NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts [ID829]

Contents:

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts [ID829]

This premeeting briefing presents:

- 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.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- Which comparator or comparators are the most appropriate for azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts in people not suitable for haematopoietic stem cell transplantation?
  - The company presented clinical effectiveness evidence from AZA-AML-001 which compared azacitidine with a combined conventional care regimen (CCR). The CCR comprised intensive chemotherapy with anthracycline and cytarabine plus best supportive care (IC), low dose chemotherapy with cytarabine plus best supportive care and best supportive care (BSC) alone.

- Does the committee consider that the proportions of chemotherapy use in AZA-AML-001 are representative of NHS clinical practice?
  - The proportion of patients pre-selected to each CCR therapy in AZA-AML-001 is 18% IC, 64% LDAC and 18% BSC
  - The ERG present data from a registry in Yorkshire that suggest more patients may receive BSC [redacted] and fewer LDAC [redacted], while clinical expert advice is that more patients would be expected to receive IC.
- What is the Committee's view about the lack of statistical significance in AZA-AML-001 for the primary efficacy endpoint of overall survival (OS)?
  - The primary efficacy endpoint for AZA-AML-001 was an ITT comparison of overall survival for azacitidine versus combined CCR. An improvement was demonstrated but it did not reach statistical significance. Statistical significance was also not reached for other outcomes assessed and reported.
  - The company argued that the lack of statistical significance in OS was as a result of confounding from treatment switching and heterogeneity in the baseline characteristics of the clinical trial population.
- Is it appropriate to adjust estimates from AZA-AML-001 to account for treatment switching and differences in baseline covariates? Were appropriate methods used to make the adjustments?
  - The company presented post-hoc analyses in order to address confounding effects of subsequent therapy and baseline covariates on overall survival (OS).
  - The company health economic base case analysis included estimates where only the CCR arm was adjusted for subsequent treatment with azacitidine.
  - The ERG commented that an analysis which adjusted for subsequent AML treatment in both arms would have been more appropriate.

Cost effectiveness

- Is the company's model robust and valid to support decision making?
- Should use of subsequent treatments have been incorporated in the model?
  - The company model did not include healthcare resource utilisation associated with switching to subsequent treatments

  - The estimates of effect for azacitidine used in the economic model included some people who in AZA-AML-001 received subsequent treatments.
- Did the company use appropriate extrapolation models in order to model overall-survival, progression-free survival and relapse-free survival?
  - Only models that implied proportional hazards treatment effects were considered (i.e., exponential, Weibull and Gompertz). Other parametric models, in particular log-logistic and log-normal models, i.e., accelerated failure time models, which allow increasing event rates over time at the start of follow-up and decreasing event rates at later times, were not considered
  - The ERG stated that statistical analyses of time-to-event outcomes relied on the proportional hazards assumption, which transpired not to be justified.
  - The ERG provided scenario analyses where extrapolation methods were changed.
- Does the Committee accept the changes made by the ERG to healthcare resource utilisation in the economic model?
  - The ERG corrected a series of implementation errors associated with the estimation of healthcare resource utilisation and costs
  - The ERG amended the model so that the mean number of treatment cycles reflected the number in AZA-AML-001
  - The ERG amended the model so that the resource use quantities within the same health state for different treatments were the same. For example in the company model the number of inpatient days per 4-week cycle was 1.73 for patients with relapsed/progressed disease who had been previously treated with azacitidine compared with 2.61 for those previously treated with CCR
- What does the Committee consider to be the most plausible ICER for azacitidine?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was to appraise the clinical and cost effectiveness of azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	Adults with acute myeloid leukaemia with bone marrow blasts more than 30%	Adults aged ≥65 years who are not eligible for haematopoietic stem cell transplant with acute myeloid leukaemia with >30% bone marrow blasts.	In line with the marketing authorisation the submission evaluates azacitidine in patients aged ≥65 years who are not eligible for haematopoietic stem cell transplant.	The ERG are satisfied this is a reasonable change
Intervention	Azacitidine		No comments	
Comparators	• Intensive chemotherapy with an anthracycline in combination with cytarabine • Non-intensive chemotherapy with low dose cytarabine • Best supportive care (which may include blood product replacement, antibiotics, antifungals and intermittent low dose chemotherapy with hydroxycarbamide)	Conventional care regimen (CCR) consisting of: • intensive chemotherapy (IC) • non-intensive chemotherapy with low dose cytarabine (LDAC) • best supportive care (BSC). Decitabine is licensed for the treatment of elderly patients as defined by the World Health Organisation. Decitabine is not recommended by NICE and therefore has not been included as a comparator.	The appropriate comparator for this appraisal is CCR rather than the individual comparators. There is currently no single standard of care for this patient group. Additionally, a number of factors including the heterogeneity of a difficult to treat population and lack of a risk algorithm to clearly guide clinicians make it difficult to assess how one treatment compares with another. The approach taken in the pivotal trial for azacitidine was to determine its efficacy and	The company have replaced three individual comparators with one composite comparator on the basis that there are no established criteria for selecting one CCR. As a result the company have not assessed whether azacitidine demonstrates clinical and cost effectiveness compared to each CCR (in patients for whom that CCR would be appropriate). The ERG considers this to be a weakness of the submission

			safety against conventional care made up of IC, LDAC or BSC alone. The trial demonstrated that patients are likely to benefit from using azacitidine regardless of the treatment regimen it is compared with. In this context it is anticipated azacitidine would be offered as a first line therapy as an alternative to all existing therapy options.	
Outcomes	• Overall survival • Progression free survival • Time to disease progression • Response rates, including haematologic response and improvement • Blood transfusion independence • Infections • Adverse effects of treatment • Health-related quality of life	The outcomes in the scope. Measures of response rates included: • Complete remission (CR) • Cytogenetic complete remission (CRc) • Partial remission (PR)	Progression free survival (PFS) was not measured in the azacitidine clinical trial as it is not a standard endpoint for acute myeloid leukaemia . For the purposes of economic modelling PFS was estimated from event free survival (EFS) and relapse free survival (RFS) data.	PFS and response rate reported by the company do not match exactly to the outcomes in the scope. Differences are either terminology or added detail for clarification. These differences are deemed acceptable.

Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: • People with acute myeloid leukaemia secondary to myelodysplastic syndrome • People with adverse-risk cytogenetics	A number of pre-defined patient- and disease-related subgroups were assessed during the pivotal trial. These included those with myelodysplastic syndrome (MDS)-related changes, and poor cytogenetic risk status, as per the scope.	No comments	Acute myeloid leukaemia secondary to MDS is a subgroup of acute myeloid leukaemia with MDS-related changes (constituting just over half), but outcomes are expected to be similar.
Source: Company submission and company decision problem proforma				

2 The technology and the treatment pathway

2.1 Azacitidine (Vidaza, Celgene) is administered subcutaneously at a recommended dose of 75 mg/m2 per day for 7 days, followed by a rest period of 21 days (28-day treatment cycles). The summary of product characteristics recommends that patients should be treated for a minimum of 6 cycles. In October 2015 azacitidine received a marketing authorisation for treating 'adult patients aged ≥65 years who are not eligible for haematopoietic stem cell transplant with acute myeloid leukaemia with >30% bone marrow blasts.'

2.2 Azacitidine also has a marketing authorisation for adults who are not eligible for haematopoietic stem cell transplantation and have:

- intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS) or
- chronic myelomonocytic leukaemia (CMML) with 10–29% marrow blasts without myeloproliferative disorder or
    - acute myeloid leukaemia (AML) with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification

These indications are subject to NICE technology appraisal guidance 218.

2.3 Acute myeloid leukaemia (AML) is a haematological bone marrow cancer affecting the myeloid line of blood cells. In AML, myeloid stem cells in the bone marrow produce immature blood cells (usually myeloblasts) which do not develop fully and build up in the bone marrow. These immature blood cells are not able to function properly and they reduce the ability of the bone marrow to produce other cells the body needs. The World Health Organisation (WHO) system requires involvement of at least 20% of blood and/or bone marrow by myeloblasts for AML diagnosis. AML can develop following myelodysplastic syndrome (MDS), or as a result of therapy (e.g. cytotoxic therapy) or it can arise without previous associated disease or treatment (primary AML). The company stated that around three quarters

(73%) of all diagnoses occur in people over 60 years and that there are approximately 1,777 new cases of AML annually.

2.4 Treatment decisions are based on a number of patient and disease related prognostic factors. As shown in figure 1, intensive chemotherapy (IC) with cytarabine is offered to people who are able to tolerate it. People considered unlikely to be able to tolerate intensive chemotherapy are usually offered less intensive chemotherapy options such as low dose chemotherapy (LDAC) with cytarabine. People unable to tolerate chemotherapy or who choose not to have chemotherapy receive best supportive care (BSC). BSC can include treatment with red blood cell or whole blood transfusions, fresh frozen plasma transfusions, platelet transfusions, antibiotic and/or antifungal therapy, and nutritional support. Hydroxycarbamide may also be used. Despite this general guidance there is no widely accepted risk algorithm which clinicians use in the UK when deciding which patients are most likely to benefit from intensive or non-intensive treatment options.

Figure 1 – Acute myeloid leukaemia (AML) treatment pathway

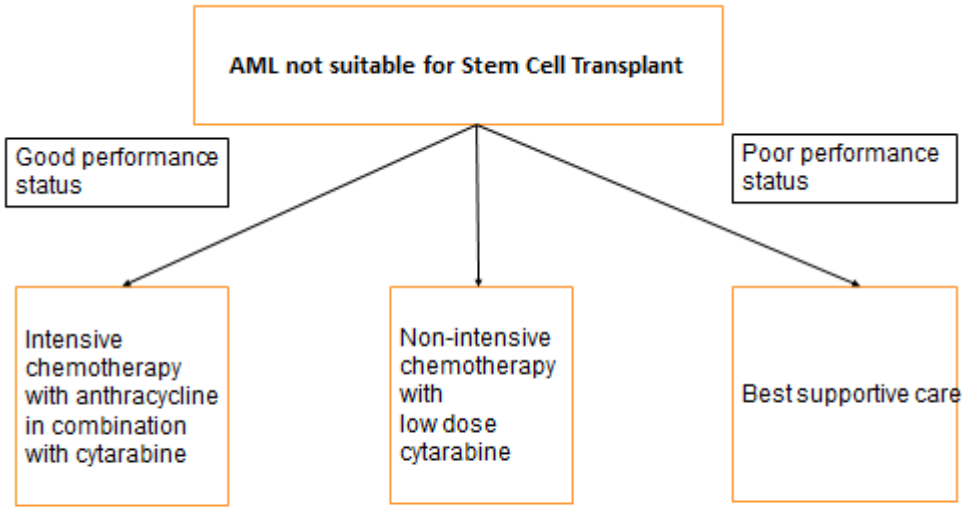


Table 2 Technology

		Conventional Care Regimen (CCR)		
	Azacitidine	**Intensive chemotherapy with cytarabine (IC)**	**Low-dose chemotherapy with cytarabine (LDAC)**	**Best supportive care (BSC)**
Marketing authorisation	Treatment of adult patients aged 65 years or older who are not eligible for HSCT with AML with >30% marrow blasts according to the WHO classification.	Cytarabine: For induction of remission in acute myeloid leukaemia in adults and for other acute leukaemia's of adults and children Idarubicin: For the treatment of acute myeloid leukaemia (AML), for remission induction in untreated patients or for remission induction in relapsed or refractory patients. Daunorubicin: Inducing remissions of acute myelogenous and lymphocytic leukaemias	Cytarabine: For induction of remission in acute myeloid leukaemia in adults and for other acute leukaemia's of adults and children	N/A
Administration method	75 mg/m2 per day administered subcutaneously daily for 7 days, followed by a rest period of 21 days (28-day treatment cycles). It is recommended that patients be treated for a minimum of 6 cycles.	In the azacitidine clinical trial those assigned to IC received cytarabine at a dose of 100-200mg/m^2 IV for 7 days in combination with anthracycline IV (daunorubicin or idarubicine) for 3 days induction, plus up to 2 consolidation cycles.	In the azacitidine clinical trial those assigned to LDAC received cytarabine at a dose of 20 mg SC twice daily for 10 days, every 28 days, until the end of the study, or study discontinuation.	In the azacitidine clinical trial BSC included, but was not limited to, treatment with red blood cell or whole blood transfusions, fresh frozen plasma transfusions, platelet transfusions, antibiotic and/or antifungal therapy, and nutritional support. Hydroxyurea use was permitted under certain conditions.

Drug cost (£)	List price: 100mg vial: £321.00 A confidential discount applies as agreed in TA218. [redacted]	Cytarabine list price: 20 mg/mL; 5 mL vial or 100 mg/mL; 1 mL vial: 100mg per vial or pack £4.95 Anthracycline list price: Daunorubicin 20 mg vial £55.00 Idarubicin: 5mg vial £87.36 / 10mg vial £170.72	Cytarabine list price: 20 mg/mL; 5 mL vial or 100 mg/mL; 1 mL vial: 100mg per vial or pack £4.95	Separate best supportive care cost not presented in the company submission

Source: Company's submission, economic model and British National Formulary (35)

See summary of product characteristics (SPC) for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 Consultees emphasised that the goal in treating acute myeloid leukaemia (AML) is not to cure but to improve progression-free and overall survival. They noted that in this population it is important to improve quality of life including more tolerable side effects and improved symptom control. Consultees noted that as around three quarters of all AML patients in the UK are over 60 years old many patients are unable to tolerate aggressive treatment options therefore treatment options are limited. Any improvement in survival rates for a patient population with a poor prognosis is welcome as AML is an aggressive fast developing cancer.

3.2 Consultees noted that no additional diagnostic or prognostic testing was required as azacitidine was already in use for myelodysplastic syndrome (MDS) and AML. They noted azacitidine was reasonably comparable in administration and supportive care requirements to low dose chemotherapy. Consultees noted the clinical trial conditions broadly reflect that observed in clinical practice. Administration of azacitidine within the key clinical trial consisted of 7 consecutive days of administration. However, it was noted that in reality few day units are open at weekends so on a worldwide basis this has led to the adoption of a '5+2+2' schedule. Azacitidine would be administered from Monday to Friday then again Monday and Tuesday to complete the 7 days of treatment.

3.3 One consultee noted that azacitidine provided a greater benefit when compared with BSC rather than LDAC and that the subgroup of patients with AML with MDS like features and adverse risk cytogenetics seemed to obtain the most benefit.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company conducted a systematic review of the literature to identify studies evaluating the efficacy and safety of azacitidine and relevant comparators. The company identified 1 phase III randomised controlled trial, AZA-AML-001.

4.2 AZA-AML-001 was an international, multicentre, controlled, Phase 3 study with an open-label, randomised, parallel-group design in 488 adults aged 65 years and above who had newly diagnosed AML with more than 30% BM blasts and an ECOG performance status of 0-2 with adequate organ function. Patients had to have newly diagnosed confirmed AML, AML secondary to primary myelodysplastic disease (MDS) not treated with azacitidine, decitabine or cytarabine, or AML secondary to exposure to potentially leukaemogenic therapy (such as radiation therapy). The trial excluded people previously treated with cytotoxic or biological treatment for AML (except hydroxycarbamide). Patients were excluded if they had received prior stem cell or bone marrow transplant. For full details of the inclusion and exclusion criteria for AZA-AML-001 see page 47 of the company submission.

4.3 Prior to randomisation patients were screened and assigned to one of three conventional care regimens (CCRs). These were

- intensive chemotherapy with anthracycline and cytarabine plus best supportive care (IC)
- low dose chemotherapy with cytarabine plus best supportive care (LDAC)
- best supportive care only (BSC).

4.4 Patients were then randomised to receive either azacitidine or the pre-selected CCR. During the trial no crossover between any treatment

groups was allowed and once randomised to a CCR patients could not change to a different CCR. However, patients who discontinued study treatment could receive subsequent AML therapy during study follow-up.

4.5 The primary outcome of the trial was overall survival (OS). The secondary outcomes of the trial included 1-year OS rate, overall remission rate, duration of remission, cytogenetic complete remission rate, partial remission, stable disease, safety and tolerability, patient-reported quality of life outcomes (using the EORTC-QLQ-30 questionnaire), measures of healthcare resource utilisation and transfusion status.

ERG comments

4.6 The Evidence Review Group (ERG) commented that there were limitations to the company's systematic review searches and inclusion criteria. However, the ERG concluded that the company did not appear to have missed any evidence.

4.7 The ERG stated that the AZA-AML-001 pivotal trial was well-designed and well conducted. They stated that although unavoidable, the open label design of the trial increased the risk of bias. The ERG noted 4 key concerns about the design of the trial:

- The primary efficacy endpoint for the RCT was an ITT comparison of overall survival for patients randomised to azacitidine versus patients randomised to the combined CCR.
- The trial was underpowered for the comparison of azacitidine to each of the individual CCR arms. Additionally, the company anticipated the selection of CCR to be 50:30:20 for IC:LDAC:BSC. The actual study recruitment to CCR has the ratio 18:64:18.
- The use of subsequent therapies following treatment assignment can result in confounded estimates for the primary efficacy endpoint and other endpoints.

- Statistical analyses of time-to-event outcomes relied on the proportional hazards assumption, which the ERG considered not to be justified.

Clinical trial results

AZA-AML-001

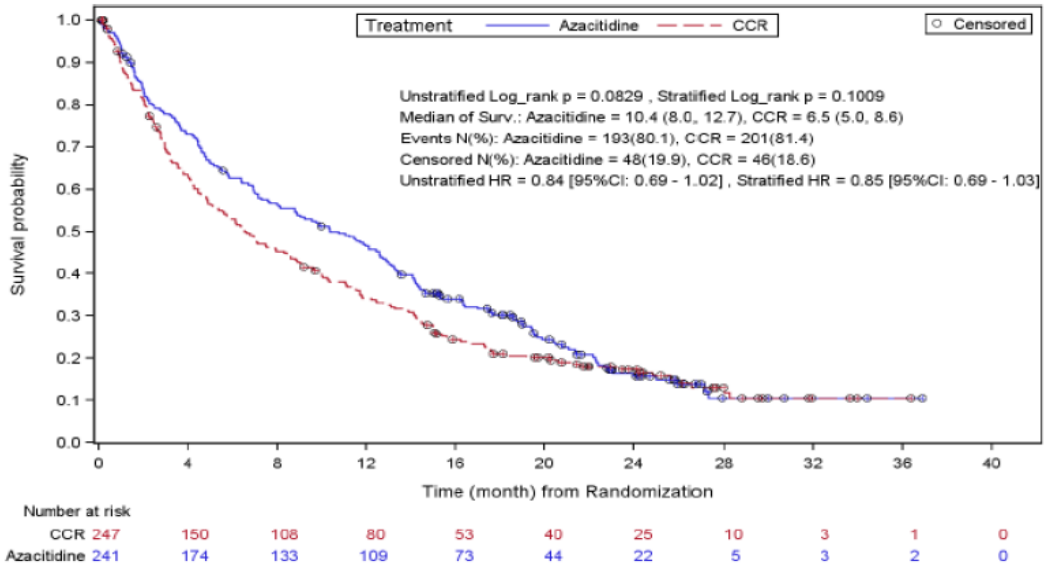
4.8 The primary outcome was overall survival (OS). The median follow-up time was 24.4 months and the median overall survival was 10.4 months (95% CI: 8.0, 12.7) in the azacitidine group (N=241) compared with 6.5 months (95% CI: 5.0, 8.6) in the CCR group (N=247) (Table 3 and Figure 2). There was a 15% reduction in the risk of death for patients on azacitidine (HR: 0.85; 95% CI: 0.69, 1.03, stratified p=0.1009, unstratified p=0.082).

Table 3 Clinical trial outcomes in AZA-AML-001. Summary of overall survival in the ITT population

Outcome	Azacitidine (N=241)	CCR (N=247)
Event, n (%)	193 (80.1)	201 (81.4)
Censored, n (%)	48 (19.9)	46 (18.6)
Median OS (95% CI), months	10.4 (8.0, 12.7)	6.5 (5.0, 8.6)
Difference (95% CI), months	3.8 (1.0, 6.5)	
HR [AZA:CCR] (95% CI)	0.85 (0.69, 1.03)	
Stratified log-rank test: p-value	0.1009	
HR [AZA:CCR] (95% CI)¶	0.84 (0.69, 1.02)	
Unstratified log-rank test: p-value	0.0829	
1-year survival, % (95% CI)	46.5 (40.1, 52.7)	34.3 (28.3, 40.3)
Difference, % (95% CI)	12.3 (3.5, 21.0)	

Source: Section 4.7.1, page 66 of the company submission

Figure 2 - Kaplan-Meier plot for overall survival (Source: Company submission, figure 8 (page 68)

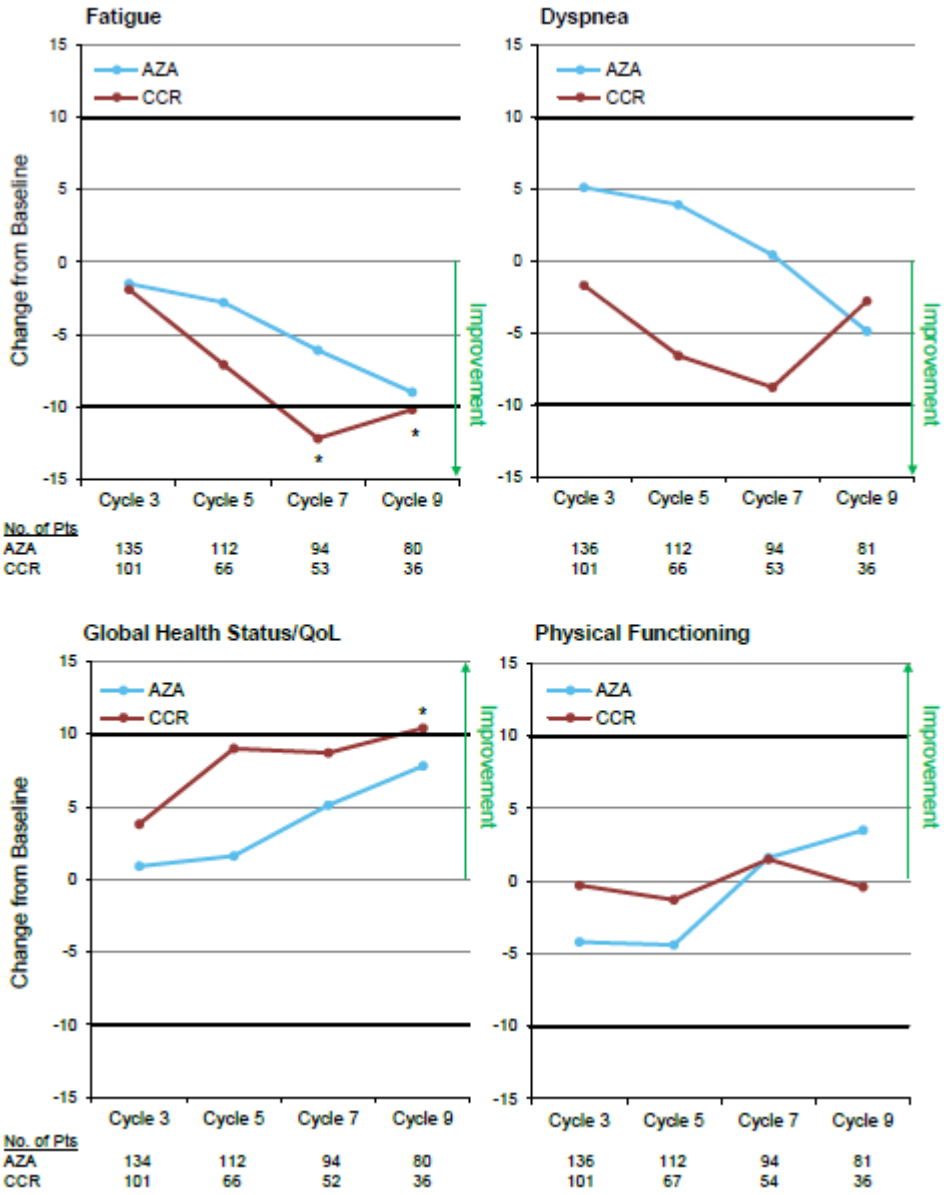


4.9 Secondary outcomes included 1 year survival, event free survival, relapse free survival, haematological status and duration of remission, transfusion status, and health related quality of life (HRQoL). Event-free survival (EFS) and relapse-free survival (RFS) are used to calculate progression-free survival estimates in the economic model. The median EFS was 6.7 months in the azacitidine group compared with 4.8 months in the CCR group. There was a 13% reduction in the risk of an event occurring for patients on azacitidine (HR:0.87; 95% CI: 0.72, 1.05; p=0.1495). The median RFS was 9.3 months in the azacitidine group compared with 10.5 months in the CCR group. There was an 11% reduction in the risk of a relapse occurring for patients on CCR (HR: 1.11; 95% CI: 0.75, 1.66; p=0.5832).

4.10 HRQoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30. The primary HRQoL endpoint was change in fatigue score; dyspnoea, physical functioning and global health status were included as secondary HRQoL endpoints. These domains either improved or did not deteriorate from baseline scores over

9 treatment cycles in both arms. Statistical tests were not reported between treatment arms for HRQoL. However, the company noted that azacitidine and CCR were associated with general improvement in HRQoL in the four pre-specified QLQ-C30 domains of fatigue, dyspnoea, global health status and physical functioning (Figure 3).

Figure 3: Mean absolute score change from baseline for primary and secondary HRQoL endpoints (HRQoL evaluable population)



Key: AZA, azacitidine; CCR, conventional care regimens.

Notes: Decreasing scores indicate improvement in the Fatigue and Dyspnoea domains of the QLQ-C30, and increasing scores indicate improvement in the Physical Function and Global Health Status/QoL domains.
The minimally important difference, defined as a mean change of at least 10 points from baseline and representing a clinically meaningful effect is denoted by bold black lines at 10 and -10 on the y-axis.
*Met the threshold for minimally important difference.
Source: Celgene Submission, Figure 10, p. 78

4.11 The company presented results from an exploratory analysis of azacitidine compared with the individual components of the CCR group. The company noted the results must be interpreted with caution as the study was not powered to detect differences between azacitidine and individual treatments.

- Median overall survival was 5.8 months (95% CI: 3.6, 9.7) in the azacitidine group (N=44) compared with 3.7 months (95% CI: 2.8, 5.7) in the BSC group (N=45). There was a 40% reduction in the risk of death for patients on azacitidine (HR: 0.60; 95% CI: 0.38, 0.95 unstratified log rank test p=0.0288).

- Median overall survival was 11.2 months (95% CI: 8.8, 13.4) in the azacitidine group (N=154) compared with 6.4 months (95% CI: 4.8, 9.1) in the LDAC group (N=158). There was a 10% reduction in the risk of death for patients on azacitidine (HR: 0.90; 95% CI: 0.70, 1.16 unstratified log rank test p=0.4270).

- Median overall survival was 13.3 months (95% CI: 7.2, 19.9) in the azacitidine group (N=43) compared with 12.2 months (95% CI: 7.5, 15.1) in the IC group (N=44). There was a 15% reduction in the risk of death for patients on azacitidine (HR: 0.85; 95% CI: 0.52, 1.38 unstratified log rank test p=0.5032).

4.12 In response to the use of subsequent therapies in the clinical trial, the company presented a series of sensitivity analyses that censored patients at the date of first subsequent therapy (table 4). The company indicated

that these results suggested the subsequent therapies may be a confounding factor in the analysis of treatment effect of azacitidine.

4.13 The company also performed more complex post-hoc analyses of OS using Cox-Proportional hazards, inverse probability of censoring weighted analysis (IPCW) and regression based imputation methods that adjusted for subsequent therapy received following the trial drug treatment. These analyses also allowed for adjustment of heterogeneity in the study population. Azacitidine was shown to statistically significantly improve OS compared with CCR. See Table 4 for full results of the post hoc analysis.

Table 4 - Overall survival estimates adjusted for baseline characteristics and/or subsequent therapy

Estimation method	HR (AZA vs CCR)	95% CI for HR	p-value
Primary ITT analysis (stratified log rank test)	*0.85*	*0.69,1.03*	*0.1009*
Sensitivity analyses censoring patients on date of first subsequent therapy			
Stratified log-rank test	0.76	0.60, 0.96	0.0190
Unstratified log-rank test	0.75	0.59, 0.95	0.0147
Cox-Proportional Hazards			
Adjusted for subsequent therapy but not baseline characteristics (time dependent) – Model 1	0.75	0.59, 0.94	0.0130
Adjusted for baseline characteristics but not subsequent therapy – Model 2	0.80	0.66, 0.99	0.0355
Adjusted for subsequent therapy and baseline characteristics (time dependent) – Model 3	0.69	0.54, 0.88	0.0027
IPCW Cox-PH Models – adjusted for subsequent azacitidine therapy in the CCR arm only			
Unadjusted for baseline characteristics	[redacted]	[redacted]	[redacted]
Adjusted for baseline characteristics	[redacted]	[redacted]	[redacted]
IPCW Cox PH Models – adjusted for any subsequent therapy in both treatment arms			
Unadjusted for baseline characteristics	0.77	0.61, 0.98	0.0310
Adjusted for baseline characteristics	0.71	0.56, 0.90	0.0047
Source: Company submission, Tables 19 – 21 (pages 68 – 72)			

4.14 The company concluded that treatment with azacitidine resulted in clinically meaningful and statistically significant increases in overall survival compared with CCR. The company noted that results from the post-hoc analysis suggest that both baseline heterogeneity and subsequent AML therapy may have confounded the primary endpoint of OS. The company stated that after adjusting for these factors azacitidine was associated with a statistically significant improvement in survival benefit compared with CCR.

4.15 The company presented subgroup analyses for patients with poor-risk cytogenetics and patients with MDS-related changes. The greatest OS benefit was observed in patients with MDS-related changes. The median OS in this sub-group was 12.7 months in the azacitidine group compared with 6.3 months in the CCR group (HR: 0.69; 95% CI: 0.48, 0.98; p=0.357). The median OS for people with a baseline cytogenetic risk rated as poor was 6.4 months in the azacitidine group compared with 3.2 months in the CCR group (HR: 0.68; 95% CI: 0.58, 0.94; p=0.0185).

ERG comments

4.16 The ERG noted that in the ITT analysis of overall survival azacitidine was not statistically significantly superior to the combined CCR. The ERG commented that measures of haematologic response, duration of remission and remission free survival were similar between azacitidine and combined CCR. Considering the individual CCR arms, it appeared (although limited statistical analysis was reported) that for some outcomes azacitidine could be inferior to IC and LDAC. The ERG suggested that although no statistical analyses were presented for the HRQOL data it appears that HRQOL outcomes for CCR were better than for azacitidine.

4.17 The ERG commented on the company's adjustments of OS as a result of subsequent therapy. The ERG noted that that the submission lacked clarity about what treatments analyses had adjusted for. The ERG stated

that the more sophisticated adjustment methods appeared to make little difference compared to the simpler censoring at switch methods.

4.18 The ERG noted that the company presented IPCW analysis where both trial arms were adjusted for treatment switching and that this appeared to adjust for any treatment switching. A further IPCW analysis was also presented where only subsequent azacitidine use in the CCR arm was adjusted for. The ERG stated that the analysis where both ams were adjusted was more appropriate in instances where the mix of subsequent treatments did not reflect that used in clinical practice. Further, in completing the analysis that adjusted only for azacitidine use in the CCR arm the company misinterpreted the NICE DSU technical support document 16. The ERG noted that the IPCW analyses rested on assumptions that they could not assess fully from the available clinical trial data.

4.19 The ERG commented on the 3 Cox proportional hazards models of survival. They noted that the different models show that adjusting or not adjusting for baseline covariates appeared to be the single structural factor to which estimate of relative effectiveness were most sensitive. They stated that the results of the 3 models were all susceptible to bias. The treatment effect in model 2 is likely to be biased from subsequent treatment use, whereas the adjustments made in models 1 and 3 for subsequent treatments assume that patients who switch have the same prognosis as those that do not switch or that their prognoses differ but they are evenly distributed across arms and that subsequent treatments have the same average effect across arms conditional on prognosis.

Adverse effects of treatment

4.20 The company presented detailed adverse event data from AZA-AML-001 in section 4.12 (page 85 - 90) of its submission. These results are summarised in Table 5. The company stated that azacitidine was generally well tolerated, with more than 50% of people in the azacitidine

treatment group receiving 6 or more treatment cycles and one-third receiving 12 or more cycles. The company reported that when adjusted for time of exposure, the incidence rates of adverse events in the azacitidine group were lower when compared with the combined care regimen (CCR) treatments. The most common haematological treatment-related adverse events with azacitidine were febrile neutropenia, neutropenia and thrombocytopenia. The most common non-haematological treatment-related adverse events were constipation, nausea and diarrhoea. The company reported that all frequent haematological adverse events were generally lower with azacitidine compared with other CCR treatments. They noted that in general non-haematological adverse events occurred more frequently in the azacitidine group compared with the CCR treatments. The most common serious adverse events (SAEs) reported in the azacitidine group included febrile neutropenia, pneumonia and pyrexia. The company stated that when adjusted for time of exposure, the overall rate per person-year of SAEs was lower in the azacitidine group compared to the CCR treatments.

Table 5 - Summary of adverse effects of treatment

Adverse events	AZA, n (%) (N=236)	CCR		
		BSC only, n (%) (N=40)	LDAC, n (%) (N=153)	IC, n (%) (N=42)
≥1 AE	234 (99.2)	36 (90.0)	153 (100.0)	42 (100.0)
≥1 treatment-related AE	188 (79.7)	0 (0.0)	124 (81.0)	39 (92.9)
≥1 Grade 3 or 4 AE	207 (87.7)	26 (65.0)	141 (92.2)	37 (88.1)
≥1 Grade 3 or 4 treatment-related AE	125 (53.0)	0 (0.0)	90 (58.8)	29 (69.0)
≥1 SAE	188 (79.7)	30 (75.0)	118 (77.1)	27 (64.3)
≥1 treatment-related SAE	87 (36.9)	0 (0.0)	56 (36.6)	14 (33.3)

ERG comments

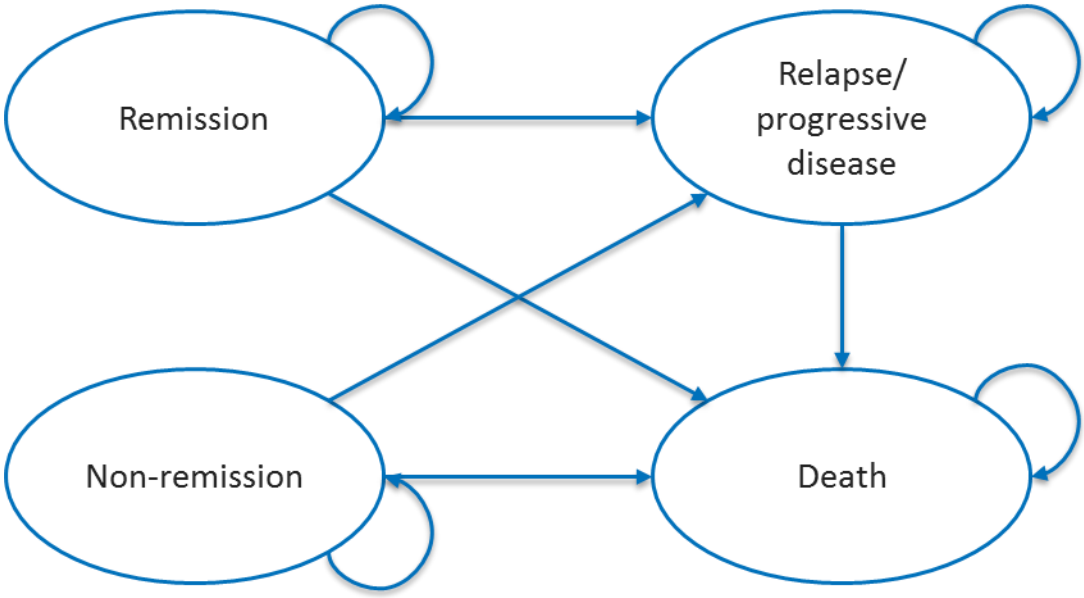
4.21 The ERG noted that treatment related adverse events were common for azacitidine, LDAC and IC but adverse events were less common for BSC.

5 Cost-effectiveness evidence

Model structure

5.1 The company presented a semi-Markov model based on 4 states: remission, non-remission, relapse or progressive disease and death. The model used a cycle length of 4 weeks with a time horizon of 10 years (lifetime). In the base case, the company compared azacitidine with the combined care regimen (CCR); a comparison with the individual CCR treatments was presented in a scenario analysis. The model perspective was the NHS and Personal Social Services, and costs and benefits were discounted at a rate of 3.5% per year.

Figure 4 - Company model structure (figure 14 on page 107 of the company submission)



ERG comments

5.1.1 The ERG noted that the model structure was transparent and simple. They did however note that some states were too broadly defined to capture important differences in costs and quality of life between the treatments being compared. The ERG commented that the main limitation of the model structure was the assumption that no subsequent active

treatment was given after the azacitidine or combined conventional care regimen (CCR). They noted that the absence of any subsequent treatment is inconsistent with the AZA-AML001 trial where a number of subsequent treatments were used. Further it was inconsistent with the approach taken by the company that used data from the AZA-AML001trial that included treatment switching in the azacitidine arm. See section 5.3.2, Table 29 (page 82) of the ERG Report for further information on the use of subsequent therapies.

Model details

5.2 The model assumes that patients have completed the first cycle of treatment (4 weeks) with either azacitidine or one of the combined care regimens (CCR) and then either respond or do not respond to treatment. Patients are then either in remission, non-remission or death. In subsequent cycles, patients can remain in these states or transition to a worse health state or die. The company estimated the proportion of people in each health state for every 4 week cycle using relapse-free survival, progression-free survival and overall survival curves. The model also allows for analysis of patients based on suitability for intensive chemotherapy (IC), low dose chemotherapy (LDAC) or best supportive care (BSC). The model included subgroup analysis for patients with cytogenetic risk and myelodysplasia-related changes.

5.3 The company identified extrapolation models based on whether the proportional hazards assumption was met, goodness of fit, clinical plausibility, and internal and external validation. For the base case, overall survival, progression-free survival and relapse-free survival were extrapolated using the Exponential, Gompertz and Weibull respectively. The company adjusted overall survival outcomes for treatment switching using a range of different methodological options. Progression-free survival and relapse-free survival were not adjusted for treatment switching (Table 6).

Table 6: Methods used to calculate survival curves in the model submitted by the company

Arm	AZA	CCR
Overall survival		
Underlying data	OS from AZA	OS from AZA
Curve fitting	Exponential	Exponential
Adjustments	—	HR of [redacted] from IPCW method (inverse HR)
Relapse-free survival		
Underlying data	EFS for CCR patients achieving CR or CRi	EFS for CCR patients achieving CR or CRi
Curve fitting	Weibull	Weibull
Adjustments	HR of 0.84 from curve fitting	—
Progression-free survival		
Underlying data	EFS for CCR patients not achieving CR or CRi	EFS for CCR patients not achieving CR or CRi
Curve fitting	Gompertz	Gompertz
Adjustments	HR of 0.85 from curve fitting	—

Source: Evidence Review Group report, section 5.2.5.2, Table 19

5.4 Health-related quality of life was incorporated into the model by applying utility scores to each health state. Utilities were derived from response status. They were mapped from trial-based disease specific EORTC QLQ-C30 data using published algorithms. Two mapping algorithms were incorporated in the model, one reported by Proskorovsky et al. 2014, which was used for the base case and the other by McKenzie and Van der Pol, 2009, used for a scenario analysis. The algorithms are presented in the company submission, Table 40 (page 128) and the corresponding utility values are shown below in Table 7. Quality of life was also affected by adverse events, by applying utility decrements for severity grade 3 or above treatment-emergent adverse events (TEAEs).

Table 7- Summary of utility values used for company cost effectiveness model

Health state	Proskorovsky et al., 2014	McKenzie and Van der Pol, 2009
Remission (CR/CRi)	0.7707	0.7400
Non-remission (PR, SD)	0.7160	0.6574
Post-progression/relapse (PD)	0.6233	0.5680
Grade 3+ AEs	− 0.0240	− 0.0207
Source: Company submission, section 5.4.4, Table 41		

Abbreviations: AE, adverse event; CR, complete remission; CRi, morphologic complete remission with incomplete blood count recovery; PD, progressive disease; PR, partial remission' SD, stable disease

5.5 The model included costs associated with acute myeloid leukaemia treatment, costs in each health state, management of adverse events (events with a severity grade of 3 or more), transfusion costs, best supportive care monitoring costs, tests to monitor diseases and care at the end of life. Treatment costs included drug acquisition, administration and dispensing for azacitidine and the combined care regimens (CCR) (Table 8). Azacitidine has a confidential patient access scheme (PAS) and the results in the model were based on this confidential discounted price. The mean number of treatment cycles from the pivotal trial are presented below in Table 9. Drug utilisation was estimated directly from the AZA-AML-001 trial and full wastage (i.e. no vial sharing) was assumed in the base case analysis. Health care resource use estimates were taken from a questionnaire the company conducted with 7 clinicians. Costs were calculated by estimating the rates of resource use per month (converted to the 4-week model cycle) for the health states induction/pre-response, remission, stable disease, and progressive disease. A weighted average of healthcare resource use was applied based on patient proportions of the combined care regimen (CCR) arm. The distribution of patients over IC, LDAC and BSC treatments (18%, 64% and 18%, respectively), modelled in the base case, was derived from the AZA-AML-001.

Table 8 - Drug acquisition cost per cycle

Treatment		Total drug cost per cycle per patient (£)		
		No wastage	*Wastage*	*Wastage with 30% tolerance*
Azacitidine		[redacted]	[redacted]	[redacted]
IC, induction	Cytarabine	£77	£105	£77
	Daunorubicin	£738	£825	£738
	Idarubicin	£1,038	£1,048	£1,038
IC, consolidation	Cytarabine	£54	£75	£54
	Daunorubicin	£550	£489	£489
	Idarubicin	£673	£699	£673
LDAC	Cytarabine	£34	£48	£34

Source: ERG report, Table 26 (page 84)

Table 9 - Mean number of treatment cycles in the AZA-AML-001 trial

Treatment		Mean number of cycles per patient
Azacitidine		8.80
IC, induction	Cytarabine	1.00
	Daunorubicin	1.00
	Idarubicin	1.00
IC, consolidation	Cytarabine	1.00
	Daunorubicin	1.00
	Idarubicin	1.00
LDAC	Cytarabine	6.1
BSC		3.60

Source: ERG report, Table 27 (page 84)

ERG comments

5.6 The ERG identified 2 key areas of concern in the company's economic modelling: extrapolation of key outcomes and health resource utilisation.

The ERG also identified issues in relation to health related quality of life estimates and costs of adverse events. However, the ERG considered that these issues had only a minor effect on the results and were secondary to the other issues identified.

5.7 The model assumed that no patients would receive active treatment following discontinuation of first-line treatment. In the AZA-AML-001 trial underpinning the analysis, 29% of participants received active second-line treatment. Advice from clinical experts suggests that active second-line treatment is considered for some patients in the NHS.

5.8 The model assumed proportional hazards for all time-to-event outcomes, even though this was not supported for overall survival and relapse-free survival by results from the AZA-AML-001 trial.

5.9 Overall survival in the AZA arm was not adjusted for subsequent active treatment, resulting in an inconsistency between the modelled health outcomes and costs, since only the costs of best supportive care were modelled following azacitidine.

5.10 There were significant differences in the costs associated with the relapsed and progressive disease state between the AZA and CCR arm, even though patients in both arms are expected to be receiving BSC at this point. The ERG noted that the biggest difference was in the number of inpatient days in the relapsed and progressed disease state which were 1.73 for azacitidine versus 2.61 for CRR, the effect of this was that cost differences accumulated at a rate of £628 per month despite all patients being managed with BSC.

5.11 The mean number of cycles of treatment in the model didn't reflect the mean number of cycles of treatment in the AZA-AML-001 trial. In the azacitidine arm the mean number of cycles of treatment was 5.6 instead of 8.8. In the CCR arm IC was calculated as 2.61 instead of 2 (initiation and consolidation), and LDAC was calculated as 4.4 when estimating

drug acquisition costs and 5.3 when calculating the costs of drug administration, tests and transfusion instead of 6.10.

Company's base-case results and sensitivity analysis

5.12 The company presented base-case results using the PAS price for azacitidine and the list prices for all other drugs. In the base case, azacitidine was associated with additional costs of [redacted] and [redacted] additional quality-adjusted life years (QALYs), compared with combined care regimens (CCR), giving an incremental cost effectiveness ratio (ICER) of £20,648 QALY gained (Table 10).

Full details of the base case results, including clinical outcomes and disaggregated costs, can be found in section 5.7 (page 142 - 146) of the company submission; details of the deterministic and probabilistic analyses can be found in sections 5.8 (pages 148–153).

Table 10: Results of the company's base case analysis (taken from section 5.7 and 5.8.1 of the company submission)

	Total cost	Total LYG	Total QALYs	Incr cost	Incr LYG	Incr QALYs	ICER (£/QALY gained)
Deterministic analysis							
Azacitidine	[redacted]	1.1820	[redacted]	[redacted]	0.2779	[redacted]	£20,648
CCR	£40,608	0.9041	0.6365				
Probabilistic analysis							
Azacitidine	[redacted]	1.1824	[redacted]	[redacted]	0.2751	[redacted]	£17,423
CCR	£41,429	0.9073	0.6386				
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CCR; conventional chemotherapy regimens,							

5.13 The company presented both deterministic and probabilistic sensitivity analyses. The deterministic sensitivity analysis showed that the model results were most sensitive to the administration costs associated with the combined care regimen (CCR), the hazard ratio of overall survival and the CCR remission rates. In the probabilistic sensitivity analysis, the additional

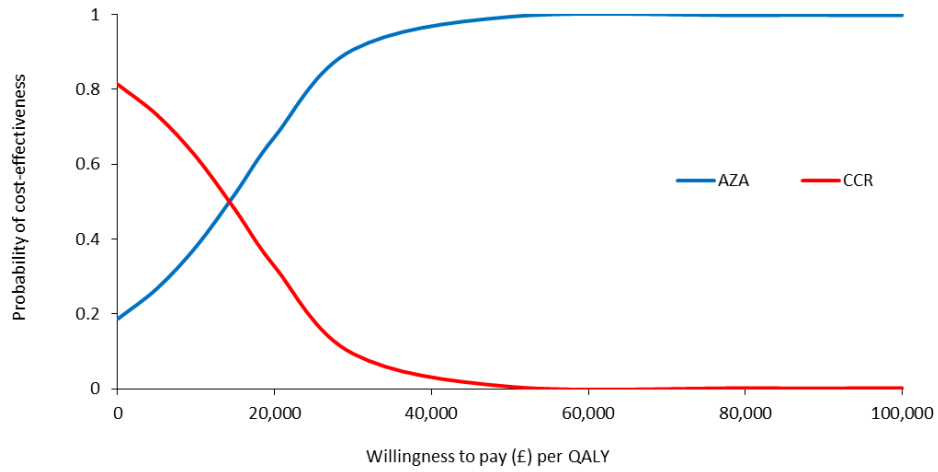
costs associated with azacitidine increased by £752 compared with the deterministic analysis and the additional QALYs increased by 0.0004; the ICER therefore decreased to £17,423 per QALY gained (Table 10); the probability of azacitidine being cost effective versus CCR at a threshold of £20,000 is 69.9%. If the threshold is increased to £30,000 or £50,000 per QALY, the probability of cost-effectiveness increases to 90.8% and 99.6% respectively (Figure 6).

5.14 The company also presented sub group analyses for patients with poor-risk cytogenetics and patients with myelodysplasia-related changes without adjustment for subsequent therapies (Table 11).

Table 11: Results of the company's subgroup analysis

	Total cost	Total LYG	Total QALYs	Incr cost	Incr LYG	Incr QALYs	ICER (£/QALY gained)
Patients with poor-risk cytogenetics							
Azacitidine	[redacted]	1.1855	[redacted]	[redacted]	0.5248	[redacted]	£20,227
CCR	£46,683	0.6607	0.4567				
Patients with MDS related changes							
Azacitidine	[redacted]	1.4050	[redacted]	[redacted]	0.4591	[redacted]	£19,175
CCR	£50,098	0.9459	0.6583				
Source: Company submission, Table 63 and 64 (page157) section 5.8.5							
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CCR; conventional chemotherapy regimens, MDS, myelodysplastic syndrome							

Figure 5: Cost-effectiveness acceptability curve for azacitidine compared with CCR



Company scenarios

5.15 The company presented a series of scenario analyses to explore the effect of assumptions about survival modelling, treatment sequences and individual treatment arm proportions using the HMRN registry (Table 12). The alternative distributions taken from the HMRN registry were [redacted]. When Kaplan Meier curves were used to extrapolate overall survival, progression-free survival and relapse-free survival the ICER increased to £32,393. The ICER decreased when overall survival data was unadjusted for treatment switching and when using the censor at switch population. The use of a shorter time horizons (1 year and 5 year) marginally increased the ICER. When using the individual treatment arms for subsequent therapies with and without adjustment the ICER's were decreased significantly with the exception of low dose chemotherapy (LDAC) which increased the ICER. The use of the HMRN registry proportions for the individual treatments reduced the ICER with and without adjustment for subsequent therapies.

Table 12 Results of the company's scenario analyses

Scenario		Incr cost	Incr QALYs	ICER (£/QALY gained)
Base case		[redacted]	[redacted]	£20,648
Scenario 1: KM curves OS, PFS and RFS		[redacted]	[redacted]	£32,393
Scenario 2: Individual treatment arms with adjustment for subsequent therapies	IC	[redacted]	[redacted]	-353%
	LDAC	[redacted]	[redacted]	£25,136
	BSC	[redacted]	[redacted]	-922%
Scenario 3: Individual treatment arms without adjustment for subsequent therapies	IC	[redacted]	[redacted]	-513%
	LDAC	[redacted]	[redacted]	£41,671
	BSC	[redacted]	[redacted]	-344%
Scenario 4: OS data unadjusted for treatment switching		[redacted]	[redacted]	£11,537
Scenario 5: OS using the censor at switch populations		[redacted]	[redacted]	£10,397
Scenario 6: Use of individual treatment arm proportions from the HMRN registry with adjustment for subsequent therapies		[redacted]	[redacted]	-380%
Scenario 7: Use of individual treatment arm proportions from the HMRN registry without adjustment for subsequent therapies		[redacted]	[redacted]	-198%

ICER, incremental cost-effectiveness ratio; Incr, incremental; LYG, life years gained; QALY, quality-adjusted life year. Source: company submission, Table 62 (page156).

ERG comments and exploratory analyses

5.16 The ERG identified 12 implementation errors in the company model (Table 57, page 127 of the ERG Report). They mainly related to the formula used to calculate health care resource use, but also to the extrapolation of outcomes. The key errors in the company model identified by the ERG were:

- In the CCR arm, patients receiving BSC are assumed to incur drug administration costs in the remission and non-remission states.

However, for other active treatments the costs of administering BSC are not included after treatment discontinuation until relapse/progression (increases ICER from £20,648 to £43,676).

- In the azacitidine and CCR arms, costs of tests and transfusions are not modelled for patients in the relapse/progressive disease state (increases ICER from £20,648 to £37,381).
- In the azacitidine and CCR arms, drug administration, monitoring tests and transfusion costs are double-counted during the 1st model cycle (increases ICER from £20,648 to £35,532).

5.17 The cumulative effect of the 12 corrections was to increase the company base case ICER from £20,648 to £62,518 (analysis A).

5.18 Having corrected the implementation errors the ERG then made a series of changes to the parameter values to reflect current UK practice and to make the model logic consistent (Table 59, page 4 of the ERG Report addendum). The effect of each of the individual changes to the ICER from analysis A is shown below. The cumulative effect of the changes is shown in table 13.

- Calibrating the number of treatment cycles
  - the mean number of treatment cycles was set to match the mean number of cycles in AZA-AML-001. This increases the ICER to £131,698 per QALY (analysis B);
- Costs of relapsed and progressive disease
  - the costs of best supportive care for relapsed and progressive disease were set to be equal across the arms. This increases the ICER to £159,352 per QALY (analysis C);
- Adjusting overall survival in both arms for subsequent active treatment
  - the method of modelling overall survival was changed to censoring for treatment switching in both arms. Due to the model coding modelling of relapse-free and progression-free survival also switches

to censor for treatment switching in both arms. The effect of this analysis is to reduce the ICER to £47,482 per QALY (analysis D)

- Fitting separate parametric survival curves to relapse-free survival and progression-free survival in each arm
  - the parametric proportional hazards progression-free survival curves were replaced with Kaplan-Meier curves. This increases the ICER to £75,471 per QALY (analysis E).
  - the relapse-free survival curves were replaced using Kaplan-Meier curves. This has little impact on the ICER (£63,569 per QALY) (analysis F).
- Adjusting overall survival for baseline covariates
  - overall survival was adjusted for treatment switching (censoring at switch in both arms) and baseline covariates. This increases the ICER to £65,188 per QALY. The method of producing this analysis does not affect relapse-free and progression-free survival and so azacitidine patients spend longer in the progressive disease model state with high costs and low utility (analysis G).

Table 13: Derivation of the ERG's base case

Analysis[a]	Outcome	Azacitidine	CCR	Difference
Celgene base case	Costs	[redacted]	£40,608	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£20,648
A = Corrected base case	Costs	[redacted]	£45,954	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£62,518
A + B	Costs	[redacted]	£50,064	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£131,698
A + B + C	Costs	[redacted]	£72,798	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per			£238,674

	QALY gained)			
A + B + C + D	Costs	[redacted]	£91,847	[redacted]
	QALYs	[redacted]	0.728	[redacted]
	ICER (cost per QALY gained)			£171,511
A + B + C + D + E	Costs	[redacted]	£92,676	[redacted]
	QALYs	[redacted]	0.727	[redacted]
	ICER (cost per QALY gained)			£174,205
A + B + C + D + E + F	Costs	[redacted]	£98,046	[redacted]
	QALYs	[redacted]	0.724	[redacted]
	ICER (cost per QALY gained)			£246,488
A + B + C + D + E + F + G = ERG preferred base case	Costs	[redacted]	£71,138	[redacted]
	QALYs	[redacted]	0.621	[redacted]
	ICER (cost per QALY gained)			£273,308

Source: ERG Report Addendum, Table 59 (page 4)

5.19 The ERG completed some exploratory assessment of the subgroup analysis by preselected CCR treatment, while acknowledging that for PFS and RFS outcomes, the sample sizes make subgroup-specific time to event data highly unreliable. Thus in these analyses subgroup specific differences in OS outcomes were allowed using censor-at-switch data, while keeping common PFS and RFS curves across the three subgroups.

5.20 Exploratory subgroup analyses by preselected CCR treatment using the changes A–F produce ICERs above £100,000 per QALY for all subgroups (Table 14). Exploratory subgroup analyses were also conducted by preselected CCR treatment using changes A, B and D–F (that is, maintaining the assumption regarding differential costs of best supportive care in relapsed and progressive disease). For patients preselected to intensive chemotherapy the ICER was £73,728 per QALY, while for other patients the ICER remained over £100,000 per QALY. An adjustment for baseline covariates, was considered not reliable because of the small

sample sizes within each group, but would be expected to increase the ICERs.

