appendix Extrapolation'!CW20,0)	=IF('Model Parameters'!$I$171="Excluded",IF(AND(B20<=('Model Parameters'!$M$48+'Model Parameters'!$M$47)),'Appendix Extrapolation'!DJ19,0),IF(AND(B20<=('Model

Description of change	Original calculation/coding	New calculation/coding
		Parameters'!$M$48+'Model Parameters'!$M$47)),'Appendix Extrapolation'!DJ19,0)*$F$13)
Maintenance dosing schedule corrected "Appendix Transition" - Col F	=IF(AND(B19<=('Model Parameters'!$M$48+'Model Parameters'!$M$47+'Model Parameters'!$F$62)),IF('Model Parameters'!$M$59="Included",'Appendix Extrapolation'!CX20,0),0)	=IF('Model Parameters'!$I$171="Excluded",IF(AND(B21<=('Model Parameters'!$M$48+'Model Parameters'!$M$47+'Model Parameters'!$F$62)),IF('Model Parameters'!$M$59="Included",'Appendix Extrapolation'!DK20,0),0),IF(AND(B21<=('Model Parameters'!$M$48+'Model Parameters'!$M$47+'Model Parameters'!$F$62)),IF('Model Parameters'!$M$59="Included",'Appendix Extrapolation'!DK20,0),0)*$F$13)
Added dose multiplier – MOID "'Appendix Transition'!F13"	NA	=IF('Model Parameters'!$I$167="Included",1,1.068)
Added dose multiplier – MOID "'Appendix Transition'!F730"	NA	=IF('Model Parameters'!$I$167="Included",1,0.971283783783784)
Drug costs – Induction and initiation - changed "Appendix Transition" - Col AR (~Col AA, CS response to clarification)	=D18*$H18*MIDO_induction+C18*AML_init	=IF('Model Parameters'!$I$169="Excluded", (AB20*$H20*MIDO_induction)+AML_init*AA20,(D20*$H20*MIDO_induction)+AML_init*C20)
Drug costs – consolidation changed - "Appendix Transition"- Col AS (~Col AB, CS response to clarification)	=E18*$H18*MIDO_conso	=IF('Model Parameters'!$I$169="Excluded",AC20*$H20*MIDO_conso,E20*$H20*MIDO_conso)
Drug costs – maintenance changed - "Appendix Transition" - Col AT (~Col AC, CS response to clarification)	=F18*$H18*MIDO_maintenance	=IF('Model Parameters'!$I$169="Excluded",AD20*$H20*MIDO_maintenance,F20*$H20*MIDO_maintenance)
Drug costs – AEs induction costs changed - "Appendix Transition" - Col AW (~Col AF, CS response to clarification)	=D18*$H18*AEC	=AB20*$H20*AEC
Drug costs – AEs consolidation costs changed - "Appendix Transition" - Col AX (~Col AG, CS response to clarification)	=E18*$H18*AEC_Con_MIDO	=AC20*$H20*AEC_Con_MIDO

Description of change	**Original calculation/coding**	**New calculation/coding**
Drug costs – AEs maintenance costs changed - "Appendix Transition" - Col AY (~Col AH, CS response to clarification)	=F18*$H18*AEC_MAIN_MIDO	=AD20*$H20*AEC_MAIN_MIDO
Medical costs - Routine care costs during drug treatment changed- "Appendix Transition" - Col AZ (~Col AI, CS response to clarification)	=(BP18*RC_induc+BQ18*RC_Conso+BR18*RC_Maintenance)*IF($B18>Threshold_routine,(1-Threshold_reduction),1)	=(AB20*RC_induc)+(AC20*RC_Conso)+(AD20*RC_Maintenance)*IF($B20>Threshold_routine,(1-Threshold_reduction),1)
Calculation of medical cost - Induc changed- "Appendix Transition" - Col CM (~Col BP, CS response to clarification)	=IF((D18*$H18-BW18-BV18)<0,0,(D18*$H18-BW18-BV18))	=D20
Calculation of medical cost - Conso changed- "Appendix Transition" - Col CN (~Col BQ, CS response to clarification)	=E18*$H18	=E20
Calculation of medical cost - Maint changed- "Appendix Transition" - Col CO (~Col BR, CS response to clarification)	=F18*$H18	=E20
Calculation of medical cost - Relapse changed- "Appendix Transition" - Col CR (~Col BU, CS response to clarification)	=IF((1-BO18-BP18-BQ18-BR18-BS18-BT18-BV18-BW18)<0,0,(1-BO18-BP18-BQ18-BR18-BS18-BT18-BV18-BW18))	=P20
Calculation of medical cost – SCT treatment added - "Appendix Transition" - Col CS	NA	=W20
Calculation of medical cost – SCT recovery added - "Appendix Transition" - Col CT	NA	=X20
Calculation of medical cost – SCT post recovery added - "Appendix Transition" - Col CU	NA	=Y20

Description of change	**Original calculation/coding**	**New calculation/coding**
KM data based on later data cut (at 05/09/2016) added	NA	Added at 'Appendix Extrapolation' Col BG and Col BH
Scenario analysis for new KM data based on later data cut added to the model	No scenario - 'Appendix Extrapolation' from Col BG to Col BR	Scenario analysis added at 'Appendix Extrapolation' from Col BI to Col BT
Percentage of patients receiving treatment in each treatment phase from original executable model added	NA	Added at 'Appendix Extrapolation' Col CZ to Col DD
Scenario analysis added to select Proportion of patients in each treatment phase	NA	Scenario analysis added at 'Appendix Extrapolation' from Col DI to Col DM
"CR at any time and censored for SCT" data replaced with the complete remission data only censored for mortality (provided initially)	CR at any time and censored for SCT at 'Appendix Extrapolation' Col DF and Col DG	Replaced with CR data only censored for mortality at Col DS and Col DT
Scenario analysis for selecting the MIDO CR data changed - 'Appendix Extrapolation' - Col DW (~Col DJ, CS response to clarification)	=IF('Model Parameters'!$E$140="CR within 60 days censored for SCT",'Appendix Extrapolation'!DH19,DF19)^DJ$15	=IF('Model Parameters'!$I$177="Original",DS19^$DW$15,DU19^$DW$15)
Scenario analysis for selecting the PBO CR data changed - 'Appendix Extrapolation' - Col DX (~Col DK, CS response to clarification)	=IF('Model Parameters'!$E$140="CR within 60 days censored for SCT",'Appendix Extrapolation'!DI19,DG19)	=IF('Model Parameters'!$I$177="Original",DT19^$DW$15,DV19^$DW$15)
Scenario analysis of assumption of "*zero cost after treatment in CR, SCT post-recovery"* implemented - 'Appendix costs'!Q65	=SUM(E65:P65)*IF(Model_type="Prob",PSA_routine_init,1)	=SUM(E65:P65)*IF(Model_type="Prob",PSA_routine_init,1)*IF('Model Parameters'!I159="Yes",0,1)
Scenario analysis of assumption of "*CR1L health state costs for patients off treatment"* implemented - 'Appendix costs'!Q66	=SUM(E66:P66)*IF(Model_type="Prob",PSA_routine_init,1)	=IF('Model Parameters'!I163="Excluded",SUM(E66:P66)*IF(Model_type="Prob",PSA_routine_init,1),RC_Maintenance)

Description of change	**Original calculation/coding**	**New calculation/coding**
Selection of "CR post 1L (No relapse)" utility changed - 'Appendix costs'!R123	=IF(Model_type="Prob",PSA_uti_cr,IF('Model Parameters'!$E$94="TTO study",'Appendix Costs'!D123,'Appendix Costs'!J123))	=IF(Model_type="Prob",PSA_uti_ind,IF('Model Parameters'!$E$94="TTO study",'Appendix Costs'!D123,'Appendix Costs'!Z123))
Selection of "Post SCT (after 1L)" utility changed - 'Appendix costs'!R127	=IF(Model_type="Prob",PSA_uti_sctpost,IF('Model Parameters'!$E$94="TTO study",'Appendix Costs'!D127,'Appendix Costs'!J127))	=IF(Model_type="Prob",PSA_uti_ind,IF('Model Parameters'!$E$94="TTO study",'Appendix Costs'!D127,'Appendix Costs'!Z127))
Selection of average age at cycle 0 changed – 'Appendix Life table'!P4	45	='Model Parameters'!I155
"% distribution at baseline" changed 'Appendix Life table'! S11 to DV11	Values	=OFFSET($R$719,MATCH($P$4,$R$720:$R$723,0), MATCH(S9,$S$719:$DV$719,0))
Utility multiplier created to adjust the utility values to decile naturally over the age	NA	=Utility!B21:E87

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Midostaurin for untreated acute myeloid leukaemia [ID894]

You are asked to check the ERG report from Centre for Reviews and Dissemination and Centre for Health Economics – York to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Monday 24 July 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 12 & 15: *Concern with age restriction.* Page 12: ERG text: "RCT evidence submitted by the company, is restricted to people aged 18-60 years, which is a sub-group of the patient population described in the final NICE scope. Older patients are not well reflected in the clinical evidence data submitted".	Page 12: To more accurately represent the available data on older patients and relevance of intensive chemotherapy we would like to suggest changing the underlined statement on page 12 and to add the following additional statement. "Older patients are not well reflected in the phase 3 clinical trial data submitted. Data on midostaurin use in older patients was documented in a single arm phase 2 study. However, it is noted that the target population for midostaurin is based on fitness for intense chemotherapy, not age".	The RATIFY study demonstrates the positive benefit risk for midostaurin in patients <60 years of age with FLT3+ AML. The phase 2 study provides single arm data illustrating the efficacy of midostaurin in patients >18 years of age with FLT3+ AML. Extrapolation from the phase 2 study demonstrates that patients >60 years of age benefit from midostaurin. The OS curves for patients treated with midostaurin in the Ratify study (<60 years) and young patients (<=60 years) in the phase 2 study are very similar. The OS observed is slightly superior to the OS observed in the phase2 study among patients >60 years. Because it is well established in the literature that the OS of patients with AML who are >60 years is notably inferior to the OS of patients <60 years, the phase 2 data provide strong evidence for the efficacy of midostaurin in young and old patients with FLT3+ AML. The recent indication granted to midostaurin by CHMP is not restricted by age. Announced 20th July 2017.	Not a factual error. The ERG is highlighting the fact that the clinical evidence was largely based on RATIFY trial and patients over 60 years of age were not represented.
Page 15: ERG text: "The results of this Phase II trial indicate that midostaurin treatment response is better in younger patients (< 60 versus > 60 years of age). "	Page 15: This statement is misleading as the response rates were not compared to a control and the responses in older patients are known to be worse than in younger patients. We suggest modifying this statement as follows "The Phase II trial reported an 8.5 % difference in CR between patients <60 versus > 60 years of age, suggesting that the response to midostaurin treatment is better in younger compared with		Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
	older patients (< 60 versus > 60 years of age) with FLT3 mutation-positive disease. However, the observed rates do not take account of key prognostic factors, e.g., FLT3 (ITD) has a considerably poorer prognosis in patients ≥ 60 vs. < 60 years. Comparison to historical controls using propensity score matching is required to accurately understand treatment differences based on age."	At the time of the RATIFY study design, age was considered the determining factor for intensive chemotherapy. However, intensive chemotherapy is increasingly being used successfully in fit older patients with AML, and age by itself is no longer considered an acceptable reason to disqualify a patient from receiving it. (Ferrara et al, Leukemia 2013). Further, on page 33, the ERG stated that the clinical advisor to the ERG agreed that "patient fitness for intensive chemotherapy is generally considered more important than age, and believed that there are older, fit patients who would also benefit from midostaurin in clinical practice." This statement supports our requested changes.	
Page 15 and Page 35: *Concern with stated chemotherapy induction practice*. ERG Text: "Patients in the RATIFY trial who did not achieve complete remission after first induction cycle underwent a second induction cycle with the same treatment whilst a different chemotherapy for the	Page: 15 and Page 35: This statement may be misleading and therefore we suggest amending it to reflect the variation in practice. Please replace "whilst a different chemotherapy for the second cycle is used in UK practices" with "whilst a different chemotherapy may be used for the second cycle in UK practice.	There is some debate regarding this point as our clinical advisors were of the opinion that the second induction therapy would comprise the same chemotherapy treatment as the first. The fact that the ERG was given a different clinical view suggests variation in UK practice.	The wording has been changed (see pages 15, 18 and 54). The wording on page 35 has not been amended as it is stating the opinion of the clinical advisor to the ERG.

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
second cycle is used in UK practices."			
Page 21: ***Concern with stated marketing authorisation.*** ERF text: "Midostaurin does not currently have UK marketing authorisation and does not have regulatory approval outside the UK."	Please replace "outside the UK" with "in the EU; however, it has been approved by the US FDA and in Switzerland" to reflect the accurate regulatory landscape.	This statement is not correct. Midostaurin was approved by US FDA on 28th April 28, 2017 and Swissmedic approval followed on 4th May 2017. Furthermore, CHMP adopted a positive opinion on 20th July 2017.	The statement has been amended (see page 21)
Page 23: ***Typo*** ER Text: "…when analysed by age, the SEER (Surveillance, Epidemiology, and End Results) data for 1988–found a median OS of 2-4 years in those under 50 years of age".	Please replace "1988-" with "1988–2012" to reflect the correct data range.	Correction of a typo.	The typo has been corrected (see page 23).
Page 26: ***Concern with relapsed/refractory patients.*** ERG text: "Furthermore, the ERG notes that the CS did not discuss or consider patients who fail to respond to induction treatment or *primary refractory* patients. "	This statement is misleading as it implies patients who failed to respond to induction treatment were not considered. We propose replacing the sentence to more accurately reflect the economic model. "The CS stated that patients who failed to respond to induction therapy (refractory) and patients who no longer responded to treatment (relapsed) were considered to be in the relapsed health state, which was	In the Phase 3 RCT, patients who failed to respond to induction, discontinued study treatment and were followed long term for SCT and OS. Our clinical experts and physicians interviewed during the course of the time trade-off (TTO) utility study advised that the health state of primary refractory patients was the same as for patients in relapse.	Not a factual error. The ERG's statement is a mere critique of the CS's description of the treatment pathway in AML (pages 31-32 of the CS). This is not related to the health states in the economic models.

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
	assumed to be the same for relapsed and refractory patients."		
Page 41: *Typo*. ERG text: "As can be seen from the results presented in Table 4 and Error! Reference source not found, …"	Please replace "Table 4 and Error! Reference source not found" with "Table 5 and Figure 1" To reflect the correct legends.	Correction of a typo.	The typo has been corrected.
Page 43: *Typo*. ERG text: "As can be seen from the results presented in Table 4"	Please replace "Table 4" with "Table 6" to reflect the table number.	Correction of a typo.	The typo has been corrected.