Table 14 ERG scenarios explored for subgroup analyses

Scenario			Pre-selected CCR therapy subgroup	Incremental		ICER (cost per QALY)[a]
Analysis	**PFS and RFS**	**OS**		**Costs**	**QALYs**	
Celgene, adjusted for subsequent therapies	Exponential and Weibull	IPCW applied to CCR arm for switching to azacitidine	IC	[redacted]	[redacted]	-£52,184
	Gompertz and Weibull		LDAC	[redacted]	[redacted]	£25,136
	Exponential and Weibull		BSC	[redacted]	[redacted]	-£169,672
Celgene, unadjusted for subsequent therapies	PH Gompertz and PH Weibull	Exponential	IC	[redacted]	[redacted]	-£85,266
		Gompertz	LDAC	[redacted]	[redacted]	£41,671
		Exponential	BSC	[redacted]	[redacted]	-£50,300
ERGb	Kaplan-Meier	Exponential, censored at switch for any active AML treatment	IC	[redacted]	[redacted]	£352,918
			LDAC	[redacted]	[redacted]	£282,589
			BSC	[redacted]	[redacted]	£152,093
ERGb,c	Kaplan-Meier	Exponential, censored at switch for any active AML treatment	IC	[redacted]	[redacted]	£73,728
			LDAC	[redacted]	[redacted]	£131,349
			BSC	[redacted]	[redacted]	£135,230
ERGb	Kaplan-Meier	ITT, Kaplan-Meier	IC	[redacted]	[redacted]	£414,304
			LDAC	[redacted]	[redacted]	£500,493
			BSC	[redacted]	[redacted]	£137,449

Source: ERG addendum, Table 60 (page 6)

Notes: a, Negative ICERs indicate azacitidine is dominant; b, Includes corrections and changes as described in Table 59 except for component 'G' (i.e., not including adjustment for baseline covariates); c, Not including component 'C' (i.e., retaining Celgene's estimates for costs in Relapse/PD)

5.21 The ERG's preferred probabilistic ICER was £277,123 per QALY (Table 15) which is similar to the ERG's preferred base case deterministic ICER of £273,308 per QALY. The cost-effectiveness acceptability curves from the probabilistic sensitivity analysis suggested that at a willingness to pay threshold of £100,000 the probability of azacitidine being cost-effective is less than 5%.

Table 15 - Cost-effectiveness results for ERG's preferred base case probabilistic sensitivity analysis

Arm	Total			Incremental			ICER (cost per QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
CCR	£73,152	0.8863	0.6218				
Azacitidine	[redacted]	1.3302	[redacted]	[redacted]	0.4439	[redacted]	£277,123

Source: ERG addendum, Table 61 (page 8)

Innovation

5.22 The company stated that azacitidine should be considered innovative in its potential to make a significant and substantial impact on health-related benefits. It noted:

- Azacitidine is an effective treatment option for a difficult to treat patient population of ≥65 years and results in a significant survival benefit
- Azacitidine provides a treatment alternative for those patients who would receive IC and LDAC and for those only eligible for BSC
- Azacitidine is an effective and generally well tolerated treatment and is likely to represent a step change in the treatment pathway

6 End-of-life considerations

6.1 The company proposed that azacitidine should be considered as an end-of life treatment.

Table 16 End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	OS for adults aged >65 years reported in the literature ranges from 1.5 months and 2 months. In AZA-AML-001 the median overall survival in the CCR arm was 6.5 months (95% CI: 5.0, 8.6).
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	Median OS based on the primary endpoint was 10.4 months in the azacitidine group, providing an OS benefit of 3.8 months with azacitidine. The company reported various pre-defined analyses demonstrating that treatment with azacitidine provided a statistically significant survival benefit versus CCR.
The treatment is licensed or otherwise indicated for small patient populations	The estimated total population for all licensed indications in England is 3,354, consisting of 1,026 covered by the proposed new indication and 2,328 for all existing indications.
Source: Company submission, section 3.1 (page 31) and section 4.7 (page 65)	

6.2 The ERG considered that the estimates of extension to life were neither plausible nor robust. The ERG conducted additional analyses of the restricted mean overall survival which they considered to be a more consistent estimator of average treatment effect. Using the ITT analysis the ERG estimated that the overall survival gain was 1.8 months using the restricted mean. When using the analysis where patients in both trial arms are censored for subsequent active treatment the estimated treatment effect was 2.5 months using the restricted mean.

7 Equality issues

7.1 No equality issues were raised during consultation. The company requested to amend the proposed remit in line with wording of marketing authorisation which specified an age cut-off of ‘65 years or more’. As NICE has an obligation towards people protected by the equality legislation; it was decided that age restriction should not be specified in the remit or scope.

8 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000978/WC500050240.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of azacitidine within its marketing authorisation for treating acute myeloid leukaemia with more than 30% bone marrow blasts.

Background

Acute myeloid leukaemia (AML) is a bone marrow cancer characterised by the overproduction of early immature myeloid cells (blasts). Myeloid neoplasms with more than 20% blasts in the peripheral blood or bone marrow are considered AML. AML is classified into several different types. In most types of AML, the leukaemia cells are immature white blood cells. In other less common types, too many immature platelets or immature red blood cells form the leukaemia cells. Anaemia, bleeding problems and serious infections are common symptoms in AML.

The incidence of AML in England is about 2500 cases per year[1]. Around three quarters of all cases occur in people over 60 years. AML is slightly more common in men than in women.

AML is classified according to the World Health Organisation (WHO) classification which takes into account morphology, cytochemistry, immunophenotype, cytogenetics and clinical information and categorises AML into several clinically distinct types. Cytogenetics is the most important prognostic factor and classifies patients into ‘favourable, intermediate or adverse risk’ groups based on the presence or absence of specific chromosomal patterns. Poor prognostic factors, including intermediate and adverse risk cytogenetics, are more common in older people and make treatment more challenging.

AML typically develops rapidly and can be fatal unless treated. People for whom intensive chemotherapy is suitable are treated with cytotoxic agents such as an anthracycline in combination with cytarabine. People in intermediate and poor-risk groups with good performance status may also receive allogeneic stem cells transplantation. People who cannot tolerate or do not wish to receive intensive chemotherapy are given non-intensive chemotherapy such as low dose cytarabine. NICE technology appraisal guidance No. 218 recommends azacitidine for adults with acute myeloid leukaemia with 20–30% blasts and multilineage dysplasia (AML that has developed from a myelodysplastic syndrome), according to the WHO

classification and who cannot have haematopoietic stem cell transplantation. Other aspects of care include blood product replacement for anaemia and thrombocytopenia, antibiotics and antifungals for infections and intermittent low dose chemotherapy with hydroxycarbamide to keep the peripheral blood blast count low.

The technology

Azacitidine (Vidaza, Celgene) is an analogue of nucleotide cytidine that reduces DNA methylation by inhibition of DNA methyltransferase. Azacitidine is administered subcutaneously.

Azacitidine does not currently have a marketing authorisation in the UK for acute myeloid leukaemia with more than 30% bone marrow blasts and when haematopoietic stem cell transplantation is not suitable. It has been studied in clinical trials in patients of age 65 years or more with acute myeloid leukaemia with bone marrow blasts more than 30%, who are not eligible for haematopoietic stem cell transplant compared with intensive chemotherapy with an anthracycline in combination with cytarabine, low dose cytarabine, or best supportive care.

Azacitidine has a UK marketing authorisation for acute myeloid leukaemia with 20-30 % blasts and multi-lineage dysplasia, according to the World Health Organisation classification.

Intervention(s)	Azacitidine
Population(s)	Adults with acute myeloid leukaemia with bone marrow blasts more than 30%
Comparators	• Intensive chemotherapy with an anthracycline in combination with cytarabine • Non-intensive chemotherapy with low dose cytarabine • best supportive care which may include blood product replacement, antibiotics, antifungals and intermittent low dose chemotherapy with hydroxycarbamide

Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • time to disease progression • response rates, including haematologic response and improvement • blood-transfusion independence • infections • adverse effects of treatment • health-related quality of life
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. 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 availability of any patient access schemes for the intervention or comparator technologies should be taken into account.
Other considerations	If the evidence allows the following subgroups will be considered. These include: • people with AML secondary to myelodysplastic syndrome • people with adverse-risk cytogenetics Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 218, March 2011, 'Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia'. Transferred to the 'static guidance list' April

	2014 Technology Appraisal No. 270, December 2012, Decitabine for the treatment of acute myeloid leukaemia (terminated appraisal). Related Cancer Service Guidance: Guidance on Cancer Services, CSGHO, October 2003, 'Improving outcomes in haematological cancers' Related NICE Pathways: NICE Pathway: Blood and bone marrow cancers, Pathway last updated: June 2015, http://pathways.nice.org.uk/pathways/blood-and-bone-marrow-cancers
Related National Policy	Blood and marrow transplantation services (all ages), Chapter 29, Manual for Prescribed Specialised Services 2013/14 http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1 and 2 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

Reference:

1. Cancer Research UK, 2014, Acute myeloid leukaemia (AML) incidence statistics (accessed on 14/09/2015)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts [ID829]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Celgene (azacitidine) Patient/carer groups • African Caribbean Leukaemia Trust (ACLT) • Anthony Nolan • Black Health Agency • Cancer Black Care • Cancer Equality • Cancer52 • Chronic Myeloid Leukaemia Support Group • Delete Blood Cancer • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Leukaemia Cancer Society • Leukaemia CARE • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care Professional groups • Association of Cancer Physicians • British Committee for Standards in Haematology • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • Accord (cytarabine, doxorubicin) • Actavis (doxorubicin) • Bristol-Myers Squibb (hydroxycarbamide) • Janssen (doxorubicin) • Hospira UK (cytarabine, doxorubicin) • Medac UK (doxorubicin, hydroxycarbamide) • Nordic (hydoxycarbamide) • Pfizer (cytarabine, doxorubicin) • Teva (doxorubicin) • Wockhardt UK (doxorubicin) • Zentiva (daunorubicin) Relevant research groups • Cochrane Haematological

Consultees	**Commentators (no right to submit or appeal)**
• British Society for Haematology • Cancer Research UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiography • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS Mid Essex CCG • NHS Thurrock CCG • Welsh Government	Malignancies Group • Institute of Cancer Research • Leuka • Leukaemia Busters • Leukaemia & Lymphoma Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing company evidence submission to the Institute.

[1] Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Leukaemia (acute myeloid, over 30% blasts) – azacitidine [ID829]

Company evidence submission

25th November 2015

File name	Version	Contains confidential information	Date
Azacitidine AML NICE STA Final CIC AIC Marked	1	Yes	25/11/15

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.

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Abbreviations

AAR	Austrian Azacitidine Registry
AE	Adverse event
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
APL	Acute promyelocytic leukaemia
BID	Twice daily
BM	Bone marrow
BSC	Best supportive care
CCR	Conventional care regimens
CI	Confidence interval
CMML	Chronic myelomonocytic leukaemia
CNS	Central nervous system
CR	Complete remission
CRc	Cytogenetic complete remission
CRi	Complete remission with incomplete blood count recovery
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EORTC	European Organization for Research and Treatment on Cancer
EU	European Union
HR	Hazard ratio
HRQoL	Health-related quality of life
HCRU	Healthcare resource utilisation
HSCT	Haematopoietic stem cell transplantation
IC	Intensive chemotherapy
IPCW	Inverse probability of censoring weighted
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWG	International Working Group
KM	Kaplan Meier
LDAC	Low-dose cytarabine
MDS	Myelodysplastic syndromes
miRNA	Micro-ribonucleic acid
mITT	Modified intent-to-treat
NYHA	New York Heart Association
OS	Overall survival

PH	Proportional hazards
PR	Partial remission
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcomes
QLQ	Quality of life questionnaire
RBC	Red blood cell
RCT	Randomised controlled trial
RFS	Relapse-free survival
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Standard deviation
SNP	Single nucleotide polymorphism
WBC	White blood cell
WHO	World Health Organization

1 Executive summary

Acute myeloid leukaemia (AML) is an aggressive haematological cancer that primarily affects older adults, with 64% of newly diagnosed cases in the UK being in patients aged ≥65 years (1). Survival in the elderly population remains very low and reflects the lack of effective treatment options. In 2003–2009, 5-year survival in patients aged <65 years were estimated to be 41.6%, but only 5.4% in patients aged ≥65 years (2). AML also significantly and negatively impacts on patients' QoL, and as the disease progresses, patients frequently suffer from bleeding, infection and pain during the final stages of disease (3-5).

Treatment choices in AML are complex as there is a high degree of heterogeneity in both disease- and patient-related factors which mean there is no single standard of care for elderly AML patients. There are also no formal risk algorithms used in UK routine practice to distinguish patients eligible for intensive versus non-intensive approaches. Treatment choices need to take into account the features of the disease, presence of comorbidities, performance status as well as patient preference (6).

Intensive chemotherapy (IC) can be used to treat older AML patients but is restricted to patients with a favourable performance status, minimal organ dysfunction and/or comorbidities (7, 8). Prognostic factors which determine poorer outcomes are proportionately over-represented in older patients and comorbidities further limit the ability to deliver IC (8). However, even when delivered, the outcomes from standard chemotherapy in elderly patients are poor (6). For patients ineligible for IC, treatment options consist of low-dose cytarabine (LDAC) or best supportive care (BSC) alone. LDAC has been shown to improve survival versus hydroxyurea. However, LDAC had little impact on the median overall survival (OS) and survival benefit was limited to only 18% of patients who achieved complete remission (CR) (9). A recent analysis of the HMRN registry highlights the current poor outcomes in UK routine practice, with a median OS of XXX months for non-transplant-eligible AML patients 65 years or older (10).

Significant efforts have been made to identify new treatment modalities in AML. However, one of the features of AML trials in the last 30 years conducted by all collaborative groups is how little improvement in OS has been observed. In the UK, sequential AML trials conducted by the Medical Research Council (now NCRI) Adult Leukaemia Working Party have seen little evidence of improvement in OS for older patients (11). As the general population lives longer, the burden of AML will further increase. Therefore, there exists a substantial unmet need for an effective therapy to improve the survival of elderly AML patients.

Azacitidine is a hypomethylating agent that has been widely used since 2008 in the European Union (EU) to treat myelodysplastic syndromes (MDS) and AML (20-30% bone marrow [BM] blasts). The pivotal AZA-AML-001 study examined the efficacy and safety of azacitidine versus conventional care regimens (IC, LDAC or BSC alone) in AML with >30% BM blasts (see section 4.7 for further details). Azacitidine demonstrated a clinically significant survival benefit versus conventional care regimens (CCR) (10.4 vs 6.5 months, p=0.1009) with a 1-year survival rate of 46.5% and 34.3%, respectively. When censored to adjust for the confounding effect of subsequent treatments post-trial,

azacitidine therapy demonstrated a statistically significant 24% reduction in the risk of death (median OS 12.1 vs 6.9 months, hazard ratio [HR] 0.76, p=0.019). The safety profile for azacitidine was consistent with previous experience in higher risk MDS and with adjustment for time of exposure on study drug, the incidence rates of AEs with azacitidine were lower versus CCR and was not associated with any detriment to QoL (see Section 4.7 and 4.12). These results have demonstrated that azacitidine is a highly effective and much needed treatment option in this difficult-to-treat elderly AML population.

On 28th October 2015, the EMA granted marketing authorisation to extend the licensed indication for azacitidine to include adult patients aged ≥65 years who are not eligible for haematopoietic cell transplantation (HSCT) with AML with >30% marrow blasts according to the World Health Organization (WHO) classification.

Both the deterministic (£20,648) and probabilistic results (£17,423) show that the ICER is well below what is usually accepted for orphan, life-extending medicines. Azacitidine also demonstrated cost-effectiveness in the hard-to-treat subgroups of poor-risk cytogenetics and MDS related changes where there is a real unmet need for an effective treatment option (ICERs £20,227 and £19,175 respectively). The PSA also demonstrates that at a willingness-to-pay threshold of £20,000 per QALY, the probability of azacitidine being cost effective versus CCR is 69.9%. If the threshold is increased to £30,000 or £50,000 per QALY the probability of cost-effectiveness increases to 90.8% and 99.6% respectively.

In conclusion, azacitidine is a cost-effective treatment option for adult patients aged 65 years or older who are not eligible for HSCT with AML with >30% marrow blasts according to the WHO classification.

1.1 *Statement of the decision problem*

The objective of this technology appraisal is to evaluate the clinical and cost effectiveness of azacitidine according to its recent licensed indication – received 28th October 2015 – allowing for its use in adult patients aged ≥65 years who are not eligible for HSCT with AML with >30% marrow blasts. The NICE decision problem is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with AML with BM blasts more than 30%	Adults aged ≥65 years who are not eligible for HSCT with AML with >30% marrow blasts	This submission specifically evaluates the efficacy and tolerability of azacitidine in patients aged ≥65 years and who are not eligible for HSCT in line with the new indication approved by the EMA
Intervention	Azacitidine	As per scope	-
Comparator(s)	• IC with an anthracycline in combination with cytarabine • Non-intensive chemotherapy with LDAC • BSC which may include blood product replacement, antibiotics, antifungals and intermittent low-dose chemotherapy with hydroxycarbamide	CCR (consisting of IC, non-intensive chemotherapy with LDAC and BSC) Decitabine is also licenced in the EU for the treatment of elderly WHO-defined AML but it is not reimbursed (TA270) and is not used in UK routine clinical practice. As agreed in scope, decitabine has therefore not been included as a comparator	There is currently no single standard of care for the treatment of elderly patients with AML with >30% BM blasts. A number of factors including the heterogeneity of this difficult-to-treat population, the lack of a risk algorithm to clearly guide clinicians in making treatment choices, subjectivity in making treatment decisions, and the impact of patient choice on treatment decisions highlight the challenges faced by clinicians in choosing appropriate therapies for this population. These factors also make it challenging to assess how one treatment compares with another in the context of technology appraisal, particularly as the patient population that may benefit from any of the current treatment options cannot be clearly and consistently defined in clinical practice. The approach taken in the pivotal trial for azacitidine (AZA-AML-001) was to determine its efficacy and safety against CCR, a conventional care arm made up of IC, LDAC or BSC alone. In doing so, the azacitidine trial demonstrated that all patients aged ≥65 years with AML (>30% marrow blasts) and ineligible for HSCT, are likely to benefit from using azacitidine, regardless of the treatment regimen it is compared with or the baseline characteristics of the patient. In this context, it is anticipated that azacitidine would be offered as a first-line therapy to patients aged ≥65 years with AML with >30% blasts and who are ineligible for treatment with HSCT, as an alternative to all existing therapy options

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			– IC, LDAC and BSC alone. As such, it is Celgene's opinion that the appropriate comparator for this appraisal is CCR rather than the individual comparators listed in the scope (see Section 3.3 for further details)
Outcomes	The outcome measures to be considered include: • OS • PFS • Time to disease progression • Response rates, including haematologic response and improvement • Blood-transfusion independence • Infections • Adverse effects of treatment • HRQoL	The outcomes measured include: • OS • PFS – estimated from EFS and RFS for the purpose of economic modelling • Time to disease progression • Response rates, including CR, CRc, and PR • Blood-transfusion independence • Infections • Adverse effects of treatment • HRQoL	A variety of endpoints are used to measure the effectiveness of treatment regimens in clinical trials for AML, including OS, EFS and RFS (12), all of which were reported in AZA-AML-001 (See Section 4.3.7). However, PFS was not measured in AZA-AML-001 as it is not a standard endpoint in AML (12). For the purposes of economic modelling PFS was estimated from EFS and RFS data (See Section 6 for more details)
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. 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 availability of any patient access schemes for the intervention or	Semi-Markov model to express cost-effectiveness in terms of cost-per -QALY	Not specified in scope but aligned to NICE reference case.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	comparator technologies should be taken into account		
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: • people with AML secondary to myelodysplastic syndrome • people with adverse-risk cytogenetics	A number of pre-defined patient- and disease-related subgroups were assessed during the pivotal trial, AZA-AML-001 and included those with MDS-related changes, and poor cytogenetic risk status, as per scope	-
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	AML presents primarily in the elderly population, with 64% of newly diagnosed cases in the UK in patients aged ≥65 years (1). Equity of treatment of the elderly is a concern, as evident from a report published by the National Audit Office in January 2015 (13). AML is also an orphan disease (14). The Cancer Patient Experience Survey in 2010 found that people with rarer forms of cancer reported a poorer experience of their treatment and care than people with more common forms of cancer (15). Therefore, access where appropriate to a treatment such as azacitidine should help to promote equality for both elderly patients and those with rarer forms of cancer	-

Abbreviations: AML, acute myeloid leukaemia; BM, bone marrow; BSC, best supportive care; CCR, conventional care regimens; CR, complete remissions; CRc, cytogenetic complete remission; EFS, event-free survival; EMA; European Medicines Agency; HRQoL, health-related quality of life; HSCT; haematopoietic stem cell transplantation; IC, intensive chemotherapy; IV, intravenous; LDAC, low-dose cytarabine; MDS, myelodysplastic syndromes; OS, overall survival; PFS, progression-free survival; PR, partial remission; RFS, relapse-free survival; SC, subcutaneous.

1.2 *Description of the technology being appraised*

Azacitidine is a nucleoside analogue of cytidine that specifically reduces deoxyribonucleic acid (DNA) methylation through the inhibition of DNA methyltransferase with antineoplastic properties. Azacitidine received approval from the EMA on 28th October 2015 for a licence variation allowing for its use in adult patients aged ≥65 years who are not eligible for HSCT with AML with >30% marrow blasts.

Table 2: Technology being appraised

UK approved name and brand name	Azacitidine (VIDAZA®)
Marketing authorisation/CE mark status	Azacitidine received EMA marketing authorisation for its new indication of AML with >30% blasts on 28th October 2015. EMA had previously provided marketing authorisation for its existing indications in MDS, CMML, and AML with 20–30% blasts
Indications and any restriction(s) as described in the summary of product characteristics	The new indication for azacitidine is as follows: • for the treatment of adult patients aged 65 years or older who are not eligible for HSCT with AML with >30% marrow blasts according to the WHO classification Azacitidine is also indicated for the treatment of adult patients who are not eligible for HSCT with: • intermediate-2 and high-risk MDS according to the International Prognostic Scoring System • CMML with 10–29% marrow blasts without myeloproliferative disorder • AML with 20–30% blasts and multi-lineage dysplasia, according to the WHO classification The contraindications are: • Hypersensitivity to the active substance or to mannitol (E421) • Advanced malignant hepatic tumours – Patients with extensive tumour burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline serum albumin <30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumours • Breast feeding – It is not known whether azacitidine or its metabolites are excreted in human milk. Due to the potential serious adverse reactions in the nursing child, breast-feeding is contraindicated during azacitidine therapy
Method of administration and dosage	SC injection (75 mg/m^2 of BSA) Daily for 7 days, followed by a rest period of 21 days (28-day treatment cycles). A delay in starting the next cycle or a dose reduction may be necessary in the case of haematologic response/toxicity and/or renal toxicity. It is recommended that patients be treated for a minimum of 6 cycles

Abbreviations: AML, acute myeloid leukaemia; BSA, body surface area; CMML, chronic myelomonocytic leukaemia; EMA, European Medicines Agency; HSCT; haematopoietic stem cell transplantation; MDS, myelodysplastic syndromes; SC, subcutaneous; WHO, World Health Organization.

1.3 *Summary of the clinical effectiveness analysis*

Evidence supporting the efficacy and safety of azacitidine comes from a single pivotal regulatory trial, AZA-AML-001. The trial was a large (n=488), international, multicentre, controlled Phase 3 study with an open-label, randomised, parallel-group design, which evaluated the efficacy and tolerability of azacitidine versus CCR (consisting of IC, LDAC or BSC alone) for the treatment of elderly patients (aged ≥65 years) with AML with >30% BM blasts who are ineligible for HSCT. The body of evidence from this study demonstrates that azacitidine provides an effective and tolerable treatment option in this difficult-to-treat patient population, and can be considered a highly effective option for elderly patients with complex patient- and disease-related prognostic factors.

1.3.1 *Efficacy demonstrated in AZA-AML-001*

In summary, AZA-AML-001 showed the following:

- Azacitidine treatment reduced the risk of death by 15% (HR: 0.85; 95% confidence interval [CI]: 0.69, 1.03, stratified p=0.1009, unstratified p=0.082), with a median OS of 10.4 months compared with 6.5 months for CCR (primary endpoint).
- Although the log-rank test did not reach statistical significance, a clinically significant improvement in OS of 3.8 months was observed. The median OS of 10.4 months represents the largest OS benefit seen with a low-intensity therapy in elderly AML (16).
- The 1-year survival estimate was 46.5% in the azacitidine arm, with a clinically meaningful benefit of 12.3% over the CCR arm. This is the greatest 1-year survival reported in an elderly population of patients with AML to date (9, 17-23).
- When censoring subjects for first subsequent AML therapy, risk of death was statistically significantly reduced by 24% (HR: 0.76; 95% CI: 0.60, 0.96, stratified p=0.019, median OS 12.1 months vs. 6.9 months), demonstrating that subsequent AML therapy has a significant impact on the results, leading to an underestimation of the effect of azacitidine.
- Post-hoc Cox proportional hazards (PH) and inverse probability of censoring weighted (IPCW)-adjusted Cox PH analyses support these results, demonstrating that when subsequent therapy and baseline prognostic factors are adjusted for, azacitidine has a statistically significant survival benefit (Cox PH analyses: risk of death reduced by 25–31%, all p<0.05; CCR-adjusted IPCW Cox PH analyses: risk of death reduced by 19–25%, all p<0.05).
- In pre-defined exploratory analyses assessing the individual treatment components of the CCR group, median OS was greater for azacitidine compared with LDAC (11.2 months vs. 6.4 months, respectively, p=0.4270), IC (13.2 months vs. 12.2 months, respectively, p=0.5032), and BSC only (5.8 months vs. 3.7 months, respectively, p=0.0288). These results must be interpreted with caution as the study was not powered to detect differences between azacitidine and individual treatments.
- Pre-defined univariate sub-group analyses showed favourable trends in survival in favour of azacitidine versus CCR across all sub-groups (HR<1), including baseline patient- and disease-related prognostic factors.
- Measures of haematologic response, duration of remission, and relapse-free survival (RFS) were similar between the azacitidine and CCR treatment arms.

- Although CR rates were similar between azacitidine and CCR (20% vs 22%), a CR was not pre-requisite for OS benefit with azacitidine. In a post-hoc analysis of patients who did not obtain a CR, median OS was significantly longer for azacitidine vs CCR (6.9 vs 4.2 months; HR 0.77, p=0.017) with estimated 1-year survival of 33.8% vs 20.4%, respectively.
- A trend for improved event-free survival (EFS) in favour of the azacitidine group compared with CCR was also observed, and azacitidine was associated with an overall benefit in achieving both red blood cell (RBC) (38.5% vs 27.6%) and platelet transfusion (40.6% vs 29.3%) independence.
- There was no meaningful deterioration in health-related quality of life (HRQoL) associated with prolongation of OS in the azacitidine group during treatment. Further, azacitidine and CCR were associated with general improvement in HRQoL in the four pre-specified HRQoL questionnaire (EORTC QLQ-C30) domains of fatigue, dyspnoea, global health status and physical functioning.

1.3.2 *Safety profile*

In AZA-AML-001 azacitidine was generally well tolerated, with more than 50% of subjects in the azacitidine treatment group receiving six or more treatment cycles, and one-third receiving 12 or more cycles.

As expected, and considering the underlying disease and the known pharmacology of azacitidine, the most common AEs in the azacitidine arm were constipation (41.9%), nausea (39.8%), pyrexia (37.7%), diarrhoea (36.9%), febrile neutropenia (32.2%), neutropenia (30.1%), and thrombocytopenia (27.1%). The most frequent serious adverse events (SAEs) reported in the azacitidine group included febrile neutropenia (25.0%), pneumonia (20.3%), AML (11.0%), and pyrexia (10.6%).

Azacitidine has been marketed and widely used in adults with MDS and AML in the EU since 2008 and the favourable tolerability profile of azacitidine observed in AZA-AML-001 is consistent with that previously observed and reported with azacitidine in these existing indications (24, 25). Given the imbalances in treatment duration between the treatment groups, when adjusting for duration of exposure, the incidence rates for the majority of AEs were either similar or lower in azacitidine-treated subjects compared to the individual CCR groups, with no additional risks observed over these currently used regimens. These results indicate that azacitidine has a favourable safety profile in the treatment of elderly patients with AML.

1.3.3 *Strengths and limitations of the evidence base*

Study AZA-AML-001 was conducted at 98 sites across 18 countries, including 5 sites in the UK and provides the pivotal evidence supporting the regulatory approval of azacitidine for the treatment of AML with BM blasts >30% in elderly patients who are ineligible for HSCT. The study successfully addresses the decision problem, providing evidence in the appropriate population versus a range of treatments currently used in clinical practice – defined as CCR – and reporting a number of efficacy, safety and quality of life endpoints.

The primary endpoint of OS is considered the most reliable endpoint for cancer studies, as it is an objective and direct measure of the treatment benefit that is most clinically meaningful to this patient population.

The patient population is representative of the population covered by the licence and the population that would be treated in clinical practice. Due to the nature of the disease and the age of the patients, this population is highly heterogeneous with a number of adverse disease- and patient-related prognostic factors associated with it. In study AZA-AML-001 >20% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 2, >50% had poor cytogenetic risk and/or MDS-related changes, and >50% were aged ≥75 years. This high degree of heterogeneity means that there is no standard of care for elderly patients with AML and there is no widely accepted risk algorithm which clinicians use when deciding which patients are most likely to benefit from intensive or non-intensive treatment options. Treatment decisions remain complex and subjective based on the judgement of the individual clinician (26, 27), and patient choice/motivation can supersede any clinical attempt to determine eligibility for various treatment options (23).

To overcome these difficulties, study AZA-AML-001 was powered to compare the efficacy and tolerability of azacitidine versus a composite comparator, CCR, combining all patients, irrespective of treatment regimen and prognostic patient- and disease-related factors, into one patient population. This approach of comparing with a composite comparator has been recognised and accepted by NICE in its previous appraisal of azacitidine (TA218) (28), as well as in other disease areas (e.g. TA254 in relapsing remitting multiple sclerosis) (29).

Limitations of the evidence supporting azacitidine stem largely from factors inherent in cancer trials, such as the impact of subsequent therapies on the results, as well as the heterogeneity of the AML patient population treated. The lack of statistical significance observed in the primary OS analysis in AZA-AML-001 may reflect the convergence of the survival curves beyond 22 months which is expected for a condition without a cure and a poor prognosis, and the choice of a non-parametric statistical test (log-rank test) in line with many clinical trials. This is likely to have led to an underestimation in the treatment effect of azacitidine. Furthermore, possible imbalances in subsequent therapy between treatment arms are recognised as a problem in cancer trials which use OS as a primary endpoint (30). When censoring patients who received a subsequent AML therapy, a statistically significant reduction in the risk of death was observed with azacitidine treatment versus CCR (OS: 12.1 vs. 6.9 months, respectively; p=0.019).

In addition, univariate analysis demonstrated the heterogeneity inherent in the elderly AML population, with a median OS between subgroups ranging from 4.8 months to 17 months (in the azacitidine arm). However, azacitidine provides a consistent survival benefit across all subgroups (HR for OS<1), with the strongest effect (HR≤0.71) seen in patients with MDS-related changes, prior MDS and poor risk cytogenetics. Cox-PH and IPCW-adjusted Cox PH analyses which adjusted for subsequent therapies and prognostic factors elicited a statistically significant reduction in the overall risk of death with azacitidine when compared with CCR.

Therefore, while the primary endpoint of the trial was not met, the study successfully demonstrated that there were a number of confounding factors which led to the

underestimation of the efficacy of azacitidine. As such, when these were accounted for, all analyses resulted in a statistically favourable outcome associated with azacitidine when compared with CCR.

1.3.4 *Conclusions*

The AZA-AML-001 trial demonstrated that treatment with azacitidine resulted in clinically meaningful and statistically significant increases in OS when compared with current treatment options (CCR). Median OS with azacitidine was 10.4 months, representing a 3.8 month (58%) increase over CCR. 1-year survival was 47%, a 36% increase compared with CCR. These findings represent the largest OS and 1-year survival benefit seen with a low-intensity therapy in elderly AML (16). With the poor survival seen for elderly AML patients treated with CCR in routine UK clinical practice (10), these results highlight that azacitidine is an effective and much needed treatment option for this difficult-to-treat population.

1.4 *Summary of the cost-effectiveness analysis*

The key features of the cost-effectiveness analysis are presented in Table 3 and replicated in Table 53.

Table 3: Summary of variables applied in the economic model

Model element	Details	Justification	Section
Population	Older patients (≥65 years old) in the UK with newly diagnosed AML who are not eligible for HSCT Patients stratified into treatment groups based on eligibility for one of three CCRs: BSC IC LDAC	Pivotal AZA-AML-001 trial	5.2
Subgroups	Population subgroups of interest: Patients with poor cytogenetic risk Patients with myelodysplasia-related changes	Pivotal AZA-AML-001 trial, NICE scoping meeting	5.3
Intervention	Azacitidine + BSC	Pivotal AZA-AML-001 trial	5.2
Comparators (treatment groups)	CCR Individual arms investigated in sensitivity analyses (but should be interpreted with caution) IC + BSC LDAC + BSC BSC alone	Pivotal AZA-AML-001 trial	5.2
Outcomes	Overall survival Progression-free survival Relapse-free survival LYs and QALYs	As per NICE reference case	

Model element	Details	Justification	Section
	Healthcare resource costs Incremental costs, LYs, and QALYs ICER		
Type of economic evaluation	Cost–utility analysis	As per NICE reference case	5.2
Method of analysis of survival	Extrapolation using regression models: Exponential Weibull Gompertz Log-logistic Log-normal Adjustment for CCR-to-azacitidine treatment switching using IPCW and inverse HRs Censor-at-switch analysis rather than ITT	NICE DSU guidance	5.3
Perspective on health effects	Direct health effects on patients	As per NICE reference case	5.2
Perspective on costs	NHS and PSS	As per NICE reference case	5.2
Time horizon	Lifetime horizon for an older patient with newly diagnosed AML (i.e., 10 years, as almost all patients have died by the end of year 10 in the model)	As per NICE reference case	5.2
Cycle length	4 weeks	Corresponding to treatment cycle length	5.2
Synthesis of evidence on health effects	Direct evidence from AZA-AML-001 trial – the evidence on the efficacy of azacitidine in the indication of interest	All comparators available in trial	5.2
Measurement and valuation of health effects	QALYs	As per NICE reference case	5.2
Source of data for measurement of health-related quality of life	Utility values mapped from trial-based EORTC QLQ-C30 data using published algorithms	As per NICE reference case when EQ-5D not collected in trial	5.4
Evidence on resource use and costs	Rates and frequencies of HCRU based on clinician survey, NICE technology appraisals, and published literature Unit costs from published NHS and PSSRU tariffs, and the BNF	Best available sources of UK data.	5.5
Discounting	Annual rate of 3.5% for both costs and health effects	As per NICE reference case	5.2

Abbreviations: AML, acute myeloid leukaemia; BNF, British National Formulary; BSC, best supportive care; EORTC, European Organisation for Research and Treatment of Cancer; HCRU, health resource use; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; LY, life-year; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life-year.

The model structure is presented in Figure 1 and replicated in Figure 14.

Figure 1: Model Structure

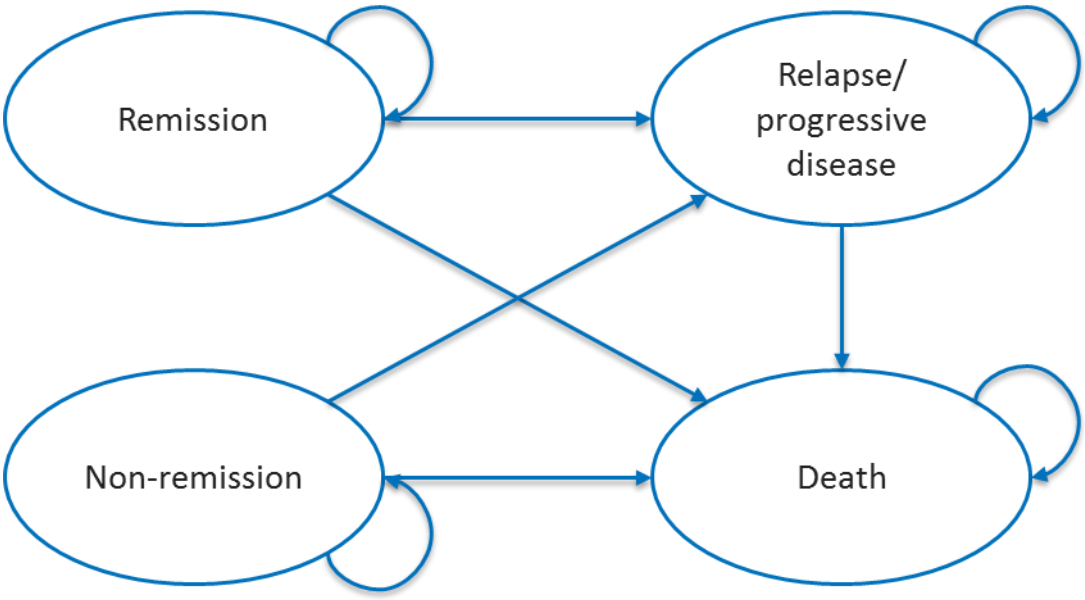


Table 4: Incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
CCR	£40,608	0.9041	0.6365	-	-	-	-
Azacitidine	XXX	1.1820	0.8212	XXX	0.2779	0.1847	£20,648

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CCR; conventional chemotherapy regimens.

2 The technology

2.1 *Description of the technology*

Brand name: VIDAZA®

UK approved name: Azacitidine

Therapeutic class: Epigenetic therapy and pyrimidine analogue

Mechanism of action: Azacitidine is a nucleoside analogue of natural occurring cytidine (31). The mechanism of action of azacitidine is not currently fully understood, but it is believed to exert its antineoplastic effects by multiple mechanisms, including (SmPC, Appendix 1):

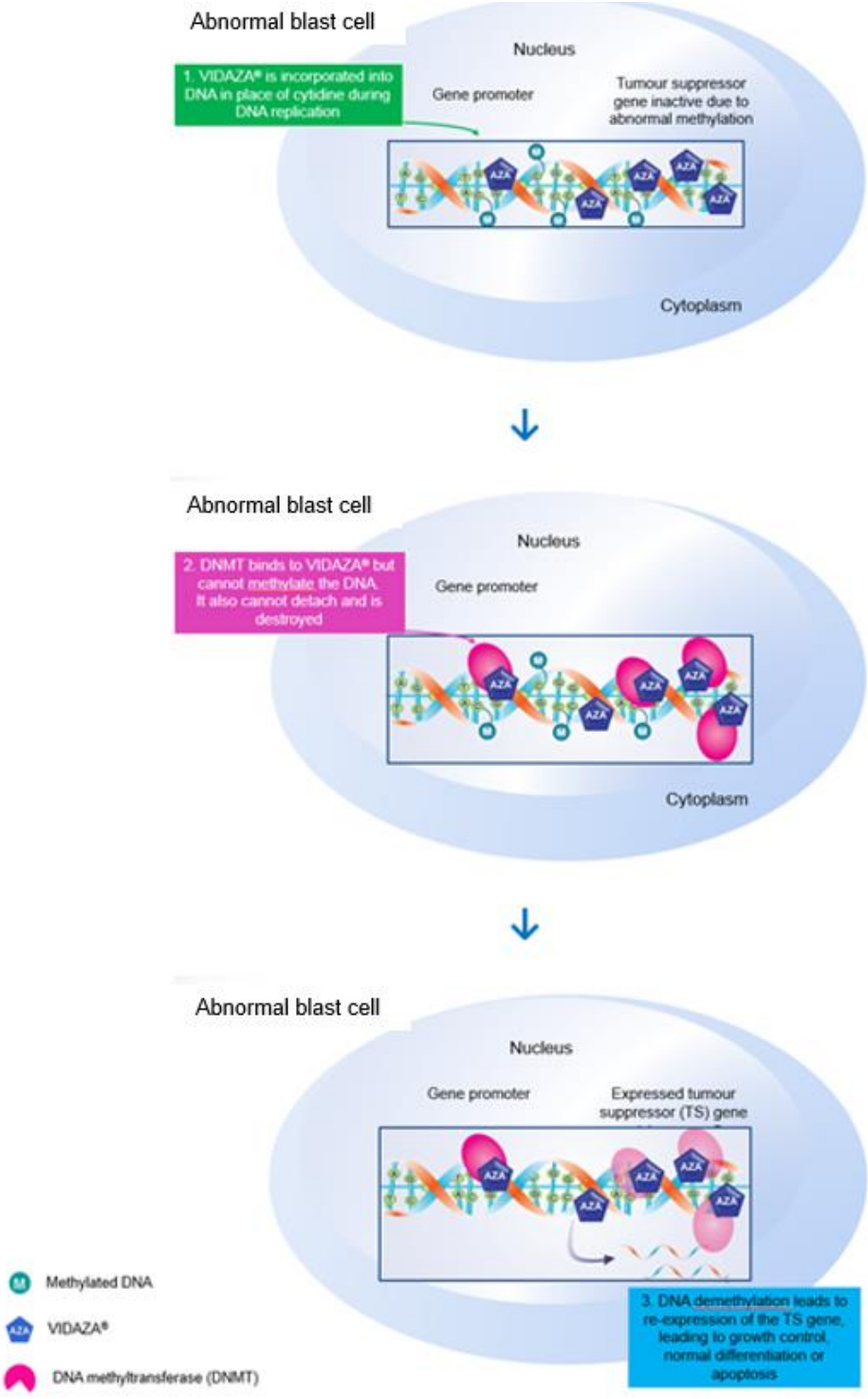
1. hypomethylation of DNA and
2. cytotoxicity on abnormal haematopoietic cells in the BM

As shown in Figure 2, in AML, blast cells undergo abnormal DNA hypermethylation, leading to the silencing of tumour suppressing genes, with a resulting loss of cell differentiation, increased proliferation, and a reduction in cell death (32). During cell division, azacitidine becomes incorporated into DNA in place of cytidine. Azacitidine cannot be methylated by DNA methyltransferase and the enzyme becomes permanently attached to the DNA (33). This abnormal DNA-protein adduct is recognised by the cell and is subsequently degraded by the proteasomal degradation pathway, leading to a further reduction in DNA methylation (33). Reducing DNA methylation leads to the re-expression of silenced tumour-suppressor genes (34), and the restoration of cancer-suppressing functions to cancer cells (31).

The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways (SmPC, Appendix 1).

Figure 2: Proposed azacitidine mechanism of action

In AML, abnormal DNA hypermethylation can lead to the silencing of important tumour suppressor genes, leading to uncontrolled cell growth. Once incorporated into DNA, azacitidine can reverse the abnormal hypermethylation, leading to the reactivation of the tumour suppressor gene and hence restoration of a normal cell cycle.



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

2.2.1 *Marketing authorisation/CE marking*

For the new indication considered in this submission:

- Regulatory submission to EMA: 23rd December 2014
- CHMP positive opinion: 24th September 2015
- Marketing authorisation: 28th October 2015

2.2.2 *Indication(s) in the UK*

The new indication is as follows:

- Azacitidine is indicated for the treatment of adult patients aged 65 years or older who are not eligible for HSCT with AML with >30% marrow blasts according to the WHO classification

Azacitidine is also indicated for the treatment of:

- intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System,
- chronic myelomonocytic leukaemia with 10–29% marrow blasts without myeloproliferative disorder,
- acute myeloid leukaemia (AML) with 20–30% blasts and multi-lineage dysplasia, according to the World Health Organization (WHO) classification.

2.2.3 *Restrictions or contraindications*

The contraindications listed in the SmPC are:

- Hypersensitivity to the active substance or to mannitol (E421)
- Advanced malignant hepatic tumours – Patients with extensive tumour burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline serum albumin <30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumours.
- Breast feeding – It is not known whether azacitidine or its metabolites are excreted in human milk. Due to the potential serious adverse reactions in the nursing child, breast-feeding is contraindicated during azacitidine therapy.

2.2.4 *SmPC/Information for use and (Draft) assessment report*

SmPC and EPAR are provided in Appendix 1.

2.2.5 *Main issues discussed by regulatory authorities*

During the regulatory process for azacitidine, three main issues were raised by the CHMP and were subsequently addressed by Celgene.

1. *Failure to meet the primary endpoint of the International, multi-centre, open-label, randomised controlled Phase 3 trial (AZA-AML-001).*

The CHMP considered the requirement for additional information about the heterogeneity of the patient population and the influence of such on the primary endpoint of OS, given that the primary endpoint of the study was not met. Celgene provided evidence that supported the notion that failure of the primary endpoint was due to an imbalance in patients' baseline characteristics/prognostic factors, and the impact of subsequent therapies. These resulted in an under-estimation of the true treatment effect of azacitidine versus CCR in elderly patients with AML. The impact of subsequent therapies has been recognised as a problem in cancer trials which use OS as a primary endpoint (30).

Celgene conveyed to the CHMP:

- the complex interaction of baseline prognostic factors that vary between subjects and influences treatment decisions and outcomes, and that the interaction of these factors change as a patient's disease progresses.
- that there was a statistically significant survival benefit in favour of azacitidine when adjustments were made for the imbalance in baseline prognostic factors
- that the subsequent therapies patients received had a significant confounding effect on the primary (survival) analysis.

2. *Inconsistent overall survival results across CCR subpopulations*

The CHMP considered the OS results across the CCR subpopulations were inconsistent and that this is of relevance considering the large heterogeneity of the study population. The CHMP asked for data on the patients' baseline characteristics, subsequent therapies, and safety profiles for each treatment group to be supplied. In addition, Celgene were asked to explain how these factors impacted the individual treatment groups and the survival outcomes from the overall CCR population. Celgene also provided a benefit/risk assessment for each treatment group and discussed the impact of this on the overall CCR population.

Celgene demonstrated that:

- data relating to each of the treatment groups were consistent with that observed in the literature which further confirmed the observed heterogeneity within each group
- the impact of subsequent therapy was deemed to have a significant influence on the survival estimates and was consistent with that reported in the CCR population
- survival estimates within each treatment group were consistent with the distribution of baseline patient- and disease related prognostic factors. For example, subjects in the BSC only group had the shortest OS, while subjects in the IC group had the longest OS
- the safety profile of azacitidine within each treatment group was consistent with the established profile of azacitidine.

3. *Clinical benefit*

The CHMP requested that Celgene further discussed the extent that azacitidine produces an additional benefit relative to existing therapy. Celgene explained that the

new indication addresses an unmet medical need at a different stage of the disease in a population with a greater incidence of poor prognostic factors and reduced survival outcomes. The CHMP had previously concluded that an additional 1-year market exclusivity could be granted for the new indication providing that azacitidine demonstrated superiority in terms of benefit-risk over existing therapies in this population. A one year marketing protection was subsequently approved by the European Commission.

2.2.6 *Anticipated date of availability in the UK*

Azacitidine was launched on 17th December 2008 for the treatment of adult patients who are not eligible for HSCT with:

- intermediate-2 and high-risk MDS
- chronic myelomonocytic leukaemia with 10–29% BM blasts without myeloproliferative disorder
- AML with 20–30% BM blasts and multi-lineage dysplasia

The UK launch for the new indication in AML >30% marrow blasts is planned for 25th January 2016.

2.2.7 *Regulatory approval outside the UK*

Table 5: Regulatory approval of azacitidine outside the UK

Indication	Locations
AML with ≥30% blasts	28 EU states, Iceland, Norway, Liechtenstein and Mexico Marketing authorisation is currently being sought in Switzerland, South Korea and Brazil
INT-2 and high risk MDS, CMML and AML with 20–30% blasts	28 European Union states, Iceland, Norway, Liechtenstein, Montenegro, Saudi Arabia, Oman, Macedonia, Bosnia and Herzegovina, Qatar, Serbia, Jordan, Vietnam, Syria, Morocco, El Salvador, Costa Rica, Nicaragua, Tunisia, Uruguay, Panama, Ecuador, Honduras, Columbia, Peru, New Zealand, Singapore, Guatemala, Russia, Chile, Dominican Republic, Malaysia, Bolivia and Australia
INT-2 and high risk MDS	Mexico
MDS	Japan
High-risk MDS	Switzerland and Turkey
INT-2 and high risk MDS, and AML	Canada
RA or RARS, RAEB, RAEB-T, and myelomonocytic leukaemia	USA, South Korea, Israel, Lebanon, Hong Kong, Thailand, Argentina, Macau and South Africa
RAEB, RAEB-T, and myelomonocytic leukaemia	Brazil and Taiwan

Abbreviations: AML, acute myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; EU, European union; INT-2, intermediate-2; MDS, myelodysplastic syndromes, RA, refractory anaemia; RARS, refractory anaemia with ringed sideroblasts; RAEB, refractory anaemia with excess blasts; RAEB-T, refractory anaemia with excess blasts in transformation.

2.2.8 *Ongoing HTAs in the rest of the UK*

A submission to the SMC is currently planned for the 1st February 2016, and a submission to the AWMSG has been ruled out after submission of a Form A due to meeting exclusion criteria number 2 for AWMSG.

2.3 *Administration and costs of the technology*

Table 6: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Powder for suspension for injection. White lyophilised powder. Each vial contains 100 mg azacitidine. After reconstitution, each mL of suspension contains 25 mg azacitidine.	SmPC
Acquisition cost (excluding VAT)†	List price: 100 mg vial: £321.00 Please note, a confidential discount applies as agreed in TA218.	BNF (35) TA218 (28)
Method of administration	Subcutaneous injection	SmPC
Doses	Azacitidine is available as 100 mg vials	SmPC
Dosing frequency	Daily for 7 days, followed by a rest period of 21 days (28-day treatment cycles). A delay in starting the next cycle or a dose reduction may be necessary in the case of haematologic response/toxicity and/or renal toxicity	SmPC
Average length of a course of treatment	It is recommended that each patient should be treated with a minimum of six cycles. Treatment should be continued for as long as the patient continues to benefit, or until disease progression. In the AZA-AML-001 trial patients received a median of 6 cycles of treatment in the azacitidine (min, max: 1, 28)	SmPC AZA-AML-001 (36)
Average cost of a course of treatment	XXX (Calculated from health economic model, using dosing from the AZA-AML-001 study and patients staying on treatment.	
Anticipated average interval between courses of treatments	Not applicable	SmPC
Anticipated number of repeat courses of treatments	None specified. Treatment is ongoing until the patient no longer benefits from treatment or until disease progression.	SmPC
Dose adjustments	Dose modifications and interruptions are specified within the SmPC for patients experiencing haematological and/or renal toxicity. Please see Section 4.2 of the SmPC for further information	SmPC

	Cost	Source
Anticipated care setting	Azacitidine treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents.	

Abbreviations: SmPC, Summary of Product Characteristics.
† Based on the reported list price on 27/10/15.

2.3.1 *Patient access scheme*

A PAS was agreed as part of TA218 (28) to be applied to all current and future indications. As such this PAS applies to the new indication of azacitidine considered in this submission.

2.4 *Changes in service provision and management*

2.4.1 *Additional test/investigations*

As seen in Table 49, azacitidine is associated with comparable monitoring requirements to CCR.

No additional tests or monitoring are required for azacitidine beyond those that are already part of current clinical practice. Therefore, it is anticipated that no additional NHS resources will be required.

2.4.2 *Main resource use to the NHS associated with the technology*

Azacitidine is administered subcutaneously for seven consecutive days during each 28-day cycle of treatment. As is standard practice for anticancer therapy, azacitidine should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents. Prior to and during treatment, patients should be monitored for haematologic response/toxicity and renal toxicities. Liver function tests, serum creatinine and serum bicarbonate should be determined prior to initiation of therapy and prior to each treatment cycle. Additionally, complete blood counts are required prior to initiation of therapy and as required to monitor response and toxicity. As a minimum, complete blood counts should be performed prior to each treatment cycle.

Monitoring of renal function is recommended in elderly patients, and is required in patients with renal impairment. In addition, patients with severe hepatic organ impairment should be carefully monitored for AEs.

As stated above, no additional tests or monitoring are required for azacitidine beyond those that are already part of current clinical practice. Therefore, it is anticipated that no additional NHS resources will be required. When compared to CCR, Table 46 shows that azacitidine requires comparable resource use. However, during induction (or early treatment), azacitidine requires considerably less inpatient days. This is mainly due to the fact that IC patients are hospitalised for a long period of time whilst receiving induction treatment.

2.4.3 *Additional infrastructure requirements*

Azacitidine is currently used in the NHS to treat patients with intermediate-2 and high-risk MDS, chronic myelomonocytic leukaemia (CMML) with 10–29% BM blasts without

myeloproliferative disorder, and AML with 20–30% BM blasts and multi-lineage dysplasia. As such no additional NHS infrastructure is required to accommodate azacitidine.

2.4.4 *Patient monitoring requirements*

The level of monitoring required for azacitidine is consistent with other treatments prescribed for AML. For an overview of the monitoring requirements associated with treatment with azacitidine, see Section 2.4.2.

2.4.5 *Need for concomitant therapies*

As per Section 4.2 of the SmPC, patients receiving treatment with azacitidine should be pre-medicated with anti-emetics to minimise nausea and vomiting. In addition, subcutaneous adverse reactions such as injection site rash/inflammation/pruritus, rash, erythema and skin lesion may require management with concomitant medicinal products, such as antihistamines, corticosteroids and non-steroidal anti-inflammatory medicinal products.

2.5 *Innovation*

Azacitidine represents a novel treatment option for this difficult to treat patient population, and results in a significant survival benefit when compared with other relevant treatments. In the pivotal azacitidine trial, AZA-AML-001, the observed median OS of 10.4 months – a 3.8 month (58%) increase over CCR – and 1-year survival of 47% – a 36% increase over CCR– represent the largest OS and 1-year survival benefit seen with a low-intensity therapy in elderly AML (16).

As well as providing an alternative treatment option for patients who would typically receive low-dose chemotherapy or IC, azacitidine represents a valuable treatment option for patients who would typically only be eligible for BSC. In this population, treatment with azacitidine resulted in a median OS of 5.8 months; representing a clinically significant improvement in OS benefit. Therefore, azacitidine offers an effective and tolerable treatment option for elderly patients with AML and is likely to represent a step-change in the treatment pathway for patients with the worst prognostic factors.

Treatment options for elderly patients with AML are limited and survival is poor. A recent analysis of the HMRN registry highlights the current poor outcomes in UK routine practice, with a median OS of XXX months for non-transplant-eligible AML patients 65 years or older (10). Therefore, there is a clear unmet need to improve treatment options and survival outcomes in the population aged 65 years and over (2). This was acknowledged by a National Audit Office report in 2015 which reported that despite improvements over recent years there remains considerable scope to improve outcomes for cancer patients, and that outcomes and access are generally poorer for the elderly population (13).

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

3.1 *Disease overview*

AML is the most frequent form of leukaemia, accounting for approximately 25% of all leukaemia cases in adults in the Western world (37). It is an aggressive, clonal myeloid neoplasm with maturation arrest of myelopoiesis, leading to an accumulation of myeloblasts in the BM and/or blood. AML is a life threatening disease that primarily affects older adults. In the UK between 2009 and 2011, an average of 40% of cases were diagnosed in men and women aged 75 years and over, and almost three quarters of cases (73%) were diagnosed in those aged 60 and over (1). The median age of diagnosis is between 65 and 72 years for the entire population, and 78 years when evaluating the population who are aged over 65 years (7, 9, 38-41).

The annual incidence rate of AML in England has been estimated to be 4.1 per 100,000 (42)). The incidence increases dramatically with older age, rising to 18.35 per 100,000 in people aged 65 years and over (42), equating to approximately 1,777 new cases of AML in this patient group in England annually (42-44) (see Section 4.13.2 for derivation of figures).

AML can arise de novo (primary AML), through transformation of existing myelodysplasia, or be secondary to previous therapy (e.g. cytotoxic chemotherapy). It is currently estimated that up to 30% of patients with MDS will progress to develop AML, with the disease often being refractory to current therapies (45). Pre-existing myelodysplastic or myeloproliferative disorders are common in elderly patients with AML, occurring in 24% to 40% of cases (46), whereas therapy-related AML accounts for approximately 5–10% of all cases (47). The prognosis for patients with MDS-related changes and/or therapy-related AML is considerably worse than that for patients with primary AML (48).

The clinical signs and symptoms of AML are diverse and non-specific, but they are usually directly attributable to the leukaemic infiltration of the BM, with resultant cytopenias (reduction in blood cell counts). Typically, patients present with signs and symptoms of fatigue, haemorrhage, and/or infections and fever due to reductions in RBCs, platelets, and WBCs (48). The corresponding impact on physical and psychological aspects of quality of life is significant and increases over the course of the condition (3).

Diagnosis of AML requires the examination of peripheral blood and BM specimens, using morphology, cytochemistry, immunophenotyping, cytogenetics, and molecular genetics. According to the WHO classification of myeloid neoplasms, a myeloid neoplasm with ≥20% blasts in the peripheral blood or BM is considered to be AML when occurring de novo, evolution to AML when it occurs with previous diagnosis of MDS or myelodysplastic/myeloproliferative neoplasm (49).

Treatment of AML is complex, and can consist of HSCT, IC, low-dose chemotherapy (e.g. LDAC), azacitidine (existing indication for patients with 20–30% BM blasts) or BSC. Clinical guidelines for the treatment of elderly patients with AML vary depending on a

variety of disease- and patient-related prognostic factors, with no pre-defined NICE clinical guidelines available for the treatment of AML.

Significant efforts have been made to identify new treatment modalities in AML. However, one of the features of AML trials in the last 30 years conducted by all collaborative groups is how little improvement in OS has been observed. In the UK, sequential AML trials conducted by the Medical Research Council (now NCRI) Adult Leukaemia Working Party has seen little evidence of improvement in OS for older patients (11).

3.2 *Burden to patients, carers and society*

Survival in patients with AML is highly dependent on a variety of patient- and disease-related prognostic factors, including increased age, reduced performance status, comorbidities, vulnerability, frailty, and genetic factors (7, 50-52). As such, elderly patients with AML face a significantly reduced chance of survival due to the combination of adverse prognostic factors. This, together with the lower likelihood of response to treatment, makes the treatment of elderly patients particularly difficult (53, 54). Over the past 30 years, limited improvement in the survival outcome of elderly AML patients have been observed. Between 2003 and 2009, 5-year survival estimates in patients aged <65 years were 41.6%. In patients aged ≥65 years only 5.4% of patients were estimated to be alive (2).

To date, the treatment option with the most favourable outcome for elderly AML patients is IC. However, in elderly patients, IC has been associated with unsatisfactory results due to the low rates of complete remission, duration of remission, disease-free survival, and increased risk of induction-related mortality (7). The combination of poor survival outcomes and limited treatment options also presents a significant emotional burden to elderly patients with AML.

When compared with the general population, patients with AML experience a significant reduction in physical functioning (as determined via the physical component domain of quality of life assessments), and experience a higher incidence of depression (3). Furthermore, quality of life deteriorates over time, with a significant reduction observed as early as 2 weeks after AML diagnosis (3). Patients with AML can also experience appetite loss and fatigue; both having a negative impact on overall measures of quality of life (4). The burden of the disease continues until death, with patients frequently suffering from open bleeding, infection, and pain during the final stages of the disease (5). The impact is far reaching with caregivers, including family or friends, often having to deal with numerous and concurrent stressful events, and often suffering negative psychological, behavioural and physiological effects on their daily lives and their health (55).

While the emotional and physical burden of the disease has been widely reported, it is difficult to determine the full economic burden of AML due to the nature of the disease (for example the variety of treatments used and observed variations in rates of remission and relapse observed), and published data are limited. For example, one study estimated the 5-year per-patient cost of medical treatment from the UK NHS perspective to vary between £8,170 and £81,636 (56). This study highlighted that the costs for medical treatment can vary significantly, and reflects the complex nature and

heterogeneity of the disease, as well as how the disease is treated. In the Netherlands the direct lifetime per-patient cost for patients with AML have been estimated at €151,827 (2001 values), with 50% of costs attributed to induction and consolidation therapy, and 20% to relapse (57). Therefore, while AML affects a relatively small proportion of the population, the costs associated with its management can be substantial.

3.3 *Clinical pathway of care*

Due to the heterogeneity of disease, there is no standard of care for elderly patients with AML, resulting in complex treatment guidelines (6, 8, 58, 59). Despite differences between published treatment guidelines, there is a general consensus that treatment decisions should be based on a number of patient- and disease-related prognostic factors. Patients with favourable prognostic factors are more likely to be assessed as "fit" to receive treatment with IC while patients with unfavourable prognostic factors, such as increased age, poor performance and/or cytogenetic risk status, and increased comorbidities are typically deemed unfit for treatment with IC. As such, these patients are usually offered less intensive chemotherapy options, such as LDAC and those unable to tolerate chemotherapy or who chose not to receive LDAC should receive BSC only.

Despite this general guidance there is no widely accepted risk algorithm which clinicians use in the UK when deciding which patients are most likely to benefit from intensive or non-intensive treatment options. A recent review further demonstrated the lack of structure when making treatment decisions, concluding that decisions remain complex and selection is subjective based on the clinician's judgement (26). Patient choice was also found to be a confounding factor, accounting for approximately 8% of treatment decisions, irrespective of the clinicians' recommendation (23).

Difficulty in classifying patients as "fit" or "unfit" for IC has been further highlighted in the National Cancer Research Institute AML and high risk MDS studies (27). Since intensive treatment may well be shortening life for some, there is the issue of which patients should be treated with an intensive approach and who should not. In the UK, older AML patients can currently be entered into one of two national studies. AML18 (formerly AML16) is for patients who are considered fit for an intensive approach whereas patients who are not considered fit for an intensive treatment approach will be eligible for the NCRI/LLR LI-1 Trial. Neither study protocol provides an objective measure of 'fit' vs 'unfit' and so eligibility is subjective and is determined by investigator and patient.

The heterogeneity of this difficult-to-treat population, the lack of a risk algorithm to clearly guide clinicians, subjectivity in making treatment decisions, and the impact of patient choice highlight the challenges faced by clinicians in treating this population effectively. These factors also make it extremely challenging to assess how one treatment compares with another in the context of technology appraisal, particularly as the patient population that may benefit from any of the current treatment options cannot be clearly and consistently defined in clinical practice. The approach taken in the pivotal trial for azacitidine (AZA-AML-001) was to determine its efficacy and safety against CCR, a conventional care arm made up of IC, LDAC or BSC alone. In doing so, the trial demonstrates that all patients aged ≥65 years with AML (>30% marrow blasts) and

ineligible for HSCT, are likely to benefit from using azacitidine, regardless of the treatment regimen it is compared with or the baseline characteristics of the patient (See section 4.7 and 4.8 for trial results). In this context, it is anticipated that azacitidine would be offered as a first-line therapy to patients aged ≥65 years with AML with >30% blasts and who are ineligible for treatment with HSCT, as an alternative to all existing therapy options – IC, LDAC and BSC alone.

3.4 *Life expectancy*

AML is a heterogeneous disease in terms of response to treatment and OS. Prognostic factors that contribute to this heterogeneity can be patient-related (such as increased age, reduced performance status, comorbidities, vulnerability, or frailty) or disease-related (such as genetic factors, adverse cytogenetics, somatic mutations, or whether the patient has MDS-related changes) (50-52).

Survival is highly age dependent with survival rates being significantly lower in older patients (7). The median OS of elderly patients with AML in population-based studies has remained unchanged since 1995 at 1.5 to 3 months (60, 61). Furthermore, a recent analysis of the HMRN registry highlights the current poor outcomes in UK routine practice, with a median OS of XXX months for non-transplant-eligible AML patients 65 years or older treated with CCR (10). There is also a clear disparity in 5-year survival rates between AML patients of different ages. Between 2003 and 2009, 5-year survival rates for patients <65 years of age was 41.6%, but just 5.4% in patients ≥65 years of age (2). In contrast, the life expectancy of people in the general population once they have reached 75 years of age is a further 10.6 years (males) and 12.9 years (females) (62). Therefore, AML represents a challenging disease to treat, and results in a significant reduction in patient's life expectancy.

Azacitidine has designated orphan status across all of its licensed indications including AML, MDS and CMML. At the time of designation by the EMA, AML affected less than 2 people in 10,000 per year and MDS affected between 1.1 and 3 in 10,000 people in the EU. N.B. At the time of orphan medicine designation, CMML was classified as a type of MDS.

Current estimates in England suggest that there are 1,777 new cases of AML each year in people aged 65 and over (42-44). When the additional criteria of ineligibility for HSCT and >30% marrow blasts are taken into account the actual number of elderly patients eligible for treatment with azacitidine under the new indication is estimated to be 1,158 (See Section 4.13.2 for further details).

In addition, it is estimated that around 2,328 adult patients would be eligible for treatment with azacitidine in England for all other licensed indications (MDS, CMML and AML with 20–30% blasts) (See Section 4.13.2 for further details).

3.5 *Relevant NICE guidance, pathways or commissioning guides*

Azacitidine was approved by NICE in 2011 within its existing indication for MDS, CMML and AML. In this appraisal (TA218) NICE recommended azacitidine as a treatment option for adults who are not eligible for HSCT and have AML with 20–30% blasts and

multilineage dysplasia, according to the WHO classification (28). The full wording of the guidance is provided below. No further technology appraisals or clinical guidelines have been published by NICE for AML.

AML is included in the NICE pathway for blood and bone cancers (63). However, the pathway provides no further recommendations on managing patients with AML beyond those provided in TA218.

NICE TA218 (28)

Azacitidine is recommended as a treatment option for adults who are not eligible for HSCT and have:

- intermediate-2 and high-risk myelodysplastic syndromes according to the International Prognostic Scoring System or
- Chronic myelomonocytic leukaemia with 10–29% marrow blasts without myeloproliferative disorder or
- AML with 20–30% blasts and multilineage dysplasia, according to the WHO classification and
- if the manufacturer provides azacitidine with the discount agreed as part of the patient access scheme.

3.6 *Clinical guidelines*

Treatment choices need to take into account the features of the disease, presence of comorbidities, performance status as well as patient preference (6). A number of guidelines provide recommendations on the treatment of elderly patients with AML, including the British Committee for Standards in Haematology (6), the European Leukaemia Net (8), the European Society for Medicinal Oncology (58), and the US National Comprehensive Cancer Network (59). These guidelines recommend that treatment should be driven by patient-related prognostic factors such as age, performance status, comorbidities (cardiovascular, cerebrovascular, pulmonary, hepatic, or renal dysfunction) and adverse disease-related prognostic factors, including unfavourable cytogenetics/molecular markers, therapy-related AML, or prior MDS.

Treatment choices will depend on the balance of patient- and disease-related prognostic factors and currently include IC ± HSCT, low-dose chemotherapy (e.g. LDAC), or BSC alone (8). HSCT however is rarely used in patients older than 65 years of age (64).

UK clinical guidelines

In guidelines published by the British Committee for standards in Haematology in 2006 (6), elderly patients with AML (defined as >60 years of age) who could tolerate IC were recommended to participate in the NCRI clinical trial, or if they were not eligible or refused to participate in the clinical trial, then treatment with standard IC (daunorubicin and cytarabine) was recommended. Treatment with LDAC was recommended for patients who opted for non-intensive chemotherapy, and BSC was recommended for all patients who were deemed unfit to tolerate chemotherapy. These UK guidelines predate the introduction of azacitidine for its existing indication of AML with 20-30% BM blasts, and have not been updated since 2006.

European clinical guidelines

European Leukaemia NET guidelines from 2010 provide treatment and management recommendations in elderly patients (defined as ≥60 years of age) with AML (8). The guidelines make specific recommendations for patients aged between 60 and 75 years of age, and for those aged ≥75 years.

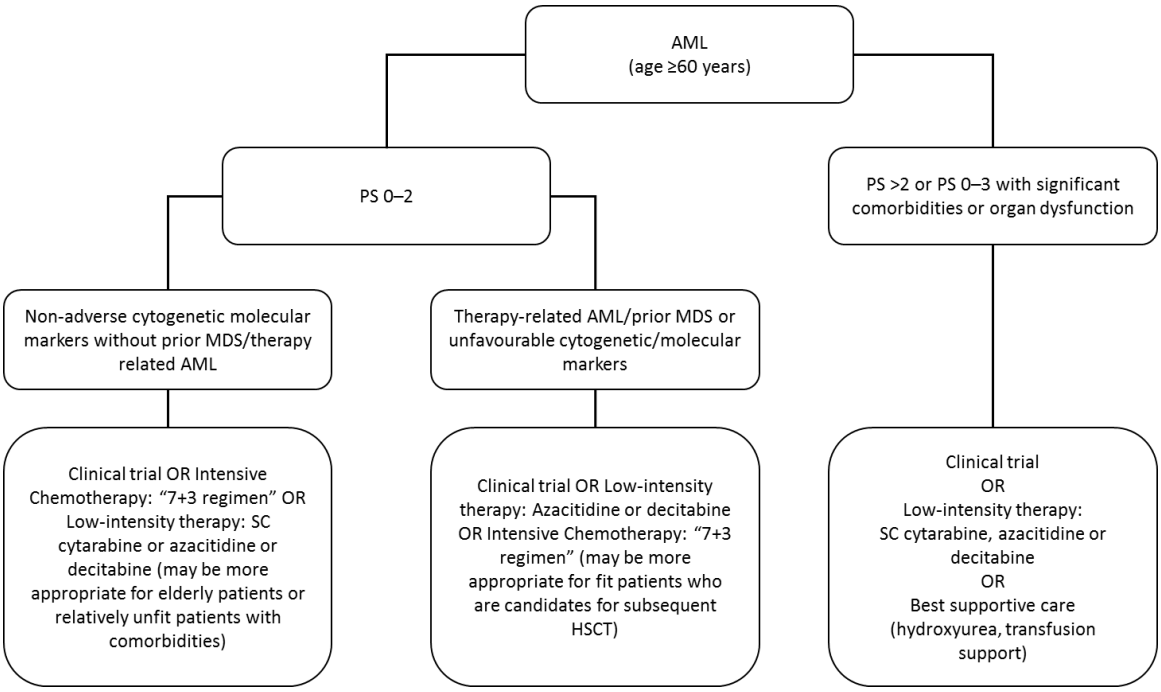
- For patients <75 years of age with good performance status (performance status<2) and no comorbidities, IC provides a favourable chance of achieving CR. The degree of cytogenetic risk will influence the acceptability of giving IC, and patients who have adverse cytogenetic risk, even those with good performance status and lacking comorbidities, may consider alternative treatments, such as investigational or low-intensity treatments. At the time azacitidine and decitabine were among the investigational hypomethylating products considered as being appropriate for use.
- For patients over 75 years of age (and probably ≥65 years) with performance status ≥2, comorbidities or organ dysfunction, IC should not be considered as these patients tend not to receive benefit from conventional chemotherapy. These patients may be considered for alternative therapies including a low-intensity dosing regimen such as LDAC, although evidence showed mortality was still high and there was no benefit of LDAC in patients with adverse cytogenetics. At that time it was recognised that other alternative options were necessary and these guidelines also recommend investigational products which at that time included azacitidine or decitabine.

More recently, guidelines published by the European Society for Medical Oncology in 2013, support the notion that treatment should be based on a number of prognostic factors, such as age, cytogenetics, molecular genetics, and comorbidity (65). The guidelines state that patients aged ≥60 years are more susceptible to treatment-related complications, and that elderly patients and patients with significant comorbidity are often not eligible for IC. Therefore, these patient populations should be offered BSC or palliative systemic treatment, such LDAC or azacitidine.

US clinical guidelines

The US 2015 National Comprehensive Cancer Network guidelines (59) have specific recommendations for newly diagnosed, older AML patients (defined as ≥60 years old). As shown Figure 3 older AML patients with an ECOG performance status of 0 to 2, with or without adverse features may be managed with a clinical trial, IC or low intensity therapy (including LDAC and azacitidine). For patients with an ECOG performance status >2 or significant comorbidities, patients are more likely to experience toxicity and less are likely to benefit from IC, so it is reasonable to offer a clinical trial, low-intensity therapies or supportive care alone. Azacitidine is therefore a recommended treatment option for both IC-eligible and IC-ineligible older AML patients.

Figure 3: Management of newly-diagnosed AML aged 60 years or more, NCCN guidelines



Abbreviations: AML, acute myeloid leukaemia; HSCT, haematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; NCCN, National Comprehensive Cancer Network; PS, performance status; SC, subcutaneous.

3.7 *Issues relating to current clinical practice*

As described previously no single treatment approach is considered standard for patients with AML, and treatment choice is driven by a number of different patient- and disease-related factors as well as patient choice. Elderly patients with AML present with a higher incidence of unfavourable cytogenetics, an increase in secondary AML, comorbidities and generally poor performance status (7, 50-52). These factors make this population more difficult to treat and one with a higher probability of having worse clinical outcomes compared with a younger population.

Treatment options for elderly patients with >30% BM blasts AML include HSCT, IC, low-dose chemotherapy (LDAC), or BSC alone (8). However, HSCT is rarely used in patients older than 65 years (64). Decitabine is also licenced in the EU for the treatment of elderly WHO-defined AML but it is not reimbursed (NICE TA270 (66)) and so is not used in UK routine clinical practice. Treatment with IC is typically contraindicated for patients aged ≥65 years with an adverse performance status, organ damage, and comorbidities (8). Treatment with IC can however be successfully used in older patients, if restricted to patients with a favourable performance status, minimal organ dysfunction and/or comorbidity, and favourable cytogenetics, but is associated with an increased risk of treatment-related mortality (7, 8). In this patient population, treatment options usually consist of LDAC or BSC and patients suffer from low survival rates, with a 26% 30-day mortality reported in patients receiving low-intensity treatment (2, 8).

In a Phase 3 trial conducted in 217 elderly AML subjects unfit for IC, treatment with LDAC was shown to prolong OS when compared with BSC including hydroxyurea (3.8

months versus 2.5 months, respectively) (9). However, long-term outcomes were poor, with only 25% of the subjects alive at 1 year (67). In addition, treatment with LDAC had no OS benefit in elderly patients with adverse cytogenetics, with an estimated survival of just 2 months.

In spite of significant efforts to identify new treatment modalities in AML, little improvement has been observed in the last 30 years in AML trials conducted by all collaborative groups; in the UK, sequential AML trials conducted by the Medical Research Council (now NCRI) Adult Leukaemia Working Party has seen little evidence of improvement in OS for older patients (11) and 5-year survival rates for patients aged ≥65 years are just 5.4%, compared with 41.6% for younger patients (aged <65 years) (2).

As such, there still exists a need for an effective therapy to improve the survival benefit and reduce the burden of disease in the elderly AML population, particularly those where existing therapeutic options are of limited value.

3.8 *Equality*

AML presents primarily in the elderly population, with 64% of newly diagnosed cases in the UK in patients aged ≥65 years (1). Equity of treatment of the elderly is a concern, as evident from a report published by the National Audit Office in January 2015 (13). AML is also an orphan disease (14). The Cancer Patient Experience Survey in 2010 found that people with rarer forms of cancer reported a poorer experience of their treatment and care than people with more common forms of cancer (15). Therefore, access where appropriate to a treatment such as azacitidine should help to promote equality for both elderly patients and those with rarer forms of cancer.

4 Clinical effectiveness

4.1 *Identification and selection of relevant studies*

A systematic review was conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of azacitidine, as well as relevant comparators, for subjects aged 65 years or over with AML with >30% BM blasts and who were not eligible for HSCT. The systematic review was designed to capture evidence in a broader population than that defined in the appraisal scope of relevance to the licenced indication for azacitidine, and included patients aged ≥55 years and with AML >20% BM blasts. Evidence specifically addressing the population considered in the scope and relevant to the licenced indication for azacitidine was then selected for inclusion in the submission.

4.1.1 *Search strategy*

Relevant studies were identified through a search of the following databases: Medline, Embase, and Cochrane Central Register of Controlled Trials (search strategies are presented in Appendix 2). Searches were initially run on 5th February 2015 and rerun on 20th November 2015 to identify additional studies published since the initial search. In addition, the conference proceedings from European Hematology Association (EHA) Annual Congress, American Society of Hematology (ASH) Annual Conference, and the British Society for Haematology (BSH) Annual Scientific Meeting were searched between January 2013 and April 2015. Finally, clinicaltrials.gov was searched for relevant, unpublished studies

4.1.2 *Study selection*

The systematic literature search was performed using a predefined search strategy to identify eligible studies. Selection of studies for inclusion was determined using the PICOS criteria in Table 7.

Two investigators independently reviewed all abstracts identified in the literature search. Abstracts were compared against eligibility criteria and if deemed eligible for inclusion, they were advanced to full-text screening. The same two investigators independently reviewed relevant full-text articles. Articles deemed eligible at this stage were included in the systematic literature review and, where possible, analyses. Discrepancies between investigators were resolved by involving a third investigator and coming to a consensus. In the event that there were multiple publications for a single trial, only those publications providing the most recent data or any other relevant data for the analyses were selected for inclusion.

Table 7: Scope of the literature review: PICOS criteria for study inclusion

Criteria	Definition
Population	Older adult AML patients† with peripheral blood or BM leukaemic myeloblasts >20%, who either: • Are newly diagnosed with AML • Have developed AML secondary to “preleukaemic” blood disorders such as MDS or myeloproliferative disease • Have developed AML secondary to exposure to leukaemogenic therapy

Criteria	Definition
	or agents with primary malignancy in remission for at least 2 years
Interventions/ comparators	• Azacitidine 75 mg/m^2 • LDAC (20 mg SC once or twice a day for 10-14 days) • Decitabine 20 mg/m^2 • Other high dose chemotherapy: ○ Combination of etoposide or fludarabine (plus granulocyte-colony stimulating factor aka "G-CSF") with cytarabine (preferred for patients with cardiac disease) ○ 7+3: continuous IV infusion of cytarabine for 7 days followed by 3 days of IV anthracycline push ○ Combination of IV mitoxantrone, etoposide IV, and cytarabine ○ Combination of IV daunorubicin, cytarabine, and etoposide ○ Combination of IV cytarabine, daunorubicin, and oral thioguanine ○ Combination of IV cytarabine and daunorubicin: 3+10 for cycle 1 followed by DA 3+8 for cycle 2 (standard for UK) • Best supportive care‡
Outcomes	Studies are eligible if at least one of the following outcomes are included:§ • Efficacy outcomes ○ Overall survival ○ Event-free survival ○ Progression-free survival ○ Relapse-free survival ○ Complete response • Safety outcomes¶ ○ Treatment-related mortality ○ Hospitalisation due to AE ○ Grade 3 or 4 haematologic AEs ○ Discontinuations due to AEs ○ Discontinuations due to reasons other than disease progression
Study Design	• Randomised controlled trials and comparative non-randomised studies (prospective and retrospective observational studies) • Studies must compare two unique treatment classes (e.g. IC vs. IC or dose-ranging studies not eligible)
Other	• English language only • Published in or after the year 2000 (Selected on the advice of a panel of haematologists who advised that there would be limited evidence of relevance pre the year 2000).

Abbreviations: AE, adverse event; AML, acute myeloid leukaemia; BID, twice daily; BM, bone marrow; CR, complete response; EFS, event-free survival; IC, intensive chemotherapy; IV, intravenous; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; SC, subcutaneous.
† Note that although the primary population of interest is those 65 years of age and older, this criteria was relaxed (e.g. 55 years of age and older) to ensure sufficient evidence was available; ‡ It was expected that definitions in best supportive care would vary; § Note that additional outcomes were of interest, but only those identified in the table above were used to guide the selection of studies; safety outcomes were extracted only for those studies providing efficacy data.

Two investigators independently extracted data on study characteristics, interventions, patient characteristics at baseline, and outcomes for the study populations of interest for

the final list of selected eligible studies. Any discrepancies found between the data extracted by the two data extractors were resolved by involving a third reviewer and coming to a consensus.

The systematic review schematic is shown in Figure 4. A total of 8,450 citations were identified through Embase, Medline, and Cochrane Central Register of Controlled Trials. Of these, 8,363 (99%) were excluded at the abstract-screening stage. This resulted in 87 studies included in full-text screening. Of these, 80 (92%) were excluded:

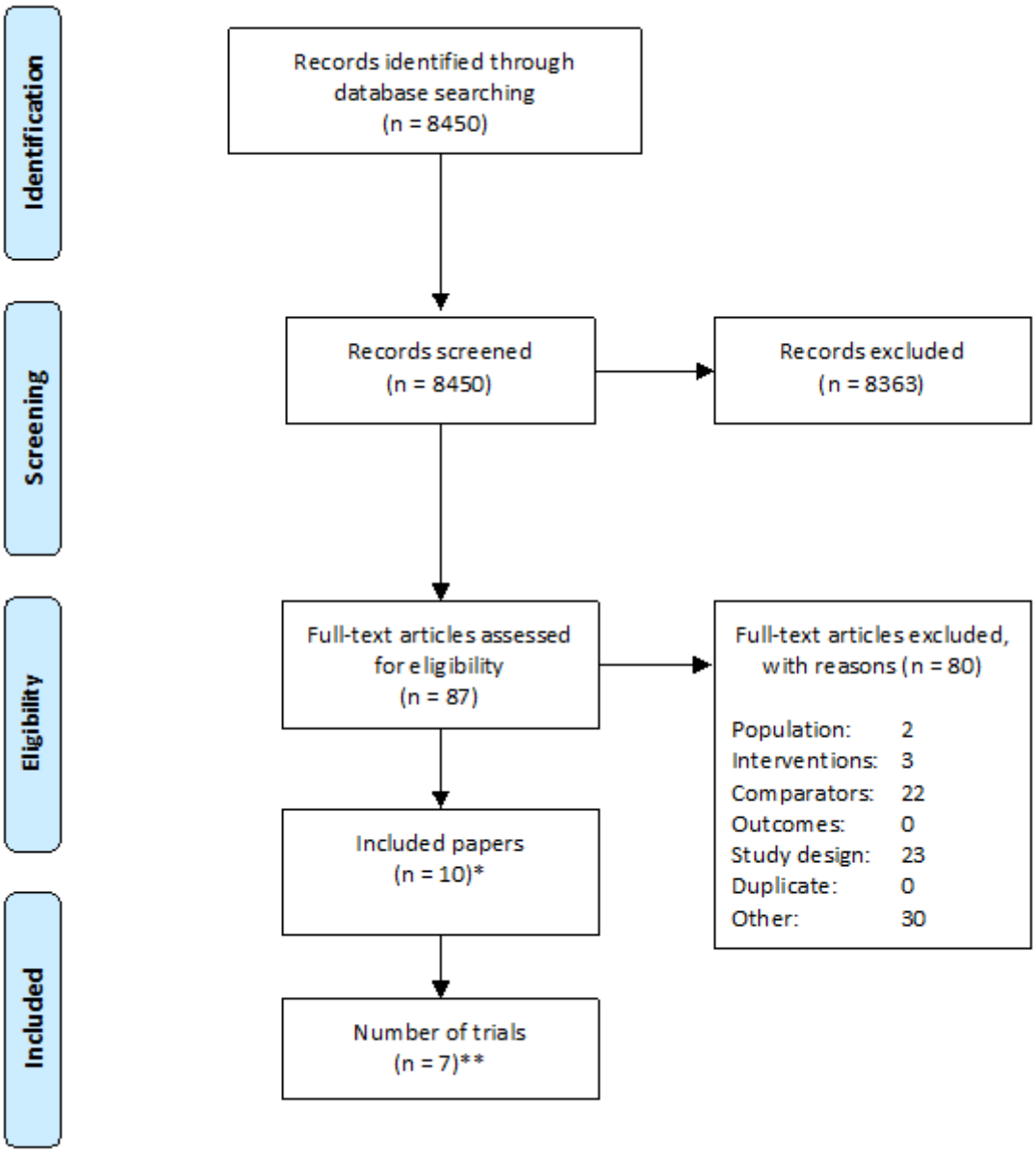
- 2 (2%) for inclusion of a population not of interest
- 25 (29%) for assessing an intervention not of interest or for inclusion of an ineligible comparator
- 23 (26%) due to ineligible study design
- 30 (34%) for other reasons (see Appendix 2 for a complete list).

Three materials were added from a manual search of literature databases and conference proceedings. This resulted in a total of 10 publications representing seven trials that were identified and met the inclusion criteria of the review consisting of four RCTs and three observation studies (22, 24, 68-75).

The systematic review was designed to identify both azacitidine and comparator studies, and also considered a broader AML population (>20% blasts aged ≥55 years) than that covered by the decision problem (≥30% blasts, aged ≥65 years). As such, the 7 identified studies were further assessed to identify those that would be of direct relevance to this submission. The resulting subset that provided evidence on the use of azacitidine in elderly patients (≥65 years) with AML with ≥30% blasts consisted of two studies: AZA-AML-001 (RCT) and Lao et al, 2015 (observational). AZA-AML-001 is summarised in Table 9 and described further in Section 4.3. The study by Lao et al is discussed further in Section 4.11.

Of the other five studies which were excluded from the submission, one RCT was identified which included azacitidine (70), but in a broader population than the scope, and another RCT included the population of interest, but the intervention (decitabine) was out of scope (22, 71, 72). The final RCT included treatment with IC, but included a population which was broader than that covered by the scope (73). The two remaining observational studies (74, 75) included azacitidine and relevant comparators (IC and BSC), but were in a population which was broader than the scope (>20% BM blasts). See Table 8 for further details.

Figure 4: PRISMA study flow diagram



* 3 materials added; ** 4 RCTs and 3 observational studies.

Table 8: Studies identified in systematic review

Study	Study design	Justification
Included in submission		
AZA-AML-001 (24, 68)	RCT	Pivotal regulatory azacitidine RCT supporting new indication (see Section 4.3 for further details))
Lao et al, 2015 (69)	Observational	Subgroup analysis in population of relevance treated with azacitidine (see Section 4.11 for further details)
Excluded from submission		
AML-MDS-001 (70)	RCT	Azacitidine study in MDS. Did not include

Study	Study design	Justification
		AML patients with blasts ≥30%
DACO-016 (22, 71, 72)	RCT	Decitabine study. Decitabine not in scope
Amadori et al, 2013 (73)	RCT	IC study and population broader than scope (AML >20% blasts)
Bories et al, 2014 (74)	Observational	Azacitidine study but population broader than scope (AML >20% blasts). No sub analysis of patients with AML ≥30% blasts)
Van Der Helm, et al 2013 (75)	Observational	IC study but population broader than scope (AML >20% blasts).

Abbreviations: AML, acute myeloid leukaemia; IC, intensive chemotherapy; IV, intravenous; RCT, randomised controlled trial.

4.2 *List of relevant randomised controlled trials*

Table 9: List of relevant RCTs

Trial no. (acronym)	Population	Intervention	Comparator	Primary study ref(s)	Is study excluded from further discussion? If yes state rationale
AZA-AML-001	Patients aged ≥65 years with newly diagnosed AML with >30% BM blasts who are ineligible for HSCT	Azacitidine (75 mg/m^2/day) SC for 7 days every 28 days	CCR, including: • BSC • LDAC: (20 mg BID) SC for 10 days every 28 days • IC: Cytarabine (100–200 mg/m^2/ day IV) in two phases (induction and consolidation)	Clinical study report (36) Dombret et al 2015 (24) Supporting information from conference poster by Minden et al 2015 (76)	No

Abbreviations: AML, acute myeloid leukaemia; BID, twice daily; BM, bone marrow; BSC, best supportive care; HSCT, Hematopoietic stem cell transplantation; IC, intensive chemotherapy; IV, intravenous; LDAC, low-dose cytarabine; RCT, randomised controlled trials; SC, subcutaneous

4.3 *Summary of methodology of the relevant randomised controlled trials*

4.3.1 *Study objectives*

The primary objective of the study was to demonstrate superiority in OS of azacitidine compared with combined CCRs in subjects aged 65 years or over who had newly diagnosed AML with more than 30% BM blasts according to the WHO criteria (49, 77), and who were not eligible for HSCT. Overall survival was defined as time from randomisation to death from any cause.

Secondary objectives included 1-year OS rate, EFS, RFS, overall remission rate, cytogenetic complete remission (CRc) rate, safety and toxicity assessments, HRQoL and health resource utilisation.

The choice of endpoints including OS, EFS and RFS is consistent with those recommended by the 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 (12). PFS is not a standard endpoint in AML trials (12), and as such was not measured in AZA-AML-001.

4.3.2 *Trial design*

Study AZA-AML-001 was an international, multicentre, controlled, Phase 3 study with an open-label, randomised, parallel-group design.

The study comprised three phases (see Figure 5):

1. **Pre-randomisation/screening phase**: Subjects were screened within 28 days prior to randomisation. Eligibility was based on local pathology and cytogenetic review. Enrolled subjects were assigned by the investigator to one of three CCRs based on local practice, clinician and patient choice, and evaluation of the subjects underlying disease condition. The three options for CCR were:

    a. IC utilising intravenous (IV) cytarabine in conjunction with an anthracycline, plus BSC

    b. LDAC plus BSC

    c. BSC only

    Baseline comorbidities were assessed using the haematopoietic cell transplantation comorbidity index (HCTCI).

2. **Treatment phase:** Subjects were randomised 1:1 to receive either:

    a. azacitidine plus BSC or

    b. pre-selected CCR

    Subjects were visited on a weekly basis during the first two treatment cycles, and then every two weeks for the remaining treatment cycles. The frequency of safety and efficacy measures ranged from weekly to every 12 weeks, depending on the procedure. During the treatment phase, a central reviewer, blinded to subject treatment, evaluated pathological samples (BM aspirates, biopsies, and peripheral blood smears) to confirm the diagnosis to be used for statistical analyses. If the central reviewer and local pathologist disagreed on the diagnosis of a subject, a third party reviewer evaluated the samples and this determination was used for statistical analyses. Subjects who were subsequently deemed not eligible to be enrolled remained in the study, but were excluded from the evaluable population for analysis.

    All cytogenetic results were confirmed by an independent central cytogenetic reviewer who was blinded to subject treatment. The central cytogenetic review

provided standardised analysis and reporting for all subjects. The central cytogenetic review was done retrospectively.

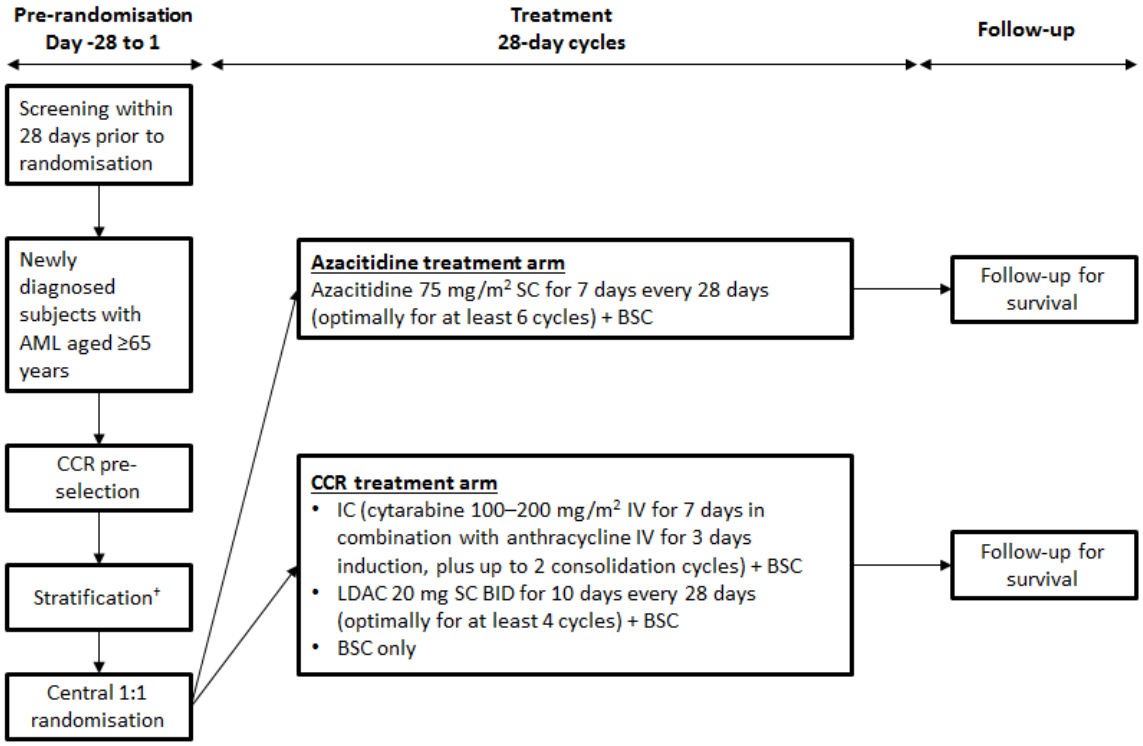
Biomarker samples were collected and a retrospective analysis was conducted following completion of the trial.

3. **Follow-up phase:** All discontinued subjects should have undergone an end-of-study procedure at the time of discontinuation. Subjects had a follow-up visit for the collection of AEs up to 28 days after the last dose of trial drug or up to the end-of-study visit, whichever period was longer. After this visit, subjects were followed for survival on a monthly basis until death, lost to follow-up, withdrawal of consent, or end of the study.

   Subjects who were randomised to receive azacitidine and who continued to receive azacitidine at the time of study closure had the option to enter an extension protocol, provided that they did not meet the criteria for withdrawal.

No cross-over was permitted between treatment groups during the trial. However, patients who discontinued randomised treatment could receive subsequent AML therapy during study follow-up according to the investigator's decision. The choice of subsequent therapy was at the discretion of the investigator.

Figure 5: Study design



Abbreviations: AML, acute myeloid leukaemia; BID, twice daily; BSC, best supportive care; CCR, conventional care regimens; ECOG, Eastern Cooperative Oncology Group; IC, intensive chemotherapy; IV, intravenous; LDAC, low-dose cytarabine; SC, subcutaneous.
† Stratification factors included CCR selection (IC vs. LDAC or BSC alone), ECOG performance status (0–1 vs. 2), and cytogenetics (intermediate-risk vs. poor-risk).

4.3.2.1 Study duration

The expected duration of the study was 31 months. This time frame consisted of a 19-month subject enrolment period, followed by 12 months of subject treatment and observation. The study was planned to conclude 12 months after the last subject was randomised.

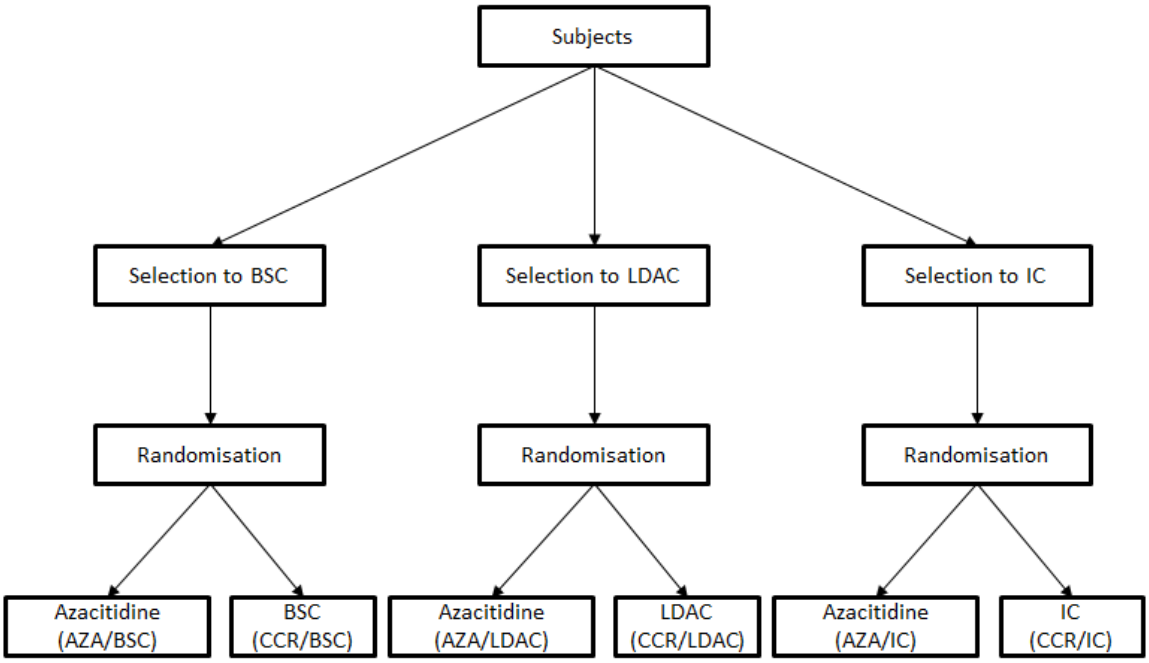
4.3.2.2 Randomisation

Subjects were randomised in a 1:1 ratio to receive either azacitidine or pre-selected CCR using an interactive voice recognition system (see Figure 6). A stratified, blocked randomisation schedule was implemented. The random treatment assignment was concealed so that investigators and subjects did not know in advance the next treatment assignment. Subjects were stratified by CCR selection (IC versus LDAC or BSC), ECOG performance status at baseline (0–1 versus 2), and cytogenetics (intermediate-risk versus poor-risk). No crossover between any of the treatment groups was permitted. Once randomised and assigned to receive one of the CCR options, a subject was not to be transferred to another treatment option within conventional care and was not to be transferred to the azacitidine treatment arm at any time during study, or treated with azacitidine following discontinuation from the originally assigned therapy, for the entire study duration. However, subjects could continue to receive the randomised study treatment for as long as was appropriate within the study duration.

4.3.2.3 Blinding

This was an open-label study. Blinding of study treatment was not feasible due to multiple comparators and routes of administration, which included intravenous infusion and subcutaneous injection over differing time periods depending on the treatment (See Section 4.3.5 for posology details). However, all central reviewers (pathology and cytogenetic) were blinded to subject treatment assignment. Evaluations by central review were used for the statistical efficacy analyses. The Independent Review Committee which reviewed and confirmed the International Working Group responses and durations was blinded to treatment, investigative site, and subject identifier.

Figure 6: Randomisation



Abbreviations: BSC, best supportive care; CCR, conventional care regimens; IC, intensive chemotherapy; LDAC, low-dose cytarabine.

4.3.3 *Eligibility criteria*

Table 10: Inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria

• Diagnosis of one of the following:
  ○ Newly diagnosed, histologically confirmed de novo AML
  ○ AML secondary to primary myelodysplastic disease not treated with azacitidine, decitabine, or cytarabine
  ○ AML secondary to exposure to potentially leukaemogenic therapy or agents† with the primary malignancy in remission for at least 2 years
• BM blasts >30%
• Adults aged ≥65 years
• ECOG performance status of 0–2
• Adequate organ function‡
• Females of child bearing potential had to have a negative pregnancy test result within 72 hours prior to starting therapy, and agree to use physician-approved contraceptive methods while taking azacitidine, and for 3 months after the final dose
• Males with a female partner of child bearing potential had to use physician-approved contraceptive methods throughout the study, and avoid fathering a child during the study and for 3 months
	• Previous cytotoxic¶ or biologic treatment for AML
	• Previous treatment with azacitidine, decitabine, or cytarabine
	• Prior use of targeted therapy agents
	• Suspected or proven promyelocytic leukaemia††
	• AML associated with inv(16), t(8;21), t(15;17), or t(9;22) karyotypes, or molecular evidence of such translocations
	• Prior BM or stem cell transplantation
	• WBC count >15x10^9/L at screening
	• Proven CNS leukaemia
	• Inaspirable BM
	• Candidate for allogeneic BM or stem cell transplant
	• Diagnosis of malignant disease within the previous 12 months‡‡
	• Malignant hepatic tumours
	• Unstable angina, significant cardiac arrhythmia, or NYHA class 3 or 4 CHF
	• Pregnant or lactating females
	• Uncontrolled systemic fungal, bacterial, or viral infection§§
	• Active viral infection with known HIV or viral hepatitis B or C
	• Known or suspected hypersensitivity to

Key inclusion criteria	Key exclusion criteria
after the final dose[§] • Able to adhere to study protocol	azacitidine or mannitol • Use of any experimental drug or therapy within 28 days prior to day 1 of cycle 1 • Unwilling or unable to complete PRO assessments without assistance or minimal assistance • Any condition, including laboratory abnormalities, which would place the subject at an unacceptable risk • Any significant medical condition, including the presence of laboratory abnormalities, or psychiatric illness which would interfere with subject participation • Any condition that confounded the ability to interpret data from the study

Abbreviations: AML, acute myeloid leukaemia; BM, bone marrow; CHF, congestive heart failure; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; NYHA, New York Heart Association; PRO, patient-reported outcomes; WBC, white blood cells.
†Such as radiation therapy, alkylating agents, and topoisomerase II inhibitors; ‡ defined as serum bilirubin ≤1.5 times the upper limit of normal, serum aspartate aminotransferase and alanine aminotransferase ≤2.5 times the upper limit of normal, and serum creatinine ≤1.5 times the upper limit of normal; § 6 months in Canada for male subjects; ¶ excluding hydroxyurea which was permitted up to 2 weeks prior to the screening haematology sample; †† based on morphology, immunophenotype, molecular assay, karyotype, or AML with previous haematologic disorder such as chronic myelogenous leukaemia or myeloproliferative neoplasms; ‡‡ excluding basal cell carcinoma of the skin without complications, in-situ carcinoma of the cervix or breast, or other local malignancy excised or irradiated with a high probability of cure; §§ defined as ongoing signs/symptoms related to the infection without improvement despite appropriate treatment.

4.3.4 *Location*

Screening was conducted in 107 investigational sites, of which, 98 sites randomised at least one patient across 18 countries in different geographic regions. Locations included: Asia (12 sites); Australia (6 sites); the US/Canada (12 sites); Eastern Europe (12 sites); and Western Europe and Israel (56 sites). These included 5 sites in the UK which in total randomised 26 patients: Oxford (n=4), Bournemouth (n=1), St Bartholomew's (n=13), King's College (n=4) and Wolverhampton (n=4).

4.3.5 *Trial drugs*

The trial drug was azacitidine and the comparators were combined CCR, including IC + BSC, LDAC + BSC, or BSC only. Full details of the trial drugs and treatment regimen are given below.

- **Azacitidine**: All subjects randomised to receive azacitidine were to receive 75 mg/m^2/day by subcutaneously (SC) for 7 days every 28 days until the end of the study, or study discontinuation. In addition, subjects were eligible to receive BSC as required.
- **IC**: All subjects who were randomised to the combined CCR arm and were assigned IC were to be treated with an induction treatment regimen (cycle 1) followed by a maximum of two consolidation cycles (cycles 2 and 3). In addition, subjects were eligible to receive BSC as required.
  - Induction therapy (cycle 1) – Cytarabine was administered at a dose of 100–200 mg/m^2/day via continuous IV infusion for a total of 7 days. Anthracycline was

given in combination with cytarabine on days 1, 2 and 3 (daunorubicin [45–60 mg/m^2/day] or idarubicin [9–12 mg/m^2/day]).
    - Consolidation therapy (cycles 2 and 3) – Subjects who attained a CR, complete remission with incomplete blood count recovery (CRi), or partial remission (PR) according to the AML response criteria (Appendix 3) were eligible to receive between one and two cycles of consolidation therapy. Cytarabine was administered at a dose of 100–200 mg/m^2/day via continuous IV infusion for 3–7 days. The anthracycline of choice was identical to that administered during cycle 1 and was administered via IV on days 1 and 2. Consolidation therapy was started between day 28 and 70 from commencement of induction therapy, and the second consolidation therapy, if given, was started between day 28 and 70 from commencement of the first consolidation therapy. Any subject who failed to attain a CR, CRi, or PR following the induction therapy was removed from the treatment phase and entered the follow-up phase of the study.
- **LDAC:** Subjects randomised to the CCR arm and assigned to LDAC were to receive cytarabine at a dose of 20 mg SC twice daily (BID) for 10 days, every 28 days, until the end of the study, or study discontinuation. In addition, subjects were eligible to receive BSC as required.
- **BSC:** All subjects who were randomised to the combined CCR treatment arm and were assigned BSC received any supportive care needed until the end of study. BSC included, but was not limited to, treatment with red blood cell or whole blood transfusions, fresh frozen plasma transfusions, platelet transfusions, antibiotic and/or antifungal therapy, and nutritional support. Hydroxyurea use was permitted under certain conditions (see Section 4.3.6). Best supportive care excluded cancer surgery, immunotherapy, biologic therapy, radiotherapy, anticancer hormonal therapy, and systemic chemotherapy where the goal was to eradicate or slow the progression of the disease.

4.3.6 *Prior and concomitant therapy*

Concomitant medications were to be kept to a minimum during the study. However, medications which were deemed to be necessary for the subject's welfare and were unlikely to interfere with the trial drugs were given at the discretion of the investigator.

- The use of hydroxyurea was permitted up to 2 weeks prior to the screening of the haematology sample. During the screening period, hydroxyurea could be given until 72 hours prior to the start of study therapy. Following the start of study therapy, transient hydroxyurea use was permitted in all treatment arms as a component of BSC. Subjects in the azacitidine treatment arm were not permitted to be given hydroxyurea within the 72 hours prior to and after azacitidine administration.
- Serotonin receptor antagonists were administered as an antiemetic approximately 30 minutes prior to administration of azacitidine. Additional doses were administered if required.
- Blood product support (red blood cells and platelets) were administered according to institutional standards.
- Myeloid growth factors could be given per investigator discretion only for the treatment of neutropenic infections, prophylactically during IC treatment, or in subjects with two or more previous episodes of neutropenic infection who were at risk of

subsequent neutropenic infection. For subjects who developed an absolute neutrophil count (ANC) <0.5 x 10^9/L, administration of prophylactic fluoroquinolone was permitted. If neutropenic infection occurred, treatment consisted of a broad-spectrum antibiotic. Myeloid growth factors were administered if deemed necessary by the investigator and infection persisted despite the use of broad-spectrum antibiotics.

- Erythropoietic agent use was allowed and was administered according to institutional practices.

The following concomitant medications were excluded during the study:

- clofarabine
- decitabine
- targeted agents (e.g. FLT-3 antagonists)
- systemic anticancer therapy (excluded hydroxyurea)
- oral retinoids (topical retinoids were permitted)
- use of any other investigation drug or therapy

4.3.7 *Study endpoints*

The study endpoints and their relevance to the decision problem are presented in Table 11. Response categories and definitions are provided in Table 12.

Table 11: Outcomes investigated in AZA-AML-001

Endpoints and measures	Included in NICE scope?	Reliability/validity/current use in clinical practice
Primary endpoint		
OS	Yes	Overall survival is considered the most reliable endpoint for cancer studies, as it is an objective and direct measure of the treatment benefit that is most clinically meaningful to the patient population. Furthermore, OS is an appropriate primary endpoint according to the "Guideline on the evaluation of anticancer medicinal products in man" CPMP/EWP/205/95 (58).
Secondary endpoints		
1-year OS rate	Yes	See OS above
EFS (defined as the interval from the date of randomisation to the date of treatment failure, progressive disease, relapse after CR or CRi, death from any cause, or loss to follow-up, whichever occurred first)	No	Secondary efficacy endpoints are based on standard AML response criteria. The attainment of CR is the standard goal in treating AML in patients with IC. However, since not all AML subjects are eligible for IC, lower intensity therapies are often now considered as treatment options for these subjects. As such, the response criteria used in this study were a version of the IWG 2003 response criteria that
RFS (defined only for subjects who achieved CR or CRi and was measured as the interval from the date of first documented CR or CRi to the date of relapse, death from any cause, or loss to follow-up, whichever	No	

Endpoints and measures	Included in NICE scope?	Reliability/validity/current use in clinical practice
occurred first)		was modified in consultation with the key opinion leaders. Progression-free survival estimates were generated from EFS and RFS to inform the economic model. See Section 5 for full details
Overall remission rate (CR + CRi)	Yes	
Duration of remission (CR + CRi) (defined as the time from the date of CR or CRi until the date of relapse from CR or CRi)	Yes	
Cytogenetic complete remission rate (defined as morphologic CR with a return to a normal karyotype at the time of CR [based on ≥10 metaphases])	Yes	
PR (defined as an ANC ≥1,000/μL and platelet count ≥100,000/μL with a >50% decrease in the percentage of BM blasts to 5–25%)	Yes	
Stable disease (defined as any evaluable time point where criteria for all other response categories [i.e, CR, CRi, PR, progressive disease, treatment failure, not assessable] are not met)	No	
Safety/tolerability (type, frequency, severity, and relationship of AEs to study treatments; physical examinations, vital signs; clinical laboratory evaluations; and concomitant medication/therapy)	Yes	All safety assessments are widely used and recognised as reliable, accurate, and relevant.
Patient-reported quality of life outcomes using the EORTC QLQ-C30 - completed on day 1 of cycle 1 (baseline), every other cycle thereafter, and at the end-of-study visit	Yes	The quality of life instrument used in this study (EORTC QLQ-C30) has been used in studies of various cancer types, and the validity has been demonstrated (78).
Measures of healthcare resource utilisation - any consumption of healthcare resources directly or indirectly related to the treatment of the subject. Five items of HCRU were collected: inpatient hospitalisations, transfusions, procedures or surgeries, and concomitant medications	No	In the HE model HCRU is based upon UK specific data from a clinician questionnaire.
Additional endpoints		
Transfusion status (RBC and platelet transfusion status [dependence or independence]) - On-treatment RBC/platelet transfusion independence was defined as the absence of any RBC/platelet transfusions for 28 or 56	Yes	The clinical consequences of abnormal haematological laboratory values, such as haemorrhages, transfusions, and infections, are routinely used as indicators of subject well-being. Peripheral blood measurements

Endpoints and measures	Included in NICE scope?	Reliability/validity/current use in clinical practice
consecutive days during the treatment period		were used in previous studies of azacitidine and the development of other treatments for MDS and/or AML.
Peripheral blood counts (platelets, ANC, Hgb, WBC, and blasts)	No	

Abbreviations: AE, adverse event; AML, acute myeloid leukaemia; ANC, absolute neutrophil count; BM, bone marrow; CR, complete response; CRi, complete response with incomplete blood count recovery; DNA, deoxyribonucleic acid; EFS, event-free survival; EORTC, European Organization for Research and Treatment on Cancer; Hgb, haemoglobin; IWG, international Working Group; MDS, myelodysplastic syndrome; miRNA, micro-ribonucleic acid; PR, partial remission; QLQ, quality of life questionnaire; RBC, red blood cell; RFS, relapse-free survival; SNP, single nucleotide polymorphism; WBC, white blood cell.

Molecular features in the BM, potentially including measures of cytogenetics, DNA methylation, single nucleotide polymorphism (SNP), gene sequencing, gene expression, micro-ribonucleic acid (miRNA) expression and/or cellular protein expression are being collected, but are not currently available.

Table 12: Response categories and definitions

Response category	Criteria for response
CR	The following conditions had to be met: • The BM should contain fewer than 5% blast cells • ANC ≥1,000/µL • Platelet count ≥100,000/µL • No RBC, platelet, or whole blood transfusions for 1-week prior to the haematology assessment used for the response evaluation.
CRi	Defined as a morphologic complete remission but the ANC count may be <1,000/µL and/or the platelet count may be <100,000/µL.
CRc	Defined as morphologic complete remission with a return to a normal karyotype at the time of CR (based on ≥10 metaphases).
PR	Defined as an ANC ≥1,000/µL and platelet count ≥100,000/µL with a >50% decrease in the percentage of BM blasts to 5–25%.
Relapse after CR or CRi	Defined as either: 1) the recurrence of >5% blasts in the peripheral blood following CR or CRi, (the percentage of peripheral blood blasts must have been ≤5% at the time of CR or CRi) or 2) a single finding of >15% blasts in the BM following a CR or CRi.
Stable disease	Any evaluable time point where criteria for all other response categories (i.e, CR, CRi, PR, progressive disease, treatment failure, not assessable) are not met.
Progressive disease	Defined as either: 1) a >50% increase in BM blast count from baseline that persists for at least 2 BM assessments separated by at least 1 month, or if the baseline BM blast count is >70% and persists for 2 post-baseline BM assessments separated by at least 1 month, or 2) a doubling of the baseline absolute peripheral blood blast count that persists for at least 7 days and the final absolute peripheral blood blast count is >10 x 10^9/L. The date of PD is defined as the first date that there was either a >50% increase in BM blast count from baseline, a persistence of BM blasts >70% in subjects with a

Response category	Criteria for response
	baseline BM blast count of >70%, or a doubling of the peripheral blood blast count.
Treatment failure	Defined as death during cycle 1 or within 28 days of the last dose and prior to day 1 of cycle 2.

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; CR, complete remission; CRc, cytogenetic complete remission; CRi, complete remission with incomplete blood count recovery; PR, partial remission, RBC, red blood cell.