Page 51: ***Concern with the presented historical controls stratified by age for the phase 2 study.*** ERG text: "The company also conducted an exploratory analysis of relapse free survival, comparing trial data with historical controls, and the presented results appear to indicate that for both age groups, patients treated with midostaurin achieved better outcomes than controls. However, the ERG believes that these comparative results may not be representative as the historical controls were not match-adjusted with the trial population."	This statement as written is misleading. Please add the following additional text to the end of the paragraph to refer to the additional analysis carried out by Novartis during the ERG review. "In response to EMA questions, Novartis has performed an additional analysis in which the historical control cohort was compared to the 223 patients treated in RATIFY using a propensity scoring technique. [redacted] The historical controls were selected from 5 successive clinical trials enrolling AML patients treated with intensive chemotherapy (Tassara et al 2014, Schlenk et al 2016b, Schlenk et al 2006a, Schlenk et al 2006b, Schlenk et al 2004a, Schlenk 2004b, Schlenk 2003).	This additional analysis provides a valid comparison as the historical controls were match-adjusted with the trial population. This analysis thus provides evidence to suggest that the addition of midostaurin to intensive chemotherapy does not adversely impact efficacy in patients age >60 years, and in fact may improve it, and that it may therefore be reasonable to extrapolate survival data from RATIFY to a broader patient population.	The statement "However, the ERG believes that these comparative results may not be representative as the historical controls were not match-adjusted with the trial population." has been removed. (see page 51-52)
Page 64: ***Concern with the relapsed transition.*** ERG text: "The model therefore assumes that all patients who enter the relapse state, even those that	Please amend the sentence in the following way to reflect the correct model transitions: "The model assumes that all patients who enter the relapse state, will either continue to stay in the relapse health state or	This statement is factually incorrect, as patients could leave the relapse health state following death or SCT in the model prior cycle 80.	The text has been edited to accommodate the possibility that patients in the relapse health state can experience a SCT.

subsequently respond to secondary therapy will continue to stay the relapse health state experiencing the morality benefits of subsequent therapy but also very low HRQoL and incurring very high care costs."	move to the SCT health state up to cycle 80 (end of the trial). Patients who are in the relapse health state at the end of the trial, remain in the relapse health state."		
Page 64: ***Concern with first and second line HRQoL used.*** ERG text: "This issue has a significant impact on the model, leading it to underestimate the ICER, and it results in the model making logically inconsistent predictions. Firstly, it implies that patients who are responders to first-line therapy experience much higher HRQoL and much lower care costs than patients who are responders to subsequent therapy. Secondly, it means that the model reacts to inputs in odd ways."	Please delete the sentence: "Firstly, it implies that patients who are responders to first-line therapy experience much higher HRQoL and much lower care costs than patients who are responders to subsequent therapy"	It is not clear why the ERG believes it is not logical for patients who are responders to first-line therapy to experience much higher HRQoL compared with responders to subsequent therapies, since this has been documented in literature. For example, Leunis, 2014 reported higher QOL in survivors without relapse vs. with relapse. Therefore, we request the ERG to remove this sentence as it is not uncommon for outcomes in second-line to be worse than in the first-line setting.	Not a factual error. The Leunis paper does not demonstrate higher QOL in survivors without relapse vs. with relapse. The observed difference of 0.05 is statistically insignificant. This decrement in HRQoL of survivors with relapse is also significantly smaller decrement than predicted by the company's model.
Page 65: ***Concern with no CR after subsequent lines of therapy*****.** ERG text: "This issue was raised with the company, at the clarification stage, and the ERG requested that the model allow patients, who have relapsed, to be able to transition to the CR health state after the induction period. <u>The company's response stated that the RATIFY trial did not collect data on CR for second and subsequent lines of</u>	Please amend the underlined sentence as follows: "The company's response stated that the RATIFY trial did not collect data on CR for second and subsequent lines of therapy and, therefore, the company's revised model <u>was not able</u> to address this issue <u>given the data available</u>"	This statement is misleading. We could not conduct this analysis robustly due to the lack of data. The revised statement reflects the fact that this not a failure from Novartis to conduct this analysis, but rather the fact that we cannot conduct such analysis robustly given the data available.	Text has been changed as suggested for clarity.

therapy and, therefore, the company's revised model failed to address this problem."			
Page 65 and Page 105: *Concern with CR data used in modified model.* **Page 65** ERG text**:** "The company, however, did modify the model to include new Kaplan-Meier data for CR, to partially respond to points raised by the ERG. These new CR data, however, lack face validity and are very different to the CR data used in the original model. The ERG, therefore, questions whether these new data are correct, and considers the original data to be the most accurate reflection of CR observed in the RATIFY trial." **Page 105** ERG text: "The revised model provided by the company at the clarification stage included new CR data, which censored the CR data for SCT events. These new data however, did not appear to be consistent with the uptake of SCT and lacked face validity."	Please remove throughout the document the text relating to the updated CR analyses provided in the response, as we only provided these analyses based on request from the ERG. As highlighted in our responses to clarification questions, we did not believe that these analyses were appropriate.	This is factually incorrect. The data on CR submitted in the original submission were correctly censored for SCT. The updated data on CR were provided following the clarification questions to reflect changes that ERG wanted to see. As highlighted in our response to the clarification questions, we did not believe that the changes requested by the ERG were correct, but provided these analyses for transparency. Therefore, we never argued that the updated analyses should be used and we agree that these analyses lack face validity.	Not a factual error. As this data were included in the revised base-case it would not be appropriate to excluded any mention of the updated CR data as this would cause confusion. The ERG have, however, add a sentence on pg. 65 to indicate that you (the company) did not consider this analyses appropriate.
Page 67, Page 72, Page 88, Page 101, and Page 117 & 118: When	For transparency, please add the following regarding the limitations of	These ERG statements are misleading on their own without a full acknowledgment of the limitations of	Not a factual error. The company is over interpreting the ERG's critique. In the ERG's report

limitations of the partition survival model are acknowledge by the ERG	using the STM when describing the limitations of the PSM. "Whilst the STM would be more flexible compared with the PSM, it should be acknowledged that the STM would not address these issues robustly given the lack of data. The STM would rely on the use of external data which is likely to introduce a number of biases and inconsistencies, and perhaps more importantly, deviate from the RATIFY trial. Therefore limitations from both approaches need to be considered when evaluating the economic assessment of midostaurin."	both the PSM and the STM approach Whilst we acknowledge there are some differences of opinion between the ERG and the company, the company attempted to address the comments from the ERG as far as possible given the available data. However, the ERG statement suggests that it was possible for the company to address all comments from the ERG. As explained in the company's response, we were not able to construct a robust STM model without relying heavily on external data. Whilst the STM may provide a better representation of the pathway (notably movement between health states), the use of external data is likely to introduce a number of biases and inconsistencies and, perhaps more importantly, deviate from our trial. This should be acknowledged by the ERG. Indeed, on page 72, the ERG acknowledges that using external data could introduce biases. The company in its response to clarification provided an exploratory analysis in order to demonstrate the complexity of constructing such a model and illustrate the potential	we state that it was suggested that a natural history model may work better after the trial period i.e. a hybrid model. We acknowledge that that the company attempted to implement this, but considered the use of data from the RATIFY probably wasn't the best way to do this. At no point do the ERG suggest that the PSM approach used in the in trial period is the wrong approach, our critique outlined in 5.2..1 instead suggests that the data used imply a model structure that is inconsistent with the care pathway for AML. With respect to the use of external data the ERG acknowledges that this may come with limitations, but as we suggest on pg. 72 using external data is often the most reasonable approach given the data available. Further, the ERG, cannot get drawn into speculating on the limitations of external data that is not presented in the CS or in the company's response to clarification questions.

		lack of face validity (when compared with the trial). The company understands that both approaches (STM or PSM) have limitations. Therefore, following assessment of the limitations of either approach, the company selected a PSM (as it was felt that it was not feasible to conduct a robust STM). Whilst we understand the ERG's preference for a STM approach, the limitations of using such an approach and its feasibility should be acknowledged. It is not clear how the company could be expected to address some of the ERG's comments given the absence of relevant data.	
Page 74 ERG text: "<u>After cycle 80, surviving patients in all health states are assumed to be cured and are considered to be survivors, who will not relapse at any time point in the future.</u>"	This statement is not correct. Please replace with "After cycle 80, some of surviving patients may relapse based on the disease free survival extrapolation."	This is factually incorrect. Health state transitions for surviving patients are models based on the extrapolation of the DFS data, hence a proportion of surviving patients transition to relapse after cycle 80. This model is not attempting to present each relapse and each treatment after relapse. This modelling is common to many oncology model whereby we do not model every relapse after 1st line.	We have altered the text to indicate that there is small risk of relapse following the cure point.

Page 77 and Page 101: ***Concern with cure approach.*** **Page 77** ERG text: "The ERG has significant concerns with regards to the cure assumption and specifically the assumption that patients revert back to general population mortality rates. The ERG acknowledges that this is a common assumption, applied within existing models, in the general area, but considers that this assumption is subject to significant uncertainty." **Page 101** ERG text: **"**The model includes a point beyond which all surviving patients have general population mortality but, there is uncertainty surrounding this. Existing epidemiological evidence suggests that patients remain at a higher mortality risk for up to 30 years after SCT. Although this risk declines with time, the risk for patients surviving at least five years after SCT, without relapse, remains considerably higher than that for the general population (between 4 to 9 times higher, irrespective of age)."	If these statements reflect the ERG's view; please add the following sentence: "Whilst the ERG have concerns with the use of a cure model to extrapolate at end of the trial, clinical advisors to the ERG considered that the cure assumption was reasonable."	This is inconsistent with ERG' clinical opinion on page 76. On page 76 the ERG says that clinical experts felt that whilst uncertain, the cure assumption was reasonable. Could the ERG clarify whether the statement on page 77 and 101 regarding the assumption of cure reflects the view of their clinical advisors or their own view?	Not a factual error. The ERG is simply stating that the literature in this area evidence do not support an assumption that patients revert to general population mortality. The ERG disagrees that the statement on pg.76 implies that the clinical advisor agreed that that patients follow general mortality as this section is dealing with timing of the cure point. The ERG has altered to the text to clarify this point. .

Page 76, page 101 and page 107: ***Concern with data cut used.*** **Page 76** ERG text**: "...**the ERG is also not clear as to why the substantially more mature data cut, made available at the clarification stage, was not used in the model. Using these data substantially reduces the uncertainty in the estimated OS differences at the base-case cure point of 80 cycles, as there are nearly four times the number of patients being observed." **Page 101** ERG text**: "**The ERG is concerned about the lack of any real justification for the 80-cycle end point assumed in the base-case, which is largely determined on the basis that this was the last observation in the RATIFY trial."	Please amend the sentence the following way for factual accuracy The updated model sent at the clarification stage did not incorporate the updated data from RATIFY as this was not requested by the ERG. However, the updated data were used in the ERG model, which reduces the uncertainty in the estimated OS differences at the base-case cure point of 80 cycles, as there are nearly four times the number of patients being observed. Page 101: Please delete the sentence: "The ERG is concerned about the lack of any real justification for the 80-cycle end-point assumed in the base-case, which is largely determined on the basis that this was the last observation in the RATIFY trial".	Page 76: This statement is misleading. The ERG did not request that the model be updated with the latest data cut-off at the clarification stage. Furthermore, we do not believe the term "substantially mature" is appropriate. Whilst more follow-up are available, we do not believe that more mature is appropriate here as this is about the number of patients at cycle 80, rather than the length of follow-up Page 101: This statement is incorrect. As we describe in our submission on page 114, we used the cure model fitted from the last event.	Text amended as suggested. The text in Page 101 has been amended as follows ""The ERG is concerned about the lack of any real justification for the 80-cycle end-point assumed in the base-case, which is largely determined on the basis that this was the last event in the RATIFY trial".
Page 107 ERG text: "In the third scenario, the point at which patients enter the cured health state is pushed back even further to the point where patients discontinue first-line therapy. This version of the model all but removes the relapse health state from the model: patients can spend only a single cycle in the	Please add if appropriate whether this has been validated with clinical experts	This is misleading on its own Could the ERG clarify whether this scenario has been validated with clinical experts .	Not a factual error. All changes to the model were based on the ERG's understanding of the appropriate pathway, following consultation with the clinical advisor and examination of previous models in AML.

relapse health state. As in scenario two, patients continue to experience mortality events in line with the OS data from the RATIFY trial up until cycle 80 and one off costs and disutility of relapse are similarly included."			
Page 81, Page 101 and Page 112: ***Concern with no utility age adjustment for CR and post-SCT***. **Page 81** ERG text: "The ERG therefore considers that the utilities used in the CR 1L and Post-SCT recovery health states should be further adjusted for age to account for age-related decline in HRQoL." **Page 101** ERG text**:** "When utility values are considered over a 60-year lifetime horizon, it is evident that the utility values assigned to the CR 1L and post-SCT recovery states may eventually exceed general population utility estimates, which naturally decline with age." **Page 112** ERG text: "The ERG believes it is appropriate to apply age adjusted utilities, to account for that fact that the benefits of cure are accrued over an extended period."	Please check the analysis and amend the text appropriately.	This is not factually correct. The ERG applied the age adjustment to all health states, and not just CR 1L and Post-SCT. Perhaps more importantly, the method used by the ERG to age-adjust is not correct. The ERG appears to multiply the discounted QALYs by the utility multiplier from the general population. This is incorrect in a number of respect. Perhaps, in simple terms, in the ERG analysis, the discounted QALYs at cycle one are multiplied by a value of 0.88 leading to an underestimation of the number of QALYs in the model. This is not appropriate.	The ERG thanks the company and acknowledges that there is an error in the executable model while implementing the utility multiplier for age-adjusted utility. The executable model has been corrected and the following sections and tables of the ERG report have been updated: Section 1.7 Section 6.3.4 Section 6.4 Section 6.5.1 Section 6.5.2 Section 6.5.3 Section 6.6 Section 8 Table 1 Table 37 Table 39 Table 40 Table 41 Table 42

Page 109: ***Concern with additional scenarios explored.*** **Page 109** ERG text**: "**Despite these strengths this version of the model also has some weaknesses. The most significant of these it that it does not properly account for QALY losses resulting from patients with refractory or relapsed disease." **Page 109** ERG text**:** "Section 6.3.1.1 and 6.3.1.2 presented scenario analyses in which the ERG modified the company's model in an attempt to address the identified flaws in the model structure. ERG considers that a combination of both scenarios 3s (only a single cycle of relapse) from sections 6.3.1.1 and 6.3.1.2 gives the nearest approximation to an appropriate model structure."	We would like to ask the ERG to add details on whether clinical expert opinion was sought on this issue and whether they felt this was a more robust scenario.	This is misleading on its own. Whilst we acknowledge some differences in opinion, the ERG should make clear whether their clinical experts felt this was more appropriate compared with the assumptions used in the company's model.	Not a factual error. All changes to the model were based on the ERG's understanding of the appropriate pathway, following consultation with the clinical advisor and examination of previous models in AML.
Page 110: ***Concern with mortality rate used.*** ERG text: **"**The ERG's preferred base case is to use a four-fold higher mortality rate, in line with the lower bound estimated in Martin et al. (2010).	Could the ERG add details on whether clinical expert opinion was sought on this issue and whether experts considered this was a more robust scenario. Please add a comparison (Plot) of the OS estimate using the company's base case and the ERG's base-case (using SMR or 4).	This is inconsistent with previous statement on Page 76, which suggested that the clinical expert believed that the assumption that patients follow general mortality is reasonable. For transparency, the ERG needs to state whether this reflect their views, or the view of their clinical experts.	Not a factual error. The ERG disagrees that the statement on pg. 76 implies that clinical advisor agreed that that patients follow general mortality as this section is dealing with timing of the cure point. The ERG has altered to the text to clarify this point.

		For transparency, the ERG should provide a comparison (Plot) of the OS estimate using the company's base case and the ERG's base-case (using SMR of 4).	
Page 121 ***Concern with End of Life Criteria*** ERG text: "However, the relevance of these estimates of median and mean OS is questionable as they are derived from 1995-2002 cancer registry data and do not identify patients' age or treatment." ERG text: "After a brief search of the literature, the ERG identified estimates of OS for AML patients that were more relevant to the current appraisal, in that they are for patients who had received the standard intensive chemotherapy that patients would receive were midostaurin not available (daunorubicin plus cytarabine). "	The statement is misleading and should be deleted. Although Maynadié study uses data from 1995 to 2002, these data were gathered from 48 population-based cancer registries from 20 European countries and as such still represents the largest database on AML. Furthermore, the treatment of AML has not changed in over 20 years, so the new data may not provide better estimates of survival. Please add the following statement. "Among the five additional studies identified by ERG, four studies are in patients under 60 years old and 1 study is in Japanese patients under 65 years old with a median age of 47. None of these studies represent Midostaurin indication population of AML patients without age restriction. Furthermore, none of these studies reported survival in FLT3+ population, which is known to be worse than that of patients without FLT3 mutations."	We believe that the Maynadié study is the only reputable source that represents AML patients without age restriction and provides accurate estimates of survival. These data are also supported by SEER data (https://seer.cancer.gov Accessed Jan 4,2017) demonstrated mean life expectancy below 2 years in AML patients. Furthermore, none of the studies noted by the ERG reported survival data in FLT3 patients. Gale et al. (Blood. 2008 Mar;111(5):2776-84) clearly showed that survival in FLT3 patients is significantly lower and further noted the 2 year survival with FLT3 mutations, which ranged from 33% to 18% depending on FLT3 level. Finally, Schlenk study in FLT3+ patients (Schlenk, Haematologica 2009) demonstrated 2 year survival in FLT3+ patients of <20%.	Not a factual error.

References:

Leunis A, Redekop WK, Uyl-de Groot CA, Lowenberg B. Impaired health-related quality of life in acute myeloid leukemia survivors: a single-center study. European Journal of Haematology. 2014;93(3):198-206.

Ferrara F, Barosi G, Venditti A, Angelucci E, Gobbi M, Pane F, Tosi P, Zinzani P, Tura S. Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. Leukemia. 2013 Apr;27(5):997-9.

Gale RE, Green C, Allen C, Mead AJ, Burnett AK, Hills RK, Linch DC; Medical Research Council Adult Leukaemia Working Party. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. Blood. 2008 Mar 1;111(5):2776-84. Epub 2007 Oct 23. PubMed PMID: 17957027.

Schlenk RF, Benner A, Hartmann F, et al. Risk-adapted postremission therapy in acute myeloid leukemia: results of the German multicenter AML HD93 treatment trial. Leukemia; 2003; 17:1521-8.

Schlenk RF, Benner A, Krauter J 2004a Individual Patient Data–Based Meta-Analysis of Patients Aged 16 to 60 Years With Core Binding Factor Acute Myeloid Leukemia: A Survey of the German Acute Myeloid Leukemia Intergroup. J Clin Oncol; 22:3741-3750.

Schlenk RF, Frohling S, Hartmann F, et al 2004b. Phase III study of all-trans retinoic acid in previously untreated patients 61 years or older with acute myeloid leukemia. Leukemia; 18:1798-1803.

Schlenk RF, Dohner K, Pralle H, et al. 2006a Risk-adapted therapy in younger adults with acute myeloid leukemia: Results of the AMLHD98A trial of the AMLSG. Blood:108:14

Schlenk RF, Frohling S, Hartmann F, et al. 2006b Intensive consolidation versus oral maintenance therapy in patients 61 years of older with acute myeloid leukemia in first remission: results of second randomization of the AML HD98-B treatment trial. Leukemia; 20:748-750.

Schlenk RF, Döhner K. Impact of new prognostic markers in treatment decisions in acute myeloid leukemia. Curr Opin Hematol. 2009 Mar;16(2):98-104. doi: 10.1097/MOH.0b013e3283257adb. Review. PubMed PMID: 19468271.

Schlenk RF, Fiedler W, Salih HR, et al. Impact of age and midostaurin-dose on response and outcome in acute myeloid leukemia with FLT3-ITD: interim-analyses of the AMLSG 16-10 trial. Blood 2016;128:449.

Tassara M, Döhner K, Brossart P, Held G, Götze K, Horst HA, Ringhoffer M, Köhne CH, Kremers S, Raghavachar A, Wulf G, Kirchen H, Nachbaur D, Derigs HG, Wattad M, Koller E, Brugger W, Matzdorff A, Greil R, Heil G, Paschka P, Gaidzik VI, Göttlicher M, Döhner H, Schlenk RF. Valproic acid in combination with all-trans retinoic acid and intensive therapy for acute myeloid leukemia in older patients. Blood. 2014 Jun 26;123(26):4027-36.,

[redacted] the chance of a successful SCT. However, the quality of remission was not studied in the RATIFY trial.

A higher proportion of the midostaurin patients achieved complete remission (CR) than placebo although the difference was not statistically significant (58.9% vs. 53.5% ; one-sided p value = 0.073). Overall, a slightly higher proportion of patients in the midostaurin group, compared with the placebo group, underwent SCT (midostaurin=59.4% and placebo=55.2%), but the trial was not designed to assess this outcome. Median event free survival was significantly longer for those randomised to midostaurin (8.2 months (95% CI 5.4–10.7 months)) than the placebo than placebo (3.0 months (95% CI 1.9–5.9 months)). The median DFS was also longer in the midostaurin than the placebo group (26.7 months vs. 15.5 months, respectively).

The RATIFY trial results show that the safety profile of midostaurin is similar to placebo. Results from the phase II trial also show that midostaurin appears to have better safety profile in the younger patients than the older patients.

No other trials that assessed the clinical effectiveness of midostaurin or standard chemotherapy in the FLT3 mutant AML patient population were identified. Hence, no meta-analysis or indirect comparison was carried out.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic review presented in the CS used adequate methods to identify relevant studies of pharmacological treatments for newly diagnosed FLT3-positive AML. The CS search did not include all chemotherapy agents, but no relevant trial will have been missed due to the absence completed/published trials in the relevant patient group.

Of the trials identified, the phase Ib trial was largely about midostaurin dosing schedule determination (concomitant or sequential) and pharmacokinetics, and the phase II trial was also non-comparative study. Hence, the CS's evidence for clinical effectiveness is based largely on the double-blind RCT (RATIFY trial).

RATIFY is a good quality study but, due to the lack of strict specification of SCT and subsequent therapies and the necessary long follow-up in the RATIFY trial, there is some uncertainty around the size of the treatment effect of midostaurin. However, there is nothing to indicate that patients in the trial were not treated according to standard guidelines.

The RATIFY trial's methods and results may not be entirely generalisable to the NHS patients who would be eligible for midostaurin. The trial's population is adults 18-60 years of age whilst a large

proportion (>60%) of AML patients to be treated in the UK are over 60 years. Therefore, the trial's results may not be generalizable to the whole eligible population, or those over 60 years of age. Given that the only available data on older patients (up to age 70 years of age, the Phase II trial) found that treatment response was better in those under 60 years of age compared with those over 60 years, there is uncertainty about the size of the treatment benefit to be achieved with midostaurin in older eligible patients, who may be older than 70 years. This means that there is also uncertainty about the size of the effect for the whole eligible population (including all ages).

Patients in the RATIFY trial who did not achieve complete remission after first induction cycle underwent a second induction cycle with the same treatment whilst a different chemotherapy for the second cycle may be used in UK practice. Hence, the treatment scheduling may not represent practice in the UK. Consequently, the effect size seen in the trial may not be achieved in clinical practice.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's economic submission included a systematic review of published evidence on the cost-effectiveness, health-related quality of life, resource use and costs associated with midostaurin in the treatment of AML. The review identified a number of economic evaluations of other therapies for AML, including UK based economic evaluations, but did not identify any relevant economic assessments of midostaurin.

The cost effectiveness of midostaurin was informed by an economic evaluation conducted by the company. The company's model uses a partition survival model approach or "area under the curve" analysis. This type of model directly uses the time-to-event data from a clinical trial to determine the distribution of patients between the health states. The model structure consisted of five health states: (i) AML diagnosis/induction; (ii) complete response/remission (CR); (iii) relapse, (iv) stem cell transplant (SCT), and (v) death. The CR health state is split into three further sub-states, indicating the phase of treatment a patients is in: consolidation, monotherapy, and CR post discontinuation of first line treatment (CR 1L). The SCT health state is similarly split into series of tunnels states, these states consisted of SCT treatment, SCT recovery, and post-SCT recovery. The efficacy data, treatment and comparator dosage, duration of primary therapy, adverse event rates and patient characteristics (age, weight, body surface area) used in the economic model were sourced from the RATIFY trial, with the remaining inputs informed by studies identified in the cost-effectiveness review and other sources Overall survival, within the first 80 cycles (~6.2 years) of the model, was estimated using Kaplan-Meier data from the RATIFY clinical trial. Thereafter, patients were assumed to be cured and experienced general population mortality.

The company found midostaurin to be more costly (cost difference of [redacted]) and more effective ([redacted] gain) compared with standard of care. The deterministic base case ICER was £33,672

There is uncertainty around the treatment effect of midostaurin in older, yet fit FLT3-positive patients, suitable for intensive chemotherapy.

It is also uncertain that the effect size seen in RATIFY would be replicated a trial that included the full age range of eligible patients, i.e. those suitable for intensive chemotherapy but not restricted to no older than 60 years of age.

It is also uncertain that the effect size seen in RATIFY would be replicated in a trial in which patients who did not achieve complete remission after first induction cycle, underwent a second induction cycle with a different chemotherapy as may happen in UK practices.

Cost-effectiveness

The principle weakness of the economic evidence submitted by the company relates to the model structure adopted and, in particular, a failure to appropriately model patients with refractory and relapsed AML. The ERG also had substantive concerns relating to the health state costs used for patients who have achieved remission and discontinued therapy/received SCT.

There are three significant areas of uncertainty in the cost-effectiveness analysis. The first relates to the additional survival gains in patients who have achieved cure for which there is limited, weak evidence to inform assumptions. The second relates to uncertainty regarding long-term health-related quality of life of patients who achieve long-term remission, both with and without SCT. The third concerns the age of the population eligible for treatment with midostaurin.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a series of exploratory analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. The most of important these scenarios related to changes made by the ERG to the model structure; the ERG analysis explored a number of iterations of the model in which alternative assumptions regarding the model structure were made. The results of this analysis demonstrated that these structural issues have a significant impact on the ICER, see Table 1. The ERG also presented an alternative base-case based on a combination of a number of these scenario analyses. The ERG's base-case makes the following amendments to the company's revised base-case:

1. Corrections for calculation errors;
2. Addition of new OS data;
3. Addition of original CR data;
4. ERG's preferred model structure;
5. Applies a four-fold risk ratio to post cure mortality;
6. Applies age adjusted utility decrement into the model;

7. Increases the maximum number of cycles of monotherapy to 18;
8. Assumes total number of units of therapy matches the original company model;
9. Incorporates adverse events resulting from SCT.

The results of these scenario analyses including the ERG's base-case are summarised in Table 1

Table 1 Summary the relevant amendments to the company's revised base-case and impact of those amendments on the ICER

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	***Midostaurin therapy***	[redacted]	[redacted]	[redacted]	[redacted]	***£28,465***	*n/a*
	SOC	[redacted]	[redacted]	-	-	-	-
ERG's preferred model structure	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£39,720	£11,255
	SOC	[redacted]	[redacted]	-	-	-	-
Four-fold increase in risk of mortality	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,899	+£434
	SOC	[redacted]	[redacted]	-	-	-	-
Up to 18 cycle of monotherapy	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,569	+£104
	SOC	[redacted]	[redacted]	-	-	-	-
Discrepancy in total units of treatment corrected	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£30,904	+£2,438
	SOC	[redacted]	[redacted]	-	-	-	-
Age adjusted utility decrement	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£30,354	+£1,889
	SOC	[redacted]	[redacted]	-	-	-	-
SCT related AE's	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£30,869	+£2,404
	SOC	[redacted]	[redacted]	-	-	-	
ERG's preferred base case	***Midostaurin therapy***	[redacted]	[redacted]	[redacted]	[redacted]	***£62,810***	***+£34,344***
	SOC	[redacted]	[redacted]	-	-	-	-

$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care

The ERG base-case analysis estimated midostaurin to be more costly ([redacted]) and more effective ([redacted] gain) compared with standard of care and suggests that the ICER for Midostaurin compared with SOC is around £62,810 per QALY.

The ERG also carried out a further series of exploratory analyses to explore the impact of alternative assumptions regarding the selected cure point, long-term health-related quality of life of patients who achieve long-term remission, and the average age of patients eligible for treatment with midostaurin. These analyses indicate that the ERG's base-case ICER is likely to represent a lower bound with the majority of analysis's resulting in increases in the ICER; range £53,718 and £92,619 per QALY, assuming the ERG's base-case assumptions.

2 Background

2.1 Description of the technology under appraisal

The company submission (CS) states that midostaurin is an oral, type III, multi-target receptor tyrosine kinase inhibitor (TKI) that acts on FMS-like tyrosine kinase 3 (FLT3) and multiple other receptor tyrosine kinases (RTKs), including fibroblast growth factor receptor 1-3 (FGFr 1-3), KIT and vascular endothelial growth factor receptor (VEGFR2). Midostaurin inhibits the FLT3-receptor signalling in leukaemic cells that express FLT3 internal tandem duplication (ITD) or tyrosine kinase domain (TKD) mutant receptors, leading to cell cycle arrest and apoptosis.

The CS also states that midostaurin is taken orally twice daily on days 8–21 of the 28-day induction and consolidation chemotherapy cycles, and twice daily as single-agent therapy for up to 12 months following combination treatment.

Midostaurin does not currently have UK marketing authorisation and does not have regulatory approval in the EU; however, it has been approved by the US FDA and in Switzerland. Midostaurin was granted orphan status for the treatment of acute AML by the European Medicines Agency (EMA) in 2004 and by the US Food and Drug Administration in 2009. A marketing authorisation application for midostaurin, in combination with chemotherapy followed by midostaurin monotherapy as treatment for adult patients with newly diagnosed AML who are FLT3 mutation-positive, was submitted to the EMA in July 2016. The CS states that an opinion from the EMA is expected in October 2017.

2.2 Critique of company's description of underlying health problem.

The manufacturer presented a brief definition, epidemiology, diagnosis and prognosis of the health problem.

2.2.1 Definition and pathophysiology of AML

The CS states that AML is an aggressive haematological malignancy and is usually considered as a clinical emergency.[1, 2] Without treatment, patients would die within 11–20 weeks of diagnosis; treatment should therefore be initiated as soon as possible, ideally within a matter of days of diagnosis.[3]

The CS also states that AML develops as a consequence of a series of genetic changes in haematopoietic precursor cells. In AML, immature monocytes and granulocytes are overproduced by the bone marrow and do not develop into leukocytes. Normal white blood cells (WBCs) are therefore replaced by leukaemic cells that have a diminished ability to defend against infection. The production of normal blood cells is decreased – resulting in anaemia, thrombocytopenia and neutropenia – and

Based on current guidelines, [13] the CS indicates that a definitive diagnosis of AML requires examination of peripheral blood and bone marrow specimens to assess cell morphology. It involves cytochemistry, immunophenotyping, cytogenetics and molecular genetics to describe the features of AML.

FLT3 mutation testing

The CS assumes that testing for FLT3 mutations is recommended and is often performed routinely in the prognostication of patients with AML; thus, no additional tests over those required for initiating standard chemotherapy will be associated with midostaurin in the UK. The CS also states that no additional tests or investigations are needed for the selection of FLT3-mutant AML patients However, the clinical advisor to the ERG stated that FLT3 testing up-take may vary across different practices in the UK: whilst the up-take of the test is considered standard practice it still may not be routinely performed on all patients although this is (rapidly) changing.

2.2.4 Prognosis of AML patients

The CS suggests that AML usually develops fast and is a fatal disease; without treatment, patients would die within 11–20 weeks of diagnosis, with mortality being due to complications (such as serious infection or haemorrhage) that are associated with the fundamental bone marrow failure. [14] The clinical advisor to the ERG agrees with this characterisation of the disease.