4.4 *Statistical analysis and definition of study groups in the relevant randomised controlled trials*

4.4.1 *Analysis populations*

Intent-to-treat population: all subjects who were randomised, independent of whether or not they received study treatment. The intent-to-treat (ITT) population was used for the analysis of the primary and secondary efficacy endpoints. Subjects in the ITT population were analysed as randomised.

Evaluable population: all subjects who had at least 1 efficacy assessment performed, did not meet any of the exclusion criteria (see Table 13), and had received a minimum of one cycle of treatment (or 28 days of treatment with blood products or antibiotics as needed) were considered to be in the evaluable population.

Modified ITT population: ITT subjects who received at least 1 dose of study medication and had a diagnosis of AML with >30% blasts confirmed by retrospective central review of an evaluable BM aspirate.

HRQoL evaluable population: all randomised subjects who completed the baseline HRQoL assessment (day 1) and had at least one follow-up assessment.

Safety population: all randomised subjects who had received at least one dose of trial drug and had at least one post-dose safety assessment. Subjects who were randomised to BSC within the CCR group were considered to be included in the safety population is that had at least one post-randomised safety assessment. Drug exposure and all safety analyses were based on the safety population. All subjects were analysed according to the initial treatment they received.

Table 13: Criteria leading to exclusion from the evaluable population

Criteria
• AML diagnosis not confirmed by central review • Cytogenetic risk stratification category not confirmed by central review • Randomised in error (had at least 1 inclusion or exclusion criteria violation) • Did not receive at least 1 cycle of randomised study medication • Initial treatment given was not treatment assigned in randomisation • Did not have at least 1 post-randomisation efficacy assessment performed • Received protocol prohibited concomitant therapy • Azacitidine was not administered after reconstitution within the protocol defined timeframe for > 1/3 of days dosed • Study medication compliance was <80% or >120%

4.4.2 *Primary hypothesis*

The null hypothesis for the primary efficacy endpoint was that the OS distributions between the azacitidine and CCR treatment groups were equivalent.

All hypothesis testing were carried out at the 5% (2-sided) significance level and designed to evaluate the superiority of azacitidine relative to CCR. Secondary endpoints were not adjusted for multiplicity.

4.4.3 *Determination of sample size*

The equality of OS curves was to be compared between the azacitidine and combined CCR groups using a stratified log-rank test. The planned sample size was approximately 480 subjects (240 per treatment arm), calculated on the assumption of a median OS of 10.5 months in the azacitidine arm and 7.5 months in the combined CCR arm (40% improvement), with a dropout rate of 1% from both treatment groups. The investigator selection of CCR was anticipated to be 50%, 30%, and 20% of subjects to the IC, LDAC, and BSC groups, respectively. This design required 374 deaths to allow the demonstration of a statistically significant difference in OS at a one-sided significance level of 0.025 with at least 90% power to detect a constant HR of 0.71.

Power calculations were based on comparisons made between the azacitidine group and the CCR group. The study was not prospectively powered to statistically compare the individual CCR treatment selections.

The final analysis, planned after 374 events had been observed, was expected approximately 31 months following randomisation of the first subject into the study.

4.4.4 *Primary efficacy analysis*

The primary efficacy analysis was performed using the ITT population. The analysis of the primary efficacy endpoint was conducted using an unstratified log-rank rest and a stratified log-rank test (stratified by CCR selection, ECOG performance status, and cytogenetic risk status). The Kaplan Meier (KM) method was used to estimate the survival distribution functions for each treatment group. KM estimates for median OS, 25th and 75th percentiles, and associated two-sided 95% CIs were summarised for each treatment group (both unadjusted for the stratification variables and within strata). Additionally, the numerical difference and associated 95% CI in the median, and the 25th and 75th percentiles between the two treatment groups (azacitidine vs. CCR) were presented for the unstratified KM estimates.

Cox proportional hazards models (unstratified and stratified) were used to estimate the hazard rate ratio and the corresponding 95% CI for azacitidine vs CCR.

Surviving subjects were censored upon study discontinuation (loss to follow-up, withdrawal of consent) or at the end of the post-study follow-up.

4.4.4.1 Sensitivity analysis

The following sensitivity analyses were performed.

Using the evaluable population

The primary efficacy analysis was repeated using the evaluable population.

Analyses to evaluate any impact of subjects receiving other cancer therapy after study therapy

- **Censoring for the use of any subsequent therapy for AML**
  Subjects who received follow-up therapy for AML following discontinuation from trial drug were censored from the date on which the first subsequent therapy was started. The modified time-to-death endpoint was based on the ITT population and analysed as per primary analysis of the primary endpoint.

4.4.4.2 Exploratory analyses

In support of the primary analysis, the following analyses were conducted on the ITT population using the same methods as the primary analysis, without stratification:

- azacitidine versus BSC only among subjects pre-selected to BSC only
- azacitidine versus LDAC among subjects pre-selected to LDAC
- azacitidine versus IC among subjects pre-selected to IC

4.4.4.3 Post-hoc analyses

Impact of subsequent therapy and/or baseline characteristics

In post-hoc multivariate efficacy analyses OS with azacitidine compared with CCR was estimated by using Cox proportional hazards models to adjust for variables that were preselected on the basis of their known potential to influence outcomes because of confounding and/or heterogeneity. These Cox models were adjusted for (1) covariates for subsequent therapy (time-varying; yes or no) and treatment-by-subsequent-therapy (time-varying) interaction, (2) selected baseline demographic and disease covariates known to influence prognosis (e.g. cytogenetic risk), and (3) all covariates in models (1) and (2). HRs, 95% CIs, and p values were estimated.

In addition, the influence of subsequent therapy on median OS was evaluated by using an IPCW adjusted Cox PH model. The IPCW approach computes adjusted HR estimates which allow for a correction for dependent censoring (79). This approach allows for the detection of improved survival that the standard ITT comparison fails to detect when a large proportion of the subjects receive subsequent therapy.

For regulatory purposes, an initial IPCW analysis was undertaken in which both treatment arms were adjusted. A further IPCW analysis was conducted in line with the NICE DSU TSD16 in which adjustments were only made to the comparator treatment arm (CCR) (80).

Impact of subsequent therapy on overall survival

To further explore the impact on OS of subsequent therapies, estimates of OS for azacitidine versus CCR were also generated for subjects who did not receive any subsequent therapy and for those subjects who received any subsequent therapy.

Modified intent-to-treat population

Considering the criteria used to select the evaluable population were very restrictive, a post-hoc analysis for the OS endpoint was conducted in a modified ITT (mITT) population, with less extensive criteria than for the evaluable population.

4.4.5 *Secondary efficacy analysis*

All secondary endpoints were analysed using the ITT population, except for HRQoL and healthcare resource utilisation (HCRU). Analyses for both HRQoL and HCRU were conducted using a HRQoL evaluable population, defined as all randomised subjects who completed the baseline HRQoL assessment (day 1) and had at least one follow-up assessment.

Kaplan-Meier methods were used to estimate the 1-year survival probabilities for time to death from any cause and death probabilities at 30 and 60 days.

Time-to-event endpoints (EFS and RFS) were analysed using the same methods as the primary efficacy analysis, but without stratification. For EFS, subjects who were alive and event-free were censored at the date of their last response assessment, and for RFS, subjects who were in continuous CR or CRi were censored at the date of their last response assessment.

Haematologic status was explored by examining the percentage of responders, defined as CR and CRi, and the duration of remission, CRc, peripheral blood counts, and transfusion requirements. All responses were based on the modified International Working Group (IWG) response criteria for AML, and are defined in Table 12.

For duration of remission, subjects who were lost to follow-up or were alive at follow-up without documented relapse were censored at the date of their last response assessment. Summary statistics included KM estimates of median duration of remission, and 1-year cumulative incidence of relapse for each treatment group.

For transfusion status, subjects who maintained red blood cell/platelet transfusion independence to the end of the treatment period were censored at the date of treatment discontinuation or death, whichever was sooner. Duration of transfusion independence was estimated and summarised using KM methods.

For HRQoL analyses, the mean change from baseline for each domain at each time point was compared with the minimal important difference to determine whether the change was clinically meaningful. A mean change of at least 10 points on the standardised domain scores was required to be considered meaningful (81).

All reported log-rank or Fisher's exact test p values for secondary endpoints are nominal.

4.5 *Participant flow in the relevant randomised controlled trials*

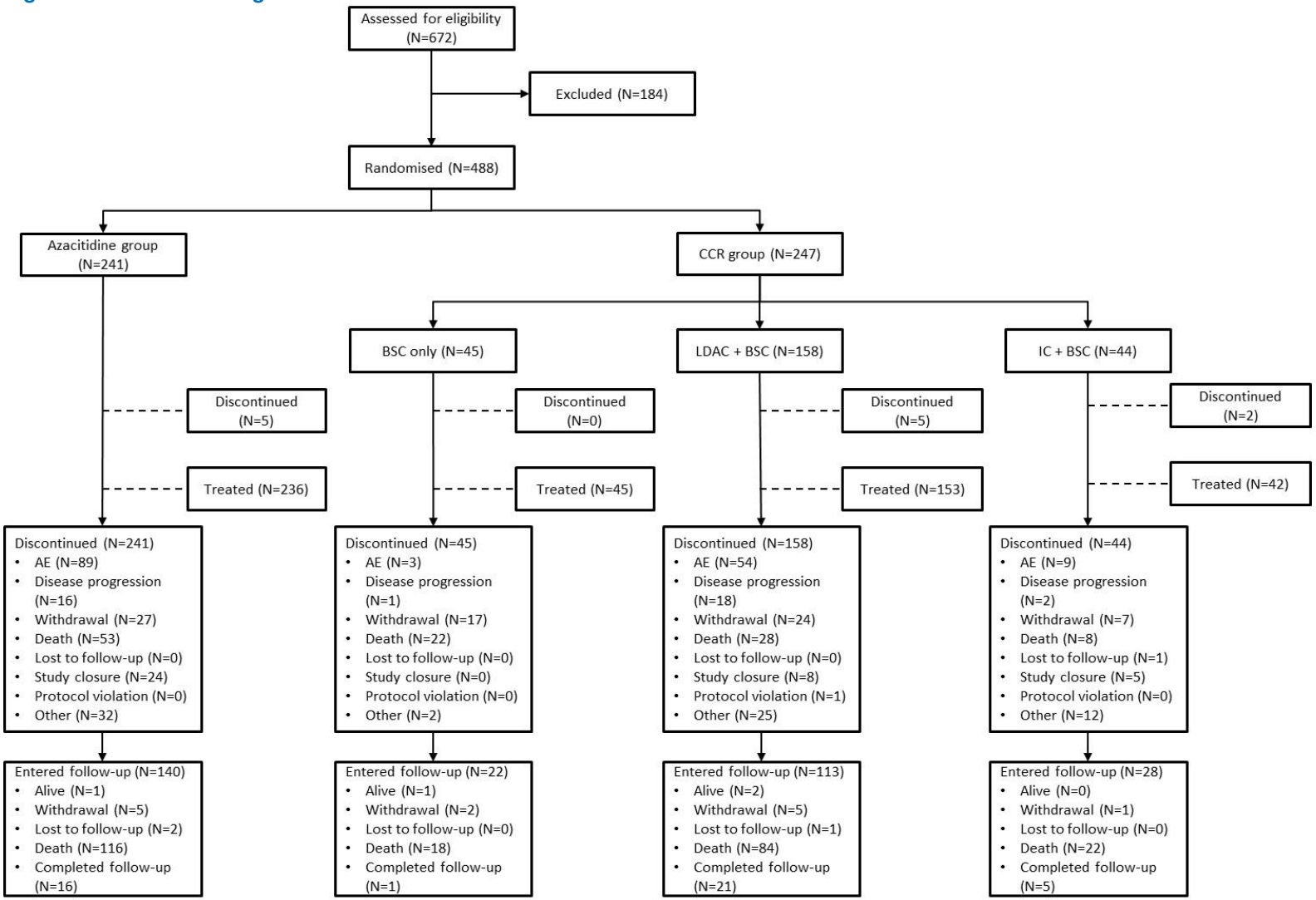
4.5.1 *Patient disposition*

In total, 488 subjects were randomised. Of these, 241 subjects were randomised to receive azacitidine, and 247 subjects were randomised to receive conventional care treatment.

- Within the group pre-selected to BSC only, 44 subjects were randomised to azacitidine and 45 subjects were randomised to BSC alone.
- Within the LDAC group, 154 subjects were randomised to receive azacitidine and 158 subjects were randomised to LDAC.
- Within the IC group, 43 subjects were randomised to azacitidine and 44 subjects were randomised to IC.

A CONSORT flow diagram for AZA-AML-001 is presented in Figure 7 and the data sets analysed are presented in Table 14.

Figure 7: CONSORT diagram for AZA-AML-001



Abbreviations: AE, adverse event; BSC, best supportive care; CCR, conventional care regimens; IC, intensive chemotherapy; LDAC, low-dose cytarabine.

Table 14: Analysis populations

Analysis population	Azacitidine				CCR				Total (N=488)
	BSC only (N=44)	LDAC (N=154)	IC (N=43)	Total (N=241)	BSC only (N=45)	LDAC (N=158)	IC (N=44)	Total (N=247)	
ITT	44	154	43	241	45	158	44	247	488
Safety	42	151	43	236	40	153	42	235	471
Evaluable	35	114	30	179	25	132	34	191	370
HRQoL evaluable	-	-	-	157	-	-	-	134	291

Abbreviations: AZA. azacitidine; BSC, best supportive care; CCR, conventional care regimens; IC, intensive chemotherapy; ITT, intent-to-treat; LDAC, low-dose cytarabine.

4.5.2 *Baseline characteristics and demographics*

4.5.2.1 Baseline patient demographics

Patient characteristics at baseline are summarised in Table 15. In the ITT population (N=488), the median age of the subjects was 75.0 years with 54.3% of the subjects ≥75 years of age. There were 288 (59.0%) male subjects and the majority of subjects (75.2%) were white.

Demographic data are well balanced between the azacitidine and the combined CCR treatment groups.

As expected, within the CCR treatment group, subjects in the IC group were slightly younger (median age, 70.5 years; 72.7% of subjects <75 years) than any of the other treatment groups and subjects in the BSC only group were slightly older than subjects in any of the other treatment groups (median age, 78.0 years; 28.9% of subjects <75 years). Baseline characteristics of subjects in the LDAC group were similar to those of subjects in the azacitidine group.

Table 15: Demographics of participants in the RCT across randomised groups (ITT)

Baseline characteristics	Azacitidine (N=241)	CCR			Total (N=488)
		BSC only (N=45)	LDAC (N=158)	IC (N=44)	
Median age (range), years	75.0 (64[†], 91)	78.0 (67, 89)	75.0 (65, 89)	70.5 (65, 81)	75.0 (64, 91)
Age group, n (%)					
<75 years	103 (42.7)	13 (28.9)	75 (47.5)	32 (72.7)	223 (45.7)
≥75 years	138 (57.3)	32 (71.1)	83 (52.5)	12 (27.3)	265 (54.3)
Male, n (%)	139 (57.7)	29 (64.4)	94 (59.5)	26 (59.1)	288 (59.0)
Geographical region, n (%)[‡]					
North America/Australia	45 (18.7)	13 (28.9)	29 (18.4)	5 (11.4)	92 (18.9)
Western Europe/Israel	116 (48.1)	26 (57.8)	74 (46.8)	22 (50.0)	238 (48.8)

Baseline characteristics	Azacitidine (N=241)	CCR			Total (N=488)
		BSC only (N=45)	LDAC (N=158)	IC (N=44)	
Eastern Europe	46 (19.1)	0	37 (23.4)	7 (15.9)	90 (18.4)
Asia	34 (14.1)	6 (13.3)	18 (11.4)	10 (22.7)	68 (13.9)
Race, n (%)					
White	185 (76.8)	37 (82.2)	116 (73.4)	29 (65.9)	367 (75.2)
Black	2 (0.8)	0	1 (0.6)	0	3 (0.6)
Asian	37 (15.4)	6 (13.3)	18 (11.4)	10 (22.7)	71 (14.5)
Hawaiian/Pacific Islander	1 (0.4)	0	0	0	1 (0.2)
Other	1 (0.4)	0	0	0	1 (0.2)
Not applicable	15 (6.2)	2 (4.4)	23 (14.6)	5 (11.4)	45 (9.2)
Median weight (range), kg	71.8 (36, 141)	73.0 (44, 108)	70.7 (34, 125)	71.1 (43, 120)	71.1 (34, 141)
Median BSA (range), kg/m^2	1.8 (1, 2)	1.8 (1, 2)	1.8 (1, 2)	1.8 (1, 2)	1.8 (1, 2)

Abbreviations: BSA, body surface area; BSC, best supportive care; CCR, conventional care regimens; IC, intensive chemotherapy; ITT, intent-to-treat; LDAC, low-dose cytarabine.
† one subject was 64 years and 11 months old at study entry; ‡ North America = United States and Canada, Western Europe = Austria, Belgium, France, Germany, Italy, Spain, The Netherlands, United Kingdom; Eastern Europe = Czech Republic, Poland, and Russia; Asia = China, South Korea, and Taiwan.

4.5.2.2 Baseline disease characteristics and prior therapies

The baseline disease characteristics are summarised by treatment group and overall for the ITT population in Table 16.

The azacitidine and combined CCR treatment groups were comparable for all baseline disease characteristics, including AML classification, prior history of MDS, time since AML diagnosis, ECOG performance status and cytogenetic status, except prior anticancer systemic therapies.

Table 16: Disease characteristics and prior therapies (ITT)

Parameter	Azacitidine (N=241)	CCR			Total (N=488)
		BSC only (N=45)	LDAC (N=158)	IC (N=44)	
WHO AML classification, n (%)					
AML with MDS-related changes	75 (31.1)	20 (44.4)	50 (31.6)	13 (29.5)	158 (32.4)
Therapy-related myeloid neoplasms	8 (3.3)	2 (4.4)	9 (5.7)	1 (2.3)	20 (4.1)
AML with recurrent genetic abnormalities	5 (2.1)	1 (2.2)	4 (2.5)	4 (9.1)	14 (2.9)
AML not otherwise specified	153 (63.5)	22 (48.9)	95 (60.1)	26 (59.1)	296 (60.7)
Prior history of MDS, n (%)					
Yes	49 (20.3)	11 (24.4)	23 9 (14.6)	4 (9.1)	87 (17.8)
Primary	46 (19.1)	11 9 (24.4)	20 (12.7)	4 (9.1)	81 (16.6)
Secondary	3 (1.2)	0 (0.0)	3 (1.9)	0 (0.0)	6 (1.2)
No	192 (79.7)	34 (75.6)	135 (85.4)	40 (90.9)	401 (82.2)
Time since AML diagnosis, months					
Median (range)	0.3 (0.0, 19.8)	0.7 (0, 20.1)	0.3 (-0.2, 20.2)[†]	0.2 (0.0, 4.4)	0.4 (-0.2, 20.2)[†]
ECOG performance status, n (%)[‡]					
Grade 0	54 (22.4)	11 (24.4)	36 (22.8)	10 (22.7)	111 (22.7)
Grade 1	132 (54.8)	19 (42.2)	87 (55.1)	26 (59.1)	264 (54.1)
Grade 2	55 (22.8)	15 (33.3)	35 (22.2)	8 (18.2)	113 (23.2)
Cytogenetic risk status – local, n (%)[‡]					
Intermediate	159 (66.0)	28 (62.2)	102 (64.6)	29 (65.9)	318 (65.2)
Normal	118 (49.0)	22 (48.9)	65 (41.1)	18 (40.9)	223 (45.7)
Poor[§]	82 (34.0)	17 (37.8)	56 (35.4)	15 (34.1)	170 (34.8)
Cytogenetic risk status – central, n (%)[‡]					
Intermediate	155 (64.3)	29 (64.4)	104 (65.8)	27 (61.4)	315 (64.5)
Normal	113 (46.9)	23 (51.1)	65 (41.1)	17 (8.6)	218 (44.7)
Poor[¶]	44 (18.3)	6 (13.3)	29 (18.4)	9 (20.5)	88 (18.0)
Very poor[††]	41 17.0)	10 (22.2)	25 (15.8)	6 (13.6)	82 (16.8)

Parameter	Azacitidine (N=241)	CCR			Total (N=488)
		BSC only (N=45)	LDAC (N=158)	IC (N=44)	
Prior therapies, n (%)					
≥1 systemic anticancer therapy	8 (3.3)	4 (8.9)	19 (12.0)	2 (4.5)	33 (6.8)
≥1 radiation therapy	17 (7.1)	2 (4.4)	13 (8.2)	2 (4.5)	34 (7.0)
BM blasts – local, n (%)‡‡					
Subjects sampled	241	45	158	44	488
Mean (SD)	56.9 (20.90)§§	51.2 (16.79)	56.6 (19.45)	55.6 (20.72)	56.2 (20.08)§§
≤50%	113 (46.9)	25 (55.6)	80 (50.6)	20 (45.5)	238 (48.8)
>50%	128 (53.1)	20 (44.4)	78 (49.4)	24 (54.5)	250 (51.2)
BM blasts – central, n (%)‡‡					
Subjects sampled	238	44	155	44	481
Mean (SD)¶¶	66.6 (24.71)	70.8 (22.76)	71.3 (21.29)	65.9 (25.11)	68.5 (23.56)
≤50%	65 (27.0)	8 9 (17.8)	27 9 (17.1)	15 (34.1)	115 (23.6)
>50%	173 (71.8)	36 (80.0)	128 (81.0)	29 (65.9)	366 (75.0)
Peripheral blood blasts, n (%)‡‡					
Subjects sampled	228	42	153	40	463
Mean (SD)	16.8 (21.75)	13.5 (22.42)	17.5 (22.52)	16.8 (24.52)	16.7 (22.26)
Peripheral blood blasts (10^9/L)‡‡					
Subjects sampled	228	42	153	40	463
Mean (SD)	1.3 (2.61)	1.1 (2.87)	1.3 (3.81)	3.3 (12.32)	1.4 (4.69)
Number of RBC transfusions, n†††					
Number of subjects	169	31	103	29	332
Mean (SD)	2.8 (1.91)	4.4 (4.98)	2.4 (1.63)	2.6 (1.35)	2.8 (2.31)
Number of RBC units transfused, n†††					
Number of subjects	169	31	103	29	332
Mean (SD)	4.7 (3.06)	7.6 (7.09)	4.3 (2.72)	4.1 (2.19)	4.8 (3.58)
Number of platelet transfusions, n†††					
Number of subjects	101	13	53	16	183
Mean (SD)	3.7 (4.11)	2.9 (2.74)	3.6 (5.61)	2.6 (1.85)	3.4 (1.59

Parameter	Azacitidine (N=241)	CCR			Total (N=488)
		BSC only (N=45)	LDAC (N=158)	IC (N=44)	
Number of platelet units transfused, n†††					
Number of subjects	101	13	53	16	183
Mean (SD)	18.0 (39.26)	6.0 (8.46)	6.9 (6.84)	10.7 (11.28)	13.3 (30.08)

Abbreviations: AML, acute myeloid leukaemia; BM, bone marrow; BSC, best supportive care; CCR, conventional care regimens; ECOG, Eastern Cooperative Oncology Group; IC, intensive chemotherapy; ITT, intent-to-treat; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; RBC, red blood cell; SD, standard deviation; WHO, World Health Organization.
† Two subjects received their formal AML diagnosis after informed consent, but prior to study treatment; ‡ status at randomisation; § includes -5, -7, 5q-, 7q-, 11q23 abnormalities, inv(3), t(3;3), t(6;9), t(9;23) and complex (≥abnormalities) that were not considered monosomal karyotype; ¶ includes -5, -7, 5q-, 7q-, 11q23 abnormalities, inv(3), t(3;3), t(6;9), and complex (≥abnormalities); †† includes t(9;22), and monosomal karyotype and are included in the poor-risk category based on National Comprehensive Cancer Network Guidelines; ‡‡ baseline as the last non-missing assessment on, or prior to the date of randomisation; §§ One subject had acute myelomonocytic leukaemia where the bone marrow differential was 18.5% blasts and 21.5 % promonocytes, for a total leukaemic cell count of 40%. The CRF did not allow the entry of the bone marrow promonocyte cell count; ¶¶ Subjects were randomized based on local pathology assessment of baseline bone marrow blast count. Baseline BM slides were retrospectively reviewed by the central pathology reviewer. In some cases, the baseline BM blast count was found to be less than 30% by the central pathology reviewer. These subjects were not removed from the study and were allowed to continue assigned treatment; ††† based on transfusion history for the 8 weeks immediately prior to randomisation.

4.5.2.3 Treatment exposure

The median number of azacitidine cycles received was 6 (range: 1–28). This was consistent with the AZA-AML-001 protocol recommendation to aim to treat patients with azacitidine for a minimum of 6 cycles. In the CCR group, the median number of LDAC cycles was 4 (range: 1–25). This compares favourably to the UK NCRI LI-1 study where the median duration of treatment with LDAC has consistently ranged from 2 to 3 cycles (17-20, 23, 82). The median number of IC cycles was 2 (range: 1–3), and the median duration of BSC was 65 days (range: 6–535 days). Six or more cycles of treatment were received in 52.5% of subjects in the azacitidine group and in 35.9% of subjects in the LDAC groups, and 12 or more cycles were received by 32.2% of subjects in the azacitidine group and in 17.6% of subjects in the LDAC group. Cumulative patient-years of study drug exposure were 174.9 for azacitidine, 82.9 for LDAC, 14.1 for IC, and 9.6 for BSC only.

4.6 *Quality assessment of the relevant randomised controlled trials*

Table 17: Quality assessment results for parallel group RCTs

	AZA-AML-001
Was randomisation carried out appropriately?	Yes Patients were randomised in a 1:1 ratio. Randomisation was performed using an IVRS. Patients were stratified at randomisation by: • CCR selection (IC, LDAC or BSC), • ECOG performance status at baseline (0–1 versus 2) • cytogenetics (intermediate-risk versus poor-risk)
Was the concealment of treatment allocation adequate?	Open-label study. Blinding of study treatment was not feasible due to multiple comparators and routes of administration. However, all central reviewers were blinded to subject treatment assignment.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Patient demographics in the azacitidine and combined CCR groups were well balanced in terms of age, age distribution, sex, geographic location, race, weight and BSA. The azacitidine and combined CCR groups were also comparable for all baseline disease characteristics (including AML classification, prior history of MDS, time since AML diagnosis, ECOG performance status and cytogenetic status), with the exception of prior anticancer systemic therapies.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Although the trial was open-label, all central reviewers were blinded to subject treatment assignment. Evaluations by central review were used for the statistical efficacy analyses. The independent review committee which reviewed and confirmed the haematologic responses and durations was blinded to treatment, investigative site, and subject identifier.
Were there any unexpected imbalances in drop-outs between groups?	No. The most common reasons for discontinuation from the treatment phase in both the azacitidine and CCR groups were occurrence of an AE (36.9% and 26.7%, respectively) or death (22.0% and 23.5%, respectively). Discontinuations due to occurrence of an AE or study closure were more common in the azacitidine group whereas discontinuations due to withdrawal of consent were more common in the CCR group, with the highest percentage in the BSC group. The percentages of subjects who were discontinued from treatment because of death or disease progression were comparable between the azacitidine and the CCR treatment groups. No subject discontinued due to loss of follow-up or protocol violation in the azacitidine group. One subject discontinued due to loss of follow-up in the IC group and one subject discontinued due to protocol violation in the LDAC treatment group.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All treatment outcomes were reported other than those that are not currently available for analysis (exploratory molecular markers).
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The ITT population was used for the analysis of the primary and secondary efficacy endpoints. The ITT population was the most appropriate population as it included all randomised patients.

Abbreviations: AE, adverse event; AML, acute myeloid leukaemia; BSA, body surface area; BSC, best supportive care; CCR, conventional care regimens; IC, intensive chemotherapy; ITT, intent-to-treat; IVRS, interactive voice recognition system; LDAC, low-dose cytarabine; MDS, myelodysplastic syndromes. Clinical effectiveness results of the relevant randomised controlled trials.

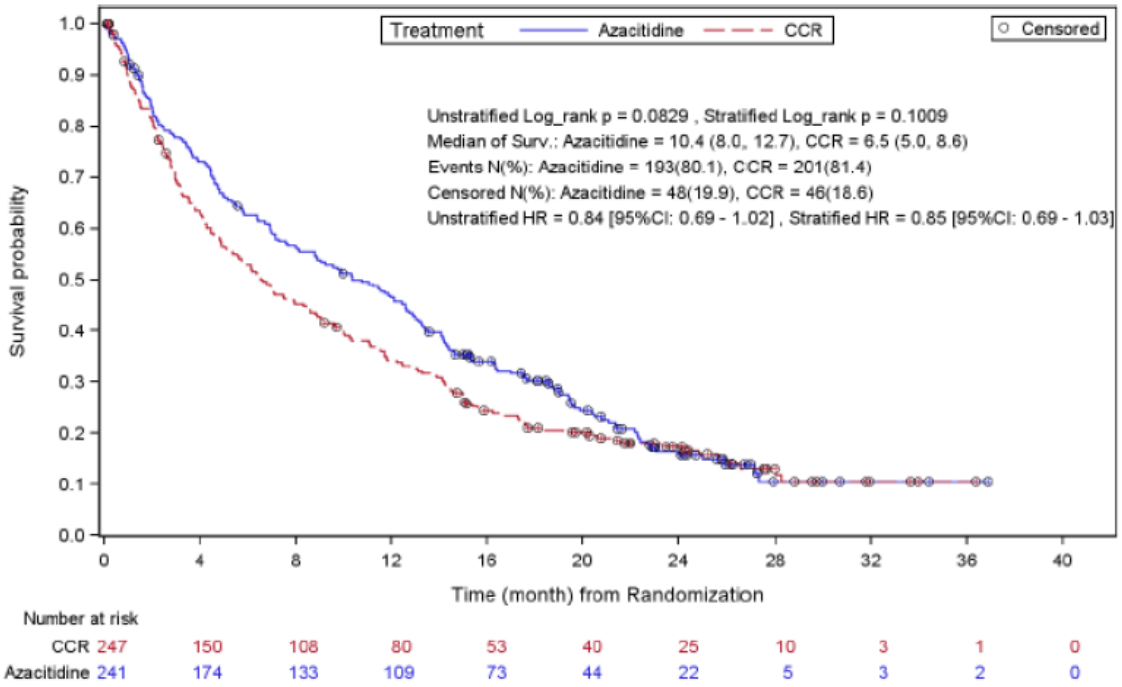
4.7 *Clinical effectiveness results (AZA-AML-001)*

4.7.1 *Primary efficacy analysis – overall survival*

The median duration of follow up was 24.4 months. Overall, 394 deaths (80.7%) occurred in the ITT population: 193 (80.1%) in the azacitidine group and 201 (81.4%) in the CCR group. The KM plot of time to death from any cause is presented in Figure 8 and a summary of OS is presented in Table 18. The primary OS analysis was performed with and without stratification. Stratification minimises the potential for bias by restricting comparisons to more homogeneous patient groups. Pre-specified stratification factors were: preselected CCR (IC versus LDAC or BSC); ECOG performance status (0–1 versus 2); and cytogenetic risk (intermediate versus poor).

- After a median follow-up time of 24.4 months, the median OS was 10.4 months (95% CI: 8.0, 12.7) in the azacitidine group (N=241) compared with 6.5 months (95% CI: 5.0, 8.6) in the CCR group (N=247), with a clinically meaningful benefit in OS of 3.8 months with azacitidine treatment.
- The azacitidine group had a 15% reduced risk of death compared with subjects in the CCR group (stratified HR= 0.85; 95% CI: 0.69, 1.03).
- Although there was a clinically meaningful improvement in the azacitidine group, the log-rank test did not meet the predefined level of significance (stratified p=0.1009 and unstratified p= 0.083).
- The survival curves show clear separation between 2 and 22 months, with convergence thereafter. The convergence of the curves is not unexpected in a condition without a curative therapy and a poor prognosis. The lack of statistical significance in OS may reflect the convergence and the statistical methods used to compare the OS curves. As with most randomised trials, the log-rank test was used to compare OS. This is a non-parametric test that compares proportions of patients surviving across the whole follow-up period; in this trial subjects were to be followed up until death, withdrawal of consent or study termination. The test does not compare survival at discrete time points, e.g. after one year (83). Therefore, data collected after 2 years' follow-up (when the curves converged) were included when calculating overall hazard ratios (HRs) and p value.
- Additional pre-defined analyses were used to explore the impact of various parameters on OS curves (Section 4.7.2).

Figure 8: Kaplan-Meier plot of overall survival



Abbreviations: CCR, conventional care regimens; CI, confidence interval; HR, hazard ratio.

Table 18: Summary of overall survival in the ITT population

	Azacitidine (N=241)	CCR (N=247)
Event, n (%)	193 (80.1)	201 (81.4)
Censored, n (%)	48 (19.9)	46 (18.6)
Median OS (95% CI), months†	10.4 (8.0, 12.7)	6.5 (5.0, 8.6)
Difference (95% CI), months†	3.8 (1.0, 6.5)	
HR [AZA:CCR] (95% CI)‡	0.85 (0.69, 1.03)	
Stratified log-rank test: p-value§	0.1009	
HR [AZA:CCR] (95% CI)¶	0.84 (0.69, 1.02)	
Unstratified log-rank test: p-value††	0.0829	
1-year survival, % (95% CI)	46.5 (40.1, 52.7)	34.3 (28.3, 40.3)
Difference, % (95% CI)	12.3 (3.5, 21.0)	

Abbreviations: AZA, azacitidine; CCR, conventional care regimens; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; KM, Kaplan Meier; OS, overall survival; PH, proportional hazards.
† median, 25th, and 75th percentile estimates of OS are from an unstratified KM analysis. Differences were calculated as AZA:CCR. The CIs for the differences were derived using Kosorok's method; ‡ the HR is from a Cox PH model stratified by ECOG performance status and cytogenetic risk status; § p-value is two-sided from a log-rank test stratified by ECOG performance status, and cytogenetic risk status; ¶ the HR is from an unstratified Cox PH model; †† p-value is two-sided from an unstratified log-rank test; ‡‡ CI for the difference in the 1-year survival probabilities was derived using Greenwood's variance estimate.

4.7.2 *Sensitivity analyses*

4.7.2.1 Evaluable population

In the evaluable population (N=370), 146 (81.6%) deaths were reported in subjects treated with azacitidine and 157 (82.2%) deaths in subjects treated with CCR. The median OS was 9.2 months (95% CI: 7.0, 12.6) in the azacitidine group (N=179) compared with 7.1 months (95% CI: 5.6, 9.6) in the CCR group (N=191), with a HR of 0.93 (95% CI: 0.74, 1.17) and two-sided p=0.5239 based on a stratified log-rank test. Similar results were obtained when evaluated using the unstratified log-rank test.

4.7.2.2 Modified intent-to-treat population (post-hoc)

Considering the criteria used to select the evaluable population were very restrictive, a post-hoc analysis for the OS endpoint was conducted in a mITT population, with less extensive criteria than for the evaluable population. In the mITT population (N=446), 175 (80.3%) deaths were reported in subjects treated with azacitidine and 190 (83.3%) deaths in subjects treated with CCR. Results in the mITT population were comparable with the primary analysis (ITT), median OS was 10.4 months (95% CI: 8.0, 12.9) in the azacitidine group (N=218) compared with 6.4 months (95% CI: 4.9, 8.8) in the CCR group (N=228), with a HR of 0.84 (95% CI: 0.69, 1.04) and two-sided p=0.1088 based on a stratified log-rank test. Similar results were recorded using an unstratified log-rank test.

4.7.2.3 Analyses to evaluate any impact of subjects receiving other cancer therapy after study therapy

Subsequent therapies can be a major problem in cancer trials using OS as a primary endpoint, particularly given the recent rise in experimental treatment options (30). This was recognised during the design of this trial; consequently, it was pre-specified that OS would also be analysed after censoring patients for treatment following the discontinuation of trial drug. This means that once patients started a subsequent therapy, although they were included in the OS analysis up to this time point (considered a patient at risk), they were precluded from subsequent analysis. This allows for a more rigorous comparison of the effects of the two treatment arms on OS.

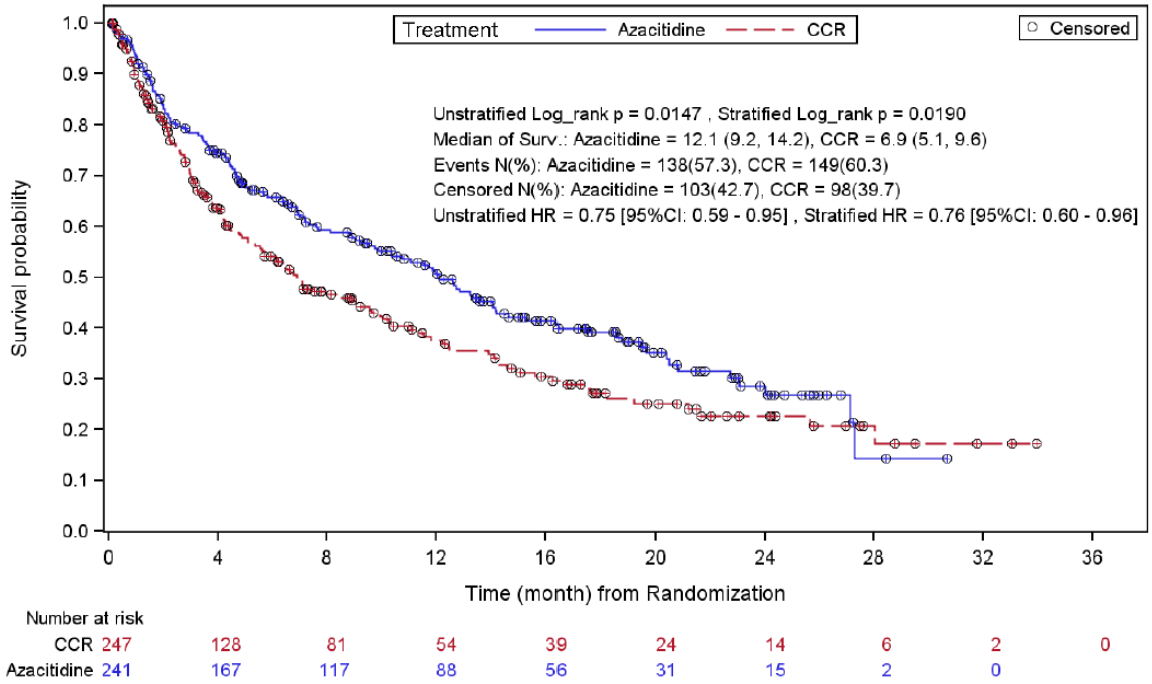
A total of 69 patients (28.6%) in the azacitidine group and 75 patients (30.4%) in the CCR group received subsequent AML therapy after discontinuing randomised study treatment. Subjects treated with azacitidine received mainly cytarabine (40 out of 67 subjects, 59.7%) as subsequent therapy, whereas subjects treated with CCR mainly received azacitidine (32 out of 74 subjects, 43.2%).

Censoring for the use of any subsequent therapy for AML

When censoring on the date of first subsequent therapy, median OS was increased in the azacitidine group (12.1 months; 95% CI: 9.2, 14.2) compared with the CCR group (6.9 months; 95% CI: 5.1, 9.6), with a HR of 0.76 (95% CI: 0.60, 0.96) and a two-sided p=0.0190, based on a stratified log-rank test. Similar results were obtained when using unstratified data (Table 19). The results from this analysis support the OS benefit of azacitidine compared with CCR and shows the robustness of the results of the primary analysis. In particular, these results indicate that subsequent therapy may be one confounding factor in the assessment of the treatment effect on OS between azacitidine and CCR in the primary analysis, resulting in an underestimation of the treatment effect

of azacitidine. Approximately 30% of subjects received subsequent AML treatment, and of these, 59.7% subjects treated with azacitidine received cytarabine as subsequent therapy, whereas 43.2% subjects treated with CCR received azacitidine.

Figure 9: Kaplan-Meier plot of overall survival censored for first subsequent AML therapy



Abbreviations: CCR, conventional care regimens; CI, confidence interval; HR, hazard ratio.

Table 19: Summary of sensitivity analyses on overall survival (ITT)

	Azacitidine	CCR
Censored for subsequent AML therapy		
Median OS (95% CI), months	12.1 (9.2, 14.2)	6.9 (5.1, 9.6)
HR [AZA:CCR] (95% CI)	0.76 (0.60, 0.96)	
Stratified log-rank test: p-value	0.0190	
HR [AZA:CCR] (95% CI)	0.75 (0.59, 0.95)	
Unstratified log rank test: p value	0.0147	

Abbreviations: AZA, azacitidine; CCR, conventional care regimens; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

Sensitivity analysis conclusion: All sensitivity analyses support the OS benefit of azacitidine versus CCR. The analysis where subjects were censored for use of any subsequent AML therapy suggests that subsequent therapy may be one confounding factor in the assessment of OS benefit of azacitidine compared with CCR.

4.7.3 *Exploratory analyses*

4.7.3.1 Azacitidine versus individual conventional care regimens

AZA-AML-001 was not designed so that azacitidine could be compared to the individual components of the CCR arm meaningfully. However, this was evaluated in an

exploratory analysis that was not powered to detect statistical differences between treatments.

Median OS was longer in each of the azacitidine groups compared with the corresponding BSC (5.8 versus 3.7 months, respectively; p=0.0288) and LDAC groups (11.2 versus 6.4 months, respectively; p=0.4270) and similar to the IC group (13.3 versus 12.2 months, respectively; p=0.5032) (Table 20). The largest difference in OS between azacitidine and CCR occurred within the LDAC pre-selection group (4.8 months), although the difference was not statistically significant.

Table 20: Summary of time to death within CCR selection (ITT)

	BSC		LDAC		IC	
	Azacitidine (N=44)	CCR (N=45)	Azacitidine (N=154)	CCR (N=158)	Azacitidine (N=43)	CCR (N=44)
Events, n (%)	38 (86.4)	42 (93.3)	124 (80.5)	126 (79.7)	31 (72.1)	33 (75.0)
Median OS, months (95% CI)†	5.8 (3.6, 9.7)	3.7 (2.8, 5.7)	11.2 (8.8, 13.4)	6.4 (4.8, 9.1)	13.3 (7.2, 19.9)	12.2 (7.5, 15.1)
HR (95% CI)‡	0.60 (0.38, 0.95)		0.90 (0.70, 1.16)		0.85 (0.52, 1.38)	
Unstratified log-rank test: p-value §	0.0288		0.4270		0.5032	
1-year survival, % (95% CI)	30.3 (17.5, 44.2)	18.6 (8.7, 31.4)	48.5 (40.3, 56.2)	34.0 (26.6, 41.6)	55.8 (39.8, 69.1)	50.9 (35.2, 64.6)
Difference, % (95% CI)	11.7 (-6.3, 29.8)		14.5 (3.5, 25.5)		4.9 (-16.2, 26.0)	

Abbreviations: BSC, best supportive care; CCR, conventional care regimens; CI, confidence interval; HR, hazard ratio; IC, intensive chemotherapy; KM, Kaplan Meier; LDAC, low-dose cytarabine; OS, overall survival; PH, proportional hazards.
† median, 25th, and 75th percentile estimates of OS are from an unstratified KM analysis. Differences are calculated as AZA:CCR. The CIs for the differences were derived using Kosorok's method; ‡ HR is from an unstratified Cox PH model; § p-value is two-sided from an unstratified log-rank test.

4.7.4 *Post-hoc analyses: impact of subsequent therapy and/or baseline characteristics*

4.7.4.1 Estimate of treatment effect on overall survival by adjusting for baseline covariates and/or subsequent therapy (post-hoc)

In order to assess the possible impact of heterogeneity within the study population and confounding due to subsequent therapy, three methods – Cox PH models, IPCW, and regression based imputation method – were used to estimate the treatment effect for azacitidine versus CCR on OS by adjusting for various baseline covariates and/or for subsequent therapy received following trial drug treatment.

Of the predefined subgroups, the baseline factors that contributed most to the heterogeneity of the AML population and were therefore included in the Cox PH models were cytogenetic risk, ECOG performance status, BM blast count, investigator

preselection of CCR, geographic region, age, and AML WHO classification. The baseline factors of white blood cell (WBC) count, prior history of MDS, and gender did not meet the criteria for selection into the model.

Cox PH

Using the Cox PH models, azacitidine was shown to statistically significantly improve OS versus CCR, with a 25% reduced risk of death when adjusting for subsequent therapy, and 31% reduced risk of death when adjusting for subsequent therapy and baseline characteristics. HRs for azacitidine versus CCR were:

- 0.75 (95% CI: 0.59, 0.94; p=0.0130) when adjusted for subsequent therapy (but not baseline characteristics)
- 0.80 (95% CI: 0.66, 0.99; p=0.0355) when adjusted for baseline characteristics
- 0.69 (95% CI: 0.54, 0.88; p=0.0027) when adjusted for subsequent therapy and baseline characteristics (Table 21).

IPCW adjusted Cox PH

Results of the IPCW analysis are shown in Table 21. The calculations are explained in detail in section 5.3. In the IPCW analysis following the NICE DSU TSD16 guidance, which adjusted for the influence of subsequent therapy in only the CCR treatment arm, the HRs for azacitidine versus CCR were XXX when adjusted, and XXX when not adjusted for baseline characteristics. The IPCW analysis adjusted in both treatment arms generated similar statistically significant results.

Table 21: Post-hoc overall survival estimates adjusted for baseline characteristics and/or subsequent therapy

Estimation method	HR (AZA vs CCR)	95% CI for HR	p-value
Cox-PH unadjusted for baseline characteristics			
Adjusted for subsequent therapy (time dependent) – Model 1	0.75	0.59, 0.94	0.0130
Cox-PH adjusted for baseline characteristics			
Unadjusted for subsequent therapy – Model 2	0.80	0.66, 0.99	0.0355
Adjusted for subsequent therapy (time dependent) – Model 3	0.69	0.54, 0.88	0.0027
IPCW Cox-PH Models – adjusted in the CCR arm[†]			
Unadjusted for baseline characteristics	XXX	XXX	XXX
Adjusted for baseline characteristics	XXX	XXX	XXX
IPCW Cox PH Models – adjusted in both treatment arms			
Unadjusted for baseline characteristics	0.77	0.61, 0.98	0.0310
Adjusted for baseline characteristics	0.71	0.56, 0.90	0.0047

AZA, azacitidine; CCR, conventional care regimens; CI, confidence interval; HR, hazard ratio; IPCW, Inverse Probability of Censoring Weighted; PH, proportional hazards.

† In line with DSU TSD16, adjustment for subsequent therapy was only applied to the comparator arm (CCR); ‡ For regulatory purposes, adjustments for subsequent therapy was applied to both treatment arms.

Regression based imputation analysis adjusting for subsequent therapy

The adjusted median OS was significantly improved in the azacitidine group (11.7 months; 95% CI: 8.8, 13.3) compared with the CCR group (6.5 months; 95% CI: 4.9, 8.3), with a HR of 0.76 (95% CI: 0.62, 0.93) and with a log-rank p value of 0.007.

4.7.4.2 Impact of subsequent therapy on overall survival (post-hoc)

Two further analyses were performed comparing OS between the azacitidine and CCR group in subjects who did not receive any subsequent therapy (approximately 70% of subjects) and in subjects who received subsequent therapy (approximately 30% of subjects). In subjects who did not receive subsequent AML therapy, OS was statistically significantly improved with azacitidine: the median OS was 6.9 months (95% CI: 4.8, 9.7) in the azacitidine group (N=174) versus 4.0 months (95% CI, 3.0, 5.1) in the CCR group (N=172) (HR 0.69; 95% CI: 0.55, 0.87; p=0.0019, stratified log-rank).

In subjects who received subsequent AML therapy, the median OS was 16.3 months (95% CI: 13.3, 19.0) in the azacitidine group (N=67) versus 15.1 months (95% CI: 12.8, 20.3) in the CCR group (N=75) (HR = 1.20, 95% CI: 0.81, 1.77; p=0.3542, stratified log-rank). Subjects in both the azacitidine and CCR treatment groups who received subsequent therapy had a longer OS than those subjects who did not receive subsequent therapy.

A further analysis on all randomised subjects censoring for subsequent cytarabine-based therapy in the azacitidine group and subsequent azacitidine in the CCR group, assessed the impact of specific subsequent therapies. In this analysis, the median OS was 11.9 months (95% CI: 8.9, 14.1) in the azacitidine group versus 6.6 months (95% CI: 5.1, 9.0) in the CCR group (HR: 0.76; 95% CI: 0.62, 0.95; p=0.0132).

Conclusion from post-hoc analyses: These analyses suggest that both baseline heterogeneity and subsequent AML therapy may have confounded the primary endpoint of OS. Adjusting for these factors demonstrated that azacitidine was associated with significant improvement in survival benefit compared with CCR.

4.7.5 *Secondary efficacy endpoints*

A summary of 1-year survival can be found in Table 18 and Table 20. A summary of the remaining secondary efficacy endpoints for azacitidine versus CCR can be found in Table 22 and based on investigators pre-selection in Table 23.

Table 22: Secondary endpoints: azacitidine versus CCR

	Azacitidine (N=241)		CCR (N=247)		HR	95% CI	p value
	N	%	N	%			
Death estimates							
30-day	16	6.6	25	10.1	–	–	–
60-day	39	16.2	45	18.2	–	–	–
Haematologic response†							
CR + CRi	67	27.8	62	25.1	–	–	0.5384
CR	47	19.5	54	21.9	–	–	0.5766
CRc-20	5	2.1	14	5.7	–	–	0.0589
PR	3	1.2	3	1.2	–	–	1.0
Progressive disease	20	8.3	20	8.1	–	–	1.0
Stable disease	71	29.5	59	23.9	–	–	0.1833
Other secondary endpoints							
EFS‡							
Median, months	6.7		4.8		0.87	0.72, 1.05	0.1495
RFS							
Median, months	9.3		10.5		1.11	0.75, 1.66	0.5832
Relapse after CR or CRi	43	63.2	35	56.5	–	–	0.4712
Duration of remission							
Median, months	10.4		12.3		–	–	–
Transfusion independence§							
RBC	65	38.5	45	27.6	–	–	–
Platelets	41	40.6	24	29.3	–	–	–

Abbreviations: CCR, conventional care regimens; CI, confidence interval; CR, complete response; CRc-20, complete cytogenetic remission in at least 20 metaphases; CRi, complete remission with incomplete blood count recovery; EFS, event-free survival; PR, partial remission; RBC, red blood cell; RFS, relapse-free survival.
† defined by International Working Group criteria and was adjusted by an independent review committee; ‡ events included treatment failure, progressive disease, relapse after CR or CRi, or death; § defined as no transfusions for 56 consecutive days on study for patients who were transfusion dependent at baseline.

Table 23: Secondary endpoints – investigators pre-selection

	BSC					LDAC					IC				
	AZA (N=44)	CCR (N=45)	HR	95% CI	p value	AZA (N=154)	CCR (N=158)	HR	95% CI	p value	AZA (N=43)	CCR (N=44)	HR	95% CI	p value
Haematologic response, n (%)[†]															
CR + CRi	7 (15.9)	0 (0.0)	–	–	–	42 (27.3)	41(25.9)	–	–	–	18 (41.9)	21 (47.7)	–	–	–
CR	6 (13.6)	0 (0.0)	–	–	–	28 (18.2)	38 (24.1)	–	–	–	13 (30.2)	16 (36.4)	–	–	–
CRc-20	1 9 (2.3)	0 (0.0)	–	–	–	3 (1.9)	8 (5.1)	–	–	–	1 (2.3)	6 (13.6)	–	–	–
PR	0 (0.0)	0 (0.0)	–	–	–	3 (1.9)	1 (0.6)	–	–	–	0 (0.0)	2 (4.5)	–	–	–
Progressive disease	4 (9.1)	5 (11.1)	–	–	–	10 (6.5)	14 (8.9)	–	–	–	6 (14.0)	1 (2.3)	–	–	–
Stable disease	14 (31.8)	6 (13.3)	–	–	–	47 (30.5)	46 (29.1)	–	–	–	10 (23.3)	7 (15.9)	–	–	–
Other secondary endpoints[‡]															
EFS															
Median, months	4.5	3.1	0.67	0.43, 1.04	0.0756	7.3	4.8	0.89	0.70, 1.13	0.3563	8.1	9.7	1.02	0.64, 1.63	0.9196
RFS															
Median, months	–	–	–	–	–	8.6	9.9	1.11	0.68, 1.81	0.6638	10.8	12.1	1.21	0.58, 2.51	0.6135
Relapse after CR or CRi, n (%)	2 (28.6)	N/A	–	–	–	31 (73.8)	25 (61.0)	–	–	–	10 (55.6)	10 (47.6)	–	–	–

	BSC					LDAC					IC				
	AZA (N=44)	CCR (N=45)	HR	95% CI	p value	AZA (N=154)	CCR (N=158)	HR	95% CI	p value	AZA (N=43)	CCR (N=44)	HR	95% CI	p value
Duration of remission															
Median, months	N/A	N/A	–	–	–	17.3	19.8	–	–	–	17.3	19.8	–	–	–

Abbreviations: AZA, azacitidine; CCR, conventional care regimens; CI, confidence interval; CR, complete response; CRc-20, complete cytogenetic remission in at least 20 metaphases; CRi, complete remission with incomplete blood count recovery; EFS, event-free survival; PR, partial remission; RBC, red blood cell; RFS, relapse-free survival.
† defined by International Working Group criteria and was adjusted by an independent review committee; ‡ events included treatment failure, progressive disease, relapse after CR or CRi, or death.

4.7.5.1 1-year survival

- Azacitidine improved 1-year survival compared with CCR (46.5% vs. 34.3%, respectively), resulting in a clinically meaningful difference of 12.3% in favour of azacitidine (95% CI: 3.5, 21.0).
- 1-year survival was also improved for azacitidine when compared with each of the CCR therapies (within investigator pre-selection) (BSC only: 30.3% vs. 18.6%, LDAC: 48.5% vs. 34.0%, and IC: 55.8% vs. 50.9%, respectively), and in a post-hoc analysis, when compared with BSC plus LDAC (within investigator pre-selection) (44.5% vs. 30.6%, respectively).
- Results for azacitidine versus CCR were similar in the evaluable population (44.2% vs. 36.8%, respectively), in the mITT population (46.9% vs 34.6%, respectively), and in the post-hoc regression-based imputation analysis (48.3% vs. 33.4%, respectively).
- When excluding subjects where their best response was a CR, the 1-year survival estimate was 33.8% in the azacitidine group and 20.4% in the CCR group.

All analyses, pre-specified or post-hoc, showed a consistent 1-year survival benefit in favour of azacitidine when compared with CCR.

4.7.5.2 30-day and 60-day death estimates

The 30-day and 60-day KM death estimates were 6.6% and 16.3%, respectively in the azacitidine group and 10.3% and 18.6%, respectively in the CCR group.

4.7.5.3 Event-free survival

Overall, 212 (88.0%) events (defined as treatment failure, progressive disease, relapse after CR or CRi, death from any cause, or loss to follow-up) were reported in subjects treated with azacitidine and 216 (87.4%) events in subjects treated with CCR.

There was a trend for improved EFS with azacitidine when compared with CCR. The median EFS was 6.7 months in the azacitidine treatment group and 4.8 months in the CCR treatment group (HR: 0.87; 95% CI: 0.72, 1.05; p=0.1495).

When considering investigator pre-selection, median EFS was:

- 4.5 months for azacitidine (BSC pre-selected) and 3.1 months for BSC (HR: 0.67; 95% CI: 0.43, 1.04; p=0.0756)
- 7.3 months for azacitidine (LDAC pre-selected) and 4.8 months for LDAC (HR: 0.89; 95% CI: 0.70, 1.13; p=0.3563)
- 8.1 months for azacitidine (IC pre-selected) and 9.7 months for IC (HR: 1.02; 95% CI: 0.64, 1.63; p=0.9196)

4.7.5.4 Relapse-free survival

In subjects with CR or CRi, 53 (79.1%) events (relapse or death from any cause) were reported in the azacitidine arm and 47 (75.8%) events in the CCR arm.