The CS states that FLT3 mutations are a particularly aggressive form of AML, with inferior overall survival (OS) and duration of remission. The expected 5-year survival for younger patients with AML is lower among those with FLT3 mutation-positive AML than among those without such mutations (wild-type FLT3 AML).[6] An analysis of data for a young UK cohort (median age, 43 years) reported a 5-year OS of 15–31% among patients with FLT3 mutations compared with 42% among those without such mutations.[6]

The CS also indicates that the most important factors predicting treatment outcomes in AML patients are: age, karyotype, and molecular genetics. [15, 16] Age or fitness has an influence on survival and prognosis, in part related to the fact that initial treatment with intensive chemotherapy may not be tolerated by many older and less healthy patients.[17]This is important given that the majority of AML patients are aged over 75.[7]

The CS reports estimates of 5-year OS for patients with newly diagnosed AML in the UK that range from 12–27% overall, and may be as low as 5% in individuals aged 65 years or older, and only 3% in patients aged 70 or older.[18, 19] The CS reports estimates of median OS for newly diagnosed AML patients as less than 12 months[18, 20] However, when analysed by age, the SEER (Surveillance, Epidemiology, and End Results) data for 1988–2012 found a median OS of 2-4 years in those under

Table 5 Summary of the overall survival data for the RATIFY trial (adapted from CS Table 11, page 55 and text)

Outcome	Midostaurin (N=360)	Placebo (N=357)	Hazard Ratio and/or p-value
Patients undergoing SCT			
All patients, %	59.4	55.2	
Patients with SCT in the 1st CR	[redacted]	[redacted]	
Median OS, months	74.7	25.6	HR= 0.77 (95% CI 0.63-0.95); p=0.0078
3-year, %	54 (95% CI 0.49–0.59)	47 (95% CI 0.41–0.52)	
5-year, %	51 (95% CI 0.45–0.56)	43 (95% CI 0.38–0.49)	
Mean overall survival, months	[redacted]	[redacted]	
Median OS censored at SCT, months (sensitivity analysis)	NE	NE	HR=0.745 (95% CI 0.54-1.03), p=0.0373
3-year, %	65	58	
5-year, %	64 (95% CI 0.56–0.71)	56 (95% CI 0.47–0.63)	
Median OS SCT only in first CR	[redacted]	[redacted]	HR=0.63 (95% CI:0.38-1.05)
Mean OS SCT only in first CR	[redacted]	[redacted]	
Median OS censoring for SCT, months	[redacted]	[redacted]	[redacted]
Mean OS censoring for SCT, months [c]	[redacted]	[redacted]	
Median OS only received SCT, months	[redacted]	[redacted]	[redacted]
Mean OS only received SCT, months [c]	[redacted]	[redacted]	
Median OS not received SCT, months	[redacted]	[redacted]	[redacted]
Mean OS not received SCT, months [c]	[redacted]	[redacted]	

Key: [a] CRs within 60 days of therapy initiation; [b] All CRs during protocol treatment and those in the 30 days following treatment discontinuation; [c] Reconstructed from respective Kaplan-Meier graphs; CR, complete remission; NE, not estimable (or not reached)

As can be seen from the results presented in Table 5 and Figure 1, OS was significantly longer for midostaurin than placebo and both the three-year and five-year survival rates were higher for midostaurin than placebo. The company also provided OS results for the most recent data cut (5th September 2016): median OS and the hazard ratio results remained similar to those from the original data cut ([redacted]). In order to calculate the mean OS from this latest data cut, the ERG reconstructed individual patient data (IPD) using the Kaplan-Meier graphs included in the company's clarification response. The ERG adapted the Guyot et al.[31] method of reconstructing data from published Kaplan-Meier survival curves, and used WebPlotDigitizer (http://arohatgi.info/WebPlotDigitizer/app/) to generate plot points and Excel

Complete remission, Event-free survival, disease free-survival and duration of remission

A summary of the other key effectiveness results is presented in Table 6 below (based on Table 11, page 55 of the CS and results reported in the CS text).

Table 6 Summary of the key effectiveness data for the RATIFY trial (adapted from Table 11, pages 55 of the CS and CS text)

Outcome	Midostaurin (N=360)	Placebo (N=357)	Hazard Ratio and/or p-value
Complete remission, %			
Protocol defined [a]	58.9	53.5	p=0.073
Expanded definition [b]	65.0	58.0	p=0.027
After 1st induction only	[redacted]	[redacted]	[redacted]
Median event-free survival, months	8.2 (95% CI 5.4–10.7)	3.0 (95% CI 1.9–5.9)	HR=0.78 (95% CI 0.66-0.93), p=0.002
1-year, %	43 (95% CI 0.38–0.49)	31 (95% CI 0.27–0.36)	
5-year, %	28 (95% CI 0.23–0.33)	19 (95% CI 0.15–0.24)	
Median event-free survival censored at SCT, months (sensitivity analysis)	8.3	2.8	HR=0.81 (95% CI 0.68–0.98), p=0.0124
1-year, %	43 (95% CI 0.38-0.49)	30 (95% CI 0.25-0.35)	
5-year, %	25 (95% CI 0.20-0.31)	21 (95% CI 0.16-0.27)	
Median disease-free survival [a], months	26.7 (95% CI 19.4-NE)	15.5 (95% CI 11.3 -23.5)	HR=0.714 (95% CI 0.55-0.92), p=0.0051
1-year, %	71 (95% CI 0.64-0.76)	57 (95% CI 0.49-0.64)	
5-year, %	48 (95% CI 0.41-0.54)	37 (95% CI 0.29-0.44)	
Median disease-free survival [a] censored at SCT, months	[redacted]	[redacted]	[redacted]
3-year, %	[redacted]	[redacted]	
5-year, %	[redacted]	[redacted]	
Median duration of remission, months	[redacted]	[redacted]	[redacted]
Median duration of remission censoring for SCT, months	[redacted]	[redacted]	[redacted]

Key: [a] CRs within 60 days of therapy initiation

Rates of complete remission

As can be seen from the results presented in Table 6, a higher proportion of the midostaurin patients achieved CR within 60 days of treatment initiation (protocol-defined CR), than did placebo patients, although the difference was not statistically significant (one-sided p value = 0.073). The

total of [redacted]

The ERG believes that the flow diagram and accompanying text provides sufficient information on the flow of participants during the follow-up period.

4.2.5.2 Baseline patients' characteristics of the Phase II trial

The baseline characteristics based on sex, age, ECOG performance status, and FLT3 mutation status were presented in the CS (Table 17, page 78 of the CS). [redacted]

2.2.1.2 Effectiveness results of Phase the II trial

A summary of the key effectiveness results is presented in Table 8 (Table 18, page 79 of the CS).

Table 9 Summary of the efficacy results for the phase II trial (Table 18, page 79 of the CS)

Endpoint	All patients (N=145)	Aged ≤60 years (N=99)	Aged >60 years (N=46)
CR, n (%)	[redacted]	[redacted]	[redacted]
EFS	[redacted]	[redacted]	[redacted]
Median EFS, months	[redacted]	[redacted]	[redacted]
2-year EFS, %	[redacted]	[redacted]	[redacted]
OS	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]
2-year OS, %	[redacted]	[redacted]	[redacted]
RFS	[redacted]	[redacted]	[redacted]
Median RFS, months	[redacted]	[redacted]	[redacted]
2-year RFS, %	[redacted]	[redacted]	[redacted]
Cumulative incidence of relapse, %	[redacted]	[redacted]	[redacted]
Cumulative incidence of death, %	[redacted]	[redacted]	[redacted]

Key: CR, complete remission; CSR, clinical study report; EFS, event-free survival; OS, overall survival; RFS, relapse-free survival.

The results show that younger FLT3positive AML patients (≤60 years old) appeared to have better median overall survival [redacted] than those who were older (>60 year old).

The company also conducted an exploratory analysis of relapse free survival, comparing trial data with historical controls, and the presented results appear to indicate that for both age groups, patients treated with midostaurin achieved better outcomes than controls.

4.2.6 Adverse events of midostaurin

Adverse events from the RATIFY trial

Adverse events of the RATIFY trial were presented in the CS (Tables 20-22, pages 84-89 of the CS). The key reported adverse events are summarised below in Table 10. The results show that the safety profile of midostaurin is similar to that of placebo.

Table 10 Key adverse events reported from the RATIFY trial

	Grade 3/4 AEs suspected be related to treatment	SAEs	Grade 3/4 infections	Withdrawal due to Grade 3/4 AEs	Death within 30 days of starting treatment	Deaths at anytime
Placebo (N=335)	[redacted]	163 (48.7%)	[redacted]	15 (4.5%)	21 (6.3%)	[redacted]
Midostaurin (N=345)	[redacted]	162 (47%)	[redacted]	21 (6.1%)	15 (4.3%)	[redacted]

Key: AEs, adverse events; SAEs, serious adverse events; SCT, stem cell transplant

Adverse events from the phase II trial

Safety results of the phase II trial were reported in Table 19, page 81 of the CS. Midostaurin appear to have a better safety profile in the younger patients than the older patients (see Table 11 below).

Table 11 Key adverse events reported from the phase II trial

	Treatment related AEs	SAEs	Withdrawal due to AEs	Death during treatment 30-day follow-up period
Aged ≤60 years (N=98)	[redacted]	[redacted]	[redacted]	[redacted]
Aged >60 years (N=46)	[redacted]	[redacted]	[redacted]	[redacted]

Key: AEs, adverse events; SAEs, serious adverse events

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No trials were identified by the company's searches.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The company did not carry out indirect comparison and/or multiple treatment comparison analyses, due to the absence of data on the comparators that targeted the FLT3 mutant AML population. The ERG did a preliminary search and agrees with the company that no trials or data were available for the analyses.

The RATIFY trial lacks generalisability to FLT3-positive AML patients in the UK, due to the age of the included population (restricted to 60 years, with a mean age of 45 years. Given that the only available data on older patients (up to age 70 years of age, the Phase II trial) found that the treatment response was better in those under 60 years of age compared with those over 60 years, there is uncertainty about the size of the treatment benefit to be achieved with midostaurin in eligible patients who may be older than 70 years. This means that there is also uncertainty about the size of the effect for the whole eligible population (including all ages).

Patients in the RATIFY trial who did not achieve complete remission after first induction cycle underwent a second induction cycle with the same treatment whilst a different chemotherapy for the second cycle may be used in UK practices. Hence, the treatment scheduling may not represent practice in the UK. Consequently, the effect size seen in the trial may not be achieved in clinical practice.

ERG Comment

The structure of the model, although accommodating a number of key clinical elements of the treatment of AML patients, has a number of significant weaknesses. In particular, there are a number of issues relating to how patients progress through the model; these mostly result from the clinical data used to populate the model. These issues result in several inconsistencies in the model and mean that the model exhibits a lack of face validity. These issues are discussed in turn below.

Possibility of response to subsequent therapy, for refractory or relapsed patient

As described above, patients who fail or relapse following first-line therapy, move to the relapse health state. On entering the relapse health state, patients cannot return to the CR health state and can only move to the SCT or death states. Patients in the relapse health state therefore have two treatment pathways. The first is to receive subsequent therapy followed by SCT, which is allowed for in the model. The second is receive subsequent therapy, but no SCT. This latter pathway is not full accounted for in the model. Within the model patients, as in RATIFY patients could and did receive subsequent therapies (as they would in clinical practice). The model, however does not accommodate response to this subsequent therapy and these patients are assumed to remain in the relapse health state with their mortality determined by observed by OS in the RATIFY trial. As consequence of this patients tend to stay in the relapse health state for a long time. This is evidenced by the fact that, at cycle 130 (~10 years), 15% of the patients initiating midostaurin are in the relapse health state. The consequence of this failure to accommodate response to subsequent therapies is very significant: the relapse heath state is defined, with low utility (0.53 QALYs per year) and very high health state costs (~60,000 per annum). The model therefore assumes that all patients who enter the relapse state and do not subsequently receive SCT, even those that subsequently respond to secondary therapy will continue to stay the relapse health state experiencing the morality benefits of subsequent therapy but also very low HRQoL and incurring very high care costs. The ERG considers it implausible that patients would continue to experience such low HRQoL and such high health care costs over such an extended period.

This issue has a significant impact on the model, leading it to underestimate the ICER, and it results in the model making logically inconsistent predictions. Firstly, it implies that patients who are responders to first-line therapy experience much higher HRQoL and much lower care costs than patients who are responders to subsequent therapy. Secondly, it means that the model reacts to inputs in odd ways. One of the clearest examples of this can be observed in a scenario analysis, carried out by the company, in which an alternative extrapolation point for OS data was chosen. In this scenario, the OS benefits of midostaurin were reduced and, in such a scenario, we would expect the ICER to increase to reflect these reduced benefits, yet it results in a significant drop in the ICER (£34,327 vs £21,552 per QALY). This reduction in the ICER is observed because, in this scenario, fewer

midostaurin patients are in the relapse health state and, therefore, this avoids the significant costs associated with this state.

This issue was raised with the company, at the clarification stage, and the ERG requested that the model allow patients who have relapsed, to be able to transition to the CR health state after the induction period. The company's response stated that the RATIFY trial did not collect data on CR for second and subsequent lines of therapy and, therefore, the company's revised model was not able to address this issue given the data available.

The company, however, did modify the model to include new Kaplan-Meier data for CR, to partially respond to points raised by the ERG. These new CR data, however, lack face validity and are very different to the CR data used in the original model. The company also expressed doubts regarding the validity of using this data and suggested that they may underestimate the prevalence of CR. The ERG, therefore, questions whether these new data are correct, and considers the original data to be the most accurate reflection of CR observed in the RATIFY trial. The ERG, therefore, reincorporated the original CR data in the model, as part of the exploratory analysis carried out by the ERG. Further, the ERG presents a scenario analysis, in Section 6, which attempts to address the identified issues with the relapse health state, by amending the model structure, so that patients do not remain in the relapsed health state in perpetuity.

Health state costs for the CR 1l and post-SCT recovery health states

The health states CR 1L (Complete remission post discontinuation of first-line treatment) and post-SCT recovery represent the terminal alive health states for patients who have successfully been treated and who have discontinued therapy. The company's model, however, assumes that both these health states are associated with significant ongoing health state costs, equivalent to approximately £8,000 per annum. This means that even decades after diagnosis patients are still accruing significant costs. The ERG considers that these ongoing health state costs are unjustified and are inconsistent with previous economic evaluations, in similar therapeutic areas. For example, in NICE TA [ID893], which evaluated inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia (ALL), no ongoing health state costs were assumed after discontinuation of treatment.[35] The impact of this assumption significantly overestimates the ICER, because patients in midostaurin have a greater chance of achieving a CR on primary therapy and a greater chance of receiving SCT.

At the clarification stage, the ERG requested that the company comment on the ongoing health costs associated with the CR 1L and SCT post-recovery health states. The company's response to this question outlined an additional scenario, in which the routine care costs for patients after 26 cycles were 50% reduced for all surviving patients. This scenario was justified on the basis that after 2 years the rates of relapse and mortality begin to plateau and, therefore, monitoring costs will fall after this

5.2.8 Treatment effectiveness and extrapolation

As stated previously, to establish the cost-effectiveness of Midostaurin, the company used a partition survival approach, which used the RATIFY trial to provide a direct comparison of the timing and rates of complete remission, relapse, SCT, and death. For details of the RATIFY trial, see section 4. The company used the data cut-off 01 April 2015 for the primary efficacy analyses to inform the base-case. As noted in section 4, a further data cut for the RATIFY trial is now available and this was requested by the ERG, at the points for clarification stage. These data were not included in the company's revised economic model as part the company's clarification response; but are explored as part of the additional analysis, carried out by the ERG, see Section 6 for details.

Within the first 80 cycles (~ 6.2 years), the model calculated the proportion of patients in each health state, by treatment, at 28-day intervals, using Kaplan-Meier data on OS, CR, SCT and time on primary therapy. The calculation of the proportion of patients in each of the five health states was as follows:

- **AML diagnosis/induction** – All patients enter the model in the AML diagnosis health state and is calculated as the proportion of patients on treatment, but not in CR. Note all patients who do not achieve CR by cycle two discontinue therapy and, therefore, patients can only stay in the AML diagnosis health state for a maximum of two cycles.
- **Complete Response/remission (CR) –** Time-to-event data on CR and time on treatment.
- **Relapse –** This a residual health state and calculated as one minus the AML diagnosis, CR, SCT and death health states.
- **Stem cell transplant (SCT) –** Time-to-event data on SCT censored for OS.
- **Death –** The proportion of dead patients is calculated as one minus the OS curve.