No difference was observed for RFS between treatment groups; median RFS was 9.3 months in the azacitidine group compared with 10.5 months in the CCR group (HR: 1.11; 95% CI: 0.75, 1.66; p=0.5832).

When considering investigator pre-selection:

- No subjects pre-selected and randomised to BSC achieved a CR or CRi.
- Median RFS was 8.6 months for azacitidine (LDAC pre-selected) compared with 9.9 months for LDAC (HR: 1.11; 95% CI: 0.68, 1.81; p=0.6638).
- Median RFS was 10.8 months for azacitidine (IC pre-selected) compared with 12.1 months for IC (HR: 1.21; 95% CI: 0.58, 2.51; p=0.6135).

4.7.5.5 Haematologic response and duration of remission

Overall response rates (CR+CRi) were comparable between treatment groups (27.8% in the azacitidine group vs 25.1% in the CCR group), as were rates of CR, PR, stable disease, progressive disease and cytogenetic complete remission (Table 22). In subjects who achieved a CR or CRi, the median duration of remission was 10.4 months for the azacitidine subjects and 12.3 months for CCR subjects. The rate of relapse after CR or CRi was 64.2% in the azacitidine group and 56.5% subjects in the CCR group. The 1-year cumulative relapse estimate was 52.2% in the azacitidine group versus 46.6% in the CCR treatment group.

In the individual components of the CCR arm, the rate of CR/CRi was: 15.9% vs 0% for azacitidine vs. BSC, respectively; 27.3% vs 25.9% for azacitidine vs. LDAC, respectively; 41.9% vs. 47.7% for azacitidine vs. IC, respectively (Table 23).

4.7.5.6 Overall survival according to haematologic response (post-hoc)

When excluding subjects who achieved a CR (47 and 54 patients in the azacitidine and CCR arms, respectively), median OS in the azacitidine group was 6.9 months compared with 4.2 months in the CCR group (HR: 0.76; 95% CI: 0.61, 0.94, p=0.017). When excluding subjects with a best response of CR, CRi, and PR, the median OS was 5.5 months in the azacitidine groups versus 4.0 months in the CCR group (HR: 0.86; 95% CI: 0.69, 1.07).

4.7.5.7 Transfusion status

A higher proportion of patients in the azacitidine treatment group who were transfusion dependent at baseline achieved RBC transfusion independence during treatment compared with CCR (38.5% vs. 27.6%, respectively). Similar results were obtained in those who were transfusion dependent at baseline and became platelet transfusion independent during treatment (40.6% vs. 29.3%, respectively).

With comparable baseline rates of RBC transfusion dependence, the total number of subjects who remained or became independent of transfusions while on treatment was 105 (43.6%) in the azacitidine group and 76 (30.8%) in the CCR group. With slightly higher baseline rates of platelet transfusion dependence in the azacitidine group (41.9% versus 33.2%), the total number of subjects who remained or became independent of platelet transfusions was 142 (58.9%) in the azacitidine group and 106 (42.9%) in the CCR group.

There were a greater proportion of subjects in the azacitidine group versus those receiving BSC only or IC who were RBC transfusion dependent at baseline and became transfusion independent during treatment. Similar analysis evaluating platelet transfusion dependence showed a greater proportion of subjects receiving azacitidine versus those receiving BSC only or LDAC who were transfusion dependent at baseline became platelet transfusion independent during treatment.

4.7.5.8 Health-related quality of life

HRQoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (78), which was to be completed by each patient at baseline, on day 1 of every other cycle and at the end-of-study visit. The HRQoL evaluable population included patients with a baseline assessment, and at least one post-baseline assessment and initially comprised 291 patients (azacitidine, N=157; CCR, N=134) (Table 24). This patient population decreased in size over time in both groups, but more rapidly in the CCR arm after cycle 3, and there was large variation in QLQ-C30 responses within each treatment group.

The primary HRQoL endpoint was change in fatigue score; dyspnoea, physical functioning and global health status were included as secondary HRQoL endpoints. These domains either improved or did not deteriorate from baseline scores over 9 treatment cycles in both arms (Figure 10; tabulated data presented in Appendix 4). The few changes that met the minimally important difference threshold were fatigue (cycles 7 and 9) and global health status/QoL (cycle 9) in the CCR group. Generally, some degree of deterioration from baseline was observed in both groups by the time of the end-of-study visit, which occurred at different time points for each patient. A mixed model analysis failed to reveal any statistically significant differences in the impact of treatment on all domains between treatment arms.

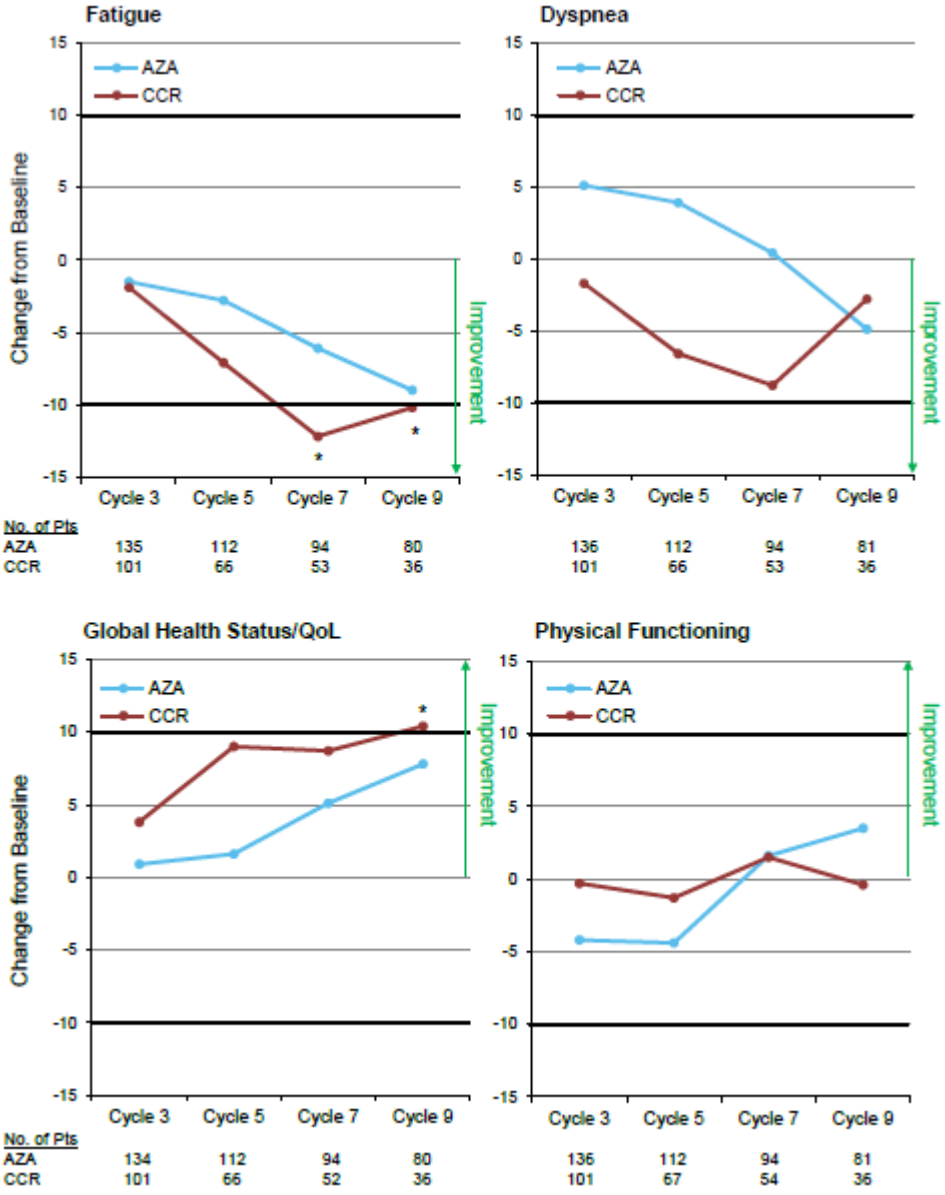
In conclusion, there was no meaningful HRQoL deterioration associated with prolongation of OS in the azacitidine group during treatment. Further, azacitidine and CCR were associated with general improvement in HRQoL in the four pre-specified QLQ-C30 domains of fatigue, dyspnoea, global health status and physical functioning.

Table 24: HRQoL assessment rates

HRQoL assessment	AZA (n=241)			CCR (n=247)		
	Treated	Assessed†	Evaluable	Treated	Assessed†	Evaluable
Cycle 1 (Baseline)	237	210 (89)	157 (66)	236	210 (89)	134 (57)
Cycle 3	174	152 (87)	137 (79)	131	113 (86)	102 (78)
Cycle 5	146	127 (87)	112 (77)	86	72 (84)	67 (78)
Cycle 7	118	105 (89)	94 (80)	67	58 (87)	54 (81)
Cycle 9	98	89 (91)	81 (83)	49	38 (78)	36 (73)

Abbreviations: AZA, azacitidine; CCR, conventional care regimens; CI, confidence interval; HR, hazard ratio.
† HRQOL assessment rates = number of patients with an EORTC QLQ-C30 assessment ÷ the total number of patients receiving treatment at the scheduled cycle visit. Numbers reported in this table represent all HRQOL assessments at each cycle; some patients may not be included in HRQL analyses due to missing baseline HRQOL assessments. Evaluable patients completed an HRQL assessment at baseline and had ≥ 1 post-baseline assessment.

Figure 10: Mean absolute score change from baseline for primary and secondary HRQoL endpoints (HRQoL evaluable population)



Abbreviations: AZA, azacitidine; CCR, conventional care regimens.
Decreasing scores indicate improvement in the Fatigue and Dyspnoea domains of the QLQ-C30, and increasing scores indicate improvement in the Physical Function and Global Health Status/QoL domains.
The minimally important difference, defined as a mean change of at least 10 points from baseline and representing a clinically meaningful effect is denoted by bold black lines at 10 and -10 on the y-axis. *Met the threshold for minimally important difference.

4.8 *Subgroup analysis*

4.8.1 *Methodology*

Due to the known heterogeneity of the AML population, well established patient- and disease-related prognostic factors were identified prospectively in the trial protocol. Data were collected at baseline and subgroup analyses on OS were pre-specified in the statistical analysis plan. Overall survival was analysed and summarised separately within each subgroup using KM and Cox PH methods as described in Section 4.4.4, but without

stratification. Variables included in the analysis which are of relevance to the decision problem were baseline cytogenetic risk status and WHO classification of AML. The full list of variables included in the univariate analysis were:

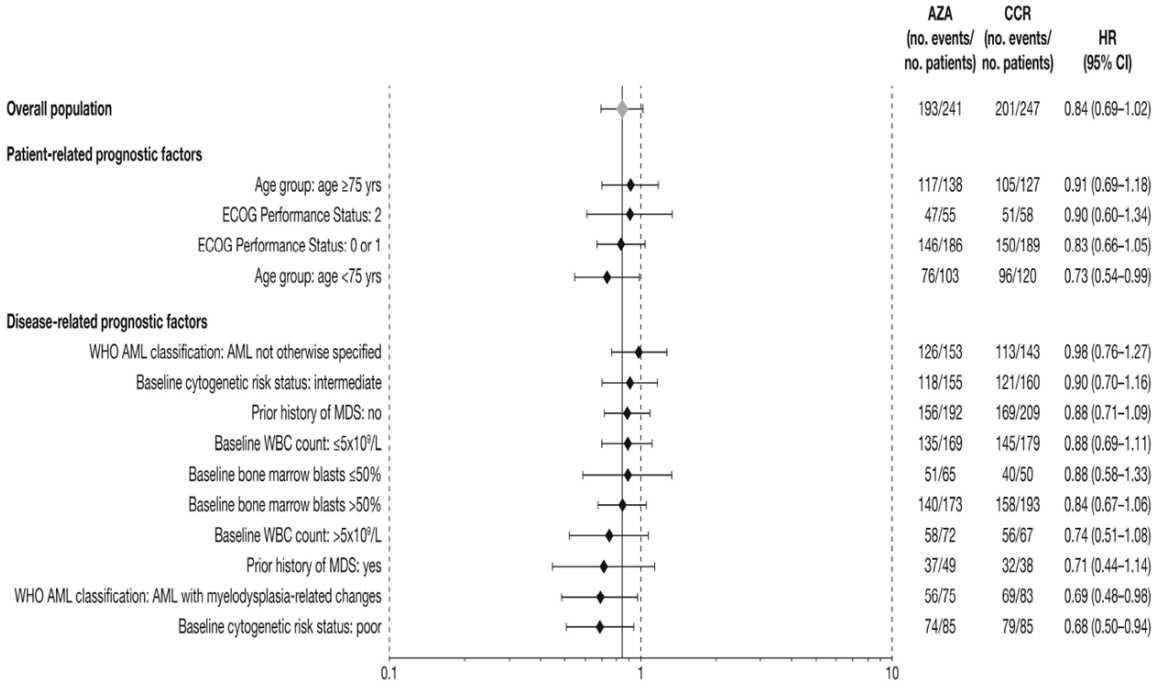
- Age group (<75 and ≥75 years old)
- Gender
- Race (White, Asian, others)
- ECOG performance status (0–1, 2)
- Baseline cytogenetic risk status (intermediate or poor)
- Geographic region (North America [US and Canada]/Australia, Western Europe [Germany, Italy, France, United Kingdom, Spain, Austria, Belgium, The Netherlands]/ Israel, Eastern Europe [Poland, Russia, and Czech Republic], Asia [China, South Korea, and Taiwan]
- WHO classification (AML with recurrent genetic abnormalities, AML with MDS-related changes, therapy-related myeloid neoplasms, and AML not otherwise specified)
- Baseline WBC count (≤5x10^9/L or >5x10^9/L)
- Baseline percentage BM blasts (≤50% or >50%)
- Prior history of MDS (yes or no)

4.8.2 *Results*

Figure 11 shows the results of the univariate analysis, illustrating the HR for each patient-related or disease-related prognostic factor. There was a consistent trend in OS benefit across all pre-specified subgroups in favour of azacitidine. The strongest effect was seen in patients with MDS-related changes, and in those with a baseline cytogenetic risk rated as poor. In subjects with MDS-related changes, the median OS was 12.7 months in those receiving azacitidine and 6.3 months in those receiving CCR (HR: 0.69; 95% CI: 0.48, 0.98; p=0.0.357). In subjects with a baseline cytogenetic risk rated as poor, the median OS was 6.4 months in those receiving azacitidine and 3.2 months in those receiving CCR (HR: 0.68; 95% CI: 0.68, 0.94; p=0.0185). There was also a statistically significant effect of age, gender, and race.

Tabulated results for all sub-groups are available in Appendix 5.

Figure 11: Overall survival by patient related- or disease-related prognostic factor: azacitidine versus CCR



Abbreviations: AML, acute myeloid leukaemia; AZA, azacitidine; CCR, conventional care regimens; CI confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MDS- myelodysplastic syndromes; WBC, white blood cell.
Plot shows HRs for patient-related and disease-related prognostic factors only. Analysis for all sub-groups is provided in Appendix 5.

4.9 *Meta-analysis*

A meta-analysis was not performed.

4.10 *Indirect and mixed treatment comparisons*

The pivotal trial for this submission included all data on the relevant population and comparators of interest, in line with the decision problem. Therefore, an indirect and mixed treatment comparison is not considered in this submission.

4.11 *Non-randomised and non-controlled evidence*

No observational studies were identified in the systematic review described in Section 4.1 that specifically evaluated the population of relevance to the decision problem (>30% blasts). However, one observational study (69) was identified in the systematic review which considered a broader population (>20% blast) but provided a subgroup analysis of the population of relevance (>30% blasts). This study by Lao et al (69) included patients aged over 60 years with AML and >20% blasts. A non-comparative subgroup analysis was performed by the authors in patients with >30% blasts, which included a total of 12 patients. Due to the small sample size, difference in age (>60 vs >65 years), and non-comparative nature of this analysis, this study has been excluded from further discussion. The systematic review did not include a search for single-arm studies, and an updated systematic review and NMA including these data may be available at the time of the first committee meeting dependant on the plausibility of running the NMA.

4.11.1 *Single arm registries*

Although single arm registries were excluded from the systematic review, there are several 'real-world' azacitidine AML registries that are of importance to this submission. The possibility of conducting a matched-adjusted indirect comparison to utilise the single-arm data is currently being explored and may be available at time of first Committee Meeting.

4.11.1.1 Austrian Azacitidine Registry

The largest study examining the effectiveness and safety of azacitidine in AML is the Austrian Azacitidine Registry (AAR; NCT01595295). This was initiated to gain a comprehensive view of the use, safety and efficacy of azacitidine in patients with AML in a 'real world' clinical practice setting. No formal exclusion criteria existed, as the aim was to include all WHO-AML patients treated with azacitidine, irrespective of age, comorbidities, and/or previous lines of treatment (25, 84).

- The patient population was elderly with a number of comorbidities. The median age was 73 years, with 43% ≥75 years, 79% had ≥1 comorbidity, 54% had received prior disease modifying treatment and 24% had an ECOG performance status of ≥2. This cohort included 172 patients with >30% BM blasts.
- Patients received a median of 4 cycles (range 1-37) and overall response to treatment, defined as complete response, marrow complete response, partial response and haematological improvement, was documented in 48% of the total ITT cohort and in 72% of patients evaluable.
- Median OS was 9.6 months (95% CI: 8.53, 10.7) from initiation of treatment with azacitidine in the entire cohort. A clinically relevant OS benefit was observed with any form of disease stabilisation (marrow stable disease [8.1 months], haematological improvement [9.7 months] or a combination thereof [18.9 months]) as compared to patients without response and/ or without disease stabilization (3.2 months). Median progression-free survival in responding patients was 9.1 months (95% CI: 0.9, 39.9). Median OS was 16.1 months for responders and 3.7 months for non-responders. Baseline age </≥75, age </≥80, WBC count </≥30 G/l or BM blast count ≤30/>30% did not impact on OS. Azacitidine treatment schedule (5 days vs 7 days) also did not impact on OS (8.9 vs 9.7 months, p=0.677).
- The authors' concluded that azacitidine is safe and effective in elderly, comorbid AML patients treated in an everyday life setting, irrespective of BM blast count (25).

A recent updated analysis of the AAR assessed the efficacy and safety of 1st line azacitidine therapy in 95 patients who fulfilled the BM blast percentage and WBC count entry criteria of the AZA-AML-001 trial (BM blasts >30% and WBC <15G/L) (85).

- Baseline patient and disease characteristics were similar (Table 25). Patient status at data cut-off, reasons for azacitidine discontinuation and treatment characteristics were also similar: median number of azacitidine cycles was 5 (1–51) and 6 (1–28), respectively (Table 25).
- Patient outcomes in terms of overall response according to International Working Group criteria (31.5% vs 29.0%), red blood cell (42.1% vs 38.5%) and platelet transfusion independence (34.5% vs 40.6%) did not differ significantly between the AAR and the AML-001 trial. Event-free survival was 5.5 months (range: 0–35.3) vs 6.7 months (range:

5–8.8) in the AAR and AML-001 trial, respectively. The 30-day (8.4% vs 6.6%; p=0.642) and 60-day (15.5% vs 16.2%; p=0.903) mortality rates were comparable.

- The incidence of febrile neutropenia (24.2% vs 28.0%) and Grade 3–4 treatment-emergent neutropenia were similar between the AAR and AML-001; however, higher rates of treatment-emergent thrombocytopenia (47.4% vs 15.7%; p=0.023) and anaemia (31.6% vs 26.3%; p<0.001) were observed in the AAR. Significantly, median OS was highly concordant between the AAR and AML-001 overall (10.8 vs 10.4 months; Figure 12A) as well as for various patient subgroups: 12.2 vs 12.7 months for patients with AML with myelodysplasia-related changes (Figure 12B); 14.6 vs 14.1 months for patients with normal cytogenetics; 13.1 vs 13.0 months for patients with intermediate-risk cytogenetics; and 7.2 vs 6.4 months for patients with high-risk cytogenetics (Figure 12C). After 1 year, 47.4% of patients were still alive in the AAR cohort compared with 46.5% in the AML-001 trial (p=0.924).

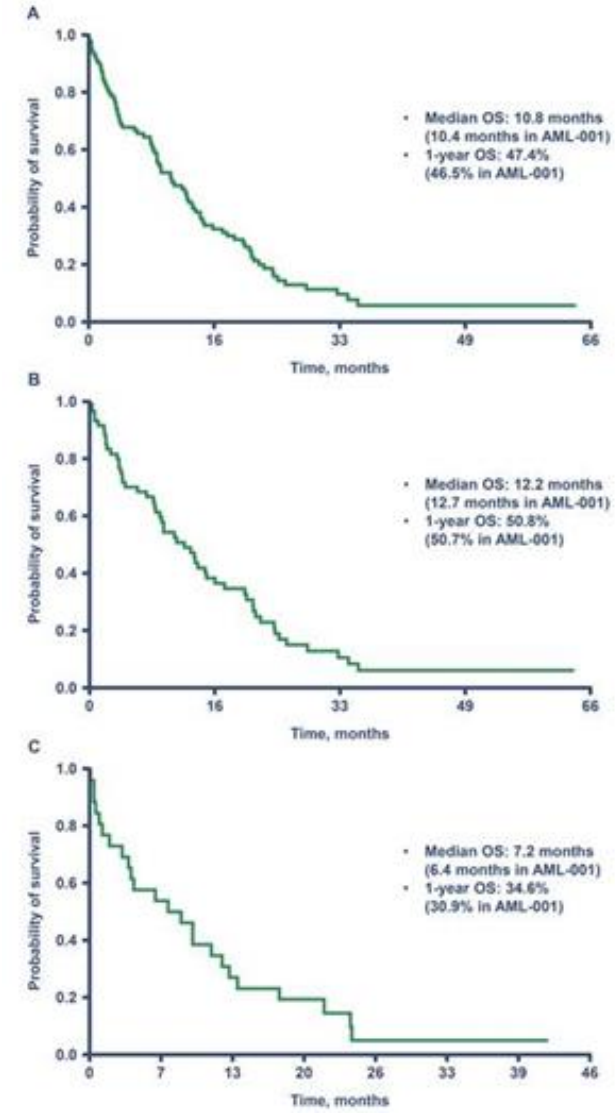
Table 25: Baseline and treatment characteristics of patients from the AAR (BM blasts >30% and WBC <15G/L) and the AML-001 trial

	AAR (n=95)	AML-001 (n=241)	p-value
Baseline characteristics			
BM blasts >30%, %	100	92.5	0.589
WBC <15G/L, %	100	99.2†	0.956
Median age (range), years	77 (23-93)	75 (64–91)	0.872
Aged ≥75 years, %	56.8	57.3	0.964
Male, %	54.7	57.7	0.777
AML classification, %			
AML-NOS	24.2	63.5	<0.001
AML-MRF	66.3	31.1	<0.001
t-AML	5.3	3.3	0.495
AML-RCA	4.2	2.1	0.403
Prior MDS, %	21.1	20.3	0.903
Median BM blasts (range), %	59 (32-100)	70 (2–100)	0.333
≥50% BM blasts, %	65.3	71.8	0.579
ECOG PS, %			
Grade 0–1	67.4	77.2	0.415
Grade 2	53.2	22.8	0.956
Grade 3	9.5	0‡	0.002
Cytogenetic risk group,§ %			
Good	2.4	0	NA
Intermediate	66.7	64.6	0.854
Normal karyotype	47.6	47.1	0.956
Poor	31.0	35.4	0.589
RBC transfusion dependent, %	60.0	70.1	0.376
PLT transfusion dependent, %	30.5	41.9	0.180

	AAR (n=95)	AML-001 (n=241)	p-value
Median WBC (range), G/L	2.1 (0.6–14.4)	3.1 (0–33)	0.661
Median ANC (range), G/L	0.5 (0–7.7)	0.3 (0–12)	0.823
Median Hb (range), g/dL	9.1 (5.8–13.6)	9.5 (5.0–13.4)	0.924
Median PLTs (range), G/L	49 (7–1270)	52 (3–585)	0.765
Treatment characteristics			
Median Aza cycles (range), n	5 (1–51)	6 (1–28)	0.763
Mean Aza cycle, n	7.9	8.7	0.843
≥6 cycles, %	45.3	52.5	0.467
≥12 cycles, %	24.2	32.2	0.287
Reason for Aza discontinuation, %			
Adverse event/death	49.5	58.9	0.367
Progressive disease	13.7	6.6	0.121
Withdrew consent/patients wish	9.5	11.2	0.710
No response/relapse/others	21.1	13.3	0.184
Still on Aza at study closure	6.3	9.9	0.371
Patient status, %			
Dead at data cut-off	84.2	80.1	0.749
Still on Aza at cut-off	6.3	9.9	0.371
Alive/unknown and off Aza	9.5	10.0	0.909

Abbreviations: AAR, Austrian Azacitidine Registry; ANC, absolute neutrophil count; Aza, azacitidine; Hb, haemoglobin; MRF, myelodysplasia-related features; RBC, red blood cell; RCA, recurrent cytogenetic abnormalities.
†Two patients did not have <15G/L WBC; ‡ECOG performance status >2 was an exclusion criteria in AML-001; §Per modified NCCN practical guidelines, 2010, in evaluable patients (n=240/241 and n=85/95 in AML-001 and the AAR, respectively).

Figure 12: Kaplan-Meier curve showing the median OS of patients treated with first-line azacitidine in the AAR who fulfilled the BM blast percentage and WBC count entry criteria of AML-001 with A) AML; B) AML-MRC; C) AML and poor-risk cytogenetics



Abbreviations: AAR, Austrian Azacitidine Registry; AML, acute myeloid leukaemia; BM, bone marrow; MRC, myelodysplasia-related changes; OS, overall survival; WBC, white blood cell.

4.11.1.2 Spanish ALMA registry

The results of the AAR are consistent with other published, large azacitidine AML registries.

In a retrospective analysis of the Spanish ALMA registry, response and survival was evaluated in 110 unfit AML patients who received azacitidine as a front-line therapy (86, 87).

- Median age was 75 years (range 56-89).
- Ninety six (87.3%) suffered from at least one comorbid condition and 64/105 (60.1%) had >30% BM blasts at diagnosis.
- Patients received a median of 4 cycles (range 1-29). Best overall response rate according to IWG-2006 was 44.5% and 53.3% in the ITT and evaluable populations, respectively, while overall response rate according to ELN-2010 was 17.3% and 20.7%, respectively.

Complete response rate (including CRm/CRi) was 15.5% and 18.5%, respectively, with both criteria.

- Median OS was 8.1 months since azacitidine onset (CI 95%: 5.3, 10.9) and median PFS 7.2 months (CI 95%: 4.7, 9.8). The proportion of patients alive 1 year after azacitidine onset was 36.7% (CI 95%: 27.3, 46.1).
- Eighty-two patients (74.5%) received 7 days of azacitidine per cycle, 21 (19.1%) received 5 days (based on physician's decision), and 7 (6.4%) received less than 5 days because of AEs. Weekend off therapy schedule ("5-2-2") and azacitidine dosage did not show any impact on either OS or response rates in multivariate analysis in this AML population (86).

4.11.1.3 French compassionate patient named programme

In a French compassionate patient named programme, 149 previously untreated AML patient ineligible for IC received azacitidine (88). Ineligibility for intensive treatment was due to either age and/or high risk AML characteristics, including adverse cytogenetics (n=40), previous documented MDS phase (n=55), prior myeloproliferative neoplasm (n=13) or therapy related AML (n=30).

- Median age was 74 years (range 31 to 91 years), 87 patients (58%) had ≥30% BM blasts and median WBC was 3.2×10^9/L.
- Patients received azacitidine for a median of 5 cycles (range 1-31).
- Within a median follow-up of 31.5 (28-33.5) months, median OS was 9.4 months (95% CI: 6.5, 10.9) and OS at 1 and 2 years was 38% (95% CI: 30, 46) and 17% (95% CI: 11, 24), respectively.
- Two-year OS was 51% in responders vs 10% in non-responders (p<0.0001). Increasing age, AML type (de novo AML, post-MDS, AML, post-myeloproliferative neoplasm or therapy-related AML), azacitidine schedule (5 versus 7 days), daily azacitidine dose (75mg/m^2 or less than 75mg/m^2), and percentage of BM blasts (</≥30%) did not significantly influence OS. Similarly, the percentage of marrow blast count, entered as a continuous variable, did not significantly influence OS (88).

4.11.1.4 Conclusion

These registry data support the safety and effectiveness of azacitidine in an elderly, comorbid AML patient population.

Overall survival, 1-year survival and response rates are consistent with the AZA-AML-001 trial results, demonstrating the reproducibility of the AZA-AML-001 results in a less restrictive 'real-world' patient populations.

Finally, although azacitidine is licenced as a continuous 7-day administration schedule, deviation from this schedule (5-2-2 dosing) did not appear to impact on survival in any of the registries.

4.12 *Adverse reactions*

All safety data is derived from the pivotal Phase 3 study, AML-AZA-001, previously described in Section 4.3. No further studies that report additional adverse reactions to those reported in AML-AZA-001 and that are of relevance to the decision problem are available.

4.12.1 *Summary of adverse events reported in AML-AZA-001*

AML-AZA-001 included 471 subjects in the safety population who had newly diagnosed AML with >30% blast and were randomised to receive azacitidine or CCR as described in detail in Section 4.3.

Overall in the safety population (N=471), the median age was 75.0 years with 53.3% of subjects ≥75 years of age, 32.7% of subjects had AML with MDS-related changes, 18.0% had a prior history of MDS, 35.7% had a poor or very poor cytogenetic risk status, and 22.9% had ECOG performance status of 2. Median baseline BM blast count was 71.5%.

A summary of the adverse events (AEs), based on the number of events occurring in ≥10% of patients in the azacitidine group, are detailed in Table 26 and Table 27, a summary by total person-years exposure is presented in Appendix 6. Note that the list of AEs reported in this table differ slightly to those reported in the primary publication for this trial by Dombret et al 2015, where the number of AEs were reported that occurred in >10% of patients in any treatment arm (24).

Table 26: Summary of adverse events

Adverse events[†]	AZA, n (%) (N=236)	CCR			Relative risk (AZA vs CCR) (95% CI)
		BSC only, n (%) (N=40)	LDAC, n (%) (N=153)	IC, n (%) (N=42)	
≥1 AE	234 (99.2)	36 (90.0)	153 (100.0)	42 (100.0)	1.0087 (0.9882,1.0296
≥1 treatment-related AE	188 (79.7)	0 (0.0)	124 (81.0)	39 (92.9)	1.1485 (1.0323,1.2778)
≥1 Grade 3 or 4 AE	207 (87.7)	26 (65.0)	141 (92.2)	37 (88.1)	1.0104 (0.9430,1.0826)
≥1 Grade 3 or 4 treatment-related AE	125 (53.0)	0 (0.0)	90 (58.8)	29 (69.0)	1.0460 (0.8786,1.2452)
≥1 Grade 5 (leading to death) AE	56 (23.7)	23 (57.5)	38 (24.8)	9 (21.4)	0.7966 (0.5893,1.0768)
≥1 Grade 5 (leading to death) treatment-related AE	12 (5.1)	0 (0.0)	10 (6.5)	4 (9.5)	0.8535 (0.4033,1.8062)
≥1 SAE	188 (79.7)	30 (75.0)	118 (77.1)	27 (64.3)	1.0697 (0.9691,1.1808)
≥1 treatment-related SAE	87 (36.9)	0 (0.0)	56 (36.6)	14 (33.3)	1.2376 (0.9564,1.6014)
≥1 AE leading to discontinuation	110 (46.6)	0 (0.0)	68 (44.4)	11 (26.2)	1.3865 (1.1064,1.7375)
≥1 treatment-related AE leading to discontinuation	22 (9.3)	0 (0.0)	20 (13.1)	5 (11.9)	0.8763 (0.5087,1.5093)
≥1 AE leading to dose reduction only	8 (3.4)	0 (0.0)	2 (1.3)	2 (4.8)	1.9915 (0.6079,6.5240)
≥1 AE leading to study drug dose	116 (49.2)	0 (0.0)	61 (39.9)	4 (9.5)	1.7771 (1.3921, 2.2684)

Adverse events†	AZA, n (%) (N=236)	CCR			Relative risk (AZA vs CCR) (95% CI)
		BSC only, n (%) (N=40)	LDAC, n (%) (N=153)	IC, n (%) (N=42)	
interruption only					
≥1 AE leading to study drug dose reduction and interruption	13 (5.5)	0 (0.0)	7 (4.6)	0 (0.0)	1.8493 (0.7512,4.5527)

Abbreviations: AE, adverse event; AML, acute myeloid leukaemia; AZA, azacitidine; BSC, best supportive care; CCR, conventional care regimens; CI, confidence interval; IC, intensive chemotherapy; LDAC. low-dose cytarabine; SAE, serious adverse event.
† AE refers to treatment-emergent adverse events. Adverse events included events that started (1) between the date of first dose of study drug and 28 days after the date of last dose of study drug for azacitidine and LDAC (2) between the date of first dose of study drug and 70 days after the date of last dose of study drug for IC (3) between the date of randomisation and the date of discontinuation from the treatment period for BSC only. Adverse events that started outside the treatment-emergent period and assessed as related to study drug was considered treatment-emergent.

Table 27: Summary of adverse events occurring in >10% of subjects in the azacitidine treatment group

Adverse events†	AZA, n (%) (N=236)	CCR			Relative risk (AZA vs CCR) (95% CI)
		BSC only, n (%) (N=40)	LDAC, n (%) (N=153)	IC, n (%) (N=42)	
Constipation	99 (41.9)	9 (22.5)	42 (27.5)	16 (38.1)	1.4714 (1.1436, 1.8931)
Nausea	94 (39.8)	3 (7.5)	43 (28.1)	24 (57.1)	1.3372 (1.0401, 1.7191)
Pyrexia	89 (37.7)	9 (22.5)	61 (39.9)	23 (54.8)	0.9529 (0.7589, 1.1966)
Diarrhoea	87 (36.9)	5 (12.5)	35 (22.9)	21 (50.0)	1.4202 (1.0809, 1.8659)
Febrile neutropenia	76 (32.2)	12 (30.0)	51 (33.3)	17 (40.5)	0.9460 (0.7317, 1.2229)
Neutropenia	71 (30.1)	2 (5.0)	44 (28.8)	14 (33.3)	1.1783 (0.8796, 1.5786)
Thrombocytopenia	64 (27.1)	2 (5.0)	46 (30.1)	9 (21.4)	1.1180 (0.8218, 1.5212)
Decreased appetite	61 (25.8)	8 (20.0)	33 (21.6)	7 (16.7)	1.2654 (0.9077, 1.7642)
Pneumonia	57 (24.2)	3 (7.5)	36 (23.5)	6 (14.3)	1.2613 (0.8918, 1.7838)
Asthenia	55 (23.3)	9 (22.5)	32 (20.9)	5 (11.9)	1.1906 (0.8411, 1.6853)
Oedema peripheral	55 (23.3)	7 (17.5)	33 (21.6)	9 (21.4)	1.1177 (0.7955, 1.5704)
Hypokalaemia	55 (23.3)	6 (15.0)	45 (29.4)	16 (38.1)	0.8174 (0.6010, 1.1117)

Adverse events[†]	AZA, n (%) (N=236)	CCR			Relative risk (AZA vs CCR) (95% CI)
		BSC only, n (%) (N=40)	LDAC, n (%) (N=153)	IC, n (%) (N=42)	
Fatigue	54 (22.9)	10 (25.0)	20 (13.1)	5 (11.9)	1.5363 (1.0453, 2.2579)
Cough	54 (22.9)	6 (15.0)	36 (23.5)	6 (14.3)	1.1202 (0.7939, 1.5807)
Vomiting	53 (22.5)	3 (7.5)	24 (15.7)	8 (19.0)	1.5079 (1.0242, 2.2200)
Acute myeloid leukaemia	49 (20.8)	13 (32.5)	37 (24.2)	1 (2.4)	0.9567 (0.6755, 1.3549)
Anaemia	48 (20.3)	4 (10.0)	39 (25.5)	7 (16.7)	0.9559 (0.6720, 1.3599)
Dyspnoea	46 (19.5)	7 (17.5)	36 (23.5)	5 (11.9)	0.9543 (0.6646, 1.3703)
Dizziness	45 (19.1)	3 (7.5)	15 (9.8)	4 (9.5)	2.0368 (1.2643, 3.2812)
Back pain	37 (15.7)	5 (12.5)	22 (14.4)	2 (4.8)	1.2705 (0.8090, 1.9951)
Insomnia	36 (15.3)	2 (5.0)	11 (7.2)	4 (9.5)	2.1087 (1.2193, 3.6468)
Arthralgia	33 (14.0)	2 (5.0)	11 (7.2)	3 (7.1)	2.0538 (1.1625, 3.6284)
Abdominal pain	31 (13.1)	3 (7.5)	16 (10.5)	7 (16.7)	1.1873 (0.7281, 1.9359)
Injection site reaction	31 (13.1)	0 (0.0)	0 (0.0)	0 (0.0)	–
Headache	31 (13.1)	1 (2.5)	19 (12.4)	6 (14.3)	1.1873 (0.7281, 1.9359)
Weight decreased	30 (12.7)	3 (7.5)	3 (2.0)	1 (2.4)	4.2676 (1.9125,9.5227)
Epistaxis	30 (12.7)	5 (12.5)	21 (13.7)	2 (4.8)	1.0669 (0.6586, 1.7282)
Injection site erythema	29 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	–
Pain in extremity	26 (11.0)	3 (7.5)	11 (7.2)	2 (4.8)	1.6181 (0.8916, 2.9367)
Rash	26 (11.0)	0 (0.0)	14 (9.2)	8 (19.0)	1.1768 (0.6870, 2.0159)
Pruritus	25 (10.6)	1 (2.5)	10 (6.5)	6 (14.3)	1.4644 (0.8125, 2.6393)
Grade 3 or 4 AEs occurring in ≥10 of subjects in the azacitidine arm, n (%)					
Febrile neutropenia	66 (28.0)	11 (27.5)	46 (30.1)	13 (31.0)	0.9389 (0.7070, 1.2468)
Neutropenia	62 (26.3)	2 (5.0)	38 (24.8)	14 (33.3)	1.1433 (0.8327, 1.5697)

Adverse events†	AZA, n (%) (N=236)	CCR			Relative risk (AZA vs CCR) (95% CI)
		BSC only, n (%) (N=40)	LDAC, n (%) (N=153)	IC, n (%) (N=42)	
Thrombocytopenia	56 (23.7)	2 (5.0)	42 (27.5)	9 (21.4)	1.0521 (0.7569, 1.4625)
Pneumonia	45 (19.1)	2 (5.0)	29 (19.0)	2 (4.8)	1.3579 (0.9000, 2.0487)
AML	42 (17.8)	8 (20.0)	28 (18.3)	1 (2.4)	1.1303 (0.7552, 1.6919)
Anaemia	37 (15.7)	2 (5.0)	35 (22.9)	6 (14.3)	0.8568 (0.5740, 1.2791)
Treatment-related AEs occurring in ≥10% of subjects in the azacitidine arm, n (%)					
Nausea	64 (27.1)	0 (0.0)	34 (22.2)	18 (42.9)	1.2256 (0.8915, 1.6848)
Neutropenia	47 (19.9)	0 (0.0)	35 (22.9)	13 (31.0)	0.9750 (0.6807, 1.3966)
Thrombocytopenia	41 (17.4)	0 (0.0)	34 (22.2)	9 (21.4)	0.9494 (0.6442, 1.3993)
Febrile neutropenia	35 (14.8)	0 (0.0)	31 (20.3)	13 (31.0)	0.7921 (0.5280, 1.1882)
Vomiting	34 (14.4)	0 (0.0)	16 (10.5)	3 (7.1)	1.7819 (1.0472, 3.0320)
Decreased appetite	32 (13.6)	0 (0.0)	14 (9.2)	5 (11.9)	1.6771 (0.9791, 2.8726)
Constipation	31 (13.1)	0 (0.0)	10 (6.5)	5 (11.9)	2.0579 (1.1414, 3.7103)
Injection site reaction	30 (12.7)	0 (0.0)	0 (0.0)	0 (0.0)	–
Diarrhoea	29 (12.3)	0 (0.0)	8 (5.2)	9 (21.4)	1.6987 (0.9599, 3.0061)
Pyrexia	29 (12.3)	0 (0.0)	24 (15.7)	10 (23.8)	0.8493 (0.5354, 1.3472)
Injection site erythema	28 (11.9)	0 (0.0)	0 (0.0)	0 (0.0)	–

Abbreviations: AE, adverse event; AML, acute myeloid leukaemia; AZA, azacitidine; BSC, best supportive care; CCR, conventional care regimens; CI, confidence interval; IC, intensive chemotherapy; LDAC. low-dose cytarabine.
† AE refers to treatment-emergent adverse events. Adverse events included events that started (1) between the date of first dose of study drug and 28 days after the date of last dose of study drug for azacitidine and LDAC (2) between the date of first dose of study drug and 70 days after the date of last dose of study drug for IC (3) between the date of randomisation and the date of discontinuation from the treatment period for BSC only. Adverse events that started outside the treatment-emergent period and assessed as related to study drug was considered treatment-emergent.

4.12.2 *Safety overview*

In general, in AZA-AML-001, azacitidine was generally well tolerated, with more than 50% of subjects in the azacitidine treatment group receiving 6 or more treatment cycles and one-third receiving 12 or more cycles.

As expected, and considering the underlying disease and the known pharmacology of the treatments used in the study, AEs were most frequently reported from four system organ classes: general disorders and administration site conditions; gastrointestinal disorders; infections and infestations; blood and lymphatic system disorders. When adjusted for time of exposure, the incidence rates in these classes were lower in the azacitidine treatment group versus the other treatment groups. In addition, the frequency of AEs leading to study drug discontinuation was low and similar between treatment groups.

The most common haematological AEs reported in the azacitidine group were febrile neutropenia (32.2%), neutropenia (30.1%), and thrombocytopenia (27.1%). Neutropenia and thrombocytopenia occurred more frequently in the azacitidine group compared with the BSC only group. Neutropenia and febrile neutropenia were similar between azacitidine and LDAC, whereas thrombocytopenia was more frequent for LDAC. Neutropenia and febrile neutropenia were more frequent in the IC group compared with the other treatment groups. Adjusting for exposure time, all frequent haematological AEs, including Grade 3 or 4 AEs, were generally lower with azacitidine compared with other CCR treatments.

The most common non-haematological AEs reported in the azacitidine group were gastrointestinal toxicities such as constipation (41.9%), nausea (39.8%), and diarrhoea (36.9%), and general disorders, such as pyrexia (37.7%). Nausea and diarrhoea occurred more frequently in the azacitidine group than in the BSC only and LDAC groups. Constipation in the azacitidine group was more frequent than in the IC group. When adjusting for time of exposure, the incidence rates of gastrointestinal events (constipation, nausea, and diarrhoea) were equivalent between the azacitidine group and the LDAC group and lower than the IC group.

The most common SAE reported in azacitidine-treated subjects included febrile neutropenia (25.0%), pneumonia (20.3%), AML (11.0%), and pyrexia (10.6%). Similar trends were observed in LDAC-treated subjects. The percentage of subjects with SAEs was lower in the IC group, with the most frequently reported SAEs being febrile neutropenia (16.7%). In the BSC only group, the most frequently reported SAEs were AML (30.0%), febrile neutropenia (30.0%), and cellulitis (10.0%). When adjusted for time of exposure, the overall rate per person-year of SAEs was lower in the azacitidine group compared to the three other treatment groups.

The majority of deaths in the azacitidine group occurred during the post-treatment period (54.8%) with 23.2% of deaths occurring on-treatment. Similar death rates were reported in the three active treatment groups. The rate of on-treatment death was 2-fold higher in the BSC only group. The cause of on- and post-treatment death was consistent with the manifestations of AML and/or underlying disease of an elderly population.

Haematology data were consistent with the reduction in haematologic AEs over time and revealed a trend toward normalisation for haemoglobin and platelets over time. The laboratory shift data demonstrated that azacitidine had a haematological profile that was either comparable to or better than that for LDAC and IC.

In conclusion, azacitidine has been marketed and widely used for MDS and AML in the EU since 2008, and the safety profile observed with azacitidine in AZA-AML-001 was consistent with that previously observed and reported with azacitidine in its existing approved indications. When normalising for treatment exposure, azacitidine tends to have a favourable safety profile compared with the CCR treatment groups with no additional risks over currently used regimens.

4.13 *Interpretation of clinical effectiveness and safety evidence*

4.13.1 *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

Summary

- **Azacitidine significantly improved patients' overall survival (12.1 months vs. 6.9 months; p=0.019) after censoring for the first subsequent AML therapy in patients aged ≥65 years with AML in the AZA-AML-001 study**
- **Azacitidine significantly improved 1-year survival versus CCR (46.5% vs 34.3%, difference 12.3%)**
- **The AZA-AML-001 findings represent the largest OS and 1-year survival benefit seen in low intensity therapy in elderly AML and are consistent with real world registry data**
- **AZA-AML-001 shows that azacitidine is highly effective and well-tolerated and has no detrimental effect on QoL. It is therefore a much needed treatment option for elderly patients with AML**

Key efficacy findings from AZA-AML-001

The AZA-AML-001 Phase 3 study evaluated the safety and efficacy of azacitidine versus CCR for the treatment of elderly patients (aged ≥65 years) with AML with >30% BM blasts who are ineligible for HSCT. AZA-AML-001 was a large (n=488), high-quality, international, multicentre, controlled study with an open-label, randomised, parallel-group design.

Survival benefits of azacitidine versus CCR (overall population)

- AZA-AML-001 demonstrated a 15% reduction in the risk of death for patients on azacitidine was observed (HR: 0.85; 95% CI: 0.69, 1.03, stratified p=0.1009, unstratified p=0.082). The median OS was 10.4 months compared with 6.5 months for CCR (an improvement of 3.8 months).
- Although the log-rank test did not reach the pre-defined significance level, there was still a clinically significant improvement in OS of 3.8 months. These findings represent the largest median survival benefit seen with a low intensity therapy in elderly AML (16).

Survival benefits of azacitidine versus CCR (censored/adjusted analyses)

- After censoring subjects for first subsequent AML therapy, a statistically significant 24% reduction in the risk of death was observed with azacitidine treatment (HR: 0.76; 95% CI: 0.60, 0.96, stratified p=0.019, median OS 12.1 months vs. 6.9 months), demonstrating that subsequent AML therapy has a significant impact on survival.
- Post-hoc Cox PH and IPCW-adjusted Cox PH analyses support these results and show that both subsequent therapy and prognostic factors impact the results.

- In Cox PH analyses, when adjusting for subsequent therapy, baseline prognostic factors or both, the risk of death was statistically significantly reduced by 25%–31% with azacitidine treatment versus CCR (all p<0.05). In the CCR-adjusted IPCW Cox PH analyses (in line with NICE DSU TSD16 guidance (80)), the risk of death was statistically significantly reduced by XXX with azacitidine treatment versus CCR XXX

1-year survival

- The 1-year survival estimate was 46.5% in the azacitidine treatment group and 34.3% in the CCR treatment group, representing a clinically meaningful difference of 12.3% in favour of azacitidine. Consistent with this analysis, when censoring for subsequent therapy, the 1-year survival difference was 13.0%. This is the greatest 1-year survival reported in an elderly population of patients with AML (9, 17-23).

Survival benefits of azacitidine versus LDAC, IC and BSC

- In pre-defined exploratory analyses of azacitidine versus the individual components of the CCR group, median OS was greater for azacitidine versus LDAC and IC (LDAC: 11.2 months versus 6.4 months, respectively; IC: 13.2 months versus 12.2 months, respectively), and a statistically significant improvement was observed between the azacitidine group and the BSC only group (5.8 months versus 3.7 months, respectively, p=0.0288). However, these results must be interpreted with caution as the study was not powered to detect differences between azacitidine and individual treatments.

Survival benefits of azacitidine in patient sub-groups (poor-risk cytogenetics and AML patients with MDS-related changes)

- Pre-defined univariate subgroup analyses showed a consistent trend in survival benefit for azacitidine versus CCR across all subgroups (HR for OS<1), including baseline patient- and disease-related prognostic factors.
- The strongest effect (HR≤0.71) was seen in patients with MDS-related changes, prior MDS and poor risk cytogenetics.

Additional benefits of azacitidine versus CCR (overall population)

- In terms of other efficacy assessments, measures of haematologic response, duration of remission, and RFS were similar between the azacitidine and CCR treatment arms.
- In patients who did not obtain a CR, median OS was significantly longer for azacitidine versus CCR (6.9 vs 4.2 months; HR 0.77, p=0.017) with an estimated 1-year survival of 33.8% vs 20.4%, respectively. Similar observations have been made in both AML (25) and higher risk MDS (89). Therefore, attainment of a CR does not appear to be a prerequisite for a survival benefit with azacitidine.
- A trend for improved EFS in favour of the azacitidine group compared with CCR was however observed, and azacitidine was associated with an overall benefit in both RBC and platelet transfusion dependence.

Efficacy conclusion

- In summary, treatment with azacitidine resulted in clinically meaningful and statistically significant increases in OS in a number of different analyses, with associated improvements in haematologic endpoints. As shown in Section 4.11.1, similar results for OS, 1-year survival and response rates have been observed in ‘real-world’ registries with

less-stringent inclusion criteria, demonstrating the reproducibility of the AZA-AML-001 results. These analyses demonstrate that azacitidine is a highly effective and much needed treatment option in this difficult-to-treat elderly AML population.

Patient-reported outcomes

- There was no meaningful HRQoL deterioration associated with prolongation of OS in the azacitidine group during treatment. Further, azacitidine and CCR were associated with general improvement in HRQoL in the four pre-specified QLQ-C30 domains of fatigue, dyspnoea, global health status and physical functioning.

Safety & tolerability

Adverse events for azacitidine

- As expected, and considering the underlying disease and the known pharmacology of the treatments used in the study, AEs were most frequently reported from four system organ classes: general disorders and administration site conditions; gastrointestinal disorders; infections and infestations; blood and lymphatic system disorders.
- Overall, when adjusted for the time of exposure to study drug, the incidence rates were lower in these classes in the azacitidine group when compared with all other individual treatment groups. Additionally, the frequency of AEs leading to study drug discontinuation was low and similar between all treatment groups.
- The most common haematological AEs reported in the azacitidine group were febrile neutropenia (32%), neutropenia (30%), and thrombocytopenia (27%) and the most common non-haematological AEs were gastrointestinal toxicities such as constipation (42%), nausea (40%), and diarrhoea (37%), and general disorders such as pyrexia (38%).
- The most frequent SAEs reported in the azacitidine group included febrile neutropenia (25%), pneumonia (20%), AML (11%), and pyrexia (11%).

Adverse events for azacitidine adjusted for time of exposure

When adjusted for time of exposure:

- all frequent haematological AEs, including Grade 3 and 4 AEs, were generally lower in the azacitidine groups when compared with other CCR treatments
- incidence rates of gastrointestinal events were equivalent between the azacitidine group and the LDAC group, and lower than the IC group
- overall rate per person-year of SAEs was lower in the azacitidine group compared with other CCR treatments.

Rates of on-treatment and post-treatment death

- Similar death rates were reported in the three active treatment groups, and the rate of on-treatment death was 2-fold higher in the BSC only group. The cause of both on- and post-treatment death was consistent with the manifestations of AML and/or underlying disease of the elderly.

Duration of treatment

- Azacitidine was generally well tolerated, with more than 50% of subjects in the azacitidine treatment group receiving six of more treatment cycles, and one-third receiving 12 or more cycles.
- The median duration of treatment for azacitidine (164.5 days) was longer than the median duration observed for BSC only (65.0 days), LDAC (98.0 days), or IC (55.5 days) treatment groups.

Safety conclusion

- In conclusion, azacitidine has been marketed and widely used for MDS and AML in the EU since 2008, the favourable tolerability profile of azacitidine in older patients with AML is consistent with that previously observed and reported with azacitidine in its existing approved indications (24, 25). Given the imbalances in treatment duration between the treatment groups, when adjusting for duration of exposure, the incidence rates for the majority of AEs were either similar or lower in azacitidine-treated subjects compared to the individual CCR groups, with no additional risks observed over currently used regimens. These results indicate that azacitidine has a favourable safety profile in the treatment of elderly patients with AML.

4.13.2 *Strengths and limitations of the clinical evidence base for the technology*

Strengths

1. ***Design features of the AZA-AML-001 study***
   - Study AZA-AML-001 is a high quality Phase 3 RCT which provides the pivotal evidence supporting the regulatory approval of azacitidine for the treatment of AML with BM blasts >30% in elderly patients who are ineligible for HSCT. The study successfully addresses the decision problem, providing evidence in the appropriate population versus a range of treatments currently used in clinical practice – defined as CCR – and reporting a number of efficacy, safety and quality of life endpoints. The primary endpoint of OS is considered the most reliable endpoint for cancer studies, as it is an objective and direct measure of the treatment benefit that is most clinically meaningful to this patient population (see Section 4.3.7).

2. ***Representativeness of patient population & generalisability to UK clinical practice***
   - The patient population recruited to the study is representative of patients included in the licensed indication and the population that would be treated in routine clinical practice in the UK. Similar to patients in routine practice, AZA-AML-001 had a highly heterogeneous population with a high number of poor prognostic features. This included a median BM blast count of ~70%, 32% with a diagnosis of AML-MRC, 35% poor risk cytogenetics, median age of 75 years and >20% of patients had an ECOG performance status of 2.
   - When comparing AZA-AML-001 to the HMRN registry (10), it can be seen that the median age (75 years AZA-AML-001 vs 78.7 years HMRN) and frequency of poor risk cytogenetics (35% AZA-AML-001 vs 33.9% HMRN) were similar. However,

there was an increased proportion of AML-MRC in the AZA-AML-001 study (32% AZA-AML-001 vs 12.1% HMRN).

- In the HRMN, there is a different proportional uptake of CCR regimens (XXX We hypothesise this is due to WBC cut off in the trial (impact on the cost-effectiveness is explored in the sensitivity analyses in section 5.8).

3. Appropriateness of the composite comparator in the context of UK clinical practice

- As discussed in detail in section 3.3, the observed heterogeneity means that there is no standard of care for elderly patients with AML. As such, complex treatment guidelines (6, 8, 59, 65) have been developed and there is no widely accepted risk algorithm that clinicians use when deciding which patients are most likely to benefit from intensive or non-intensive treatment options.
- To overcome these difficulties, study AZA-AML-001 was powered to compare the efficacy and tolerability of azacitidine versus a composite comparator, CCR, combining all patients, irrespective of treatment regimen, into one patient population. This approach of comparing with a composite comparator has been recognised and accepted by NICE in its previous appraisal of azacitidine (TA218) (28), as well as in other disease areas (e.g. TA254 in relapsing remitting multiple sclerosis) (29). Given the difficulties described above CCR is the most appropriate comparator when assessing the efficacy of azacitidine in this difficult-to-treat patient population.

4. Value of clinical outcomes observed with azacitidine

- Outcomes for elderly AML patients treated with CCR are very poor and therefore there is an urgent unmet need for new treatment options. AZA-AML-001 has shown the highest median OS (10.4 months, a 58% increase vs CCR) and 1-year survival (47%, a 36% increase vs CCR) benefit for a non-intensive therapy in an elderly AML population and has demonstrated that azacitidine can provide a highly effective and well-tolerated treatment option for this complex and difficult-to-treat patient population.

Limitations

1. Absence of statistical significance for the primary endpoint of OS in the AZA-AML-001 study

- While the primary endpoint demonstrated a clinically meaningful increase in OS of 3.8 months in the azacitidine treatment group versus the CCR treatment group, the log-rank test failed to reach the pre-defined significance level.
- The convergence of the survival curves observed after month 22 is not unexpected in a condition without a curative therapy and a poor prognosis.
- The lack of statistical significance achieved in the primary OS analysis may reflect the convergence and the statistical methods used to compare the OS curves. In line with the majority of clinical trials, the log-rank test was used to compare OS. However, this is a non-parametric test which compares the survival across the entire follow-up period. Using this test is likely to have led to an underestimation in the survival difference between treatments in cases where patients are followed up until death, withdrawal of consent, or study termination. The test does not compare

survival at discrete time points, and therefore data after two years – when the curves converged – were included when calculating overall HRs and significance levels (83).

- Furthermore, possible imbalances in subsequent therapy between treatment arms is recognised as a problem in cancer trials which use OS as a primary endpoint (30).
- To allow for a more rigorous comparison of the effects of the two treatment arms on OS, the study included a pre-specified analysis where patients were censored upon discontinuation of study drug and initiation of subsequent therapy. This means that patients were included in OS calculations up until starting treatment with subsequent therapy, at which point they were precluded from further analysis. In total, 69 (28.6%) subjects in the azacitidine group and 75 (30.4%) subjects in the CCR group received subsequent AML therapy after discontinuing study treatment. The results from this analysis demonstrated a statistically significant reduction in the risk of death with azacitidine treatment versus CCR (OS: 12.1 vs. 6.9 months, respectively; p=0.019). Furthermore, when evaluating 1-year survival – a time point at which subsequent therapy is less likely to have an impact – there was a significant increase associated with azacitidine which was consistent with the results observed when censoring for subsequent therapy.

2. Effect of prognostic factors on observed survival outcomes from the AZA-AML-001 study

- A variety of patient- and disease-related prognostic factors are likely to influence survival outcomes. The impact of the heterogeneity of the elderly AML population was examined in univariate and multivariate analyses.
  - Univariate analysis demonstrated the heterogeneity of the elderly AML population, with a median OS between subgroups ranging from 4.8 months to 17 months (in the azacitidine arm).
  - In all subgroups there was a consistent trend in survival benefit associated with azacitidine treatment (HR for OS<1), and the strongest effect (HR≤0.71) was seen in patients with MDS-related changes, prior MDS and poor risk cytogenetics. As expected, survival was better in younger patients (<75 years) and in patients with a better performance status (ECOG performance status 0 or 1).
  - Two IPCW-adjusted Cox PH analyses were undertaken to adjust for baseline patient- and disease-related covariates and the impact of subsequent therapy. A regulatory-preferred analysis was conducted where adjustments were made to both treatment arms, and a NICE-preferred analysis was conducted where adjustments were made only to the CCR treatment arm. Both analyses revealed a statistically significant survival benefit with azacitidine versus CCR (regulatory-preferred: HR: 0.71; p=0.0047 and NICE-preferred: HR: 0.75; p=0.01). The outcomes of these analyses indicate that treatment with azacitidine results in a statistically significant reduction in the overall risk of death when compared with CCR.
- While the primary endpoint of the trial was not met, the study successfully demonstrated that there were a number of confounding factors which led to the underestimation of the efficacy of azacitidine. As such, when these were accounted

for, all analyses resulted in a statistically favourable outcome associated with azacitidine when compared with CCR.

3. Intra-comparator variability

- The absolute OS results for azacitidine between the three investigator pre-selected treatment groups that made up the CCR arm (IC, LDAC and BSC only) were not consistent. However, this finding is in line with the impact of prognostic factors on efficacy identified in univariate and multivariate analyses, and the variation in these characteristics observed across the three pre-selection groups. For example, patients who were pre-selected and randomised to receive BSC only were generally older and had more adverse prognostic factors compared with those pre-selected and randomised to receive treatment with IC. The data from these individual treatment group comparisons however do confirm a consistent improvement in OS with azacitidine, although the study was not powered to detect differences.

End-of-life criteria

Table 28: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS reported in the literature ranges between 1.5 months (aged >65 years) and 2 months (aged >55 years) (60, 61)
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	Median OS based on the primary endpoint was 10.4 months in the azacitidine group and 6.5 months in the CCR group, providing an OS benefit of 3.8 months with azacitidine. As reported in Section 4.7, various pre-defined analyses demonstrated that treatment with azacitidine provided a statistically significant survival benefit versus CCR
The treatment is licensed or otherwise indicated for small patient populations	The estimated total population for all licensed indications in England is 3,354, consisting of 1,026 covered by the proposed new indication and 2,328 for all existing indications. See additional detail provided following this table

Abbreviations: OS, overall survival; NHS, National Health Service.

The population covered by the proposed new indication was derived as follows:

- The total population with AML aged over 65 in England is estimated to be 1,777 based on a total population of 9,685,248[a] (43) over the age of 65 years in England, and an incidence rate of AML in patients aged >65 years of 18.35[b] per 100,000 (42)
- 1,282 (72.1%)[c] of those are estimated to be ineligible for HSCT (90)

[a] 2014 midyear estimates uplifted to 2015 using growth rate of 0.77% (44).

[b] Based on proportional average across age bandings (65–69, 70–74, 75–79, 80+)

- Of these, 1,026 (80%) are estimated to have BM blasts >30% (91)

The population for all other licensed indications was derived as follows:

- The total population with MDS (including patients with chronic mylomonocytic leukaemia and AML with 20–30% blasts) in adults (>18 years) in England is estimated to be 10,298 based on a total population of 55,155,788[a] (43), and an incidence rate of MDS in patients aged >18 years of 18.67[d] per 100,000 (42)
- 2,451 (23.8%)[e] of those are estimated to have intermediate-2 and high-risk MDS (92-94)
- 2,328 (95%) of those are estimated to be ineligible for HSCT (95)

4.14 *Ongoing studies*

In adults with AML with BM blasts >30%, there are no completed or ongoing company-sponsored studies from which new evidence will become available in the next 12 months.

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[c] Population estimated from total of 495 patients eligible for HSCT in England in 2013.

[d] Based on proportional average across 5-year age bandings (20–24 to 80+)

[e] Based on a proportional average.

5 Cost effectiveness

5.1 *Published cost-effectiveness studies*

5.1.1 *Identification of studies*

A systematic review was conducted to identify cost-effectiveness studies from the published literature relevant to the decision problem.

The following electronic databases were searched on the 19th October 2015: Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, EMBASE (Ovid), NHS EED (Ovid, as part of the Cochrane Library), HTA (Ovid, as part of the Cochrane Library) and Econlit (Ovid).

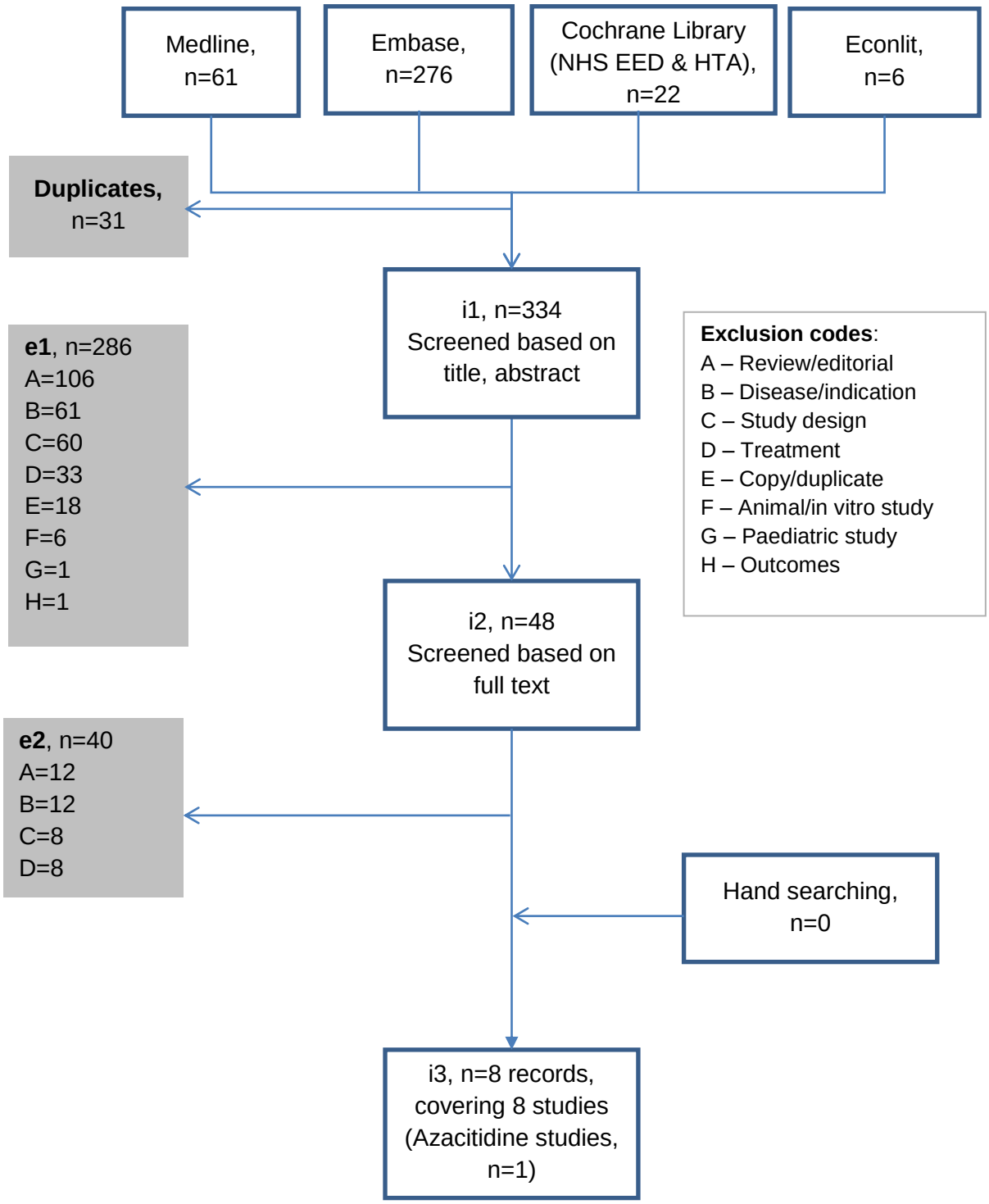
Electronic searches were supplemented by hand searching the following sources: reference lists of included publications, conference proceedings, the Cost-Effectiveness Analysis (CEA) Registry, the WHO International Clinical Trials Registry Platform (ICTRP), the HTA database of the International Network of Agencies for Health Technology Assessment (INAHTA), the NIHR HTA website, the Research Papers in Economics (RePEc) website, and previous NICE HTA submissions in the relevant disease. Any relevant abstracts identified through the electronic database search or supplementary hand searching were checked for available associated posters.

In total, 365 citations were identified through the electronic database searches. Upon the removal of duplicates, 334 titles and abstracts were screened for relevance according to eligibility criteria described in Appendix 7. Following exclusion of 286 citations, the full texts of 48 publications were reviewed, of which 40 were excluded, resulting in eight relevant papers for final inclusion (Figure 13).

No additional relevant studies were identified via hand searching.

Full details of the search, including search terms, details of the included studies and of the studies excluded on full paper review are provided in Appendix 7.

Figure 13: Schematic for the systematic review of cost-effectiveness evidence



5.1.2 *Description of identified studies*

Of the eight studies identified for inclusion, four were full publications (96-99), and four were abstracts (100-103), of which one had an available associated poster (103). Countries from which the economic data were derived included: the US (n=4) (99, 100, 102, 103); France (n=1) (96); Russia (n=1) (101); China (n=1) (97); and Italy (n=1) (98). No UK-based studies were identified.

Of the eight studies identified, three were cost-utility analyses that evaluated currently available pharmacological interventions in an active comparator setting, and reported an ICER (100, 102, 103); these studies are deemed to be most relevant to decision making in England, however, one was a poster and two were abstracts only and thus reported limited information regarding study methodology. The remaining five studies were cost-effectiveness analyses: four studies reported costs per LYG (96, 97, 99, 101), and two reported costs per complete remission (98, 99).

All of the included studies considered the treatment of patients with AML; in two studies, the FAB classification system was used to diagnose patients, and therefore it is assumed that patients had >30% blasts (96, 97). However, it was unclear in six studies if patients had >30% blasts due to a lack of reporting (98-103). One study considered only patients with acute promyelocytic leukaemia (APL) (103). The interventions investigated in the studies included: azacitidine vs low-dose cytarabine (Ara-C) (101); decitabine vs conventional induction chemotherapy with Ara-C and daunorubicin (100); chemotherapy vs autologous/allogeneic bone marrow transplantation (96); high-dose Ara-C vs daunorubicin (97); idarubicin vs daunorubicin (both in combination with Ara-C) (98, 99); chemotherapy vs allogeneic haematopoietic cell transplantation (102); and arsenic trioxide vs Ara-C in combination with chemotherapy vs idarubicin (103).

With regard to the model structures used, two studies constructed Markov models (100, 103), two studies used decision trees/analyses (98, 102), and four studies did not specify the model type used (96, 97, 99, 101). The analysis perspective was clearly reported in only one study and this was from the US third party payer perspective (103). In two studies, a payer perspective was assumed (96, 98). The time horizon was reported in three studies (100, 102, 103), and ranged from 1 year (100) to 55 years (103). Health states considered in the models included: healthy (100), death (100, 103), active disease (100), AML in remission on conventional induction chemotherapy (100), AML in remission on decitabine or high-dose Ara-C (100), AML on active treatment with conventional induction chemotherapy or decitabine (100), complete remission (98), partial remission (98), resistance (98), 1st-line stable disease (103), 2nd-line stable disease (103), and 2nd-line disease event (103).

The eight included studies are summarised in Table 29.

Table 29: Summary of included cost-effectiveness evaluations

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population	QALYs or LYG (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY/LYG)	Relevance and limitations
Batty, 2013 (100) US (abstract only)	CUA - semi-Markov model, 1 year time horizon, health states included healthy, death, active disease, AML in remission, AML in remission on various treatments	• Decitabine • Conventional induction therapy (Ara-C and DNR)	Patients with AML aged >60 years	QALYs: • Decitabine, 0.5982 • Conventional induction therapy, 0.1754	Total costs: • Decitabine, $55,777 • Conventional induction therapy, $127,867	ICER: • Reported as - $72,090/0.4228 = -$170,506/year (decitabine dominated conventional induction therapy)	• Abstract only so information reported is limited • Unclear if patients have >30% blasts so relevance of population to NICE scope is unknown • US-based analysis; generalisability to a UK setting is unknown
Dufoir, 1992 (96) France (full publication)	CEA – model type not reported, life years saved were calculated using the Kaplan Meier method, payer perspective assumed (policy perspective)	• Chemotherapy† • Auto-BMT • Allo-BMT	Adult patients aged <55 years with AML in first CR taking part in two cooperative consecutive trials (BGM 84 and BGMT 87[†]), diagnosed according to FAB criteria (M1-M5); median age, 32-34 years	Estimated survival at 5 years: • Chemotherapy, 2.84 years • Auto-BMT, 3.58 years • Allo-BMT, 3.78 years	Total costs: • Chemotherapy, FF 304,846 • Auto-BMT, FF 505,364 • Allo-BMT, FF 424,696	Mean cost per LYG: • Chemotherapy, FF 108,641 • Auto-BMT, FF 142,733 • Allo-BMT, FF 112,205	• Assumed patients have >30% blasts; population is therefore aligned with the NICE scope • Information regarding CEA methodology very limited • Based in France, conducted in 1992 and cost expressed in francs; generalisability to a current UK setting is unknown
Huang, 2011 (97) China (full publication)	CEA – model type not reported, life years saved were calculated using the Kaplan Meier method	• HiDAC • DNR-based chemotherapy‡	Adult patients aged 50-60 years with AML diagnosed according to FAB criteria (excluding APL) who achieved CR	Median event-free survival at 5 years: 1) Patients with better/intermediate cytogenic risk: • HiDAC, 27 months	Total treatment costs: 1) Patients with better/intermediate cytogenic risk: • HiDAC, $442,180.39 • DNR-based	Cost per LYG: 1) Patients with better/intermediate cytogenic risk: • HiDAC, $18,746.84 • DNR-based chemotherapy, $32,733.37	• Assumed patients have >30% blasts; population is therefore aligned with the NICE scope • Information regarding CEA methodology very limited

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population	QALYs or LYG (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY/LYG)	Relevance and limitations
			following induction therapy and with an intermediate or poor cytogenic risk profile	• DNR-based chemotherapy, 20 months 2) Patients with poor cytogenic risk: • HiDAC, 0.92 years • DNR-based chemotherapy, 1.67 years	chemotherapy, $54,644.72 2) Patients with poor cytogenic risk: • HiDAC, $94,978.68 • DNR-based chemotherapy, $53,904.15	2) Patients with poor cytogenic risk: • HiDAC, $103,237.70 • DNR-based chemotherapy, $32,277.93	• Based in China; generalisability to a UK setting is unknown
Kulikov, 2012 (101) Russia (abstract only)	CEA – model type not reported	• AZA • Low-dose Ara-C	Patients with AML or MDS in the Russian Federation	NR	Total treatment costs: • AZA, RUB 2,658,703 • Low-dose Ara-C, RUB 1,749,130	Cost per LYG: • AZA, RUB 1,303,286 • Low-dose Ara-C, RUB 1,366,507	• Abstract only so information reported is limited • Unclear if patients have >30% blasts and includes MDS patients so relevance of population to NICE scope is unknown • Based in Russia; generalisability to a UK setting is unknown
Lambertenghi-Deliliers, 1991 (98) Italy (full publication)	CEA – decision tree with health states for CR, partial remission, and resistance and 2 cycles of treatment, payer perspective assumed (perspectives of	• IDA + Ara-C • DNR + Ara-C	Adult patients with newly diagnosed AML; mean age, 49 years	CRs after 1 cycle: • IDA + Ara-C, 29.8-60.0% • DNR + Ara-C, 20.0-43.5% Total CRs: • IDA + Ara-C, 40.3-80.0%	Total induction treatment costs: • IDA + Ara-C, 2,095,000 Lira • DNR + Ara-C, 104,000 Lira Total salvage treatment costs: • IDA + Ara-C,	Cost per CR: 1) 50% resistant at 1st cycle and 50% resistant at 2nd cycle: • IDA + Ara-C, 28.7-68.4 million Lira • DNR + Ara-C, 39.5-62.5 million Lira 2) All resistant cases	• Unclear if patients have >30% blasts so relevance of population to NICE scope is unknown • Based in Italy, conducted in 1991 and costs expressed in Italian Lira; generalisability to a

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population	QALYs or LYG (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY/LYG)	Relevance and limitations
	hospital doctors and administrators were considered)			• DNR + Ara-C, 39.2-58.5%	1,429,000 Lira • DNR + Ara-C, 2,208,000 Lira	at 2nd cycle: • IDA + Ara-C, 30.1-71.0 million Lira • DNR + Ara-C, 41.5-67.6 million Lira *[Dependent on clinical data used – but IDA consistently shown to be more cost-effective than DNR]*	current UK setting is unknown
Pashko, 1991 (99) US (full publication)	CEA – model type not reported	• IDA + Ara-C • DNR + Ara-C	Patients with previously untreated AML; median age, 36 years (IDA-treated) and 41 years (DNR-treated)	Median survival: • IDA, 1.64 years • DNR, 1.13 years CRs periods 1 and 2: • IDA, 80% • DNR, 58%	Total costs per patient: • IDA, $59,687 • DNR, $59,567	Cost per LYG • IDA, $36,395 • DNR, $52,714 Total cost per CR: • IDA, $74,609 • DNR, $102,115	• Unclear if patients have >30% blasts so relevance of population to NICE scope is unknown • Information regarding CEA methodology very limited • US-based analysis conducted in 1991; generalisability of results to a current UK setting unknown
Statler, 2014 (102) US (abstract only)	CUA – simple decision analysis, 5 year time horizon, 3% discount per year of costs and QALYs	• Consolidation chemotherapy (not specified) • AHCT	Patients aged <60 years with AML in first CR	QALYs: • Chemotherapy, 2.67 • AHCT, 1.79 Overall survival: • Chemotherapy, 3.04 years • AHCT, 2.15 years	Total costs: • Chemotherapy, $163,391 • AHCT, $182,018	Chemotherapy dominated	• Abstract only so information reported is limited • Unclear if patients have >30% blasts so relevance to NICE scope is unknown • US-based analysis; generalisability of results to UK setting unknown

Study, Year, Country	Summary of model	Intervention/ comparator	Patient population	QALYs or LYG (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY/LYG)	Relevance and limitations
Tallman, 2015 (103) US (abstract and poster)	CUA – Markov model with monthly cycles and four health states (1st-line stable disease, 2nd-line stable disease, 2nd-line disease event, and dead) , US third party payer perspective, time horizon of 55 years until patient reaches 100 or have died	• ATO + ATRA • ATRA + Ara-C + chemotherapy • ATRA + IDA	Adult patients with newly diagnosed low-to-intermediate risk APL, aged 45 at model entry	Total QALYs: • ATO + ATRA, 14.33 • ATRA + Ara-C, 6.71 • ATRA + IDA, 8.13 Total LYG: • ATO + ATRA, 17.79 • ATRA + Ara-C, 8.57 • ATRA + IDA, 10.09	Total cost: • ATO + ATRA, $136,170 • ATRA + Ara-C, $96,940 • ATRA + IDA, $101,396	ICER per QALY (ref ATRA + Ara-C): • ATRA + ATO, $5,614 • ATRA + IDA, $3,122 ICER per LYG (ref ATRA + Ara-C): • ATRA + ATO, $4,512 • ATRA + IDA, $2,933 ATO highly cost-effective compared with Ara-C plus chemotherapy and IDA	• Abstract and poster only so information reported is limited • Considers only APL patients, therefore generalisability to a population defined in NICE scope is unknown • US-based analysis; generalisability of results to UK setting unknown

Abbreviations: AHCT, allogeneic hematopoietic cell transplantation; Allo-BMT, allogeneic bone marrow transplantation; AML, acute myeloid leukaemia; APL, acute promyelocytic leukaemia; Ara-C, cytarabine; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; Auto-BMT, autologous bone marrow transplantation; AZA, azacitidine; CEA, cost-effectiveness analysis; CR, complete remission; CUA, cost-utility analysis; DNR, daunorubicin; FAB, French-American-British; FF, French francs; HiDAC, high-dose arabinoside; ICER, incremental cost-effectiveness ratio; IDA, idarubicin; LYG, life years gained; MDS, myelodysplastic syndrome; NICE, National Institute for Health and Care Excellence; NR, not reported; QALY(s), quality-adjusted life year(s); RCT, randomised controlled trial; RUB, Russian ruble; US, United States.
† Chemotherapy consisted of four monthly cycles of intensive sequential chemotherapy with etoposide and amsacrine (cycle 1), cytarabine and daunorubicin (cycle 2), high-dose cytarabine (cycle 3), and 6-mercaptopurine, vincristine, methotrexate and prednisone (cycle 4) in the BGM 84 study OR five courses of daunorubicin and cytarabine given 1, 3, 6, 9, and 13 months after consolidation as well as continuous chemotherapy with 6-mercaptopurine and methotrexate in the BGMT 87 study.
‡ The daunorubicin-based regimen consisted of 2 cycles of daunorubicin in combination with arabinoside, followed by 1-2 cycles of homoharingtonine combined with arabinoside, followed by 1-2 cycles of etoposide in combination with arabinoside.

5.1.3 *Quality assessment of identified studies*

Quality assessments of the full text studies are provided in Appendix 8. Identified abstracts and posters were not quality assessed due to the limited reporting of the methodology used.

5.2 *De novo analysis*

The cost-effectiveness model was developed according to methods guidance published by NICE (104) and the NICE Decision Support Unit (DSU) (105-107) and international good research practices for modelling (108, 109), to ensure that the analysis was as methodologically rigorous as possible.

5.2.1 *Patient population*

The population in the model is the AZA-AML-001 trial population and is in line with the target indication: older patients with newly diagnosed AML and more than 30% bone marrow blasts who are not eligible for HSCT. The starting age in the model was 75 years and patients were assumed to have a body surface area (BSA) of 1.80 m^2, based on the mean age and BSA of patients in the AZA-AML-001 trial.

The distribution of patients receiving IC (18%), LDAC (64%), and BSC (18%) is slightly different to patients in UK clinical practice from the Haematological Malignancies Research Network (HMRN) data from Northern England (10). HMRN is a collaboration between researchers in the Epidemiology & Statistics Group (ECSG) at the University of York, a unified Clinical Network operating across 14 hospitals, and an integrated Haematological Malignancy Diagnostic Service at St James's Hospital in Leeds (110). The HMRN data shows that of the patients receiving the treatment options of interest, XXX. More patients in this registry received BSC and fewer LDAC than in AZA-AML-001. To access the impact of this difference, a weighted average ICER based upon this treatment distribution and calculated from the individual treatment arms in AZA-AML-001 (as undertaken by the DSU in TA218 (28)) is presented as a scenario analysis in section 5.8.

This report focuses on this overall study population (CCR). This is because, as explained in section 3.3 above, there is no clinical consensus on a criteria which makes an individual eligible to receive IC, LDAC, or just BSC. Clinical decisions are based on upon the expert judgement of the treating physician and the preferences of the patient and their individual needs.

The model also allows analysis of patients based on eligibility for IC, LDAC, or BSC, cytogenetic risk (intermediate and poor), and myelodysplasia-related changes. Subgroups on cytogenetic risk and myelodysplasia-related changes were chosen based upon a current unmet need for an effective option for patients presenting with these characteristics and the observed significant (P-values < 0.05) OS benefit of azacitidine over CCR in the AZA-AML-001 trial in these subgroups. The results from alternative and subgroup analysis are presented in in section 5.8 below.

5.2.2 *Model structure*

A semi-Markov model was developed based on the design of the AZA-AML-001 study and a targeted literature review of clinical guidelines and economic models for AML in the

published literature (section 5.1 above). Feedback on the structure, assumptions and inputs, and outputs was obtained from two UK clinical oncologists.

Figure 14 illustrates the structure of the model. Upon diagnosis with AML, patients enter the model at the first dose of either AZA or CCR (i.e., IC + BSC, LDAC + BSC, or BSC alone). The Markov model starts after patients have completed the first cycle of treatment (4 weeks), when patients either respond or do not respond to the treatment and are in one of the following health states:

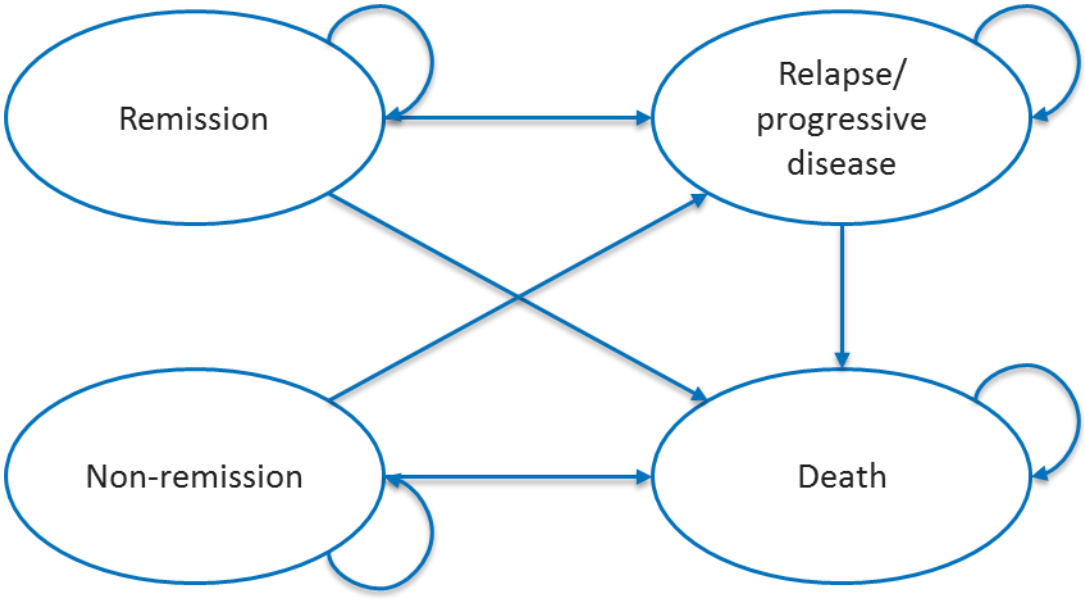
- Remission (i.e., CR or CRi)
- Non-remission (i.e., partial response [PR], stable disease)
- Death.

Patient pathways in the subsequent treatment cycles are as follows.

- Patients who have achieved remission (CR or CRi) may continue in remission, relapse, or die. Patients whose disease has relapsed after remission remain in relapse or die.
- Patients who have achieved PR or stable disease can either remain in non-remission or progress to PD or die.
- Patients whose disease has progressed can either stay in PD or die.

The model has a 4 week cycle, corresponding to the cycle length of treatments in the AZA-AML-001 study.

Figure 14: Model Structure



Using the semi-Markov approach, the proportion of the model cohort in each health state is estimated for each 4 week cycle using independent RFS, PFS and OS curves, as follows:

- Remission (CR or CRi) – RFS curve for patients who have achieved remission. RFS was adjusted in the model to ensure consistency with OS and PFS (measured from

randomisation to event, whereas in AZA-AML-001, RFS is measured from the first response to relapse).

- Non-remission (PR or SD) – PFS curve for patients who have achieved PR or SD
- PD or relapse – difference between the OS, RFS, and PFS curves
- Death – complement of the OS curve.

Table 30: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime horizon for an older patient with newly diagnosed AML (i.e., 10 years, as almost all patients have died by the end of year 10 in the model)	As per NICE reference case
Were health effects measured in QALYs; if not, what was used?	Yes. QALYs. Utility values mapped from trial-based EORTC QLQ-C30 data using published algorithms (see section 5.4 below)	As per NICE reference case
Discount of 3.5% for utilities and costs	Yes.	As per NICE reference case
Perspective (NHS/PSS)	NHS/PSS	As per NICE reference case
PSS, personal social services; QALYs, quality-adjusted life years		

5.2.3 *Intervention technology and comparators*

The model is based directly on evidence from the AZA-AML-001 trial. As described in section 1.3 above, investigators assigned patients to one of three CCRs before randomization to AZA or individual CCR regimen. The main comparator for the economic evaluation is CCR as defined in the trial. The individual components of CCR were:

- **IC**:
  - Induction therapy – Cytarabine was administered at a dose of 100–200 mg/m2/day via continuous IV infusion for a total of 7 days. Anthracycline was given in combination with cytarabine for 7 days.
  - Consolidation - Two consolidation cycles for those who responded to the treatment, followed by BSC. Those who do not respond to induction therapy receive BSC.
- **LDAC:** Cytarabine at a dose of 20 mg SC BID for 10 days, every 28 days, until disease progression or unacceptable toxicity; patients then receive BSC.
- **BSC:** Including but is not limited to red cell or whole blood transfusions, fresh frozen plasma transfusions, platelet transfusions, antibiotic and/or antifungal therapy, and nutritional support). This is continued until death.
  - The same BSC is assumed to apply to all patients who have stopped active treatment on AZA, IC or LDAC

Azacitidine is incorporated at a dose of 75 mg/m^2/day SC for 7 days every 28 days. In the basecase wastage is assumed and vials used are rounded up to the cost of the nearest full vial. Vial sharing is tested in the sensitivity analysis (this also applies to CCR regimens).

5.3 *Clinical parameters and variables*

5.3.1 *Endpoints*

As indicated above when describing the model structure, the following trial endpoints were used in the cost-effectiveness model:

- OS, defined as the time from randomization to death from any cause.
- Relapse-free survival (RFS), defined in the trial as the time from first documented CR or CRi to relapse, death from any cause, or loss to follow-up.
    - For the model this was adjusted to time from randomization until relapse or death.
- Progression-free survival (PFS), defined as the time from randomization to death or disease progression (PD) for patients who did not achieve remission (CR or CRi).
- Event-free survival (EFS; time from randomization to treatment failure, disease progression, relapse after CR or CRi, death from any cause, or loss to follow-up) was used to estimate both RFS and PFS.

PFS was not reported in the trial. This was calculated by disaggregating the data into those who did or did not achieve CR or CRi; then, patients with CR or CRi were assessed for death or relapse (i.e., RFS); patients with no CR or CRi were instead assessed for death or disease progression (i.e., PFS).

Response status was also used to allocate utilities and disease management costs; in particular, costs for consolidation IC were attributed to patients with CR, CRi, and PR. The cost of BSC was allocated to patients with PD after stopping active treatment. Response rates from the trial (after excluding non-confirmable or non-assessable subjects) used in the model are shown in Table 31.

Table 31: Response rates by arm in the AZA-AML-001 trial

Response	azacitidine response rate	CCR response rate
Remission (CR, CRi)	0.28	0.25
Relapse after remission	0.64	0.56
Non-response (PR, SD, PD, TF)	0.72	0.75
PR	0.01	0.01
SD	0.29	0.24
PD	0.08	0.08
TF	0.07	0.12

Abbreviations: CR, complete remission; CRi, morphologic complete remission with incomplete blood count recovery; PD, progressive disease; PR, partial remission' SD, stable disease; TF, treatment failure

5.3.2 *Extrapolation of data and curve fitting*

A variety of methods can be used to assess the suitability of parametric survival models, which involves fitting and testing a range of survival models and comparing internal validity (goodness of fit to the observed trial data) and external validity (the plausibility of extrapolated portions). We used the survival model selection process algorithm recommended by the NICE DSU TSD14 (106) which involves the following steps:

- examination of the log-cumulative hazard plot for each model
- testing the proportional hazards assumptions
- comparison of model fit in order to select the most appropriate model taking into account the completeness of the survival data based on:
- visual inspection
- Akaike/Bayesian information criterion (AIC/BIC)
- log-log plots
- Cox regressions
- clinical validation.

Relative efficacy is commonly used to establish differences between treatments when proportional hazards (PH) are applicable. Details are described for the extrapolation of OS in all patients below. The results of survival analysis for treatment group by pre-selected CCR treatment are presented in Appendix 9 and presented as sensitivity analyses (results based upon the individual treatment arms, should be considered however due the limitations explained throughout this document).

The following curve fits are used in the base-case:

- OS: Exponential
- RFS: Weibull
- PFS: Gompertz

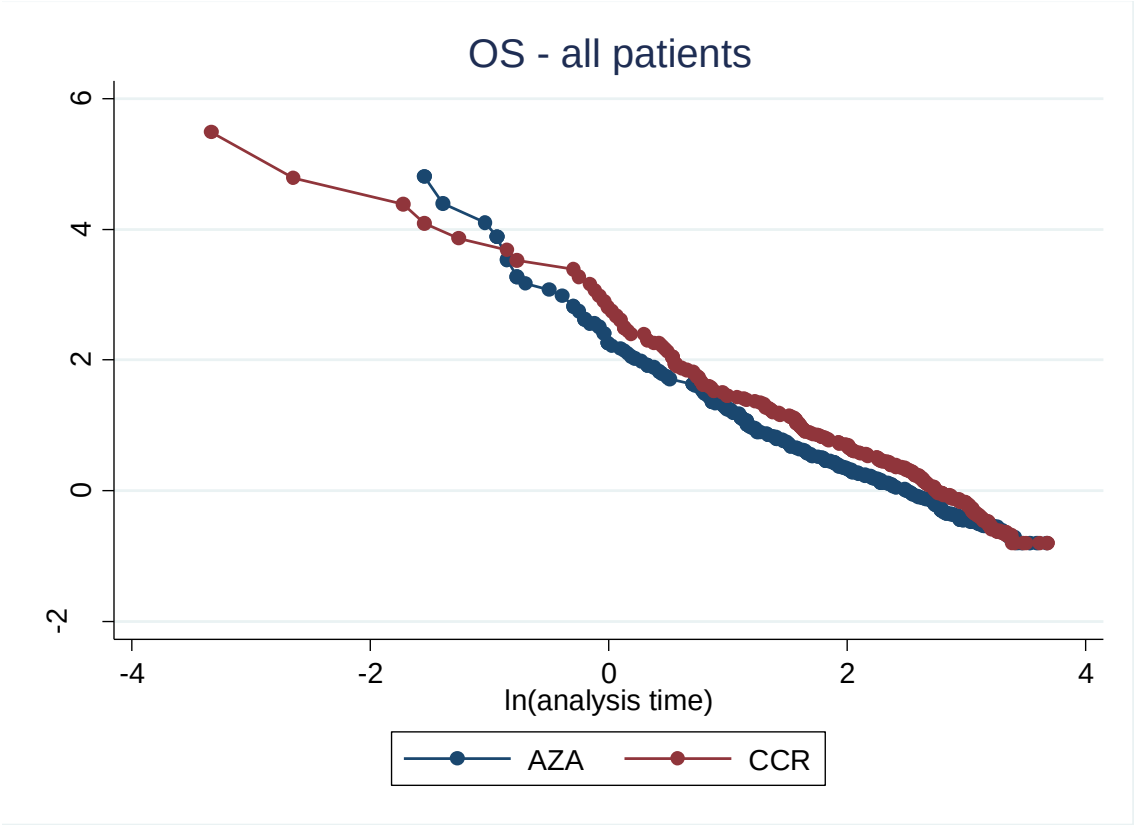
5.3.3 *Fitting of Curves*

1. OS

The Kaplan-Meier (KM) OS estimates from the AZA-AML-001 trial are shown in Figure 8. The curves start to separate after 3 months; the difference between the curves is greatest at about 13 months and then become smaller until the two curves cross at month 25. At month 40, about 10% of patients remained alive.

Using the model selection algorithm described above, the log-log plots of –ln(-ln(S)) vs ln(t), where S is survival (OS, RFS, and PFS, respectively) and t is time in months, are first plotted for OS, as shown in Figure 15. The curves are relatively straight and parallel, indicating that proportional hazards hold; moreover, a Cox regression run with an interaction between treatment group and ln(time) showed no statistically significant effect of the interaction (p-value of 0.133), also supporting the use of HRs.

Figure 15: Log-log plot for OS



HRs and their sources used for PH modelling are shown in Table 32. Following the NICE DSU recommendations (106), for exponential, Weibull, and Gompertz functions, HRs from the corresponding parametric models fitted to the survival data were used; for accelerated failure-time (AFT) models (i.e., log-logistic and log-normal) the HR is not produced, and so HRs from a Cox proportional hazards model based on KM data were used (Table 32).

Table 32: Hazard ratios for OS: azacitidine vs CCR

Source	Hazard ratio		
	Unadjusted	Subsequent treatment adjusted (see below)	Censor-at switch
Kaplan–Meier	0.84	XXX	0.75
Exponential	0.83		0.72
Weibull	0.83		0.74
Gompertz	0.83		0.74
Log-logistic[a]	0.84		0.75
Log-normal[a]	0.84		0.75

[a]From a Cox proportional hazards model fitted to KM data.

2. RFS

In the AZA-AML-001 trial, RFS was only measured for patients who achieved CR or CRi and was defined as the time from the first documented leukaemia-free state, which is different from the start of OS data (i.e., the date of randomization). To ensure consistency with OS,

RFS was redefined in the model as the time from randomization to relapse, death from any cause, or loss to follow-up, whichever occurred first, censoring for subjects alive in continuous CR/CRi. It was noted that all relapses after CR/CRi occurred before other events amongst patients who achieved CR/CRi.Figure 16 shows the KM estimates for RFS from the AZA-AML-001 trial; the curves cross after 20 months. Figure 17 shows the log-log plot for RFS hazards; unlike OS and PFS, these indicate that the PH assumption is weak, and a Cox regression run with an interaction between treatment group and ln(time) showed a statistically significant effect of the interaction (p-value of 0.011); however, the PH assumption overall has been retained for consistency. HRs are also used still for RFS in the model because the shape of the RFS curves, both overall and for treatment groups and subgroups, are not well suited for independent regression models (for illustration of this: there is no indication visually that independent regression models would better characterise observed RFS for extrapolation).Table 33 shows the HRs used in the model.

Figure 16: KM curves for RFS

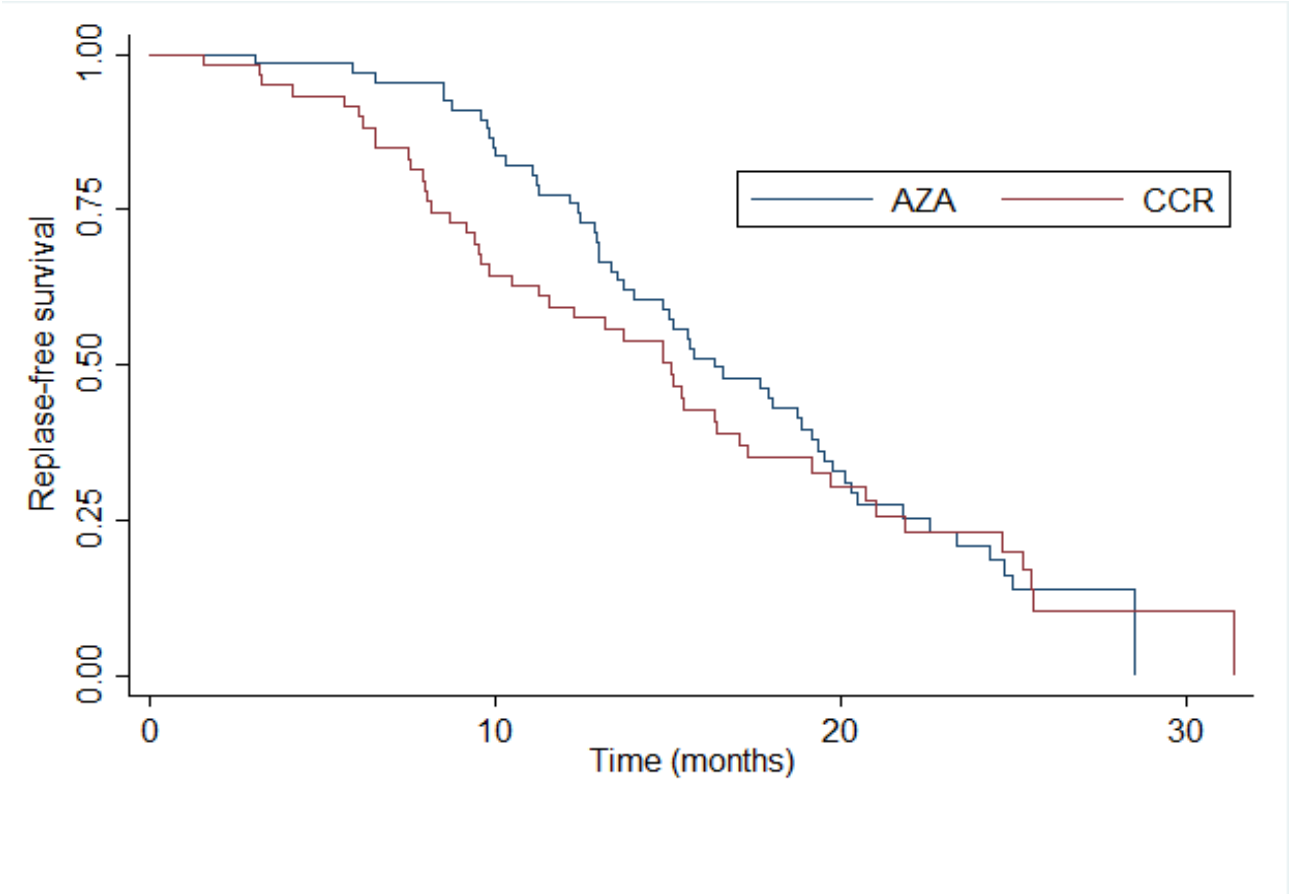


Figure 17: Log-log plot for RFS

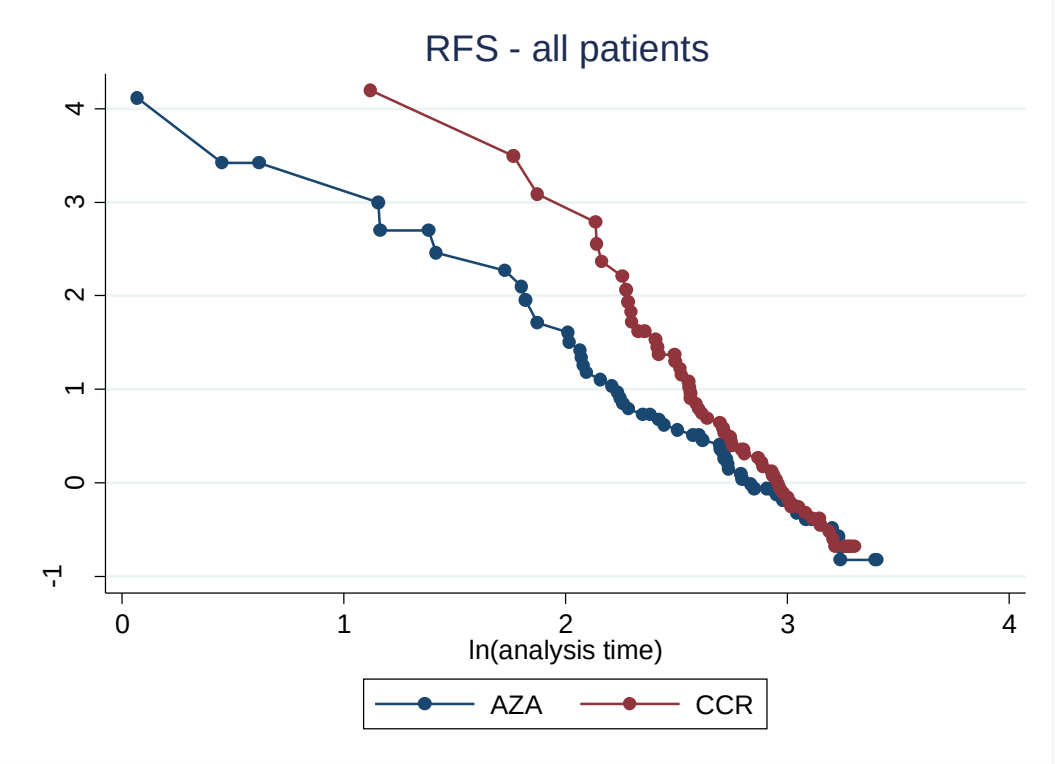


Table 33: Hazard ratios azacitidine for RFS: vs CCR

Source	Hazard ratio		
	Unadjusted	Cross-over adjusted	Censor-at switch
Kaplan–Meier	0.83	n/a	0.82
Exponential	0.86		0.86
Weibull	0.84		0.83
Gompertz	0.88		0.86
Log-logistic[a]	0.83		0.82
Log-normal[a]	0.83		0.82

[a]From a Cox proportional hazards model fitted to KM data.

3. PFS

PFS was not reported in the trial and was therefore derived from OS, PD, and EFS data. In the model, PFS was defined as the time from randomization to PD, death from any cause, or loss to follow-up, whichever occurred first. Patients who were still alive and in continuous PR or SD were censored at their last response assessment.

PFS was calculated from EFS data for patients whose best response was PR, SD, or PD and for patients who experienced TF. For these patients, all PD response assessments occurred before other events. Patients who achieved CR/CRi were excluded from the PFS analysis because they were included in the RFS analysis. Patients whose best response was non-evaluable were also excluded from the analysis as they did not fit into any category.

Figure 18 shows the KM estimates for PFS from the AZA-AML-001 trial; the curves cross after 20 months. Figure 19 shows the log-log plot for PFS hazards; as with OS, the curves are relatively straight and parallel, indicating that proportional hazards hold; moreover, a Cox regression run with an interaction between treatment group and ln(time) showed no statistically significant effect of the interaction (p-value of 0.187), also supporting the use of HRs.

Table 34 shows the HRs used in the model.

Figure 18: KM curves for PFS

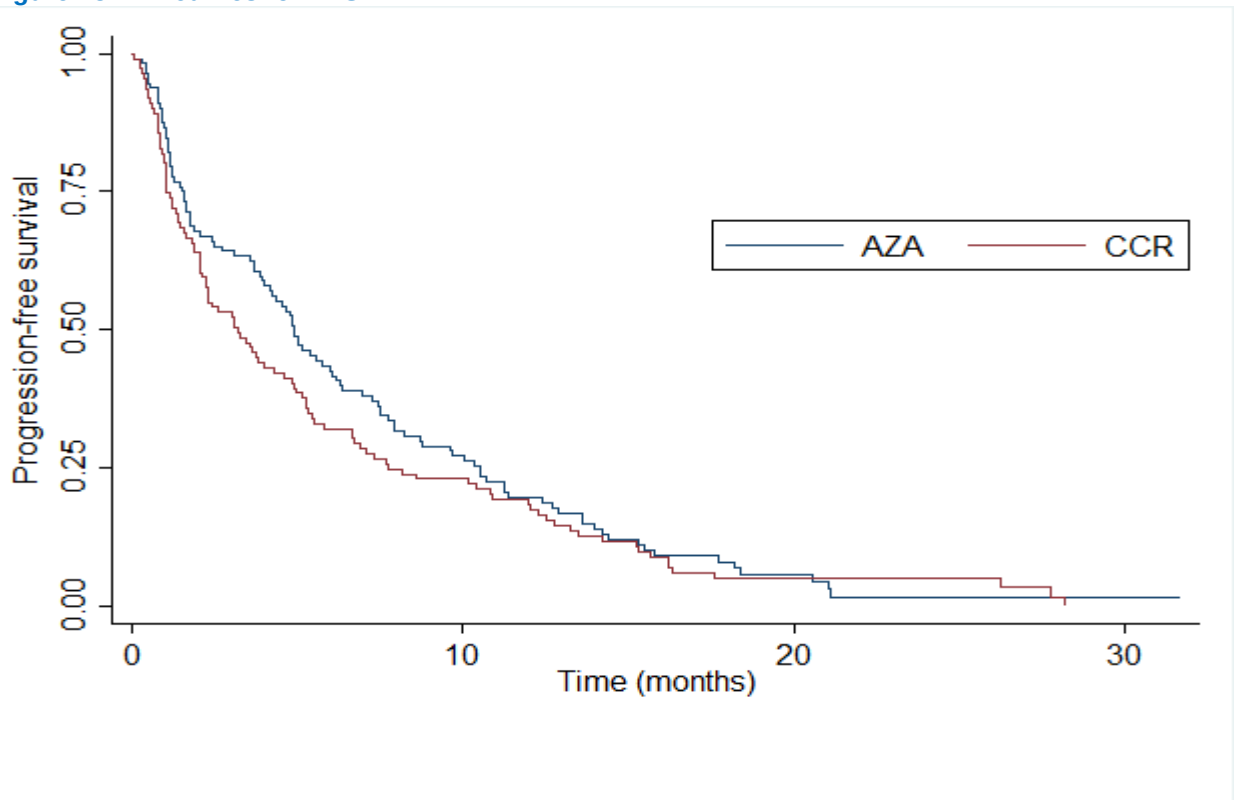


Figure 19: Log-log plot for PFS

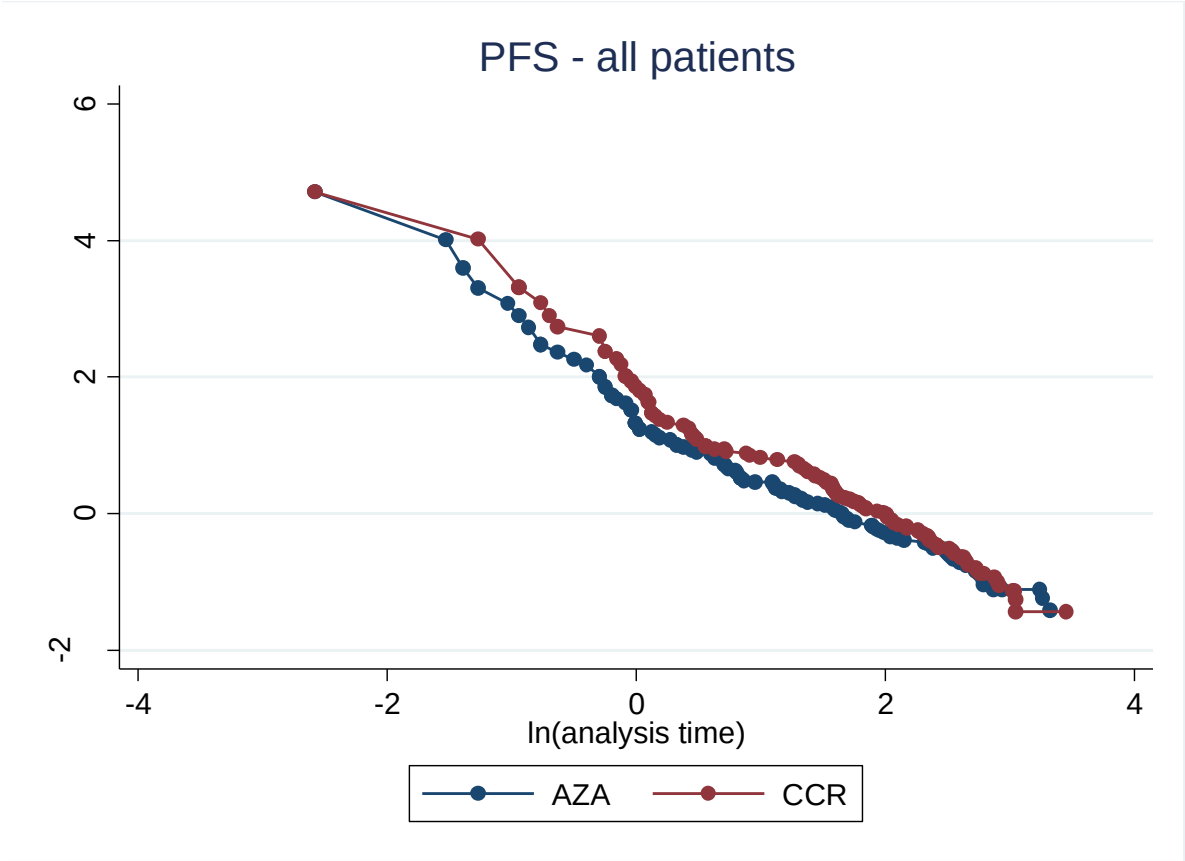


Table 34: Hazard ratios azacitidine for PFS: vs CCR

Source	Hazard ratio		
	Unadjusted	Cross-over adjusted	Censor-at switch
Kaplan–Meier	0.85	n/a	0.77
Exponential	0.85		0.75
Weibull	0.85		0.76
Gompertz	0.85		0.76
Log-logistic[a]	0.85		0.77
Log-normal[a]	0.85		0.77

[a]From a Cox proportional hazards model fitted to KM data.

5.3.4 *Curves used in the model*

All of the cases show that RFS fit was relatively poor due to the shape of the observed RFS curve; the censor-at-switch analysis also shows relatively poor fit because of the impact of the censoring overlaid on the ITT data. Table 35 and

Table 36 show the AIC and BIC goodness of fit statistics for both ITT based data and censor-at-switch data; note that the ITT data is used for both the unadjusted model (in which CCR data are the baseline and azacitidine is modelled via HR) and the cross-over adjusted model (in which azacitidine data are the baseline and counterfactual CCR is modelled via inverse HR for OS). The exponential, Weibull, and Gompertz distributions were considered as log-logistics and log-normal distributions are accelerated failure time models where hazard ratios are not established. As with the visual inspection of the curves, the AIC and BIC results suggest some uncertainty over the best fitting curve although the AIC and BIC values are close and suggest that many curves could fit with similar precision.

The extrapolated curves used in the model are shown below in Figure 20, Figure 21 and Figure 22. The base-case uses cross-over adjusted (IPCW) OS, RFS and PFS based upon HR. As such only the azacitidine curves are shown for OS as CCR is fitted via the inverse HR and CCR curves are shown for RFS and PFS as azacitidine is fitted via HR. Unadjusted (ITT) and censor-at-switch models are included in the sensitivity analyses.