After cycle 80, surviving patients in all health states are assumed to be cured and are considered to be survivors, who experience a low risk of relapse. Therefore, after cycle 80 of the model, the company assumed that surviving patients entered a phase where they followed similar characteristics to that of the general population (same mortality risk). The specific choice of cure point, selected by the company, was determined by the availability of Kaplan-Meier data from the RATIFY trial, and was when the final event was observed in the chemotherapy arm. The company also put forward a series of arguments justifying the cure assumption, based on clinical opinion which noted the following: *"(1) following the first 2 years, patients are likely to become more stable depending on their disease status, with relapse and mortality becoming less frequent …; (2) after 5 years, patients are likely to follow a natural mortality curve as most of the leukaemia relapse occurred prior to this stage; (3) 10-year survival is likely to be approximately 10% lower than at the end of the trial (about 6.7 years prior), so the mortality trend should not be too aggressively*

experience general population mortality. With regards to the latter clinical arguments, advice from the clinical advisor to the ERG, suggests that the clinical justification put forward by the company with regards to the timing of the cure point is reasonable and the ERG further notes that the selected cure point aligns with the cure point used in economic models of other therapies in similar therapeutic areas.[35]

The selection of the cure point at 80 cycles is, however, somewhat arbitrary and while the ERG consider it a reasonable base-case, due to the fact it maximises the observable data available, the ERG is concerned by the fact that the sensitivity analysis did not explore the impact of selecting alternative cure points. The exploration of this uncertainty is important for two reasons. Firstly, as stated above, survival gains observed at the cure point are extrapolated over an entire lifetime and, therefore, the cure point is an important driver of cost-effectiveness. Secondly, because, there are relatively few patients observed in the later part of the Kaplan-Meier curve, the observed differences in OS in the tail of the Kaplan-Meier curve is subject to considerable uncertainty.

The updated model sent at the clarification stage did not incorporate the updated data from RATIFY as this was not requested by the ERG. However, the updated data were used in the ERG model, which reduces the uncertainty in the estimated OS differences at the base-case cure point of 80 cycles, as there are nearly four times the number of patients being observed.

5.2.8.2 Extrapolation beyond the trial follow-up

Overall survival

As stated above, the company directly incorporates the Kaplan-Meier data available on OS into the model and extrapolates these data, assuming that patients beyond cycle 80 experience general population mortality. The company's approach, therefore, did not fit parametric curves typically used in the extrapolation of time-to event data. The company justified this approach to extrapolation by having explored a range of parametric approaches, including using piecewise extrapolation of the Kaplan-Meier data and fitting parametric functions for the whole model duration. These approaches to extrapolation were, however, considered implausible on the basis of the clinical opinion cited above, which suggested that, after 5 years, patients were likely to follow a natural mortality curve. These alternative (parametric) models, were, however, explored in the scenario analysis for completeness

1. *Model structure*

   The ERG has significant concerns regarding the model structure, and notes a number of significant structural flaws, meaning that the model lacks face validity. Most importantly, the model does not fully accommodate h subsequent therapies and implies that responders to subsequent therapy remain the relapse health state while experience the OS benefits of subsequent therapy. The ERG is also concerned about the health costs assigned to the CR 1L (patients in remission post discontinuation of treatment) and post-SCT recovery health states lack validity and have a large impact on the ICER.

2. *The cure assumption*

   The model includes a point beyond which all surviving patients have general population mortality but, there is uncertainty surrounding this. Existing epidemiological evidence suggests that patients remain at a higher mortality risk for up to 30 years after SCT. Although this risk declines with time, the risk for patients surviving at least five years after SCT, without relapse, remains considerably higher than that for the general population (between 4 to 9 times higher, irrespective of age).

3. *The choice of the cure time point*

   The ERG is concerned about the lack of any real justification for the 80-cycle end point assumed in the base-case, which is largely determined on the basis that this was the last event in the RATIFY trial. The ERG considers this to be a reasonable base-case, as it is clinically justifiable and maximises the use of the available data, but noted the available OS data at these time points is subject to significant uncertainty as and consider that the impact of selecting alternative (clinically justified) cure points should have been explored in scenario analysis.

4. *Representativeness of the modelled population*

   The patient population modelled was based on patients enrolled in the RATIFY trial, which excluded patients over the age of 60 years. Epidemiological evidence suggests that the over 60's represent a significant proportion of the patients who are potentially eligible for treatment with midostaurin. Exclusion of this high-risk group of patients is likely to significantly underestimate the ICER, and there remains significant uncertainty as to the cost-effectiveness of midostaurin in older populations.

5. *The need to age-adjust utility estimates*

   When utility values are considered over a 60-year lifetime horizon, it is evident that the utility values assigned to the CR 1L and post-SCT recovery states may eventually exceed general

Table 36 Impact of correction for discrepancy on total unit of treatment

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Discrepancy in total units of treatment corrected	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£30,904	£2,438
	SOC	[redacted]	[redacted]	-	-	-	-
$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care							

6.3.4 Age adjusted disutility

The ERG believes it is appropriate to apply age adjusted utilities, to account for that fact that the benefits of cure are accrued over an extended period (see Table 37). The resulting ICER increases by £1,889 per QALY compared to CS base case.

Table 37 Impact of age adjusted utility decrement

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Age adjusted utility decrement	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£30,354	+£1,889
	SOC	[redacted]	[redacted]	-	-	-	-
$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care							

6.3.5 Addition of adverse events related to SCT

Table 38 presents the results of incorporating adverse events associated with SCT into the model: the ICER increased from £28,465 per QALY to £30,869 per QALY.

Table 38 Impact of SCT related AE's

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
SCT related AE's	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£30,869	+£2,404
	SOC	[redacted]	[redacted]	-	-	-	-
$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care							

6.4 ERG's preferred base case

Table 39 presents the ERG's preferred base-case which combines a number of the changes to the company base-case explored in Section 6.3. Specifically, the ERG base-case makes the following amendments to the company's revised base-case:

10. Corrections for calculation errors;
11. Addition of new OS data;
12. Addition of original CR data;
13. ERG's preferred model structure;
14. Applies a four-fold risk ratio to post cure mortality;
15. Applies age adjusted utility decrement into the model;
16. Increases the maximum number of cycles of monotherapy to 18;
17. Assumes total number of units of therapy matches the original company model;
18. Incorporates adverse events resulting from SCT.

The ERG considers this alternative base-case to be superior to the company's revised base-case and that the resultant estimate of the cost-effectiveness of midostaurin more plausible, notwithstanding the remaining issues with the model structure. The impact of combining these modifications to the company model is substantial, increasing the ICER from £34,327 in the revised company model to £62,810 in the ERG's preferred base-case.

Table 39 ERG's preferred base case

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
ERG's preferred base case	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£62,810	+£34,344
	SOC	[redacted]	[redacted]	-	-	-	-

$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care

6.5 Further exploratory analysis of uncertainties

This section presents additional scenario analyses considering uncertainty surrounding three assumptions/ inputs used in the model. These concern the cure point selected, the utility values for the CR 1L and post-SCT recovery health states, and the mean age of the population eligible for treatment with midostaurin. These additional analyses are performed using the ERG's preferred base case model.

6.5.1 Alternative cure point

As noted in Section 5.2.8, the choice of cure point is very important to the outcomes of the model because the survival gains observed at that chosen time point are extrapolated over an entire lifetime. Given the influence of the cure point, the ERG considers that further exploration of alternative cure points is warranted. The ERG explores this issue by assuming the following alternative cure points 4 years, 5 years and 7 years. The results of the analysis are presented in Table 40. The alternative cure points have significant influence on resulting ICER, with all three alternatives increasing the ICER. This is because the observed difference in OS is larger at cycle 80 (~6.2 years) than at any of the alternative cure points considered.

Table 40 Impact of alternative cure points assumption

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
ERG's preferred base case [cure point ~6.2 yrs]	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£62,810	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Cure point at 4 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£70,160	+£7,351
	SOC	[redacted]	[redacted]	-	-	-	-
Cure point at 5 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£64,207	+£1,397
	SOC	[redacted]	[redacted]	-	-	-	-
Cure point at 7 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£84,161	+£21,351
	SOC	[redacted]	[redacted]	-	-	-	-

ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care; yrs, years

6.5.2 Alternative assumption of utility values for CR 1L and SCT post-recovery health states

As outlined in Section 5.2.8, there were multiple sources of utility values for several health states in the model. The company, however, presented only limited scenario analysis exploring the impact of alternative utility values. The ERG therefore presents additional scenario analyses considering alternative sources for the CR 1L and post-SCT recovery states. The ERG focus on these two health states as the model is most sensitivity to the utility values for these states. In the scenarios carried out by the ERG it is assumed that the utility values for both health states will be the same on the basis these two states represent the "remission/potentially cured" health states in the model. To explore the uncertainty in the utility values for these health states, the ERG presents three scenarios representing the range of values reported in the literature. Table 41 presents the results of this analysis. The impact of using alternative utility values for these two health states is quite significant, with the ICERs ranging from £53,718 per QALY to £66,429 per QALY.

Table 41 Impact of alternative assumption of utility values for CR and SCT post-recovery health states

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
ERG's preferred base case	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£62,810	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Pessimistic assumption (Kurosawa-2014)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£66,429	+£3,619
	SOC	[redacted]	[redacted]	-	-	-	-
Optimistic assumption (Novartis-TTO)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£53,718	-£9,092
	SOC	[redacted]	[redacted]	-	-	-	-

$, all ERG corrections and adjustments implemented to the company's base case model; ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care

6.5.3 Alternative assumptions of mean age of the AML population

One of the key issues raised in Section 4 and Section 5.2.3 concerning the trial was that it excluded patients over the age of 60. It is not possible to fully correct for the fact that the RATIFY trial excluded older patients, as there no other comparative efficacy data for midostaurin. It is however, possible to modify the model to take into account the fact that the benefit of cure will be lower in older patients due to reduced life expectancy. Table 42 presents the results of scenario analysis in which the mean age of patients is changed from 45 to 50, 55, and 60 years of age. The impact of increasing mean age is very significant, increasing the ICER substantially. This is because increasing the age of patients dramatically reduces the benefits of cure.

Table 42 Impact of alternative assumptions of mean age of the AML population

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
ERG's preferred base case [mean age – 45 yrs]	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£62,810	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Mean age – 50 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£70,513	+£7,704
	SOC	[redacted]	[redacted]	-	-	-	-
Mean age – 55 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£80,325	+£17,515
	SOC	[redacted]	[redacted]	-	-	-	-
Mean age – 60 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£92,619	+£29,809
	SOC	[redacted]	[redacted]	-	-	-	-

ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care; yrs, years

6.6 Conclusions from ERG analyses

The ERG has presented a number of additional analyses. These analyses were carried in a number of stages. The first stage addressed a number of minor calculation errors in the company's revised model and incorporated new OS data the original CR data into the revised company model. The impact of these changes was reduce the ICER from £33,672 per QALY to £28,569 per QALY.

Using the corrected and updated model the ERG then presented a number of analysis considering a range of issues raised in Section 5. These scenario analyses addressed the following issues:

- The model structure and ongoing differences in costs and QALYs.
- Assumptions regarding post cure mortality rates;
- The maximum number of cycles of monotherapy.
- Discrepancies in total units of therapy received in the original and revised company model.
- Adjusting utilities for the age of the cohort.
- Additional of SCT related AE's

The most of important these scenarios related to changes made by the ERG to the model structure and the ERG analysis explored a number of iterations of the model in which alternative assumptions regarding the model structure were made. These analysis explored two distinct issues with the company's model structure, firstly that it does not accommodate response to subsequent therapy and secondly that it assumes ongoing care costs for patients who are "cured". The results of this analysis

demonstrated that these structural issues have a significant impact on the ICER. This exploration of alternative model structures was concluded with the ERG presenting a preferred model structure. The ERG, while considering this model a more appropriate vehicle through which to assess the cost-effectiveness of midostaurin, do emphasise that this model does not represent a fully appropriate model: it still has significant limitations and weaknesses.

The ERG base-case analysis estimated midostaurin to be more costly [redacted] compared with standard of care and suggests that the ICER for Midostaurin compared with SOC is around £62,810 per QALY.

A further series of exploratory analyses explored the impact of alternative assumptions regarding the selected cure point, utility values used in the CR 1L and post-SCT recovery health state and mean age of eligible patients indicate that the ERG's base-case ICER is likely to represent a lower bound with the majority of analysis's resulting in increases in the ICER; range £53,718 and £92,619 per QALY, assuming the ERG's base case assumptions.

Based on the ERG's base case analysis midostaurin is unlikely to represent good value to the NHS considering typical WTP thresholds.

8 Overall conclusions

Clinical effectiveness

Although the results of the RATIFY trial demonstrate a clear beneficial effect of midostaurin, with a median OS benefit of 49 months (and mean OS benefit of [redacted] months), in patients who do, and do not, undergo SCT as part of first line therapy for AML, there is significant uncertainty regarding the effect size.

This uncertainty relates mainly to the age of the RATIFY trial population, which was restricted to 60 years, with a mean age of 45 years. Given that the only available data on older patients (up to age 70 years of age, the Phase II trial) found that the treatment response was better in those under 60 years of age compared with those over 60 years, there is uncertainty about the size of the treatment benefit to be achieved with midostaurin in eligible patients who may be older than 70 years. This means that there is also uncertainty about the size of the effect for the whole eligible population (including all ages).

Cost effectiveness

The economic evidence presented by the company primarily consisted of a *de novo* model. The company's model used a partition survival model approach which directly used the time-to-event data from the RATIFY trial to determine the distribution of patients between the health states. The company found midostaurin to be more costly (cost difference of [redacted]) and more effective [redacted] compared with standard of care. The deterministic base-case ICER was £33,672 per QALY.

The ERG considers that the economic analysis presented by the company was inadequate to fully address the decision problem specified in NICE's scope. The ERG's principal concerns related to the structure of the model, which contained a number of significant structural flaws meaning that the model lacks face validity. The ERG was unable to fully rectify all the identified issues with the company's model, but was able to carry out a number of analyses using assumptions and data inputs it believes are more plausible than those used in the company's base-case analysis. The ERG base-case analysis estimated midostaurin to be more costly ([redacted]) and more effective [redacted] compared with standard of care and suggests that the ICER for Midostaurin compared with SOC is around £62,810 per QALY.

8.1 Implications for research

Further RCT evidence in of older (aged > 60 years) FLT3-positive patients, who are suitable for intensive chemotherapy, is required.

Age and Outcomes in Patients with FLT3-positive AML given Midostaurin

Addendum to NICE Submission

ERG Responses regarding Age of the Target Population and Midostaurin

The ERG expressed concern for the population of the RATIFY trial (Stone, et al., 2017) These are expressed in the following statements in the ERG report:

- p.12 “The population considered in the company submission (CS) are people with newly diagnosed, FLT3 mutation-positive AML, which exactly matches that of the NICE scope. However, the anticipated product licence for midostaurin restricts the population to those suitable for intensive chemotherapy. Furthermore, the ERG notes that the RCT evidence submitted by the company, is restricted to people aged 18-60 years, which is a sub-group of the patient population described in the final NICE scope. Older patients are not well reflected in the clinical evidence submitted.”

- p.13: “It provides the only data for the use of the licensed regimen in patients aged over 60 years (up to age 70 years). The results of this Phase II trial indicate that midostaurin treatment response is better in younger patients (< 60 versus > 60 years of age).”