Figure 20: OS after adjustment for cross-over (base-case)

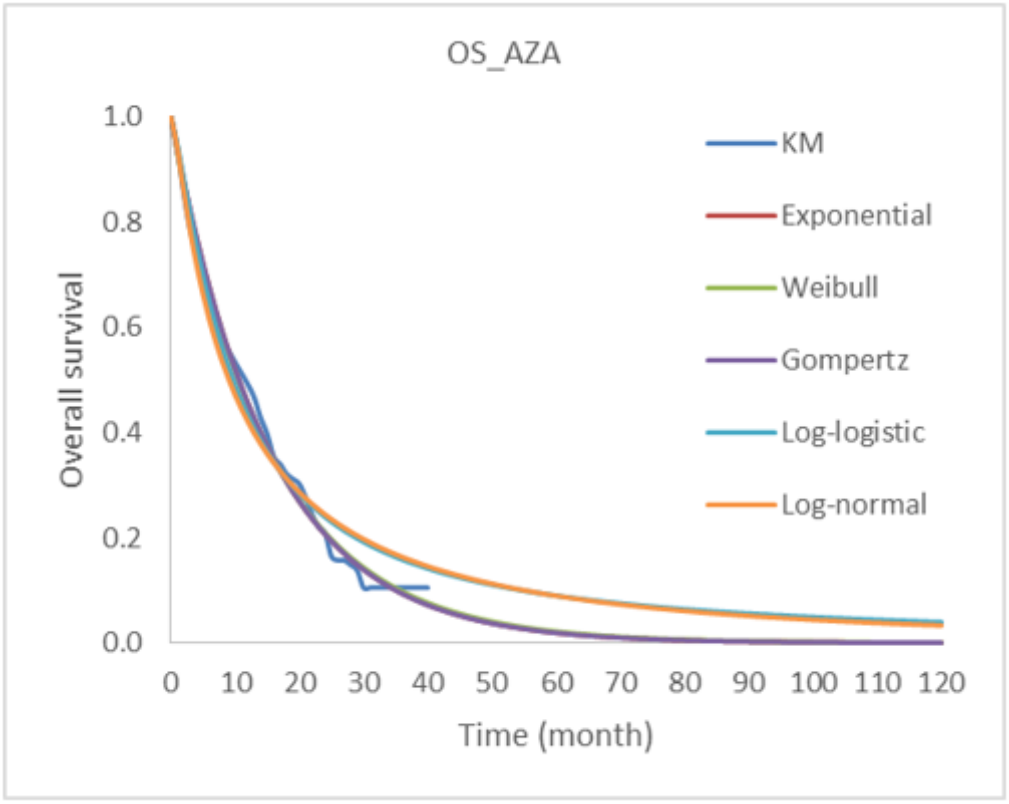


Figure 21: RFS after adjustment for cross-over (base-case)

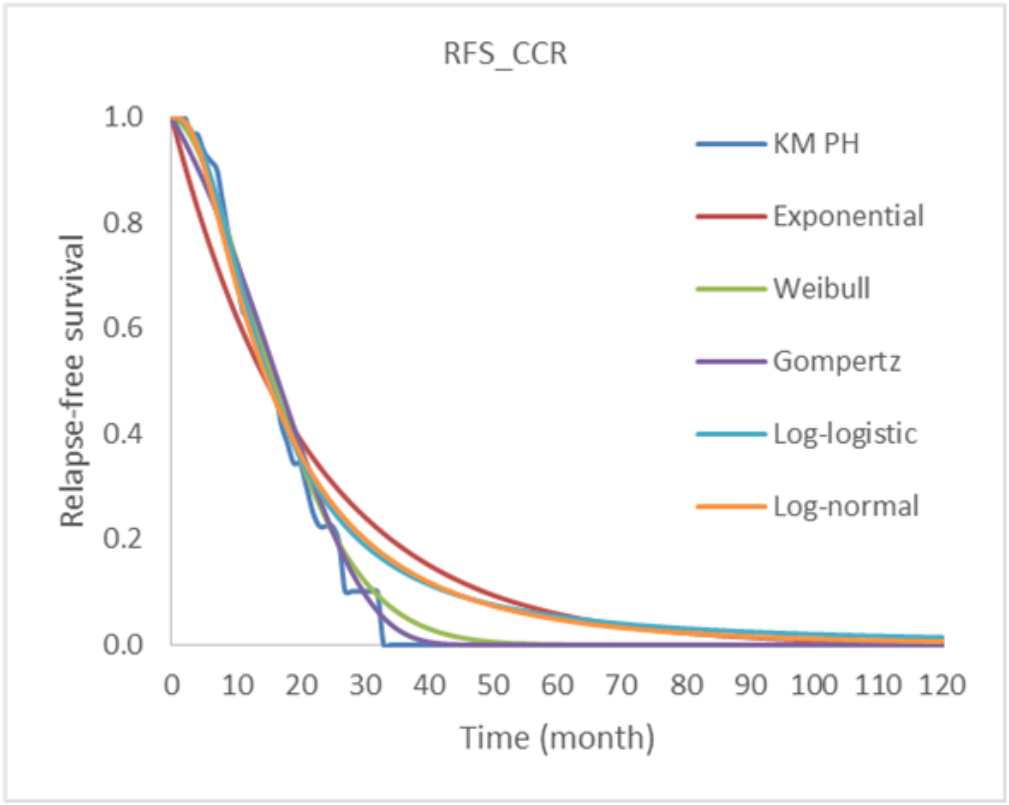


Figure 22: PFS after adjustment for cross-over (base-case)

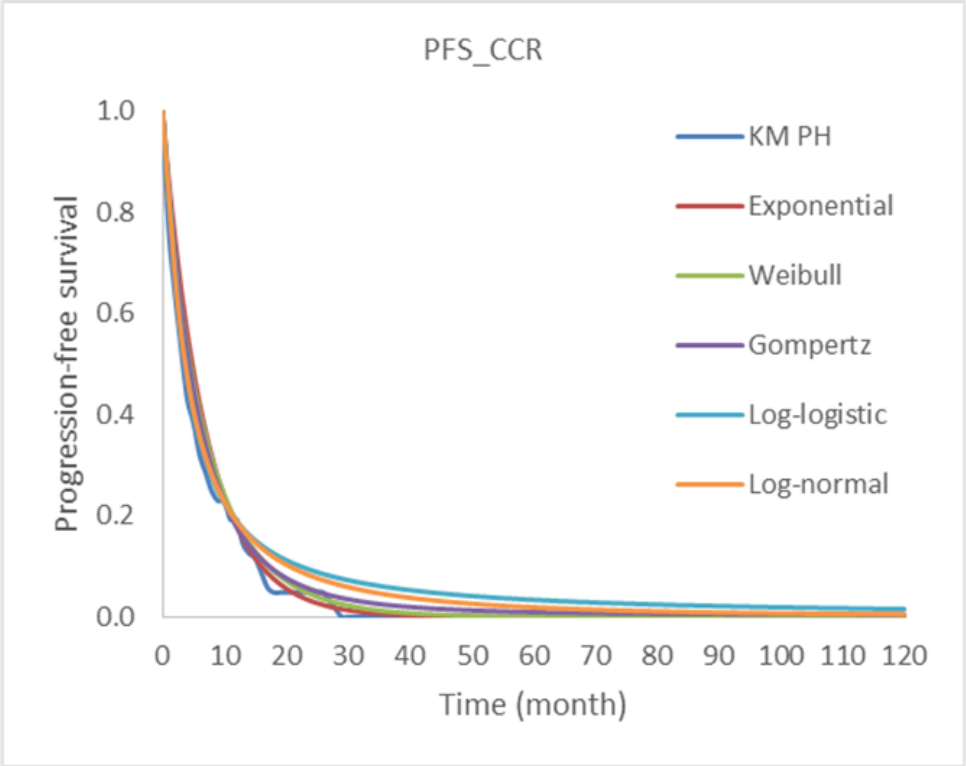
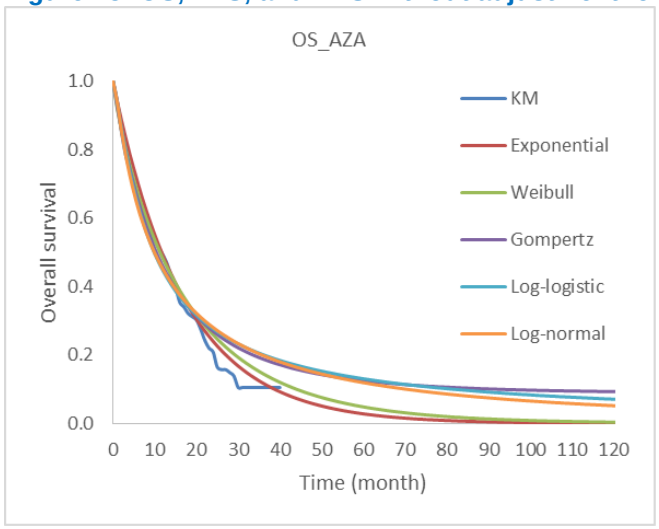
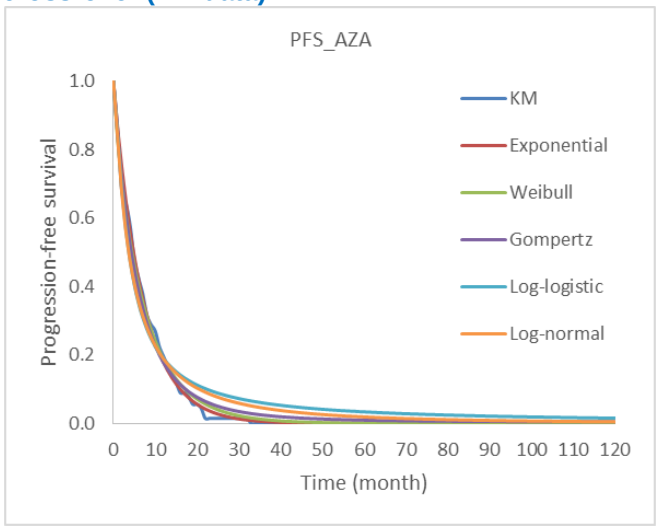
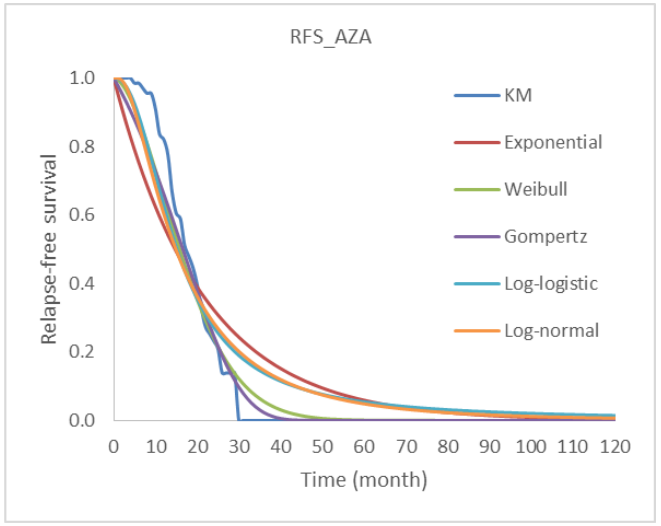
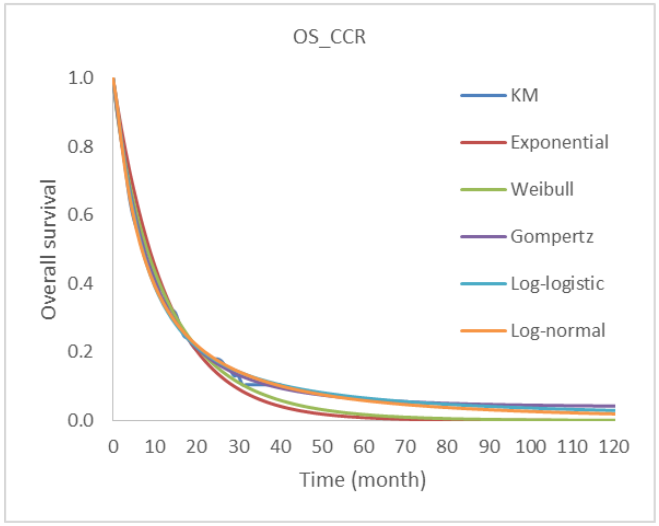


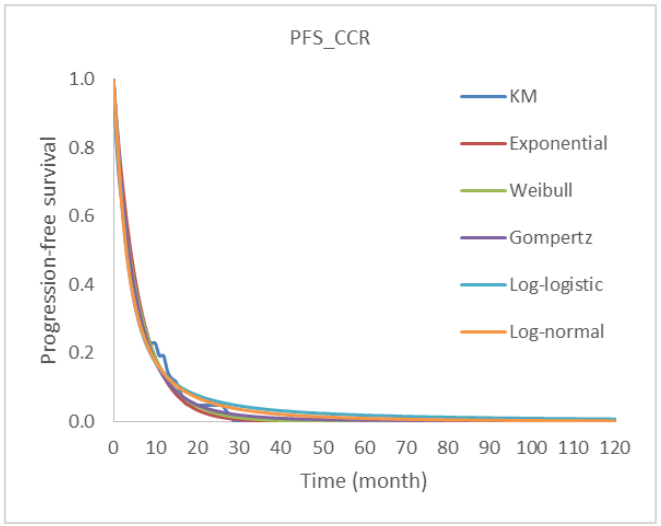
Figure 23: OS, PFS, and RFS without adjustment for cross-over (ITT data)











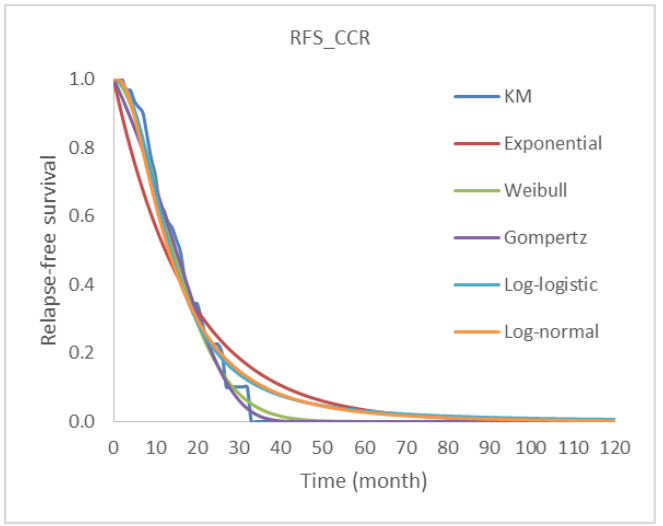


Figure 24: OS, PFS, and RFS without adjustment for cross-over (censor-at-switch data)

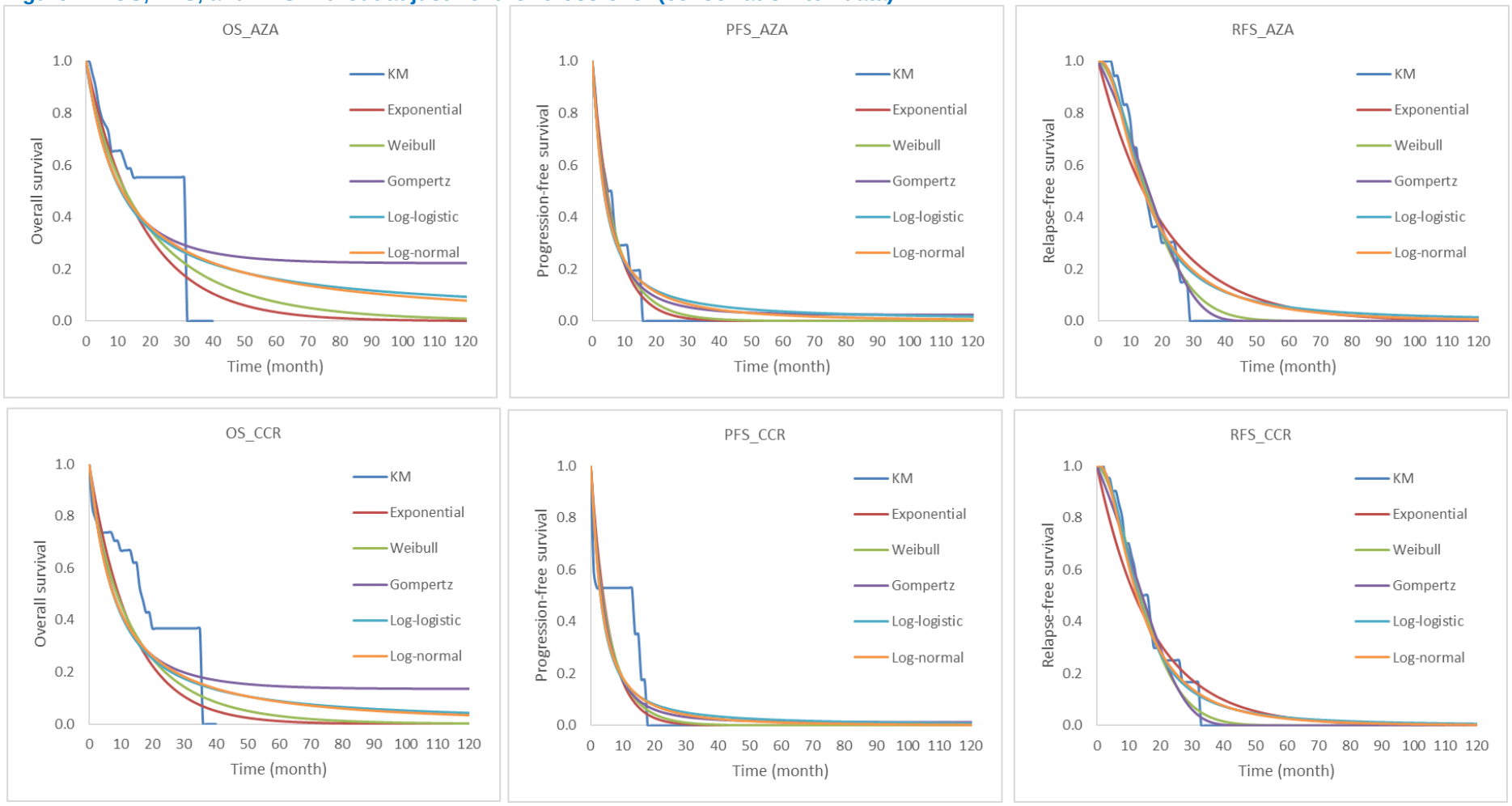


Table 35: Goodness of fit for OS, RFS, and PFS parametric functions (ITT data)

	OS	RFS	PFS

Parametric model	Azacitidine (n = 241)		CCR (n = 247)		Azacitidine (n = 67)		CCR (n = 62)		Azacitidine (n = 112)		CCR (n = 111)	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	752	759	799	806	**100**	**104**	**133**	**138**	353	359	373	378
Gompertz	752	759	**793**	**800**	108	113	137	141	353	359	**372**	378
Exponential	**750**	**754**	802	806	149	151	149	151	**351**	**354**	374	**376**

Table 36: Goodness of fit for OS, RFS, and PFS parametric functions without adjustment for cross-over (censor-at-switch data)

Parametric model	OS				RFS				PFS			
	Azacitidine (n = 241)		CCR (n = 247)		Azacitidine (n = 67)		CCR (n = 62)		Azacitidine (n = 112)		CCR (n = 111)	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	**674**	681	694	701	**103**	**108**	**137**	**141**	344	349	344	349
Gompertz	674	681	**684**	**691**	113	117	141	145	342	348	**342**	**347**
Exponential	676	**680**	700	704	150	152	150	152	**342**	**345**	344	347

5.3.5 *Subsequent Treatment Adjustment*

1. Selection of models

In the AZA-AML-001 trial a total of 67 of the 241 AZA patients received AML therapy after azacitidine, and 75 patients of the 247 CCR patients received AML therapy after CCR. The results of the pre-specified censor-at-switch analysis indicated that subsequent therapies could be affecting the OS results. To remedy this, a number of alternative methods for adjusting for treatment switching were explored. Following the NICE DSU TSD16 (80), the IPCW, Rank Preserving Structural Failure Time Model (RPSFTM) and Iterative Parameter Estimation (IPE) were estimated and tested for applicability.

The analysis was undertaken by a third party (PRMA Consulting) and involved replicating the protocol-defined analyses conducted by Celgene (primary efficacy analysis and censor-at-switch analysis), and additional analyses that adjust for treatment switching (IPCW, RPSFT and IPE). SAS v.9.3 software was used for replication of the primary efficacy and censor-at-switch analyses and for the IPCW method, but Stata v.14 was used for the remaining analyses because the RPSFT and IPE methods are not implemented in SAS. The SAS and STATA codes are available in **Error! Reference source not found.**.

All analyses were based on the ITT population. Patients were assigned to cycles where the start date of each treatment cycle was calculated based on study drug exposure records for each patient, except those who received BSC only. The start date of the first cycle was the earliest date that the patient received any study drug or the date of randomization for patients receiving BSC only. The full report is available in **Error! Reference source not found.**.

The analyses adjusted for crossover, which accounted only for switching from CCR to azacitidine, produced the following results:

- IPCW method: adjusted XXX, unadjusted XXX median OS of XXX months for CCR.
- RPSFT method: adjusted HR XXX median OS of XXX months for CCR based on counterfactual data and XXX months based on the inverse-HR.
- IPE method using an exponential distribution: adjusted HR XXX median OS of 6.49 months for CCR based on counterfactual data and XXX months based on the inverse-HR.

The two-stage method was not used because there was insufficient time-varying data to identify the “second baseline” that the method requires.

The IPCW was selected as the most realistic model (as presented in section 4.7.4.1). However, this analysis does have some limitations. The IPCW method has an underlying assumption that there are no unmeasured confounders; that is, all factors that might affect treatment switching are observed, measured, and included. In reality this is never truly the case. Every effort was made to include all relevant baseline and time-varying covariates so that no important predictors of switching are missing; the covariates were also validated by a clinical expert. However, there might be other covariates that might have an impact on switching and were not captured. A further limitation of the IPCW approach is that it does not produce counterfactual survival data directly; in order to use adjusted CCR data in

subsequent survival analysis and economic modeling, counterfactual data are required. The survivor function approach, in which the CCR hazard function is calculated using the observed azacitidine hazard function and using the inverse of the IPCW-adjusted HR, changed the shape of the CCR survival curve relative to the observed data. On the face of it, this is problematic – as well as altering the shape of the CCR survival curve, the method forces hazards to be proportional – but it must be acknowledged that the purpose of the analyses is to produce counterfactual data, which may result in counterfactual hazard functions (i.e., different KM curve shapes) and not just counterfactual hazards from curves whose shapes do not change.

These limits notwithstanding, the IPCW method and results are stronger than the alternatives. The use of RPSFT and IPE methods have an underlying assumption of a common treatment effect for patients who started treatment with azacitidine and for those who switched to azacitidine. This assumption does not hold in this case: differences in prognosis between the two groups are likely to lead to a different benefit from delayed versus immediate treatment; CCR itself, particularly LDAC and IC, is also an active treatment, so the prognosis of a patient switching from CCR will not be the same as for a patient receiving azacitidine from the start of the study.

The similarity of the results for the IPE and RPSFT analyses is likely because of violation of the key assumption, that treatment benefit in terms of OS is the same regardless of whether a patient began on azacitidine or switched; this assumption is hard to justify given the prognosis for with AML in the trial. The assumption cannot be tested in an unbiased test (i.e., the basis of the test is that patients who switched to the treatment are endogenously more or less likely to benefit, which prevents an unbiased test).

Censor-at-switch analysis is prone to selection bias, and the primary efficacy analysis (not accounting for switching) is inappropriate. The approach taken here methodically moved through the available methods.

Finally, subgroup adjustment was not feasible because of limited data on switching; however, a clinical expert consulted during this analysis stated that questions can be raised about the clinical generalizability of the results in subgroups, because clinicians can identify potential switching candidates based on observed performance, and recommended focusing on the adjusted data for overall patients.

Although there is uncertainty related to how the counterfactual CCR data must be constructed for the IPCW analysis, and the requirements for an assumption of no unmeasured confounding to hold, the assumptions underlying the IPCW method are the best supported by the data in this instance.

2. The IPCW model - Methods

A regression model is developed to estimate the probability of remaining uncensored, where in this case uncensored is defined as the CCR patient receiving no subsequent azacitidine therapy. This is then used to generate and adjust HR estimates for the difference in OS between the two treatments.

Weights relate to the probability of remaining uncensored, or having no subsequent use of azacitidine. Study patients with a low probability of remaining uncensored but who in fact remained uncensored have greater weight in the analyses than those who had a higher

probability of remaining uncensored. This is because such patients are a closer proximate match (i.e., comparing low-probability patients who are censored with low-probability patients who remain uncensored is the closest approximate comparison, and so these patients have more weight in the analysis). The basic assumption that needs to be met by applying this method is that there are no unmeasured confounders (80).This means that all relevant baseline and time-varying covariates should be correctly specified and collected, and no important predictors of switching are missing.

Patients who switch treatments are artificially censored at the time of switching, and observations for the remaining patients are weighted to adjust for censored patients. A pooled logistic model is constructed to predict the probabilities of remaining uncensored-by informative censoring (crossover) at each measurement point and must include all baseline or post-randomization variables that predict both treatment switching and outcome. Briefly, the procedure for estimation using IPCW is as follows (79, 111):

1. Panel data are created for the pooled logistic models. The follow-up period is partitioned into intervals based on follow-up measurement points (visit dates). At each measurement point, time-dependent variables that could predict treatment discontinuation, switching, and OS are assessed for all patients.

2. The probability of remaining uncensored is calculated. A logistic regression model is fitted to predict participation at each measurement (remaining uncensored) for each subject. The probability of remaining uncensored using baseline risk factors of interest (E) is estimated, as is the probability P of remaining uncensored using both baseline risk factors of interest (E) and time-dependent covariates (Z). The results of this modeling process are summarized to describe the factors associated with participation at each procedure.

3. IPCWs are calculated: the inverse probability weight for remaining uncensored (1/P) will consist of the probability for remaining uncensored estimated in step 2, using both covariates E and Z. This inverse probability is stabilized by multiplying it by the probability for remaining uncensored using covariates.

4. A standard Cox regression (i.e., in accordance with estimation with no crossover) is fitted for the current outcome using 1/P as weights. The set of covariates E and any other appropriate adjustment covariates for that outcome may also be included in a parametric regression approach. The weighted Cox regression is fitted using stabilized weights (S/P). Standard errors are corrected using sandwich estimation or bootstrapping methods.

5. An unweighted version of the Cox regression is fitted for comparison. The same models are fitted as in step 3 but without any sampling weights.

Preliminary reviews of the data suggested that subsequent use of azacitidine often closely followed relapse or progression. The model constructed had relatively short time periods (15 days) in order to capture this association. This model was constructed using the status of patients at 15 day time points. The last time period for each study subject usually contained less than 15 days.

The “numerator” model in the pooled logistic model consisted of baseline factors and the “denominator” model consisted of baseline factors and time-varying covariates. This method

provides an estimate of the adjusted HR of survival for the CCR arm in relation to the azacitidine arm but does not generate an estimate of the survival distribution (i.e., does not produce a KM curve). However, a crude estimate of the survival distribution can be obtained by applying the estimated HR to the azacitidine KM curve; this will result in an estimated CCR survival curve with a similar profile (shape) to the azacitidine curve. Similarly, the converse of the HR can be used as an estimate of the median of the adjusted survival distribution for CCR – the actual estimated values are indicative only and will reflect the estimated distribution based on the distribution of the azacitidine KM curve (112).

Baseline characteristics and time-varying variables were captured during the trial and were used in step 2 of the IPCW method in order to estimate the probabilities of remaining uncensored or having no subsequent use of azacitidine. These variables were assessed by a clinician to establish which factors would be considered relevant and appropriate for use in the crossover analysis models, and whether any of the laboratory variables collected at each visit were relevant for analysis of survival data, either as factors that influence the change in treatment or as factors that could affect the estimate of survival.

Statistical tests were then conducted to assess whether there were any statistically significant differences between CCR patients who switch and CCR patients who do not switch for the list of potential covariates to be included in the model. Means and standard deviations were calculated for numerical variables and counts and percentages for categorical variables for all patients, but also separately for patients who were censored or died. P values were determined using chi-square test for categorical variables and Student's t-test for numerical variables.

The covariates included initially in the model, are presented in Table 37. These were summarized by basic summary statistics (number and percentages for categorical variables and means and standard deviations for numerical variables).

Table 37: Covariates used in the IPCW method

Type of variable	Variable
Non time-varying covariates	
Demographic characteristics	Age at informed consent (continuous) Age (<75 years, ≥75 years)
	Sex (male or female)
	Geographic region (North America/Australia, Western Europe/Israel, Eastern Europe, or Asia)
	Race (Asian, Black or African American, White, Native Hawaiian or other Pacific islander, other, n/a)
Clinical characteristics	ECOG performance status at randomization (0–1, 2)
	AML classification (newly diagnosed, histologically confirmed *de novo* AML; AML secondary to prior myelodysplastic disease not treated with azacitidine, decitabine, or cytarabine; AML secondary to exposure to potentially leukemogenic therapies or agents with the primary malignancy in remission for at least 2 years)
	Time since initial AML diagnosis to randomization (< median; ≥ median) (derived from time since initial diagnosis and date of signed informed

Type of variable	Variable
	consent)
	Baseline comorbidity score
	Prior history of myelodysplastic syndromes (yes or no)
	Cytogenetic risk status (intermediate risk, poor risk)
Study design	Pre-randomization CCR assignment (BSC, low-dose cytarabine, intensive chemotherapy)
	International working group response assessment
Laboratory variables	Percentage bone marrow blasts (continuous) according to central review
Time-varying covariates	
Laboratory variables	WBC count
	Hemoglobin
	Platelet count
	ANC
	RBC transfusion status (independent or dependent)
	Platelet transfusion status (independent or dependent)
Adverse events	Occurrence of a grade 3/4 adverse event since last visit (yes/no)
Other	Time since last visit (in months; included at each visit)

Abbreviations: ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group; RBC, red blood cell; WBC, white blood cell

3. The IPCW model - Results

A Cox regression was approximated by using a pooled logistic model that included weighting by the stabilized weights and adjustment for the repeated study subject observations. An unadjusted HR of XXX was estimated for the model with 15 day time periods. As shown in Table 38, after adjustment for baseline factors, the HR was reduced to XXX (further details are provided in **Error! Reference source not found.**.

Table 38: Results of the IPCW models

Model	HR (95% CI)	*P* value[a]
Unadjusted	XXX	XXX
Adjusted	XXX	XXX

[a]*P* value calculated using a log-rank test

However, the IPCW method provides a KM curve associated with the counterfactual data, without itself being counterfactual data. There are various methods for producing counterfactual data. The method used here is the “survivor function” approach presented by Latimer and colleagues (113), and involves producing a counterfactual KM curve by multiplying the azacitidine hazard function (which does not require adjustment and is presumed to be unbiased by treatment switching) by the inverse of the IPCW-adjusted HR. Using the IPCW adjusted HR of XXX, this produces the observed azacitidine and counterfactual CCR data shown in Figure 25 and Table 39. Note that, because the construction of the counterfactual data alters the shape of the CCR curve to Figure 25.

Table 39 shows that this results in an increase in the median OS, but a decrease in the mean OS.

Figure 25: Kaplan–Meier plot of observed azacitidine and IPCW HR-adjusted CCR data

[redacted]

Table 39: Comparison of survival for CCR between primary efficacy and IPCW HR-adjusted analyses

Analysis	Median OS (95% CI)	Restricted mean OS[a] (95% CI)
Primary efficacy	6.49 (4.93, 8.54)	11.14 (9.26, 13.16)
IPCW	XXX	XXX

[a]Restricted mean is the mean survival within the follow-up period (24.4 months)

In the model, the cross-over adjusted hazard ratio of XXX was applied to the CCR data using the inverse. That is, trial-based, extrapolated azacitidine data is used as the reference and counterfactual CCR data is generated using inverse HRs. The implementation was conducted for all five parametric functions used to extrapolate azacitidine survival.

5.4 *Measurement and valuation of health effects*

5.4.1 *Health-related quality-of-life data from clinical trials*

5.4.1.1 Mapping

PubMed and the latest HERC database were searched to identify algorithms to map from the EORTC QLQ-C30 to EQ-5D. The HERC database lists published studies of mapping algorithms that estimate EQ-5D Health State Utility Values (HSUVs) from other HRQL measures and reports the algorithm in sufficient detail to allow other researchers to estimate utilities from other data. Ten studies that mapped between the EORTC QLQ-C30 and EQ-5D in various cancers were identified, but none in AML or haematology.

Many of the reported mapping algorithms are not applicable to other samples: the mapping function is not always provided fully for other researchers to use, the samples may have been too small, or the methodology may have produced unreliable predictions.

The mapping algorithm reported by McKenzie and Van der Pol, 2009 (114) and Proskorovsky et al., 2014 (115) were selected, based on their previous use in HTA, the large sample of older cancer patients in the UK, the good performance of the model, and its external validation by Longworth et al., 2014 (116). The more recent algorithms by Proskorovsky *et al.*, 2014 were used to derive HSUVs for the base case; HSUVs based on the algorithm by McKenzie and van der Pol, 2009 were used in scenario analysis. The mapping algorithms are presented in Table 40.

Table 40: Mapping algorithms from EORTC QLQ-C30 to EQ-5D

EORTC QLQ-C30	McKenzie and Van der Pol, 2009	Proskorovsky et al., 2014	
		Full model	Trimmed model
Constant	0.2376	0.1554	0.23004

EORTC QLQ-C30	McKenzie and Van der Pol, 2009	Proskorovsky et al., 2014	
		Full model	Trimmed model
Global health status	0.0016*	0.00198*	0.00191
Physical functioning	0.0004	0.00463*	0.00478
Role functioning	0.0022*	0.00058079	NS
Emotional functioning	0.0028*	0.00141*	0.00136
Cognitive functioning	0.0009*	−0.00048664	NS
Social functioning	0.0002	0.00059878	NS
Fatigue	−0.0021*	0.00016137	NS
Nausea/vomiting	−0.0005	0.00041262	NS
Pain	−0.0024*	−0.00249*	−0.00249
Dyspnoea	0.0004	0.00060165	NS
Insomnia	0.00004	0.00082466	NS
Appetite loss	0.0003	−0.00037029	NS
Constipation	0.0001	−0.00050445	NS
Diarrhoea	−0.0003	-	-
Financial problems	−0.0006	0.00079559	NS
Adjusted R^2	0.611	0.6956	0.6941
RMSE indices	-	0.165	0.165
No of patients (country)	199 (UK)	154 (UK and Germany)	
Disease	Inoperable oesophageal cancer	Multiple myeloma	
Validation	External validation with breast cancer	No external validation	

RMSE, root mean square error; NS, not significant

Mapping was based on subgroups of patients with EORTC QLQ-C30 values.

- Utility for remission with CR or CRi was mapped patients who achieved CR or CRi.
- Utility for non-remission with PR or SD was mapped from patients who achieved PR or SD.
- Utility for PD was mapped from the final observed data before progression as a proxy for progression.
- Utility for post-relapse after remission is assumed to be the same as for PD.

The resulting mapped HSUVs are presented in Table 41 below.

5.4.2 *Health-related quality-of-life studies*

As explained above, targeted searches were run and identified two studies which have been used to inform the HSUVs used in the model. More details on the McKenzie and Van der Pol, 2009 and Proskorovsky et al., 2014 studies are presented above.

5.4.3 *Adverse reactions*

The model also included a disutility associated with overall grade 3 or above AEs. The decrement used in the model is shown in Table 41 below. The EORTC QLQ-C30 data was used to map the EQ-5D utility for AEs are from patients who were hospitalised with and without grade 3 or higher TEAEs in the AZA-AML-001 trial. Adverse event-related QALYs were calculated by multiplying the incidence of overall grade 3 or higher AEs (i.e., the probability of occurring) by its duration in days, then multiplying the result by the day equivalent of the HSUV.

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

The HSUVs derived using the algorithm by Proskorovsky and colleagues were used in the base case analysis; results based on the algorithm by McKenzie and colleagues were explored in the scenario analysis. HSUVs are assumed to be independent of treatment. No HSUVs were applied in the death state.

Table 41: Summary of utility values for cost-effectiveness analysis

Health state	Proskorovsky et al., 2014	McKenzie and Van der Pol, 2009
Remission (CR/CRi)	0.7707	0.7400
Non-remission (PR, SD)	0.7160	0.6574
Post-progression/relapse (PD)	0.6233	0.5680
Grade 3+ AEs	− 0.0240	− 0.0207

Abbreviations: AE, adverse event; CR, complete remission; CRi, morphologic complete remission with incomplete blood count recovery; PD, progressive disease; PR, partial remission' SD, stable disease

5.5 *Cost and healthcare resource use identification, measurement and valuation*

Healthcare Resource Use (HCRU) data are taken directly from a questionnaire Celgene conducted with 7 clinicians (Appendix 12). The questionnaire includes HCRU on medical staff contacts, monitoring patients, hospital-related costs (e.g., inpatient stays and management of adverse events) by treatment arms and treatment course. Average numbers from respondents were used in the model.

Rates of resource use per month (converted to the 4-week model cycle) were collected for the health states induction/pre-response, remission, stable disease, and progressive disease. The weighted average of healthcare resource use by patient proportions of the CCR arm was used for the entire CCR arm.

The questionnaire also captured the expected number of transfusions (red blood cell and platelet) for each health state. Transfusion costs are based on types of transfusion required, the mean number of each transfusion per patient and unit cost per transfusion by type. Table 51 below provides more details.

Unit costs for HCRU are based on the BNF, NHS reference costs, and PSSRU. The costs used are presented in Table 48 below.

Patients who die are assumed to receive terminal care before death. A terminal care cost of £5,705 per patient was assumed, based on a micro-costing study by the King's Fund (117) and is applied as a single cost at the point of death.

The cost per cycle of HCRU on medical staff contacts, monitoring patients, and hospital-related costs was then calculated by multiplying RFS and PFS by the respective unit costs at each cycle. OS was used to calculate the terminal care cost per cycle. The total cost of HCRU is the sum of the costs per cycle.

The cost of managing AEs was calculated as a cost per patient, based on the average cost for managing the most frequent grade 3 or 4 TEAEs in the AZA-AML-001 trial (i.e., anaemia, neutropenia, febrile neutropenia, thrombocytopenia, pneumonia, AML. The costs are presented in Table 52 below.

5.5.1 *Resource identification, measurement and valuation studies*

Targeted searches were run to identify any costing studies for the population in question. A costing study (56) was identified which developed a model combining a decision tree with several Markov models to reflect the complexity of the prognostic factors and treatments of AML. The model was simulated with a cycle length of 1 month for a time period of 5 years and further simulated until age 100 years or death. Results were compared for two age groups and five different initial treatment intents and responses. Transition probabilities, life expectancies, and costs were derived from 2006 data from the HMRN.

However, this study was not specific to AML with >30% blasts and sufficient information on the selection and inclusion of specific costs was not available to provide useable information for the de-novo health economic model.

5.5.2 *Intervention and comparators' costs and resource use*

Drug utilization was estimated directly from the AZA-AML-001 trial. Total drug use per cycle, per patient was calculated by multiplying the average daily dose (mg/m^2), the average BSA of 1.80 m^2, and days per cycle. The base case assumes wastage (i.e., no vial sharing) and alternative scenarios of no wastage, and wastage with 30% tolerance (i.e., vial sharing assumed in 30% of cases) are explored in sensitivity analyses. For drugs with several vial or pack sizes, vial size selection was on the basis of the largest available size, rather than smaller vials as required to minimize vial wastage. The number of vials required for each drug are shown in Table 42. As can be seen, the dosing from the AZA-AML-001 trial is used where a mean of 6.9 days per cycle was observed for azacitidine.

Table 42*:* Drug utilisation per cycle (4 weeks)

Treatment	Medications (vial/pack size)		Daily dose (mg/m2)	Days per cycle	Total Dose (mg) per cycle
Azacitidine	Azacitidine (100 mg)		XXX	XXX	XXX
IC, induction	Cytarabine	100 mg	122.20	7.10	1,561.72
		500 mg			
		1,000 mg			

Treatment	Medications (vial/pack size)		Daily dose (mg/m2)	Days per cycle	Total Dose (mg) per cycle
	Daunorubicina (20 mg)		49.70	3.00	268.38
	Idarubicina	5 mg	11.00	3.00	59.40
		10 mg			
IC, consolidation	Cytarabine	100 mg	120.20	5.00	1,081.80
		1,000 mg			
	Daunorubicina (20 mg)		49.40	2.00	177.84
	Idarubicina	5 mg	10.70	2.00	38.52
		10 mg			
LDAC	Cytarabine	100 mg	84.05	10.22	696.65
		500 mg			

[a]Use of anthracycline in the trial comprised 50% idarubicin and 50% daunorubicin
Abbreviations: IC, intensive chemotherapy; LDAC, low-dose cytarabine.

Drug acquisition unit costs (Table 43) were calculated based on prices from BNF.

Table 43: Drug acquisition unit costs (£)

Drug name	Vial or pack	mg per vial or pack	Price (£) per vial/pack	Source
Azacitidine	100 mg vial	100	XXX	BNF 2015
Cytarabine (non-proprietary)	20 mg/mL; 5 mL vial or 100 mg/mL; 1 mL vial	100	4.95[a]	
	20 mg/mL; 25 mL vial or 100 mg/mL; 5 mL vial	500	19.75[a]	
	100 mg/mL; 10 mL vial	1,000	39.00	
	100 mg/mL; 20 mL vial	2,000	77.50	
Daunorubicin (non-proprietary)	20 mg vial	20	55.00	BNF 2015
Idarubicin (Zavedos®)	5 mg vial	5	87.36	
	10 mg vial	10	174.72	

[a]Average of two prices.

The drug acquisition cost per cycle was calculated based on number of vials required and unit cost per vial and is presented in Table 44.

Table 44: Drug acquisition cost per cycle

Treatment	Total drug cost per cycle per patient (£)

		No wastage	Wastage	Wastage with 30% tolerance
Azacitidine		XXX	XXX	XXX
IC, induction	Cytarabine	£77	£105	£77
	Daunorubicin[a]	£738	£825	£738
	Idarubicin[a]	£1,038	£1,048	£1,038
IC, consolidation	Cytarabine	£54	£75	£54
	Daunorubicin[a]	£550	£489	£489
	Idarubicin[a]	£673	£699	£673
LDAC	Cytarabine	£34	£48	£34

[a]Average of two prices
Abbreviations: IC, intensive chemotherapy; LDAC, low-dose cytarabine

The per cycle cost could then be applied to the treatment duration from AZA-AML-001 to calculate the total cost per patient. Table 45 shows the mean number of treatment cycles, taken from the AZA-AML-001 CSR. The trial protocol states that patients should receive at least six cycles of azacitidine. In the trial, the patients received a mean of 8.8 cycles, which was therefore used in the model. The effect of increasing the number of cycles was explored in the sensitivity analysis. For IC, the trial protocol also states that patients who achieved CR, CRi, or PR may receive one or two consolidation cycles. The mean number of cycles in the trial was 1, which was therefore used in the model.

Table 45: Mean number of treatment cycles in the AZA-AML-001 trial

Treatment		Mean number of cycles per patient
Azacitidine		8.80
IC, induction	Cytarabine	1.00
	Daunorubicin[a]	1.00
	Idarubicin[a]	1.00
IC, consolidation	Cytarabine	1.00
	Daunorubicin[a]	1.00
	Idarubicin[a]	1.00
LDAC	Cytarabine	5.21
BSC		3.60

[a]1:1 ratio was assumed for patients on daunorubicin and idarubicin.
Abbreviations BSC, best supportive care; IC, intensive chemotherapy; LDAC, low-dose cytarabine.

5.5.3 *Health-state unit costs and resource use*

HCRU associated with the different health-states depend on the health professionals involved, and the frequency and mean time (in minutes) of their involvement (Table 46 and Table 47). Unit costs for health professionals are from PSSRU and NHS reference costs (Table 48). The different monitoring and testing requirements are also captured via the clinician questionnaire and are presented in Table 49 with the unit costs in Table 50.

Table 46: HCRU (frequency per cycle) for each health state.

	Induction/pre-response		Remission		Stable disease		Progressive disease	
	Azacitidine	CCR	Azacitidine	CCR	Azacitidine	CCR	Azacitidine	CCR
CNS Haematologist	2.77	2.38	1.66	0.87	2.08	2.37	2.03	2.62
Consultant	2.58	3.52	0.92	1.13	1.29	1.66	2.03	1.60
Day Care Nurse	7.75	2.35	5.54	0.95	6.00	3.41	3.69	3.47
Day Care SpR	1.66	5.16	1.11	2.07	1.66	2.85	2.95	2.95
District Nurse	0.62	5.39	0.31	5.61	0.62	6.33	0.62	0.59
Doctor	0.85	4.95	1.23	2.21	1.54	3.04	0.92	0.88
Jnr. Doctor	0.23	17.11	0.62	21.75	2.54	17.31	2.77	2.64
Pharmacist	2.77	3.09	2.77	1.78	2.95	1.37	0.31	0.42
Oncology nurse	0.62	2.17	0.31	0.05	0.62	0.50	0.62	0.59
Inpatient day	3.16	13.91	0.25	0.90	2.30	9.20	1.73	2.61

Source: Celgene HCRU questionnaire for the resource use;
Abbreviations: CCR; conventional chemotherapy regimens; CNS, clinical nurse specialist; SpR, specialist registrar

Table 47: HCRU (mean time in minutes per frequency) for each health state

	Induction/pre-response		Remission		Stable disease		Progressive disease	
	Azacitidine	CCR	Azacitidine	CCR	Azacitidine	CCR	Azacitidine	CCR
CNS Haematologist	34.20	25.51	26.40	25.85	33.00	37.23	24.40	34.20
Consultant	25.60	20.33	20.80	16.29	24.00	16.97	20.80	25.60
Day Care Nurse	40.72	22.99	18.40	3.91	26.83	27.55	33.00	40.72
Day Care SpR	22.00	19.82	22.00	17.79	22.00	19.08	22.00	22.00
District Nurse	15.00	13.87	15.00	4.26	15.00	17.31	15.00	15.00
Doctor	12.67	13.00	12.67	9.79	12.67	12.10	9.00	12.67
Jnr. Doctor	9.00	16.01	15.00	0.94	20.00	10.76	12.67	9.00
Pharmacist	13.50	25.64	13.50	0.71	13.50	19.68	6.00	13.50
Oncology nurse	6.00	11.68	4.00	0.00	6.00	4.55	6.00	6.00
Inpatient day	1440.00	1440.00	1440.00	1440.00	1440.00	1440.00	1440.00	1440.00

Source: Celgene HCRU questionnaire for the resource use;
Abbreviations: CCR; conventional chemotherapy regimens; CNS, clinical nurse specialist; SpR, specialist registrar

Table 48: Unit costs for each item of HCRU

Staff type	Unit costs available 2013/2014 (costs including qualifications given in brackets)	Cost per minute (per day for inpatient stay)	Source
CNS Haematologist	Nurse advanced (includes lead specialist, clinical nurse specialist, senior specialist). £51 (£58) per hour; £80 (£90) per hour client contact cost	£1.33	PSSRU 2014
Consultant	Consultant: medical, £101 (£140) per contract hour	£1.68	PSSRU 2014
Day Care Nurse	Nurse, day ward (includes staff nurse, registered nurse, registered practitioner), £34 (£41) per hour; £84 (£100) per hour of patient contact	£1.40	PSSRU 2014
Day Care Specialist registrar	Registrar group, £40 (£60) per hour (48 hour week); £34 (£51) per hour (56 hour week); £48 (£71) per hour (40 hour week)	£0.80	PSSRU 2014
District Nurse	Community nurse (includes district nursing sister, district nurse), £43 (£50) per hour; £57 (£66) per hour of patient-related work.	£0.95	PSSRU 2014
Doctor	Associate specialist, £97 (£124) per hour (40 hour week). An associate specialist is a doctor who has trained and gained experience in a medical or surgical specialty but has not become a consultant.	£1.62	PSSRU 2014
Jnr. Doctor	Foundation house officer 2, £29 (£41) per hour (48 hour week); £25 (£35) per hour (56 hour week); £35 (£49) per hour (40 hour week)	£0.58	PSSRU 2014
Pharmacist	Hospital pharmacist, £42 (£48) per hour; £84 (£96) per cost of direct clinical patient time (includes travel); £60 (£68) per cost of patient-related activities.	£1.40	PSSRU 2014
Oncology nurse	Nurse team leader (includes deputy ward/unit manager, ward team leader, senior staff nurse), £42 (£48) per hour; £104 (£120) per hour of patient contact	£1.73	PSSRU 2014
Inpatient stay for IC (cost/day)	Average of "Elective Inpatients - Excess Bed Days", "Non-Elective Inpatients - (Long Stay) Excess Bed Days", "Day Case", "Non-elective Inpatients - Short Stay", "Regular Day or Night Admissions"	£714.64	SA25G/ SA25H/ SA25J/ SA25K/ SA25L/ SA25M - Because the unit cost of inpatient stay for IC is cost per day, elective inpatients and non-elective inpatients (long stay) are excluded

Abbreviations: CNS, clinical nurse specialist; SpR, specialist registrar; PSSRU, Personal Social Services Research Unit; IC, intensive chemotherapy.

Table 49: HCRU (number of tests per cycle) for drug monitoring tests

	Induction/pre-response		Remission		Stable disease		Progressive disease	
	Azacitidine	CCR	Azacitidine	CCR	Azacitidine	CCR	Azacitidine	CCR
Bone marrow aspirates	0.92	1.25	0.15	0.21	0.42	0.35	0.15	0.16
Bone marrow biopsies	0.50	0.41	0.00	0.00	0.04	0.08	0.00	0.03
Peripheral blood smears	1.08	1.01	0.77	0.59	0.77	0.83	0.77	0.74
Blood tests	9.23	13.29	1.85	3.53	6.54	7.82	7.23	8.33
DNA and RNA extractions for molecular testing	0.92	1.24	0.15	0.15	0.15	0.20	0.15	0.15
Extractions for cytogenetic testing	0.92	0.80	0.15	0.16	0.15	0.19	0.15	0.13
Serum blood chemistry	8.46	12.00	1.69	3.53	6.38	7.72	6.92	7.74

Source: Celgene HCRU questionnaire for the resource use
Abbreviations: CCR; conventional chemotherapy regimens; DNA, deoxyribonucleic acid; RNA, ribonucleic acid

Table 50: Unit Costs for drug monitoring tests

Laboratory and disease monitoring tests	Description	Cost per test	Source
Bone marrow aspirates	Clinical Biochemistry, National average cost	£1.18	DAPS04, NHS reference 2013-2014
Bone marrow biopsies	Clinical Biochemistry, National average cost	£1.18	DAPS04, NHS reference 2013-2014
Peripheral blood smears	Haematology, National average cost	£3.00	DAPS05, NHS reference 2013-2014
Blood tests	Haematology, National average cost	£3.00	DAPS05, NHS reference 2013-2014
DNA and RNA extractions for molecular testing	Clinical Biochemistry, National average cost	£1.18	DAPS04, NHS reference 2013-2014
Extractions for cytogenetic testing	Cytology, National average cost	£7.77	DAPS01, NHS reference 2013-2014
Serum blood chemistry	Clinical Biochemistry, National average cost	£1.18	DAPS04, NHS reference 2013-2014

Table 51: Unit costs and resource use (number of transfusions per cycle) of transfusions

	Induction/pre-response		Remission		Stable disease		Progressive disease		Unit cost (per transfusion)
	Azacitidine	CCR	Azacitidine	CCR	Azacitidine	CCR	Azacitidine	CCR	
Red blood cells	3.62	3.40	0.15	0.72	3.00	3.05	4.55	4.78	£121.85 (118)
Platelets	4.54	3.63	0.15	0.48	3.92	3.46	5.70	5.85	£193.15 (119)

Source: Celgene HCRU questionnaire for the resource use
Abbreviations: CCR; conventional chemotherapy regimens.

5.5.4 *Adverse reaction unit costs and resource use*

As explained above, the cost of managing AEs was calculated as a cost per patient, based on the average cost for managing the most frequent grade 3 or 4 TEAEs in the AZA-AML-001 trial (i.e., anaemia, neutropenia, febrile neutropenia, thrombocytopenia, pneumonia, AML.

Table 52: Costs of managing adverse events (≥ grade 3)

Adverse Event	Cost per inpatient episode	Source
Anaemia	£341.69	National Schedule of Reference Costs 2013-14, HRG. Currency Code: SA08J - Other Haematological or Splenic Disorders, with CC Score 0-2. Unit day case cost
Neutropenia	£341.69	National Schedule of Reference Costs 2013-14, HRG. Currency Code: SA08J - Other Haematological or Splenic Disorders, with CC Score 0-2. Unit day case cost
Febrile neutropenia	£341.69	National Schedule of Reference Costs 2013-14, HRG. Currency Code: SA08J - Other Haematological or Splenic Disorders, with CC Score 0-2. Unit day case cost
Thrombocytopenia	£316.46	National Schedule of Reference Costs 2013-14, HRG. Currency Code: SA12K - Thrombocytopenia with CC Score 0-1. Unit Day case cost
Pneumonia	£143.64	National Schedule of Reference Costs 2013-14, CL. Currency Code: WF01A, Service Code 300 - General Medicine. National average unit cost
Acute myeloid leukaemia	£377.01	National Schedule of Reference Costs 2013-14, CL. Currency Code: SA25M - Acute Myeloid Leukaemia with CC Score 0-1. Unit day case
Grade ≥ 3 TEAEs	£310.36	Average

Abbreviations: HRG, Health Resource Group; TEAE, Treatment Emergent Adverse Events.

5.5.5 *Miscellaneous unit costs and resource use*

There are no additional or miscellaneous costs considered in the economic evaluation.

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

5.6.1 *Summary of base-case de novo analysis inputs*

Table 53: Summary of variables applied in the economic model

Model element	Details	Justification	Section
Population	Older patients (≥65 years old) in the UK with newly diagnosed AML who are not eligible for HSCT Patients stratified into treatment groups based on eligibility for one of three CCRs: • BSC	Pivotal AZA-AML-001 trial	5.2

	• IC • LDAC		
Subgroups	Population subgroups of interest: • Patients with poor cytogenetic risk • Patients with myelodysplasia-related changes	Pivotal AZA-AML-001 trial, NICE scoping meeting	5.3
Intervention	Azacitidine + BSC	Pivotal AZA-AML-001 trial	5.2
Comparators (treatment groups)	CCR Individual arms investigated in sensitivity analyses (but should be interpreted with caution) • IC + BSC • LDAC + BSC • BSC alone	Pivotal AZA-AML-001 trial	5.2
Outcomes	Overall survival Progression-free survival Relapse-free survival LYs and QALYs Healthcare resource costs Incremental costs, LYs, and QALYs ICER	As per NICE reference case	
Type of economic evaluation	Cost–utility analysis	As per NICE reference case	5.2
Method of analysis of survival	Extrapolation using regression models: • Exponential • Weibull • Gompertz • Log-logistic • Log-normal Adjustment for CCR-to-azacitidine treatment switching using • IPCW and inverse HRs • Censor-at-switch analysis rather than ITT	NICE DSU guidance	5.3
Perspective on health effects	Direct health effects on patients	As per NICE reference case	5.2
Perspective on costs	NHS and PSS	As per NICE reference case	5.2
Time horizon	Lifetime horizon for an older patient with newly diagnosed AML (i.e., 10 years, as almost all patients have died by the end of year 10 in the model)	As per NICE reference case	5.2

Cycle length	4 weeks	Corresponding to treatment cycle length	5.2
Synthesis of evidence on health effects	Direct evidence from AZA-AML-001 trial – the evidence on the efficacy of AZA in the indication of interest	All comparators available in trial	5.2
Measurement and valuation of health effects	QALYs	As per NICE reference case	5.2
Source of data for measurement of health-related quality of life	Utility values mapped from trial-based EORTC QLQ-C30 data using published algorithms	As per NICE reference case when EQ-5D not collected in trial	5.4
Evidence on resource use and costs	Rates and frequencies of HCRU based on clinician survey, NICE technology appraisals, and published literature Unit costs from published NHS and PSSRU tariffs, and the BNF	Best available sources of UK data.	5.5
Discounting	Annual rate of 3.5% for both costs and health effects	As per NICE reference case	5.2

Abbreviations: AML, acute myeloid leukaemia; BNF, British National Formulary; BSC, best supportive care; EORTC, European Organisation for Research and Treatment of Cancer; HCRU, health resource use; HSCT, haematopoietic stem cell transplantation; ICER, incremental cost-effectiveness ratio; LY, life-year; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life-year

5.6.2 *Assumptions*

The following key assumptions have been made:

Table 54: Assumptions used in the economic model

Assumption	Justification
Patients are not eligible for HSCT at any point	Azacitidine's license extension excludes those patients who are eligible for HSCT. Patients in AZA-AML-001 were ineligible for HSCT.
Patients who do not achieve remission in the treatment phase do not subsequently achieve remission	Clinical expert advice. Once off treatment and not in remission, a patient will not achieve remission.
Once in the PD state, patients either remain in PD or die.	Clinical expert opinion and previous TAs in similar end-of-life cancers.
There is no treatment switching	Clinical expert opinion. Only a very small percentage of patients at this stage of disease would be fit for a second treatment after failing their first.