- p. 14-15: “The trial’s population is adults 18-60 years of age whilst a large proportion (>60%) of AML patients to be treated in the UK are over 60 years. Therefore, the trial’s results may not be generalizable to the whole eligible population, or those over 60 years of age. Given that the only available data on older patients (up to age 70 years of age, the Phase II trial) found that treatment response was better in those under 60 years of age compared with those over 60 years, there is uncertainty about the size of the treatment benefit to be achieved with midostaurin in older eligible patients, who may be older than 70 years. This means that there is also uncertainty about the size of the effect for the whole eligible population (including all ages).”

- p. 16-17: “The population recruited to the RATIFY trial excluded patients over the age of 60 and therefore excluded a significant proportion of patients potentially eligible for treatment with midostaurin. Exclusion of this high-risk group of patients is likely to have created a more favourable treatment effect for midostaurin in the primary efficacy analysis, with a commensurate effect on cost-effectiveness.”

- p. 18: “There is uncertainty around the treatment effect of midostaurin in older, yet fit FLT3-positive patients, suitable for intensive chemotherapy.”

We would like to present multple lines of evidence that this is not case, and that the effectiveness of midostaurin is demonstrated across both age groups.

Evidence 1: FLT3-positive AML has homogenous biology regardless of age group.

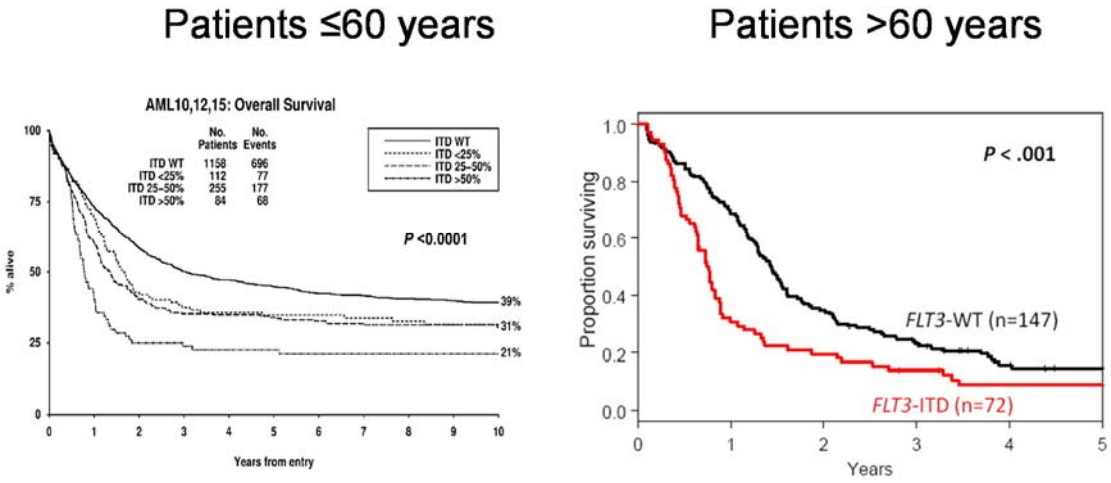
Elderly patients with AML tend to have an increase in unfavourable or complex cytogenetics. (Creutzig, Zimmermann, & Reinhardt, 2016) However, these complex cytogenetics are generally infrequent in patients with FLT3 mutations.

As detailed in a recent landmark article looking at mutations and molecular subgroups, FLT3 mutations and other “driver” mutations did not overlap with others in most cases. (Papaemmauil, Gerstung, & Bullinger) This included FLT3-ITD mutations as well, which was used as an inclusion criterion in the RATIFY trial. In that study, only 39 patients (7.1%) exhibited complex cytogenetics. (Stone, et al., 2017) This was consistent with a prior study that also showed the rarity of complex cytogenetics in patients with FLT3 mutations.

Thus, it is not expected that patients in our target population will have differing prognosis based on age alone.

Evidence 2: The prognosis of patients with FLT3-positive AML is similarly poor across differing age groups.

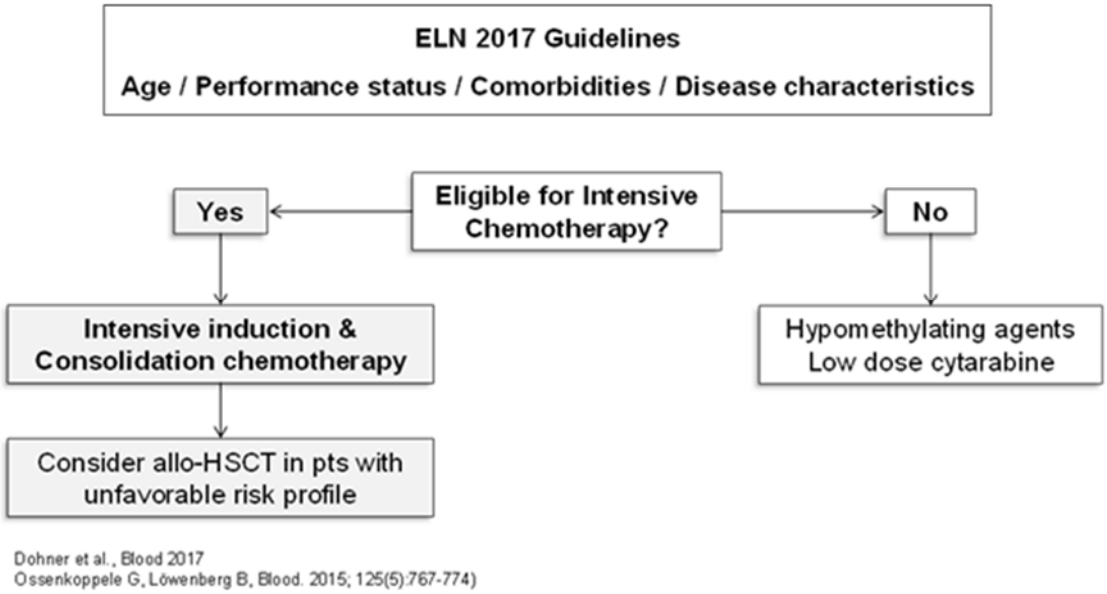
Studies have been consistent in illustrating the uniformly poor prognosis of patients in our target population.



The data above shows that there is no fundamental change in disease risk and biology based on age alone among patients with FLT3-positive AML. (Linch, Hills, & Brunett, 2014; Whitman, Maharry, & Radmacher, 2010)

Evidence 3: Due to shifts in clinical practice, age is no longer the only factor for eligibility in chemotherapy.

The current standard of care no longer limits induction chemotherapy to patients < 60 years of age. The NCCN Guidelines recommends that performance status, functional status, and comorbid conditions be considered as well if the patient is 60 years old and above. (National Comprehensive Cancer Network, 2016) A similar model is used by the European Leukemia Network, where chemotherapy is considered even in patients > 60 years of age if these patients prove eligible based on those other factors. (Döhner, Estey, & Grimwade, 2017)



The same network has observed that treatment-related mortality has decreased due to better supportive care, wiser patient selection, and improved general health status even in older patients. (Döhner, Estey, & Grimwade, 2017) This trend has been observed in countries that were early adopters of intensive induction chemoterhapy (e.g. Sweden and the Netherlands). A study that included 11,598 patients from the Swedish Cancer Registry showed that relative survival ratios (ratio of observed all-cause survival in the AML population compared to general population) have increased the most for patients aged between 61-70 years, from 0.16 (95% CI 0.13-0.19) in 1997-2005, to 0.28 (95% CI 0.23-0.33) in 2006-2011. ([Bower, Andersson, & Björkholm, 2016) A more recent study in Denmark also showed better relative survival rations in patients with AML aged 70 years and below, attributing these effectes to better management of induction chemotherapy. (Dinmohamed, Visser, & van Norden, 2016)

Evidence 4: Data from the original submission showed that Midostaurin is effective in patients more than 60 years of age

In our submission dated 2nd March 2017, we included the first report of an open label, single-arm, phase 2 study by Schlenk, et al (2015), enrolling patients with FLT3-positive AML. The inclusion criteria for age was 18 to 70 years. The primary objective of the study was explicitly to compare outcomes between patients 18 to 60 years of age, and those aged 61 to 70 years.

As reported in the paper, the study was able to enrol 149 patients with an age range between 20 to 70 years, with 34% of these patients being age ≥ 60 years. Median age was 54 years.

After induction therapy, the study showed complete response in 74.8%, which is comparable to the 80% response rate in the RATIFY trial. Refractory disease remained in 17.7% of patients, and deaths in 7.5%. At 25 months, complete response was at 74%. When this was classified by age, there was a complete response in 77% of patients < 60 years, and 67% of patients ≥ 60 years.

The second report of the same study had 284 patients, with 32% of those patients having an age ≥ 60 years. (Schlenk, Fiedler, & Salih, Impact of age and midostaurin-dose on response and outcome in acute myeloid leukemia with FLT3-ITD: interim-analyses of the AMLSG 16-10 trial., 2016) Overall response to induction was the same for patients < 60 and ≥ 60 years old, at 76% (p = 0.81). Death in patients < 60 years was 4%, and 10% in patients ≥ 60 years. The cumulative incidence of relapse and death after transplant in both age groups were also without differences, at 13% (p = 0.97) and 16% (p = 0.41) respectively. Median overall survival (OS) for all patients was 25 months. For patients < 60 years, median OS was 26 months, while for patients ≥ 60 years, it was 23 months, with no statistical difference (p = 0.15).

Evidence 5: When comparing trial data with propensity score-matched historical controls, midostaurin demonstrated efficacy in patients > 60 years old.

An interim analysis was performed on the ongoing study reported previously. This analysis was conducted independently and sent by the German-Austrian Acute Myeloid Leukemia Study Group (AMSLG). (Novartis Pharmaceuticals UK, 2017)

The historical controls were selected from 5 successive clinical trials conducted by AMSLG enrolling AML patients treated with intensive chemotherapy (Schlenk, Frohling, & Hartmann, 2004; Schlenk, Döhner, & Salih, 2015; Schlenk, Fiedler, & Salih, 2016; Schlenk, Frohling, & Hartmann, 2006; Tassara, Dohner, & Brossart, 2016)

Across these trials, a total of [redacted] patients with FLT3 ITD mutations were identified. The baseline characteristics of these data are presented in Table 2-2 (Average age older: Response to 2nd LoOI – clinical aspects, Rydapt (midostaurin)/PKC412). These AMLSG studies included: 06-04, [redacted]; 07-04, [redacted]; 93, [redacted]; 98A, [redacted] and 98B, [redacted].

These historical controls were compared to the [redacted] patients treated in study ADE02T using a propensity scoring technique. A propensity score is the probability of treatment assignment conditional on observed baseline characteristics. With the propensity score, one can design and analyze an observational (nonrandomized) study so that it is similar to the characteristics of a randomized controlled trial. The propensity score acts as a balancing score so that the distribution of observed baseline covariates will be similar between treated and untreated subjects. The inverse probability of treatment weighting method was utilized (Williamson 2014).

The propensity score was calculated with a logistic regression model which regressed the following baseline variables: age, gender, NPM1 mutation status, white blood cell count and percentage of bone marrow blasts. (Williamson, Forbes, & White, 2014)

Using the aforementioned method, midostaurin treatment demonstrated benefit, with OS Hazards Ratio (HR) (95% CI) = [redacted] and Event-free survival (EFS) HR (95%CI) = [redacted]. (See figures below; historical = propensity score matched historical cohort; 16-10 = population in Schlenk et al, 2016)

Overall survival

[redacted]

Event-free survival

[redacted]

This survival benefit was seen in age groups above and below 60 years. OS hazards ratio between those on midostaurin and those on standard of care was [redacted] in patients ≤ 60 years, and [redacted] in patients > 60 years.

EFS hazards ratio between those on midostaurin and those on standard of care was was likewise [redacted] in patients ≤ 60 years and [redacted] in patients > 60 years. (See figures on succeeding pages)

Overall Survival – Age ≤ 60

Overall Survival – Age > 60

Event-Free Survival – Age ≤ 60

Event-Free Survival – Age > 60

Because Schlenk, et al (2016) is a publication of interim results, we plan to submit for your consideration a full CSR once the study is completed. A sample size of 440 patients has been calculated, with an estimate 150 being older than 60 years. Additionally, 2 additional phase 3 studies may be initiated in 2017 which will generate additional efficacy and safety data. These are described as follows:

- Study A2408 is a single-arm multi-center study to assess safety and efficacy of midostaurin in combination with standard chemotherapy during induction and consolidation, followed by 12 months of midostaurin monotherapy in adult patients with newly diagnosed FLT3-mutated AML. The study enrolls patients who are eligible for "7+3" or "5+2" chemotherapy; patients have to be fit to receive intensive induction and consolidation chemotherapy. The planned sample size is 300 patients, with the first patient expected to be enrolled in Q3 2017.
- Study E2301 is a randomized, double-blind study of midostaurin vs placebo in combination with chemotherapy during induction and consolidation, followed by 12 months of midostaurin monotherapy in adult patients with newly diagnosed AML, without FLT3 mutation. Patients have to be suitable for intensive induction chemotherapy. The protocol includes a comprehensive collection of baseline data (including biomarkers), post-study treatments, and evaluation of minimal residual disease (MRD). The planned sample size is 502 patients; the first patient is expected to be enrolled by the end of 2017.

Evidence 6: The ICER given the new age adjustments recommended by the ERG

The ICER submitted in version 2_2 was of £33,672. This model was created in answer to the ERG comments. The following model includes some additional changes and options.

	ICER	Description
Initial ICER (Model 2_2)	£33,672	
Return to the initial CR data	£18,712	In their comments, ERG requested for SCT censoring as well as other adjustments to the CR data. As explained in our response, we consider the initial CR data more accurate as the SCT, relapsing and death patients were already taken out. The initial 60 days CR data was imported in this model.
Dosing adjustment to return to the initial submission (avoid the 1.06 adjustment)	£19,820	In their first review, the ERG wanted to split the treatment phase. We submitted this data, but the ERG noted a smaller overall area under the curve for primary treatment duration. In this model, we re-

		analysed data to match the initial submission.
Include GVHD complications	£21,548	SCT complications were not initially included. In this version of the model, we have added a complication cost and a complication disutility.
SCT costs	£17,398	In this version of the model we have used the NHS blood and transplant 2014 cost.
Threshold for routine care cost	£25,503	We applied a 50% reduction to routine care costs after 26 cycles to reduce the impact of long term relapse.
Updated OS data	£13,588	In this version, we have included the Kaplan-Meier extracted using digitalization identical to the ERG model. Note that this data can only be used for the cure model.
Age related adjustment (based on new Schleck data)	£27,754	We added an exploratory age adjustment based on the Schleck study. More data is now available on the performance of MIDO by age group, mainly the hazard ratio in comparison to an historical comparator created using propensity score matching.

After all these modifications, our final ICER is £27,754.

Explaining the new age adjustment

Model 2_2 had two age adjustments. The first adjusted the cure model standardized mortality rate (risk ratio). This adjustment only affected the cure model, and relevant literature data proved difficult to find. The trial did not provide this long-term information either. The second adjustment for age was only relevant for the transition tail option. This adjustment was based on patient level data. Similarly, a multiplication of the mortality rate was applied on the transition rate.

The new age adjustment takes advantage of the newly available Schleck data. The new data provided in *Response to 2nd LoOI – clinical aspects, Rydapt (midostaurin)/PKC412* was used, primarily for the digitalization of the SOC and MIDO for the older population.

Adjustment	*Description*	*Source*
Younger population Kaplan-Meier	*The ITT data is used for the younger population.*	
Older population Kaplan-Meier (SOC)	*The patient level data was not available for this population. Therefore, we digitalized the OS data of the SOC. The adjustment was only performed for OS.*	*Response to 2nd LoOI – clinical aspects, Rydapt (midostaurin)/PKC412*
Older population Kaplan-Meier (MIDO)	*The patient level data was not available for this population. Therefore, we digitalized the OS data of the MIDO. The adjustment was only performed for OS. This adjustment leads to an ICER of £27,754.* *The hazard ratio generated by the cox model presented in the new Schleck document was applied to the SOC using hazard mapping to generate the MIDO arm OS data. This adjustment lead to an ICER of £25,044.* *We retained the digitalization approach as the base case adjustment, as it was more conservative.*	*Response to 2nd LoOI – clinical aspects, Rydapt (midostaurin)/PKC412*
Extrapolation for younger and older population	*For the younger population, i.e. based on the ITT data, the initial cure model was used. For the older population, the OS was also extrapolated with a cure model, but the average age at baseline was considered at 65, versus 45 used in the initial model.*	*Average age older: Response to 2nd LoOI – clinical aspects, Rydapt (midostaurin)/PKC412*
Pooled Kaplan-Meier	*A weight of 59% was applied to the older population. Consequently, a weight of 41% was applied to the younger population Kaplan-Meier.*	*Patient between 60-74 / all patients between 16-74; Cancer research UK, Acute Myeloid Leukaemia (C92.0, C92.4, C92.5, C92.6, C92.8 C93.0, C94.0, C94.2), Average Number of New Cases per Year and Age-specific Incidence Rates, UK, 2012-2014*
Utilization in the model	*The new Kaplan-Meier and its cure extrapolation are used to replace the ITT data when the option is selected.*	

Adjusted Kaplan-Meier – Short term

Adjusted Kaplan-Meier – Long term

References

[Bower, H., Andersson, T.-L., & Björkholm, M. (2016). Continued improvement in survival of acute myeloid leukemia patients: an application of the loss in expectation of life. *Blood Cancer, 6*, e390.

Creutzig, U., Zimmermann, M., & Reinhardt, D. (2016). Changes in cytogenetics and molecular genetis on acute myeloid leukemia from childhood to adult age groups. *Cancer, 122*, 821-830.

Dinmohamed, A., Visser, O., & van Norden, Y. (2016). Treatment, trial participation and survival in adult acute myeloid leukemia: a population-based study in the Netherlands, 1989–2012. *Leukemia, 30*, 24-31.

Döhner, H., Estey, E., & Grimwade, D. (2017). Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood, 129*, 424-427.

Linch, D., Hills, R., & Brunett, A. (2014). Impact of FLT3(ITD) mutant allele level on relapse risk in intermediante-risk acute myeloid leukemia. *Blood, 124*, 273-276.

National Comprehensive Cancer Network. (2016). *Guidelines for AML treatment*. Abgerufen am 21. September 2017 von NCCN: www.nccn.org/professionals/physician_gls/f_guidelines.asp

Novartis Pharmaceuticals UK. (2017). *Data report - Midostaurin.*

Papaemmauil, E., Gerstung, M., & Bullinger, L. (kein Datum). Genomic classification and prognosis in acute myeloid leukemia. *New England Journal of Medicine, 374*, 2209-2221.

Schlenk, R., Döhner, K., & Salih, H. (2015). Midostaurin in combination with intensive induction and as single agent maintenance therapy after consolidation therapy with allogeneic hematopoietic stem cell transplantation or high-dose cytarabine. *Blood, 126*, 322.

Schlenk, R., Fiedler, W., & Salih, H. (2016). Impact of age and midostaurin-dose on response and outcome in acute myeloid leukemia with FLT3-ITD: interim-analyses of the AMLSG 16-10 trial. *Blood, 128*, 449.

Schlenk, R., Frohling, S., & Hartmann, F. (2004). Phase III study of all-trans retinoic acid in previously untreated patients 61 years or older with acute myeloid leukemia. *Leukemia, 18*, 1798-1803.

Schlenk, R., Frohling, S., & Hartmann, F. (2006). Intensive consolidation versus oral maintenance therapy in patients 61 years of older with acute myeloid leukemia in first remission: results of second randomization of the AML HD98-B treatment trial. *Leukemia, 20*, 748-750.

Stone, R., Mandrekar, S., Sanford, B., Laumann, K., Geyer, S., & Bloomfield, C. (2017). Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. *New England Journal of Medicine, 377*, 454-464.

Tassara, M., Dohner, K., & Brossart, P. (2016). All-trans retinoic acid as adjunct to intensive treatment in younger adult patients with acute myeloid leukemia: results of the randomized AMLSG 07-04 study. *Annals of Hematology, 95*, 1931-1942.

Whitman, S., Maharry, K., & Radmacher, M. (2010). FLT3 internal tandem duplication associates with adverse outcome and gene- and microRNA-expression signatures in patients 60 years of age or older with primary cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. *Blood, 116*, 3622-3626.

Williamson, E., Forbes, A., & White, I. (2014). Variance reduction in randomised trials by inverse probability weighting using the propensity score. *Statistics in Medicine, 33*, 721-737.

Single Technology Appraisal (STA)

Midostaurin for untreated acute myeloid leukaemia [ID894]

ERG's commentary on the addendum submitted by the company

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD
Date	31/10/2017

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

Table of Contents

Table of Tables

1 Introduction

The evidence review group (ERG) was requested by NICE to provide a critique of additional evidence submitted by the company in response to ERG's concerns regarding the representativeness of the population recruited to the RATIFY trial .

The company's addendum included:

- Evidence to support the CS statement that FLT3-positive AML has homogenous biology regardless of age group;
- Evidence to support the CS assumption that prognosis of patients with FLT3-positive AML is similarly poor across differing age groups ;
- Evidence that older patients will be eligible for midostaurin therapy;
- Evidence supporting the effeteness of midostaurin in older patients;
- A new propensity score matched analysis of historical control data estimating the clinical effectiveness of midostaurin in older patients.
- New economic evidence incorporating a new age adjustment scenario in which the cost-effectiveness of midostaurin in older patients is estimated.

2 Critique of the additional evidence submitted by company after FAC to support "Age and Outcomes in Patients with FLT3-positive AML given Midostaurin"

2.1 Evidence 1. FLT3-positive AML has homogenous biology regardless of age group.

The argument presented here by the company is that the higher mortality seen in elderly AML patients is due at least in part to unfavourable cytogenetics, but that these unfavourable cytogenetics are rare in FLT3+ve patients. Hence older FLT3+ve patients would not be expected to have a more unfavourable prognosis than younger ones (based on age alone).

The ERG cannot comment in detail on this, but would point out that it does not resolve the uncertainty that arises from the lack of older (aged > 60 years of age) patients in the RATIFY trial.

2.2 Evidence 2. The prognosis of patients with FLT3-positive AML is similarly poor across differing age groups.

The company addendum presents additional evidence to support the argument that the prognosis of patients with FLT3-positive AML is uniformly poor across differing age groups and that disease risk and biology is unrelated to age. The ERG notes that the graphs presented are from unrelated cohorts: that for the $\leq$60 years is of a UK cohort (n=1609) (Linch et al.2014), the > 60 years cohort is for the

USA (n=243)(Whitman et al. 2010). The company did not confirm that these cohorts are essentially similar apart from age. The ERG notes that the Linch et al. 2014 cohort is divided into different % of FLT 3ITD, whilst the Whitman et al. 2010 cohort is not. The company addendum does not make clear how these cohorts should be compared. Assuming that the > 60 years FLT3-ITD cohort is to be compared with the highest % FLT3 cohort in the study of younger patients, the ERG estimates the following % alive numbers (Table 1). (Note these estimates were generated by a manual reading from the graphs, and the ERG fully acknowledges these are rough estimates.) If other % ITD data are used, then the % alive in the younger cohort is higher and the difference between the younger and older groups is greater.

Table 1: Overall survival in the <60 and >60 cohorts

	≤60 years cohort (Linch et al.2014)	**≥60 years cohort (Whitman et al. 2010)**
	FLT3 ITD >50%	FLT3 ITD
1 year	40%	33%
2 years	25%	20%
5 years	22%	10%

The ERG's interpretation of the data presented in the two graphs does not strongly support the conclusion drawn by the company that there is no fundamental change in disease risk and biology based on age alone among patients with FLT3-positive AML. Further, the ERG notes that rates of OS are uniformly lower in the >60 cohort. Therefore, while the ERG agrees that the prognosis of patients with FLT3-positive AML is poor in all ages, it does not agree that age is not a prognostic factor.

2.3 Evidence 3: Due to shifts in clinical practice, age is no longer the only factor for eligibility in chemotherapy.

The ERG made this point in their report: older patients are not necessarily unfit and some will be eligible to receive treatment. The ERG concurs with this statement and this is why the ERG questions the generalisability of the RATIFY population results: RATIFY excluded patients aged > 60 years.

2.4 Evidence 4: Data from the original submission showed that Midostaurin is effective in patients more than 60 years of age

The ERG agrees that the data in the original submission from a single-arm Phase II study showed that midostaurin was effective in older patients. However, the results also showed that younger FLT3 positive AML patients (≤60 years old) appeared to have better median overall survival ([redacted]), complete remission rate ([redacted]) median event-free survival ([redacted]

[redacted]), and median relapse free survival ([redacted]) than those who were older (>60 year old).

In the addendum the company present additional data from an expanded version of the Phase II study. The first patient entered the original study in June 2012 and in April 2014, after recruitment of n=147 pts, the study was amended including a sample size increase to 284 pts and a dose reduction to 12.5% of the initial dose of midostaurin in case of co-medication with strong CYP3A4 inhibitors (e.g. posaconazole). This study is available only as a conference abstract which focuses on age and the comparison between the first (n=147) and the second cohort (n=137) of the study in terms midostaurin dose-adaptation.

Unlike the results of the original study, the results from the expanded cohort were similar in patients aged younger and older than 60 years. Overall response to induction was the same for patients < 60 and ≥ 60 years old, at 76% (p = 0.81. The cumulative incidence of relapse and death after transplant in both age groups were also without differences, at 13% (p = 0.97) and 16% (p = 0.41) respectively. For patients < 60 years, median OS was 26 months, while for patients ≥ 60 years, it was 23 months, with no statistical difference (p = 0.15). However, death in patients < 60 years was 4%, and 10% in patients ≥ 60 years.

It is unclear to the ERG how long the later recruited patients were followed up for (the median follow-up for the whole cohort was 18 months), or how many events those patients contributed to the analysis. In addition, this analysis was an interim analysis and so the results are uncertain. Furthermore, the ERG is uncertain about the significance of the dose reduction in the expanded cohort and whether this is more or less reflective of clinical practice than the full dose. Finally, it must be noted that the cohort does not include any patients aged over 70 years.

2.5 Evidence 5: When comparing trial data with propensity score-matched historical controls, midostaurin demonstrated efficacy in patients > 60 years old.

From the addendum the ERG understands that the 223 patients from the expanded Phase II study (interim data only) were compared and matched, using propensity score matching, to 415 patients with specifically FLT3 ITD mutations selected from 5 successive clinical trials.

The results of this analysis found OS hazards ratio (HR) (95% CI) = [redacted] and event-free survival (EFS) HR (95%CI) = [redacted] When analysed by age group the results suggest that the treatment effect of midostaurin is greater in those aged over 60 years than in younger patients: OS hazards ratio between those on midostaurin and those on standard of care was [redacted] in patients ≤ 60 years, and [redacted] in patients > 60 years.

The ERG attempted to check this analysis but were unable to do so fully because the citations given in the addendum do not relate to all 5 trials and therefore information pertaining to only two trials could be checked by the ERG: HD 98-B (Schlenk et al. 2004 and Schlenk et al. 2006) and AMLSG 07-04 (Schlenk et al. 2016).

The ERG has the following comments.

1. Information from the publications of these two studies suggests that the historical control may not be reflective of current clinical practice. The treatment regimen does not match that given in the RATIFY trial, in particular the historical cohort trials induction included a lower dose of cytarabine, but also included etoposide (Table 2).

Table 2: Summary of historical control data

	HD 98-B	**07-04**
Date of recruitment	Feb 1998 to Sept 2001 (Schlenk 2004) or Aug 1997 to April 2003(Schlenk 2006)	Aug 2004 to Jan 2006
Number of patients contributing to historical control	23	203
Age range of total cohort	61-84.5 years	≤60 years
Age range of patients contributing to historical control	unknown	unknown
Induction:	Idarubicin 12mg.m^2 IV days 1+3 Cytababine 100mg/m^2 days 1-5 Etoposide 100 mg days 1+3 If response achieved a 2nd cycle was given, if not a more intensive regimen was given.	2 cycles of Idarubicin 12mg/m^2 IV days 1+3+5 Cytababine 100mg/m^2 days 1-7 Etoposide 100 mg days 1-3
Consolidation	First consolidation cycle: Cytarabine 0.5 g/m2/12 h i.v. days 1–3, mitoxantrone 10 mg/m2 i.v. days 2 and 3). SCT was permitted if there was a HLA-identical family donor on the decision of the local investigator Second randomization was performed after completion of first consolidation	3 cycles of high dose cytarabine – 3g/m^2 bid on days 1, 3, 5 (or 1,2 3) High risk patients received HCT. NB from Dec 2006 all FLT3 patients given HSCT as consolidation (number of patients not known). If MRD available HSCT in 1st CR to most patients

	therapy for patients in CR. Patients were randomized to either a second intensive consolidation therapy IEiv (idarubicin 12 mg/ m2 i.v. days 1 and 3, etoposide 100 mg/m2 i.v. days 1–5) or to a 1-year oral maintenance therapy IEpo (idarubicin 5mg p.o. days 1, 4, 7, 10, 13, etoposide 100 mg p.o. days 1 and 13; repeated on day 29 for 12 courses).	

2. Neither the characteristics of the controls nor the 223 Phase II study patient cohort are reported, though as the Phase II cohort included patients up to age 70 only it can be assumed that this analysis is also limited to patients of 70 years or younger. From the K-M plots provided, 62 (15%) were aged over 60 (up to 70 years) and 353 (85%) were 60 years or younger. This does not reflect clinical practice where >55% of patients are diagnosed aged >70 years.

3. This analysis is an observational study and therefore, is subject to bias. Whilst the propensity score matching may improve the comparability of the cohorts on known factors, it cannot account for unknown confounders. Furthermore, the method of propensity score matching is best applied to very large observational studies, rather than single arm studies of limited size.

4. The ERG notes that it is unclear if the analysis of OS was censored for SCT (the main analysis of RATIFY was not).

5. These results are much more favourable to midostaurin than are the results of the RATIFY trial. This appears to be due to the poorer survival results in the historical cohort than in the control arm of RATIFY. The ERG rough estimates (from manual reading off graphs provided) for OS and EFS are given in Table 3.

Table 3: Comparison of EFS and OS in the RATIFY trial and in the historical controls

	Control arm RATIFY	**Historical control**
EFS		
EFS at 12 mths	36%	30%
EFS at 24 mths	28%	22%
EFS at 48 mths	27%	20%
OS		
OS at 12 mths	64%	60%
OS at 24 mths	50%	35%
OS at 48 mths	44%	30%

The ERG notes that the OS control in the >60 years comparison is very much poorer than that in the ≤60 years one and also notes that the sample size in the older age group comparison is very much smaller.

In summary, these additional analyses do indicate that there is uncertainty around the midostaurin treatment effect in older patients. However, the inherent uncertainty in the analysis of observational data, means that there is still no reliable estimate of the treatment benefit of midostaurin in patients aged up to 70 years. Furthermore, there is still no estimate of the treatment benefit of midostaurin in the full population who would be eligible for this treatment in the NHS (i.e. including patients aged over 70 years).

Given the limitations of the propensity score analysis the ERG does not believe it provides a more reliable estimate of treatment effect than does the results of the RATIFY trial.

2.6 Evidence 6: The ICER given the new age adjustments recommended by the ERG

The addendum presents additional economic evidence exploring the impact of a number of alternative assumptions. This additional evidence consists of a number revisions to the company base-case model based on responses to questions raised by the ERG at the points for clarification stage and the incorporation of an age adjustment scenario which seeks to respond to the ERG's concerns regarding the representativeness of the population recruited to the RATIFY trial. The ERG considers the revisions based on the previously presented analysis, a new company preferred base-case, and

discusses these changes to the model, before proceeding to assess the validity of the new age adjusted scenario.

2.6.1 Revised company base-case

Table 4 provides a brief summary of the assumptions made in the company's revised base-case and those made in the ERG's base-case analysis.

Table 4: Comparison of Company revised base-case and ERG base-case

	Company revised base-case	**ERG base-case**
ERG calculation corrections	Not included	Included
Model structure/health state costs	50% reduction to routine care costs after 26 cycles.	Zero health state costs after treatment. Utilities all equal to CR1L health state following treatment
Complete response data	As per the original company base-case	As per the original company base-case
Time on treatment	As per the original company base-case	As per the original company base-case
Mortality: trial period	Updated OS data cut	Updated OS data cut
Mortality: post-trial period	General population	Four fold multiplier applied
Age adjusted utilities	Not included	Included
GVHD complications	Included	Included
SCT costs	Based on NHS blood and transplant 2014 cost	Based on NHS reference costs as per the company base-case.
Maximum number of cycles of monotherapy	Set to 12 as per the market authorisation	Set to 18 as per RATIFY trial.

As can be seen from Table 4, in its revised base-case the company rejects a number of changes made by the ERG in its base-case analysis. The company presents no additional evidence or argument relating to these issues, but presumably contests the appropriateness of these assumptions. For completeness the ERG presents a brief restatement of the ERG's position with regard these ERG base-case assumptions.

ERG calculation errors: The ERG identified a small number of inconstancies and calculation in the original company model. These corrections were not adopted by the company in its addendum submission. It is not clear whether the company is in disagreement with regards of the validity of these corrections, but the notes that the company did not raise any concerns with respect to the ERG's calculation corrections in its factual accuracy report. The ERG considers the company's decision to not include these calculation corrections to be highly problematic as it means there is not a mutually agreed model in which alternative assumptions can be explored.

Model structure health state costs: In the ERG's original report a number of significant issues with the company's base-case model structure were noted. Of primary concern was the fact that the model assumes significant ongoing routine care costs for patients in the relapse, CR 1L (patients in remission post discontinuation of treatment) and post-SCT recovery health states. The ERG made a number changes to the company's base-case model to ameliorate the impact of these assumptions by assuming zero routine care costs after discontinuation of treatment. However, the company chose not to adopt any of these changes and instead applied a 50% reduction in routine care costs after 26 cycles (months). As noted in our original report, the ERG consider this scenario inappropriate as it does not address the underlying issues identified with the company base-case and still implies significant ongoing health state costs for patients; ~£3000 per annum in the CR1L Post SCT recovery health states and ~£30,000 in the relapse health state. This scenario also implies that patients who relapse will continue to experience lower HRQoL even if they are successfully treated.

Mortality in the post-trial period: In the post-trial period the company base-case assumed that all surviving patients have general population mortality after the cure point (6.2 years). Existing epidemiological evidence, however, suggests that the mortality risk for patients surviving at least five years after SCT, without relapse, remains considerably higher than that for the general population (between 4 to 9 times higher, irrespective of age). The ERG therefore considered that the company's base-case was overly optimistic.

Age adjusted utilities: When utility values are considered over a 60-year lifetime horizon, it is evident that the utility values assigned to the CR 1L and post-SCT recovery states may eventually exceed general population utility estimates, which naturally decline with age. The ERG thus considers that utilities in the CR 1L and post-SCT recovery state should be further adjusted for declining HRQoL with age.

SCT costs: The company's original base-case included the costs of SCT from NHS reference costs. The ERG, however, noted alternative costs were available from NHS blood and transplant (2014). At the clarification stage, the company provided a scenario analysis implementing the values from the NHS Blood and Transplant (2014), which have now been adopted in its revised base-case. As part of their response the company, however, stated a preference for using NHS reference costs noting the following: "SCT process has evolved substantially since 2002 and is currently far more common. Therefore, inflating a 2002 cost to 2017 may overestimate the SCT cost. On the other hand, however, the NHS reference cost potentially excludes some of the SCT costs, though the more recent cost source is likely to be more accurate than the inflation of 2002 costs used in the NHS publication." The ERG considered the arguments provided by the company in its response persuasive and therefore retained the assumptions used in the original company base-model (NHS reference costs). It is not clear why the

company chose to adopt NHS blood and transplant (2014) as source of SCT costs in its revised base-case given their previously stated preference for using NHS reference costs.

2.6.2 Age related adjustment

To address the ERG's concerns regarding the representativeness of the modelled population the company presents a new age adjustment scenario. This new analysis makes two separate changes to the company's base-case analysis, these consist of changes to the OS data and changes to the average age of the population modelled.

Revisions to OS data: The age adjustment scenario incorporates new OS data into the model based on analysis of the propensity score matched historical controls described above (Evidence 5). To incorporate this new OS data the company splits the modelled population into two groups young (<60) and old (>60). Overall survival data for the young group are sourced from the RATIFY trial as per the original base-case. Overall survival data from the old cohort are sourced from the new comparison with historical controls (Evidence 5). To estimate cost-effectiveness for the combined cohort the OS data are weighted assuming 41% of patients are young and 59% are old. The weights are derived from age-specific incidence rates. Only the OS data used in the model is changed and all other clinical data are sourced from the RATIFY trial as per the original base-case.

Average age of cohort: In the post-trial period the overall survival of patients in the model is assumed to follow that of the general population with mortality rates determined by the mean age of the cohort. To account for the fact that this scenario assumes a greater number of older patients the model assumes that the mean age of the patients receiving midostaurin is 65 years.

The ERG has a number of substantive concerns regarding the age adjustment scenario. These issues concern the reliability of the data used to model OS; inconsistencies in the clinical data used; the proportion of older patients assumed; and the average age of the cohort assumed. These are discussed in turn below.

- **Reliability of OS data:** As described above the ERG has significant concerns relating to the reliability of the new propensity score matched historical control analysis noting that this comparison estimates that OS benefits are much larger than suggest by the RATIFY trial.
- **Inconstancies in clinical data:** While the age adjustment scenario incorporates new OS data into the model it does adjust the other clinical data used in the model including the response/relapse, rate of SCT or time on treatment. It is highly likely that are significant differences between younger and older patients with respect to these clinical parameters. For example, older patients are significantly less likely to receive a SCT than younger patients. These inconstancies are likely to have a significant impact on the cost-effectiveness estimates

and therefore caution should be used in interpreting the results of this analysis as they are subject to very significant uncertainty.

- **Proportion of older patients:** The proportion of older patients assumed by the company in the scenario is based on the incidence of AML in patients over the age of 60. The ERG considers that this approach is likely to overestimate the proportion of older patients. This is because not all older patients will be eligible for treatment with midostaurin treatment due to the requirement that patients be able to tolerate intensive chemotherapy. In the company model increasing the proportion of older patents acts to increase the ICER. This effect is, however, reversed in the ERG base-case model as a result of the ERG's changes to the model structure.
- **Mean age of cohort:** The mean age of the cohort is used to determine the mortality of patients post the cure point. In the company's age adjustment scenario the mean age of is assumed to be 65. The ERG considers this assumption to be inconsistent with the OS data used as only 59% of patients are assumed to be between the ages of 60 and 70, with the remaining 41% having a mean age of 45. If the mean age of the older age cohort is assumed to be 65 and the appropriate weighting applied, the mean age of the whole cohort is instead 56.8. The impact of reducing the mean age of the population modelled is to reduce the ICER

In summary while the ERG acknowledges the difficulties of modelling the effectiveness of midostaurin in more representative populations of young and older patients, the ERG considers that the additional age adjustment scenario is subject to a number of significant limitations. Particularly, the ERG considers it likely that the new OS data incorporated into the model is likely to significantly overestimate the benefits of midostaurin.

2.6.3 Additional ERG analysis

To allow the committee to understand the impact of the new age adjustment scenario the ERG present additional analysis in which this scenario is incorporated into the ERG's base-case. Results of this additional analysis are presented in Table 5. The results of this analysis show that incorporating the new age adjustment scenario into the ERG base-case substantially reduces the ICER (note this is the reverse of incorporating it into the company's revised base-case where the ICER increases). The reduction in the ICER observed in the ERG base-case is because the propensity score matched analysis estimates that midostaurin provides much greater OS benefits in the older cohort than in the younger cohort.

Table 5: Incorporating the new age adjustment scenario in ERG's base-case

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS revised base case without age related adjustment	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£13,588	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
CS revised base case (with age related adjustment: mean age 57)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	24,001	+£10,413
	SOC	[redacted]	[redacted]	-	-	-	-
CS revised base case (with age related adjustment: mean age 65)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£27,754	+£14166
	SOC	[redacted]	[redacted]	-	-	-	-
ERG's preferred base case (without age related adjustment)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£62,810	+£49,222
	SOC	[redacted]	[redacted]	-	-	-	-
ERG's preferred base case (with new adjustment: mean age 57)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£35,999	+£22,411
	SOC	[redacted]	[redacted]	-	-	-	-
ERG's preferred base case (with new adjustment: mean age 65)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£45,060	+£31,472
	SOC	[redacted]	[redacted]	-	-	-	-

3 References

Linch, D., Hills, R., & Brunett, A. (2014). Impact of FLT3(ITD) mutant allele level on relapse risk in intermediate-risk acute myeloid leukemia. *Blood, 124*, 273-276.

National Health Service Blood and Transplant. *Unrelated donor stem cell transplantation in the UK. A report from the UK stem cell strategy oversight committee*; 2014. Available from: nhsbt.nhs.uk

Schlenk, R., Frohling, S., & Hartmann, F. (2004). Phase III study of all-trans retinoic acid in previously untreated patients 61 years or older with acute myeloid leukemia. *Leukemia, 18*, 1798-1803.

Schlenk, R., Frohling, S., & Hartmann, F. (2006). Intensive consolidation versus oral maintenance therapy in patients 61 years of older with acute myeloid leukemia in first remission: results of second randomization of the AML HD98-B treatment trial. *Leukemia, 20*, 748-750.

Schlenk, R., Fiedler, W., & Salih, H. (2016). Impact of age and midostaurin-dose on response and outcome in acute myeloid leukemia with FLT3-ITD: interim-analyses of the AMLSG 16-10 trial. *Blood, 128*, 449.

Whitman, S., Maharry, K., & Radmacher, M. (2010). FLT3 internal tandem duplication associates with adverse outcome and gene- and microRNA-expression signatures in patients 60 years of age or older with primary cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. *Blood, 116*, 3622-3626.

Single Technology Appraisal (STA)

Midostaurin for untreated acute myeloid leukaemia [ID894]

Results of additional analysis requested by committee

Produced by **CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD**

Date **14/11/2017**

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

Table of Tables

Table 1 presents the results of revised base case. The revised base case included revised model structure using ERG's model structure scenarios:

- Cure health state after 3 years, and
- Zero CR 1L and post-SCT recovery health state costs after cure point

The difference between the ICER produced by this scenario and the ERG base-case can be almost entirely attributed to changes to routine care costs which are now substantially higher in the standard care arm (incremental routine care costs = -£14,926 in the new scenario vs -£289 in the ERG base-case).

Table 1 ERG's base-case including revised model structure

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
CS base case[$] (corrected)	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£28,465	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
ERG's base case	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£62,810	+£34,344
	SOC	[redacted]	[redacted]	-	-	-	-
ERG's base-case including revised model structure *	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,924	+£16,458
	SOC	[redacted]	[redacted]	-	-	-	-

$, all ERG corrections and adjustments implemented to the company's base case model;

* The ERG's base-case was revised only for the model structure assumption.

ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care;

Table 2 presents the results of ERG's exploratory analysis sequentially applied to the revised model structure changes.

Table 2 ERG's exploratory analyses and base-case

Amendment	**ICER**	**Change in ICER**
Company's base-case (response to clarification) – corrected by ERG	***£28,465***	***n/a***
1. Model structure (cure health state after 3 years, and zero CR 1L and post-SCT recovery health state costs after cure point)	£29,014	+£548
Amendment 1 and 2. Maximum number of cycles of monotherapy increased to 18 (based on RATIFY)	£29,121	+£656
Amendment 1 and 3. Units of treatment received based on company's original model (discrepancy corrected)	£31,545	+£3,080
Amendment 1 and 4. Age-adjusted utilities	£31,010	+£2,545
Amendment 1 and 5. Adverse events associated with stem cell transplant	£31,548	+£3,083
Amendment 1 and 6. Applying 4 fold risk to general population mortality	£36,215	+£7,750
1 to 6: ERG's base-case including revised model structure	**£44,924**	**+£16,458**
Key: n/a, not applicable		

Table 3 presents the results of ERG's exploratory applied cumulatively to the revised model structure changes.

Table 3 ERG's exploratory analyses and base-case (amendment to the CS base-case added cumulatively)

Amendment	**ICER**	**Change in ICER**
Company's base-case (response to clarification) – corrected by ERG	***£28,465***	***n/a***
1. Model structure (cure health state after 3 years, and zero CR 1L and post-SCT recovery health state costs after cure point)	£29,014	+£548
Amendment 1 and 2. Maximum number of cycles of monotherapy increased to 18 (based on RATIFY)	£29,121	+£656
Amendments 1 to 2 and 3. Units of treatment received based on company's original model (discrepancy corrected)	£31,660	+£3,195
Amendments 1 to 3 and 4. Age-adjusted utilities	£33,840	+£5,375
Amendments 1 to 4 and 5. Adverse events associated with stem cell transplant	£36,705	+£8,240
Amendments 1 to 5 and 6. Applying 4 fold risk to general population mortality	£44,924	+£16,458
1 to 6: ERG's base-case including revised model structure	**£44,924**	**+£16,458**
Key: n/a, not applicable		

Table 4 presents impact of the alternative cure point assumptions.

Table 4 Impact of alternative cure point assumptions.

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
ERG's base-case including revised model structure [cure point ~6.2 yrs]	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,924	n/a
	SOC	[redacted]	[redacted]	-	-	-	
Cure point at 4 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£46,387	+£1,464
	SOC	[redacted]	[redacted]	-	-	-	-
Cure point at 5 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,531	-£393
	SOC	[redacted]	[redacted]	-	-	-	-
Cure point at 7 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£56,079	+£11,155
	SOC	[redacted]	[redacted]	-	-	-	-

Key: ICER, incremental cost effectiveness ratio; Inc. incremental; n/a, not applicable; n/a: not applicable; QALY, quality adjusted life year; SOC, standard of care; yrs, years

Table 5 presents impact of alternative assumptions of mean age of the AML population.

Table 5 Impact of alternative assumptions of mean age of the AML population

Scenarios	Treatments	Costs	QALYs	Inc. cost	Inc. QALY	ICER	Change in ICER
ERG's base-case including revised model structure [mean age – 45 yrs]	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,924	n/a
	SOC	[redacted]	[redacted]	-	-	-	-
Mean age – 50 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£49,679	+£4,755
	SOC	[redacted]	[redacted]	-	-	-	-
Mean age – 55 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£55,600	+£10,676
	SOC	[redacted]	[redacted]	-	-	-	-
Mean age – 60 yrs	Midostaurin therapy	[redacted]	[redacted]	[redacted]	[redacted]	£62,818	+£17,895
	SOC	[redacted]	[redacted]	-	-	-	-

Key: ICER, incremental cost effectiveness ratio ; Inc. incremental; n/a, not applicable; QALY, quality adjusted life year; SOC, standard of care; yrs, years