Assumption	Justification
In any cycle, patients can only be in one of the health states	Markov model Structure

Abbreviations: HSCT, haematopoietic stem cell transplantation; BSC, best supportive care; TAs, technology appraisals; PD, progressive disease.

5.7 *Base-case results*

5.7.1 *Base-case incremental cost effectiveness analysis results*

The base-case results are presented in Table 55 below.

Table 55: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
CCR	£40,608	0.9041	0.6365	-	-	-	-
Azacitidine	XXX	1.1820	XXX	XXX	0.2779	XXX	£20,648

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CCR; conventional chemotherapy regimens

5.7.2 *Clinical outcomes from the model*

The OS curves from the model for the CCR arm are compared to real world data from the HMRN registry in section 5.9 below.

The Markov traces are presented in Figure 26 to Figure 30.

Figure 26: Markov Trace - RFS

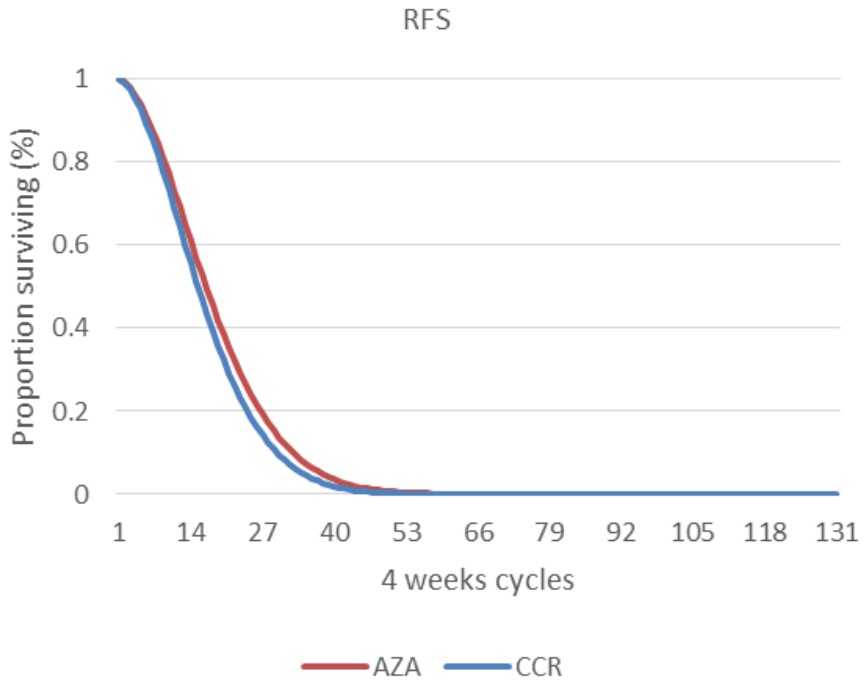


Figure 27: Markov Trace - PFS

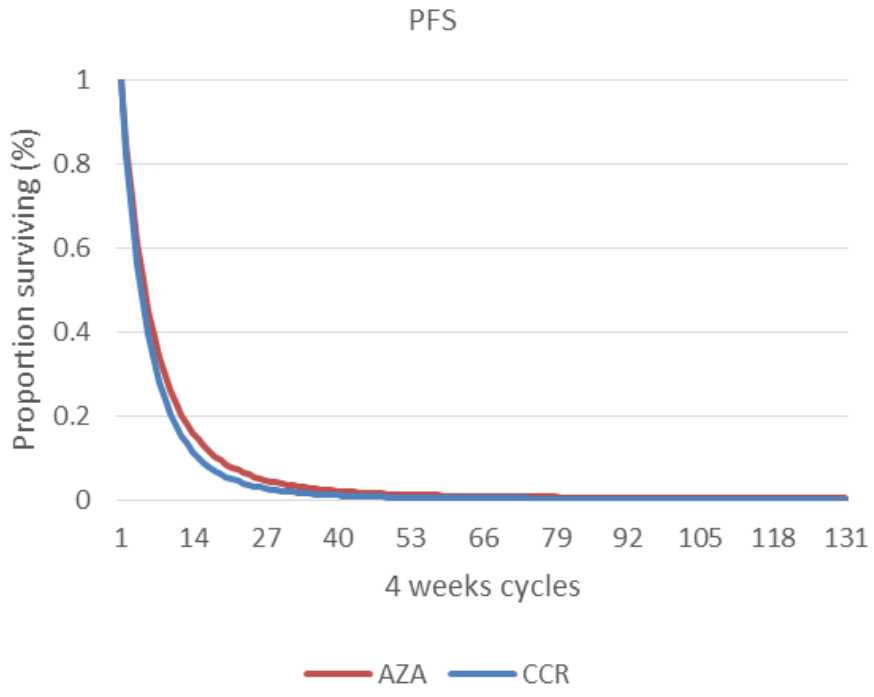


Figure 28: Markov Trace - OS

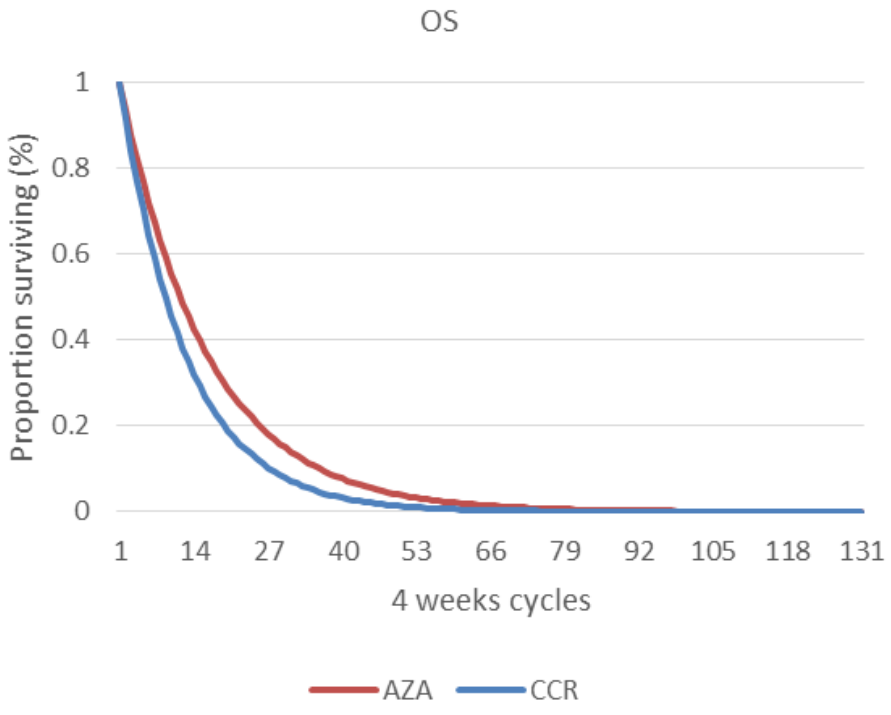


Figure 29: Markov Trace - azacitidine

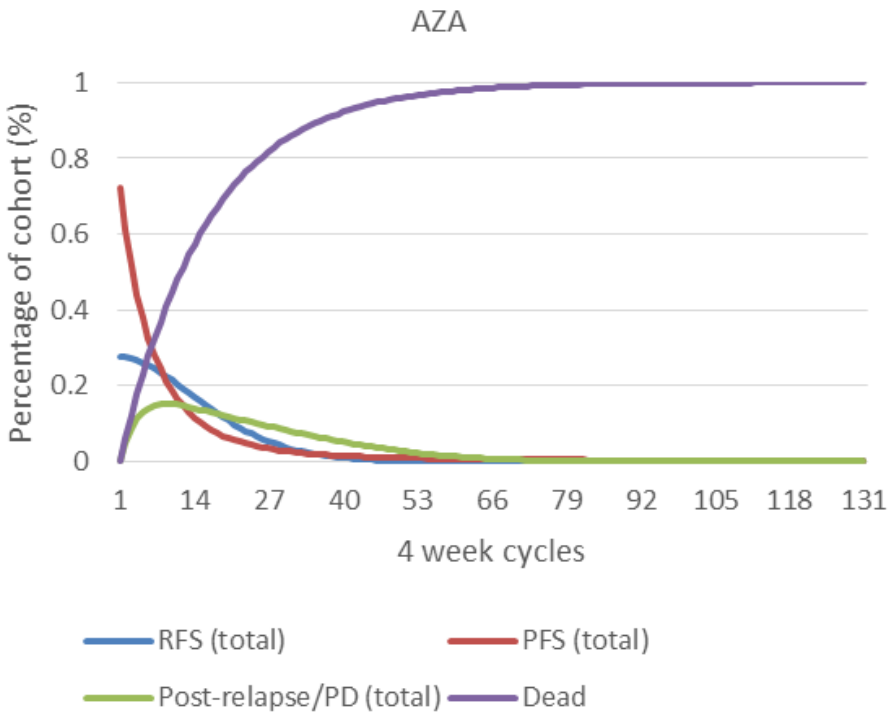
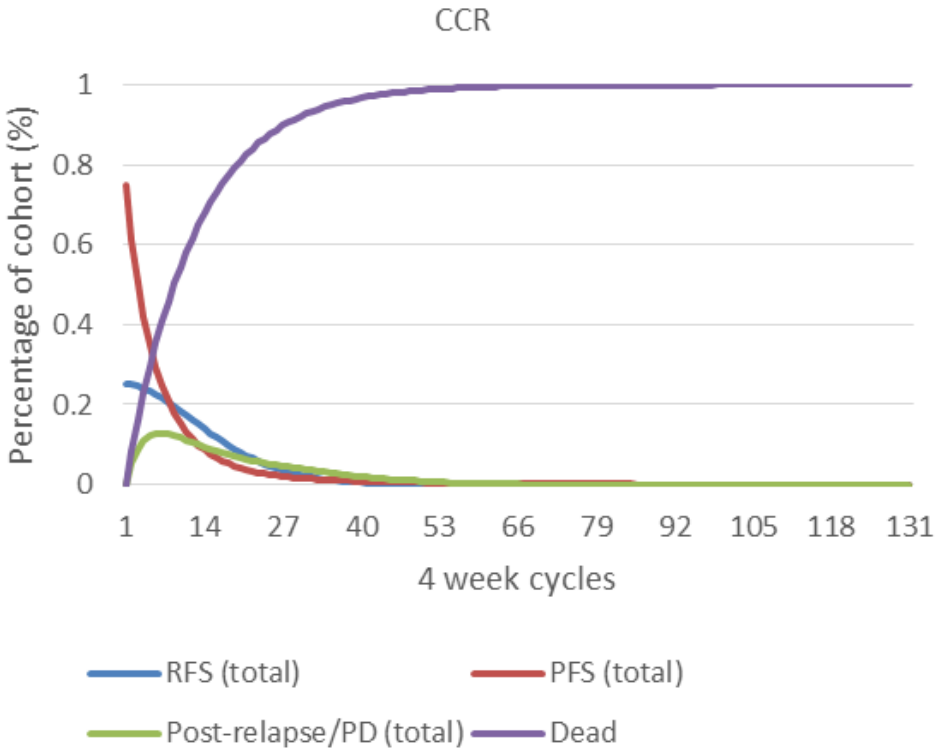


Figure 30: Markov Trace - CCR



5.7.3 *Disaggregated results of the base case incremental cost effectiveness analysis*

The disaggregated QALYs and costs are presented below.

Table 56: Summary of QALY gain by health state

Health state	QALY azacitidine	QALY CCR	Increment	Absolute increment	% absolute increment
RFS	XXX	XXX	0.047	0.048	26%
PFS	XXX	XXX	0.049	0.049	26%
PD	XXX	XXX	0.088	0.088	48%
Total	XXX	XXX	0.185	0.185	100%

Abbreviations: QALY, quality-adjusted life-year, CCR; conventional chemotherapy regimens, RFS; relapse free survival, PFS; progression free survival PD, progressive disease

Table 57: Summary of Costs by health state

Health state	Cost azacitidine	Cost CCR	Increment	Absolute increment	% absolute increment
RFS	XXX	£6,503	XXX	XXX	XXX
PFS	XXX	£22,235	XXX	XXX	XXX
PD	XXX	£6,260	XXX	XXX	XXX
Terminal care	XXX	£5,609	XXX	XXX	XXX
Total	XXX	£40,608	XXX	XXX	XXX

Abbreviations: CCR; conventional chemotherapy regimens, RFS; relapse free survival, PFS; progression free survival PD, progressive disease

Table 58: Summary of predicted resource use by category of cost

Item	Azacitidine	CCR	Increment	Absolute increment	% absolute increment
Drug acquisition	XXX	£370	XXX	XXX	XXX
Drug administration	XXX	£23,316	XXX	XXX	XXX
Tests to monitor disease	XXX	£157	XXX	XXX	XXX
Transfusions	XXX	£4,624	XXX	XXX	XXX
Management of AEs	XXX	£269	XXX	XXX	XXX
BSC/Monitoring costs	XXX	£6,260	XXX	XXX	XXX
Terminal care	XXX	£5,609	XXX	XXX	XXX
Total cost	XXX	£40,608	XXX	XXX	XXX

Abbreviations: CCR; conventional chemotherapy regimens; AEs, adverse events; BSC, best supportive care

5.8 *Sensitivity analyses*

5.8.1 *Probabilistic sensitivity analysis*

Uncertainty in a model can arise from parameter precision, which can be addressed via probabilistic sensitivity analyses (PSA). In PSA preferably all parameters are varied simultaneously and multiple sets of parameter values are sampled from predefined probability distributions (120). Distributions should be assigned to characterize the uncertainty associated with the precision of mean parameter values.

Parameters were varied according to their sampling distributions as shown in Table 59. A distribution of the (incremental) costs and benefits (QALYs) was determined by sampling a value from each input parameter distribution, calculating the results with the model, and repeating this process 2,000 times. Results are presented with a point estimate and 95% uncertainty interval, and with a joint-distribution of incremental costs and QALYs on the cost-effectiveness plane. The probability of cost-effectiveness was expressed with cost-effectiveness acceptability curves.

Table 59: Probabilistic distributions for model parameters

Beta distribution	Gamma distribution
Response rate HSUVs HSUVs for adverse events Incidence of adverse events	Patients' weight and height Drug usage and number of treatment cycles Healthcare resource use

Abbreviation: HSUV, health state utility value.

Table 60: PSA results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
CCR	£41,429 (£34,562, £49,698)	0.9073 (0.6970, 1.1358)	0.6386 (0.5047, 0.7924)	-	-	-	-
Azacitidine	XXX	1.1824 (1.0337, 1.3468)	XXX	XXX	0.2751	XXX	£17,423

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CCR; conventional chemotherapy regimens

Figure 31: Cost-effectiveness Plane – Incremental Costs vs. Incremental QALYs

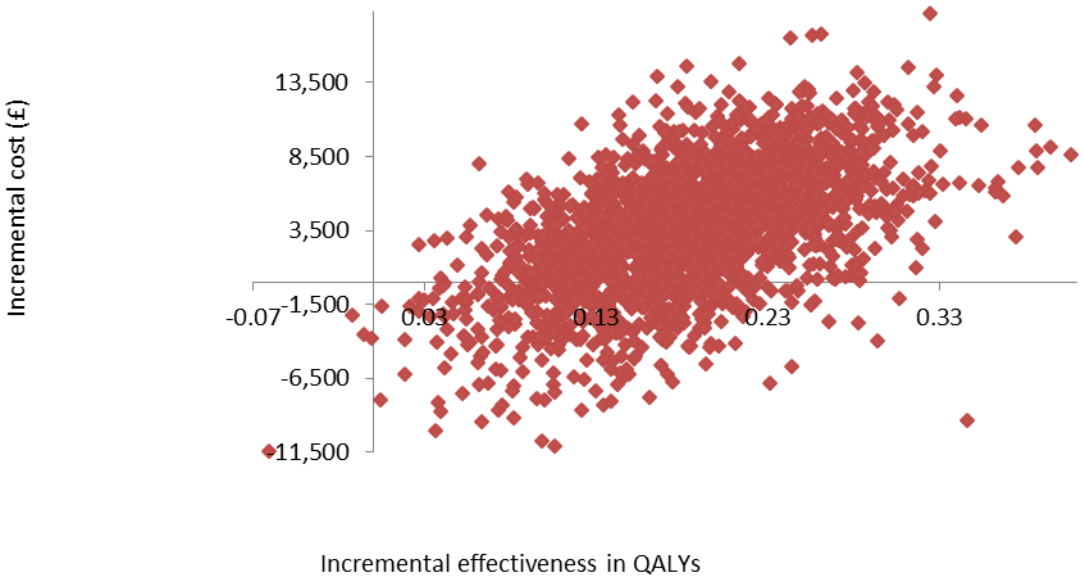


Figure 32: Cost-effectiveness Plane – Incremental Costs vs. Incremental LYs

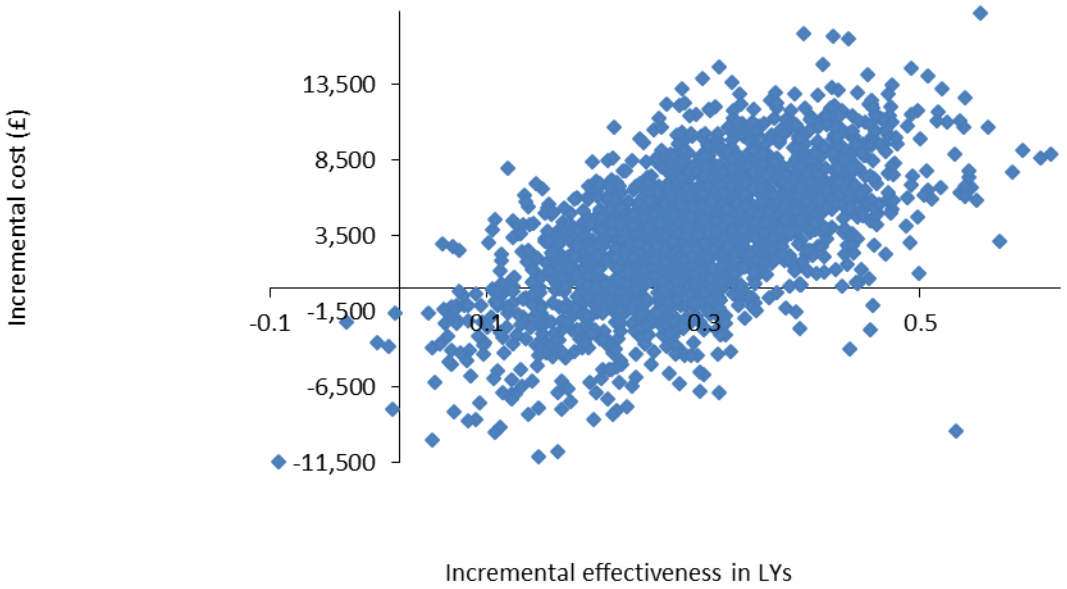
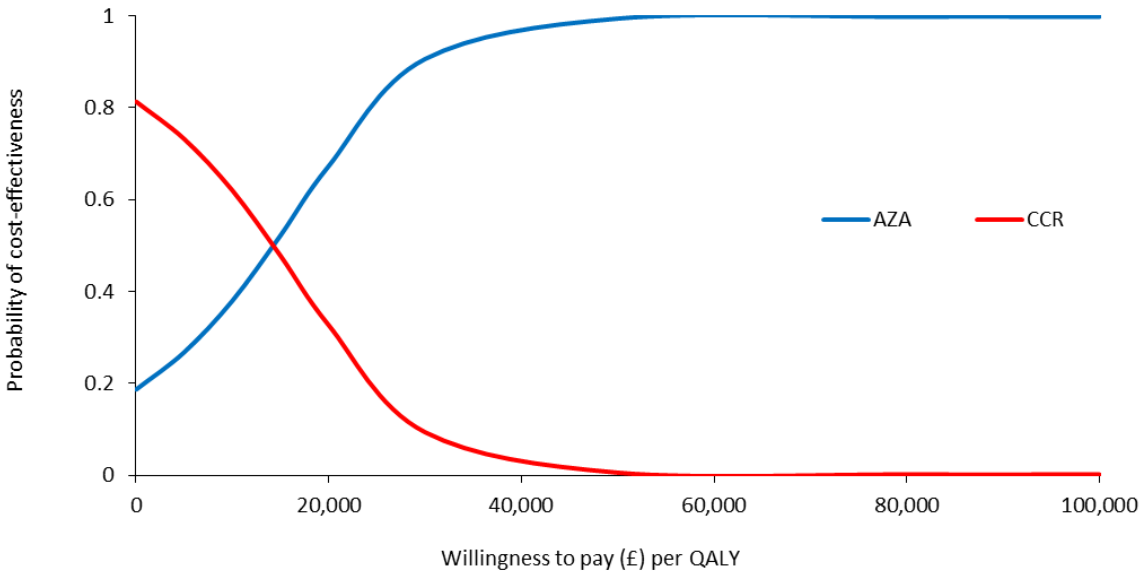


Figure 33: Cost-effectiveness Acceptability Curve



The PSA shows that at a willingness-to-pay threshold of £20,000 per QALY, the probability of azacitidine being cost effective versus CCR is 69.9%. If the threshold is increased to £30,000 or £50,000 per QALY, the probability of cost-effectiveness increases to 90.8% and 99.6% respectively.

5.8.2 *Deterministic sensitivity analysis*

Parameter uncertainty may be represented via deterministic sensitivity analysis (DSA). In a DSA, parameter values are varied manually to test the sensitivity of the model's results to specific parameters or sets of parameters. One-way SA is a form of DSA in which one parameter value is varied while keeping all other parameter values constant, to investigate the impact of individual parameters on the base case ICER (120).

In this model, the base case value of the following parameters were varied by ±20% or around a confidence interval (for HRs) to evaluate this impact:

- drug utilization costs
- drug administration costs
- drug monitoring cost (transfusion and tests)
- BSC/palliative care costs
- HRs
- safety
- response rate
- HSUVs

Figure 34: Tornado Diagram for DSA

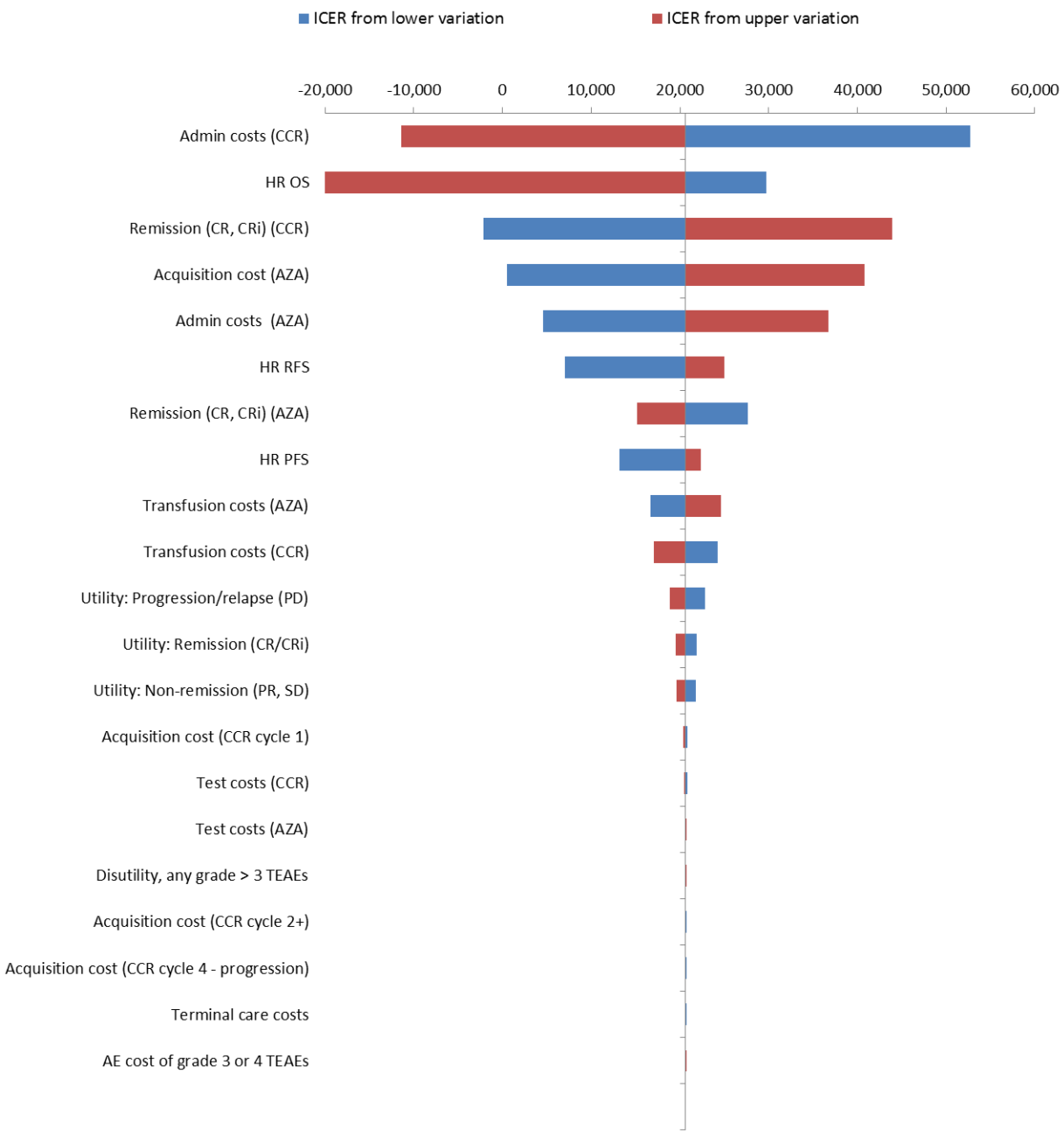


Table 61: DSA results

Base Case		£20,479
Variable	**ICER (£ per QALY)**	**Variation from Base case ICER**
Admin costs (CCR)	£52,681	155%
	-£11,385	-155%
HR OS	£29,691	44%
	-£22,222	-208%
Remission (CR, CRi) (CCR)	-£2,156	-110%
	£43,951	113%
Acquisition cost (Azacitidine)	£464	-98%
	£40,832	98%
Admin costs (Azacitidine)	£4,554	-78%
	£36,743	78%
HR RFS	£7,049	-66%
	£25,045	21%
Remission (CR, CRi) (Azacitidine)	£27,681	34%
	£15,209	-26%
HR PFS	£13,214	-36%
	£22,362	8%
Transfusion costs (Azacitidine)	£16,688	-19%
	£24,608	19%
Transfusion costs (CCR)	£24,230	17%
	£17,066	-17%
Utility: Progression/relapse (PD)	£22,823	11%
	£18,852	-9%
Utility: Non-remission (PR, SD)	£21,888	6%
	£19,541	-5%
Utility: Remission (CR/CRi)	£21,814	6%
	£19,601	-5%
Acquisition cost (CCR cycle 1)	£20,883	1%
	£20,414	-1%
Test costs (CCR)	£20,819	1%
	£20,478	-1%
Disutility, any grade > 3 TEAEs	£20,519	-1%
	£20,778	1%
Acquisition cost (CCR cycle 2+)	£20,538	-1%
	£20,760	1%
Terminal care costs	£20,757	1%

	£20,540	-1%
Acquisition cost (CCR cycle 4 - progression)	£20,707	0%
	£20,590	0%
Test costs (Azacitidine)	£20,703	0%
	£20,593	0%
AE cost of grade 3 or 4 TEAEs	£20,645	0%
	£20,651	0%

5.8.3 *Scenario analysis*

Uncertainty in a model can arise from structural assumptions relating to quantitative judgments that cannot be measured empirically (such as discount rates and time horizon). The impact of structural uncertainty on estimates of cost-effectiveness should be explored by separate analyses of a representative range of plausible scenarios.

The following alternative scenarios were evaluated:

- KM curves for RFS, PFS and OS
- OS data unadjusted for treatment-switching
- OS using the censor at switch population
- EQ-5D based on the mapping algorithm from McKenzie et al
- Vial Sharing
- Vial sharing in 30% of cases
- 1 year and 5 year time horizons
- Discount rate at 1.5% and 6%
- Individual treatment arms with adjustment for subsequent therapies
- Individual treatment arms without adjustment for subsequent therapies
- Use of individual treatment arm proportions from HMRN registry.
  - This was estimated using the following proportions (XXX as calculated from data on file. A weighted average ICER was calculated by multiplying the total costs and QALYs from the individual CCR and azacitidine arms (azacitidine results from individual arms not CCR population) by these proportions and then summing the resulting totals. i.e.,

$$Incremental\ XXX)$$

$$ICER = \frac{incremental\ costs}{incrementalQALYs}$$

Abbreviations: TC, total costs; AZA, azacitidine; BSC, best supportive care; IC, intensive chemotherapy; LDAC, low-dose cytarabine; TQ, total QALYs; QALYs, quality-adjusted life years

The model is not set up with this as a default option, but this can be replicated using the steps described above.

Table 62: Results of the scenario analyses

					Base Case	£20,648
Scenario		**Incremental Cost**	**Incremental LYs**	**Incremental QALYs**	**ICER (£ per QALY)**	**Variation from Base case ICER**
KM curves for RFS, PFS and OS		XXX	0.1485	XXX	£32,393	57%
OS data unadjusted for treatment-switching		XXX	0.3630	XXX	£11,537	-44%
OS using the censor at switch population		XXX	0.8309	XXX	£10,397	-50%
EQ-5D based on the mapping algorithm from McKenzie et al		XXX	0.2779	XXX	£22,243	8%
Vial Sharing		XXX	0.2779	XXX	-£13,300	-164%
Vial sharing in 30% of cases		XXX	0.2779	XXX	-£9,323	-145%
Time Horizon	1 year	XXX	0.0791	XXX	£30,305	47%
	5 year	XXX	0.2673	XXX	£20,860	1%
Discount Rate	1.5%	XXX	0.2861	XXX	£20,604	0%
	6%	XXX	0.2685	XXX	£20,704	0%
Individual treatment arms with adjustment for subsequent therapies	IC	XXX	0.3759	XXX	-£52,184	-353%
	LDAC	XXX	0.2729	XXX	£25,136	22%
	BSC	XXX	0.2095	XXX	-£169,672	-922%
Individual treatment arms without adjustment for subsequent therapies	IC	XXX	0.2449	XXX	-£85,266	-513%
	LDAC	XXX	0.2600	XXX	£41,671	102%
	BSC	XXX	0.3386	XXX	-£50,300	-344%
Use of individual treatment arm proportions from HMRN registry with adjustment for subsequent therapies		XXX	0.2665	XXX	-£57,756	-380%
Use of individual treatment arm proportions from HMRN registry without adjustment for subsequent therapies		XXX	0.2874	XXX	-£20,218	-198%

5.8.4 *Summary of sensitivity analyses results*

PSA results are slightly lower than the deterministic ICER with reasonable variation in the incremental costs, incremental QALYs, and ICERs overall and all of the parameters converge.

Deterministic sensitivity analyses showed that the greatest uncertainty is around CCR administration costs, HR for OS, CCR remission rates, AZA acquisition and administration costs, and the HR for RFS – i.e., factors generally tied to the difference in total costs between AZA and CCR.

Alternative scenarios were also tested to investigate the uncertainty around the model structure and assumptions. Vial sharing assumptions had the greatest effect on cost-effectiveness producing dominant ICERs. Using Kaplan-Meier curves without extrapolation also had a noticeable impact, increasing the ICER to £32,393. Use of a shorter time horizon (1 year) also increased the ICER to £54,376.

All but one of the sensitivity analyses produced ICERs below £50,000 per QALY. This was only crossed when the administration costs of CCR were reduced by 20% (ICER £52,681).

5.8.5 *Subgroup analysis*

The results of the two subgroups (patients with poor-risk cytogenetics and patients with MDS related changes) are presented below. As subsequent-treatment adjustment was not possible for these subgroups, results are presented without adjustment.

Table 63: Results for patients with poor-risk cytogenetics (without adjustment for subsequent therapies)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
CCR	£46,683	0.6607	0.4567	-	-	-	-
Azacitidine	XXX	1.1855	XXX	XXX	0.5248	XXX	£20,227

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CCR; conventional chemotherapy regimens

Table 64: Results for patients with MDS related Changes (without adjustment for subsequent therapies)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
CCR	£50,098	0.9459	0.6583	-	-	-	-
Azacitidine	XXX	1.4050	XXX	XXX	0.4591	XXX	£19,175

Abbreviations: MDS, Myelodysplastic; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CCR; conventional chemotherapy regimens.

5.9 *Validation*

The model was validated through a multistep process to verify the structure and underlying modelling and economic assumptions; this was followed by verification of all numerical data included in the model and mark-up of the reference publication.

5.9.1 *Validation of assumptions*

The model structure and underlying assumptions were assessed at four levels.

- An internal clinical validation was performed by PRMA Consulting's Senior Medical Director, Professor Deborah Saltman.
- PRMA Consulting's senior management and expert health economists performed an internal validation.
- The validity of the model was confirmed by XXX, an external technical advisor with extensive experience of NICE HTAs.
- Externally, two UK clinical oncologists validated the model structure and key assumptions; one of them also validated HCRU inputs (types of HCRU involved) and model outputs on effectiveness.
- The model was also reviewed by the Celgene team.

5.9.2 *Internal model validation*

Internal validation involved checking the model for face validity (plausibility) and technical validity (verification).

The model developers used a checklist to ensure that the model generates accurate results and that these are consistent with input data and robust to extreme values. The checks are documented in Table 65.

A health economist who was not involved in development of the cost-effectiveness analysis checked the formulas.

Table 65: Checklist used to check the model inputs and results

Check	Purpose
Set discount rate to 0	To confirm that discounted and non-discounted results are equal
Set main HSUVs to 0	To confirm that QALYs are zero, or can be explained by utility decrements associated with adverse events
Set all HSUVs to 1	To confirm that LYs are equal to QALYs, or that any difference can be explained by utility decrements associated with adverse events
Set drug costs to 0	To confirm that drug costs are zero
Set admin costs to 0	To confirm that administration costs are zero
Set all non-drug costs to 0	To confirm that non-drug costs are zero
Manually confirm tornado diagram calculations by changing user-	To confirm that that tornado diagram calculations are correct

Check	Purpose
altered cells	

Abbreviations: HSUV, health state utility value; LY, life-year; QALY, quality-adjusted life-year.

5.9.3 *Validation of model outcomes*

The overall survival from the model for the CCR arm has been compared to UK specific real world data from the HMRN registry (data on file). Figure 35 provides a comparison for all patients and Figure 36 for those patients with poor-risk cytogenetics.

Figure 35: Comparison of CCR OS data to HMRN

XXX

Figure 36: Comparison of CCR OS data for patients with poor-risk cytogenetics to HMRN

XXX

It can be seen that the model predicts slightly better outcomes than have been seen for patients treated with CCR in UK clinical practice. When adjustment is made for subsequent therapies, the survival curves move closer to that seen in the real world. This further emphasises that CCR survival in AZA-AML-001 could have benefited from patients switching treatment to receive azacitidine which they currently cannot do in clinical practice in the UK.

The similar curve shapes suggest the model is replicating real life experience plausibly and that the results of AZA-AML-001 can be interpreted with a degree of comfort once adjustments have been made for subsequent treatments.

5.10 *Interpretation and conclusions of economic evidence*

The model has a number of strengths and weakness which should be considered when interpreting the results.

5.10.1 *Strengths*

The model was developed according to published methodological guidance and includes advanced modelling techniques. All model inputs have been based on the AZA-AML-001 trial, published sources (such as NHS reference costs), or inputs from key opinion leaders.

The model is user-friendly, transparent, and flexible. It allows the user to compare azacitidine and CCR in the overall population, or individually by preselected CCR. The model has built-in functionalities to run a range of sensitivity analyses including one-way SA via variation of key inputs, PSA, and alternative scenario analyses.

The model structure, clinical assumptions underlying the model, and model outputs for effectiveness have been validated by two UK clinicians with input from a further 7 UK clinicians.

5.10.2 *Limitations*

Although a systematic approach to survival modelling approach was taken, and a range of sensitivity analyses have addressed the uncertainty in model parameters and structure, the results should be treated with caution because of some limitations.

The impact of disutility of AEs may have been underestimated because it was based on grade 3 or worse AEs, although this is a common assumption in oncology modelling, and should reflect impactful AEs.

HCRU and costs are comprised of a combination of trial data, published unit costs, and a survey of clinicians with experience treating patients with AML; the latter is an uncertain source of input data mainly because azacitidine itself is not a part of usual clinical practice to treat AML >30% blasts in England and Wales. However, in the absence of trial-based or observational data on HCRU, it is considered to be a representative dataset for England and Wales.

Finally, comparison is limited across types of survival analysis, treatment groups for IC, LDAC, and BSC, and subgroups for cytogenetic risk and myelodysplasia-related changes by the fact that HRs adjusted for subsequent treatments are only able to be estimated for the overall patient population, not subgroups or other treatment groups and it has been shown above that it is important to adjust the OS results of AZA-AML-001 for the impact of subsequent treatments.

5.10.3 *Conclusion*

One-way Sensitivity analysis has shown that the ICER is most sensitive to the administration costs, assumptions on vial sharing and to rates of remission – i.e., to factors linked to the difference in total costs between AZA and CCR. However, the majority of sensitivity analyses tested produced ICERs around £30,000 per QALY and very few rose above £50,000 per QALY.

Both the deterministic (£20,648) and probabilistic results (£17,423) show that the ICER is well below what is usually accepted for Orphan, life-extending medicines and azacitidine also demonstrated cost-effectiveness in the hard-to-treat subgroups of poor-risk cytogenetics and MDS related changes where there is a real unmet need for an effective treatment option (ICERs £20,227 and £19,175 respectively). The PSA also demonstrates that at a willingness-to-pay threshold of £20,000 per QALY, the probability of azacitidine being cost effective versus CCR is 69.9%. If the threshold is increased to £30,000 or £50,000 per QALY, the probability of cost-effectiveness increases to 90.8% and 99.6% respectively.

Azacitidine should be reimbursed for the treatment of adult patients aged 65 years or older who are not eligible for HSCT with AML with >30% marrow blasts according to the WHO classification.

6 Assessment of factors relevant to the NHS and other parties

6.1 The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical and cost effectiveness. This will allow subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

Provide the information specified in sections 6.2–6.10.

6.2 State how many people are eligible for treatment in England. Present results for the full marketing authorisation or CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Table 66: Eligible Population for the full marketing authorisation

Year	2016	2017	2018	2019	2020
Population aged over 65	9,685,248	9,759,824	9,834,975	9,910,704	9,987,016
Prevalent population	-	-	-	-	-
Incident population	1,777	1,791	1,805	1,819	1,833
Incident population less those eligible for HSCT (from 2013)	1,282	1,296	1,310	1,324	1,338
AML ineligible for HSCT cases with blasts > 30% (80%)	1,026	1,037	1,048	1,059	1,070

Abreviations: HSCT, haematopoietic stem cell transplantation; AML, Acute Myeloid Leukaemia

Table 67: Subgroup Population with poor risk cytogenetics

Year	2016	2017	2018	2019	2020
Population	9,685,248	9,759,824	9,834,975	9,910,704	9,987,016
Prevalent population	-	-	-	-	-
Incident population	1,777	1,791	1,805	1,819	1,833
Incident population less those eligible for HSCT (from 2013)	1,282	1,296	1,310	1,324	1,338
Population with poor risk cytogenetics (34.8%)	446	451	456	461	465
AML ineligible for HSCT cases with blasts > 30% (80%)	357	361	365	368	372

Abreviations: HSCT, haematopoietic stem cell transplantation; AML, Acute Myeloid Leukaemia

Table 68: Subgroup Population with MDS related changes

Year	2016	2017	2018	2019	2020
Population	9,685,248	9,759,824	9,834,975	9,910,704	9,987,016
Prevalent population	-	-	-	-	-
Incident population	1,777	1,791	1,805	1,819	1,833
Incident population less those eligible for HSCT (from 2013)	1,282	1,296	1,310	1,324	1,338
Population with MDS related changes (32.4%)	415	420	424	429	433
AML ineligible for HSCT cases with blasts > 30% (80%)	332	336	339	343	347

Abreviations: HSCT, haematopoietic stem cell transplantation; MDS, Myelodysplastic; AML, Acute Myeloid Leukaemia

6.3 Explain any assumptions that were made about current treatment options and uptake of technologies.

No assumptions have been made. As the comparison is versus CCR, all patients within license will either receive CCR or azacitidine.

6.4 When relevant, explain any assumptions that were made about market share in England.

Market share has been estimated using internal assumptions around uptake. The estimates no not account for the impact of azacitidine coming off patent at the end of 2019 and the possibility of generics entering the market in 2020. This is because the level of generic entry and potential costings are unknown at this point.

6.5 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, administration costs, monitoring costs and the costs of managing adverse reactions).

The following costs are included within the budget impact calculations:

- Drug costs
- Administration (HCRU) costs

- Tests
- Transfusions
- Treatment of AEs
- Monitoring
- Terminal Care

6.6 State what unit costs were assumed and how they were calculated. If unit costs used in health economic modelling were not based on national reference costs or the payment-by-results tariff, explain how a cost for the activity was calculated.

As described above in section 5.5, costs used within the health economic model are taken from recognised sources such as the national schedule for reference costs, BNF and PSSRU. The budget impact model is built onto the health economic model and the same unit costs as described above are used.

6.7 If there were any estimates of resource savings, explain what they were and when they are likely to be made.

When compared to CCR, Table 46 shows that azacitidine requires comparable resource use. However, during induction (or early treatment), azacitidine requires considerably less inpatient days. This is mainly due to the fact that IC patients are hospitalised for a long period of time whilst receiving induction treatment.

6.8 State the estimated annual budget impact on the NHS in England.

Table 69: Budget Impact for the full marketing authorisation

	2016	2017	2018	2019	2020
Drug Cost	XXX	XXX	XXX	XXX	XXX
Drug Administration	XXX	XXX	XXX	XXX	XXX
Tests	XXX	XXX	XXX	XXX	XXX
Transfusions	XXX	XXX	XXX	XXX	XXX
Treatment of AEs	XXX	XXX	XXX	XXX	XXX
BSC / Monitoring	XXX	XXX	XXX	XXX	XXX
Terminal Care	XXX	XXX	XXX	XXX	XXX
Total Net Budget Impact	XXX	XXX	XXX	XXX	XXX
Cumulative Budget Impact	XXX	XXX	XXX	XXX	XXX

Abreviations: AEs, Adverse Events; BSC, Best Supportive Care

Table 70: Budget Impact for the Subgroup Population with poor risk cytogenetics

	2016	2017	2018	2019	2020
Drug Cost	XXX	XXX	XXX	XXX	XXX
Drug Administration	XXX	XXX	XXX	XXX	XXX
Tests	XXX	XXX	XXX	XXX	XXX
Transfusions	XXX	XXX	XXX	XXX	XXX
Treatment of AEs	XXX	XXX	XXX	XXX	XXX
BSC / Monitoring	XXX	XXX	XXX	XXX	XXX
Terminal Care	XXX	XXX	XXX	XXX	XXX
Total Net Budget Impact	XXX	XXX	XXX	XXX	XXX
Cumulative Budget Impact	XXX	XXX	XXX	XXX	XXX

Abreviations: AEs, Adverse Events; BSC, Best Supportive Care

Table 71: Budget Impact for the Subgroup Population with MDS related changes

	2016	2017	2018	2019	2020
Drug Cost	XXX	XXX	XXX	XXX	XXX
Drug Administration	XXX	XXX	XXX	XXX	XXX
Tests	XXX	XXX	XXX	XXX	XXX
Transfusions	XXX	XXX	XXX	XXX	XXX
Treatment of AEs	XXX	XXX	XXX	XXX	XXX
BSC / Monitoring	XXX	XXX	XXX	XXX	XXX
Terminal Care	XXX	XXX	XXX	XXX	XXX
Total Net Budget Impact	XXX	XXX	XXX	XXX	XXX
Cumulative Budget Impact	XXX	XXX	XXX	XXX	XXX

Abreviations: AEs, Adverse Events; BSC, Best Supportive Care

6.9 Identify any other opportunities for resource savings or redirection of resources that it has not been possible to quantify.

There are no additional potential resource saving identified outside of those incorporated within the budget impact calculations.

6.10 Highlight the main limitations within the budget impact analysis.

As the budget impact model is built around the cost-effectiveness model, the same uncertainties as described in section 5.9 apply equally. A further limitation is that the market share estimates are uncertain and rely on assumption as described in section 6.4

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116. Longworth L, Yang Y, Young T, Mulhern B, Hernandez Alava M, Mukuria C, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. Health Technol Assess. 2014 Feb;18(9):1-224.
117. Addicott R, Dewar S. Improving choice at end of life. King's Fund. Accessed on: 05/09/15 http://www.kingsfund.org.uk/sites/files/kf/improving-choice-end-of-life-descriptive-analysis-impact-costs-marie-curie-choice-programme-lincolnshire-rachael-addicot-steve-dewar-april-2008.pdf. 2008.
118. NHS Blood and Transplant. Price List 2015/16; Code BC001; http://hospital.blood.co.uk/media/27457/price_list_2015-16.pdf, accessed on: 15/11/15.
119. NHS Blood and Transplant. Price List 2015/16; Code BC04; http://hospital.blood.co.uk/media/27457/price_list_2015-16.pdf, accessed on: 15/11/15.
120. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD, et al. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. Med Decis Making. 2012 Sep-Oct;32(5):722-32.

8 Appendices

[List the titles of the appendices here. All appendices should be provided as separate documents to the main submission.]

Abacus guidance: see separate appendices template to help complete appendices as appropriate

Appendix 1: SmPC and EPAR

Appendix 2: Search strategy for relevant studies

Appendix 3: AWG 2003 response criteria

Appendix 4: HRQoL results from AZA-AML-001

Appendix 5: Subgroup analyses from AZA-AML-001

Appendix 6: Adverse reactions by patient exposure from AZA-AML-001

Appendix 7: Search strategy for cost-effectiveness studies

Appendix 8: Quality assessment of cost-effectiveness studies

Appendix 9: Extrapolation of data

XXX

Appendix 10: HCRU questionnaire

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Single technology appraisal

Leukaemia (acute myeloid, over 30% blasts) – azacitidine [ID829]

Dear [Insert name],

The Evidence Review Group, the Peninsula Technology Assessment Group (PenTAG), and the technical team at NICE have looked at the submission received on 25th November 2015 from Celgene. 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 8th January 2016. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed NICE DOCS LINK].

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.

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If you have any queries on the technical issues raised in this letter, please contact Nicola Hay, Technical Adviser (Nicola.Hay@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

On behalf of
Dr Frances Sutcliffe

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Section A: Clarification on clinical effectiveness data

A1. **Priority question:** Patient level transcripts have been received. Please provide a data dictionary for the variables in the data files `ID829 azacitidine AML 3245 trial data 141215 SY [CIC].dta`, `ID829 azacitidine AML os_blxt 141215 SY [CIC].dta`, and `ID829 azcitidine AML wgtanalaealt 141215 SY [CICC].dta`.

Literature searching

A2. Please clarify the host platform through which EMBASE was searched? If it was not OVID, please separate out the MEDLINE searches from the EMBASE search, thereby providing MEDLINE OVID searches in one annex and the EMBASE search in another.

A3. **Priority Question:** The literature searches exclude studies reporting meta-analyses or systematic reviews. Please provide the rationale for this decision**.**

A4. Page 41 of the company submission states that '*three materials were added from a manual search of literature databases and conference proceedings*.'

a. Please provide the complete citations for the materials that were added.

b. Please clarify which literature databases were searched manually.

A5. Page 85 of the company submission states that *'no further studies that report additional adverse reactions… and that are of relevance to the decision problem are available.'*

a. Please clarify if separate literature searches been undertaken to identify studies reporting adverse effects.

b. If a separate literature search has been undertaken, please provide the search strategies and a table of studies excluded.

c. If no separate searches were undertaken, please provide further commentary to support the statement that 'no further studies that report additional adverse events …that are of relevance to the decision problem are available.'

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A6. Page 98 of the company submission states that *'there are no completed or ongoing company-sponsored studies from which new evidence will become available in the next 12 months.*' Please confirm whether there are any such studies from which new evidence will become available beyond 12 months.

A7. Please provide full citations for the 15 studies excluded as they were published pre-2000 (Appendix 2.4, Table 1).

AZA-AML-001 trial

Methods

A8. Page 54 of the company's submission: Please clarify why the sample size calculations assumed a split of 50:30:20 for intensive chemotherapy: low-dose cytarabine: best supportive care.

A9. Please confirm whether loss to follow-up was treated as an event rather than censored for relapse-free survival, event- free survival (Table 11, page 50 of the company's submission) and progression-free survival (page 112 of the company's submission).Please provide justification as to why loss to follow-up was treated as an event if applicable.

A10. Please clarify why event-free survival, relapse-free survival and progression-free survival were not adjusted for treatment switching.

A11. Last row of Table 17, (page 64 of the company's submission) '*Did the analysis include an intention-to-treat analysis*? *If so, was this appropriate and were appropriate methods used to account for missing data*?' In response to the question, it is stated that '*the ITT population was the most appropriate population as it included all randomised patients*.' Please clarify how missing data were dealt with in the analysis of primary and secondary outcomes, including the post-hoc analysis to adjust for treatment switching.

A12. Section 4.7.4, pages 69-71 of the company's submission:

a. Please clarify how covariates were selected for the analyses.

b. Please clarify why no time-varying covariates (e.g. bone marrow or peripheral blood blast count) were included in the propensity score for the Inverse probability of censoring weighted method.

A13. Section 4.7.4.1, pages 65-66 of the company's submission: Please provide a description of the methods used to perform the regression-based imputation analysis adjusting for subsequent therapy.

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A14. Section 4.7.5.8, Health-related quality of life, page 77 of the company's submission: states that '*A mixed model analysis failed to reveal any statistically significant differences in the impact of treatment on all domains between treatment arms.'* Please clarify what statistical distribution was used for this analysis, any if there were any stratification and fixed and time-varying covariate adjustment and adjustment for differential drop-out across treatment arms.

A15. Please provide a table giving the counts and incidence rates for each treatment arm of the AZA-AML-001 trial (azacitidine, intensive chemotherapy, low-dose cytarabine, best supportive care) of the grade ≥3 treatment related adverse events that occurred in >10% of patients in any treatment arm.

Results

A16. Please state the number of UK patients (26 in total) randomised to azacitidine, intensive chemotherapy, low-dose cytarabine, and best supportive care.

A17. Table 16, page 61 of the company submission: Please provide a corrected version of Table 16 (The numbers in 'Cytogenetic risk status – local/central' do not appear to sum to the number of patients randomised [unless 'Normal' patients are excluded – perhaps these should be indicated as a subset of 'Intermediate'?]). There also appears to be some inaccuracies in the 'Prior history of MDS' when compared with Dombret et al. 2015 and the AZA-AML-001 clinical study report.

A18. Table 22, page 72 of the company's submission: Please confirm whether the proportion of patients randomised to azacitidine experiencing relapse after complete remission or complete remission with incomplete blood count recovery is 63.2% or 64.2% (as per Dombret et al. 2015 and the AZA-AML-001 clinical study report).

A19. Please confirm whether the age range of patients randomised to low-dose cytarabine is 65–89 years (as per page 59 of the company submission) or 65–88 years (as per Dombret et al. 2015 and the AZA-AML-001 clinical study report).

A20. Please complete the table below for event-free survival and relapse-free survival.. For each treatment arm (azacitidine [AZA], intensive chemotherapy [IC], low-dose cytarabine [LDAC], best supportive care [BSC]). Please provide a tabulation of the count of each event type (at the latest snapshot), for example for relapse-free survival.

Arm	**AZA**	**CCR**		
		IC	**LDAC**	**BSC**
Relapse	XX	XX	XX	XX
Death from any cause	XX	XX	XX	XX

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Loss to follow-up	XX	XX	XX	XX
Total	**53**	**XX**	**XX**	**XX**

Section B: Clarification on cost-effectiveness data

Literature searches

B1. Please provide further details summarising the company's approach to identifying studies reporting health-related quality of life. If separate literature searches were undertaken, please provide the search strategies.

Methods

B2. Please confirm that event free survival was used directly (without any further adjustment) for relapse-free survival (in patients achieving complete remission or complete remission with incomplete blood count recovery) and progression-free survival (in patients not achieving complete remission or complete remission with incomplete blood count recovery), that is, if relapse-free survival and progression-free survival were recombined, event-free survival would be obtained for the full population.

B3. Please confirm that the following methods were used to calculate different survival curves in the model, and if so whether the curves for relapse-free survival and progression-free survival were fitted to azacitidine (AZA) and conventional care regimen (CCR) patients with a proportional-hazards azacitidine treatment variable, or if these were fitted only to CCR patients. Please see the table below.

Arm	AZA	CCR
Overall survival		
Underlying data	OS from AZA	OS from AZA
Curve fitting	Exponential	Exponential
Adjustments	—	HR of 1/0.75 from IPCW method (inverse HR)
Relapse-free survival		
Underlying data	EFS for CCR patients achieving CR or CRi	EFS for CCR patients achieving CR or CRi
Curve fitting	Weibull	Weibull
Adjustments	HR of 0.84 from curve fitting	—
Progression-free survival		
Underlying data	EFS for CCR patients not achieving CR or CRi	EFS for CCR patients not achieving CR or CRi
Curve fitting	Gompertz	Gompertz

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Adjustments	HR of 0.85 from curve fitting	—

B4. Page 112 of the company's submission: Please clarify whether the results using the Iterative Parameter Estimation (IPE) method are correct, as there appears to be some disparity between these results and the results in Appendix 11 and other sources.

B5. **Priority question:** Please provide a copy of the Statistical Analysis Plan cited in Appendix 11 of the company's submission.

B6. Page 123 of the company's submission states that '*subgroup adjustment was not feasible because of limited data on switching; however, a clinical expert consulted during this analysis stated that questions can be raised about the clinical generalizability of the results in subgroups, because clinicians can identify potential switching candidates based on observed performance, and recommended focusing on the adjusted data for overall patients*.'

a. Please clarify what baseline patient characteristics were used to define the subgroups and why particular baseline characteristics were chosen.

b. Please provide further details on the reasons why the results of the subgroup analysis were not considered to be clinically generalizable.

c. Please provide details of the number of patients who switched treatments and the number who did not.

B7. Table 37, page 125 of the company's submission. Please clarify whether the information about covariates used in the Inverse probability of censoring weighted analysis in Table 37 is correct as there appears to be discrepancies between Table 37 and Table 14 of Appendix 11.

B8. Page 130 of the company's submission: Please explain why the adverse events which are costed on page 130 of the company's submission appear to differ from the adverse events for which disutilities are measured (page 129 of the company's submission).

B9. Please explain what the 'Acute myeloid leukaemia' adverse event refers to, and what the cost represents.

B10. **Priority question:** Please explain how mean treatment duration for azacitidine from the AZA-AML-001 trial was applied in the model. Please confirm that the model only includes costs for 8 cycles of treatment although 32% of patients were still receiving azacitidine after 12 cycles.

Single technology appraisal

Leukaemia (acute myeloid, over 30% blasts) – azacitidine [ID829]

Dear Matthew,

The Evidence Review Group, the Peninsula Technology Assessment Group (PenTAG), and the technical team at NICE have looked at the submission received on 25th November 2015 from Celgene. 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 Friday 8 January 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

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Yours sincerely
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Section A: Clarification on clinical effectiveness data

A1. Priority question: Patient level transcripts have been received. Please provide a data dictionary for the variables in the data files `ID829 azacitidine AML 3245 trial data 141215 SY [CIC].dta`, `ID829 azacitidine AML os_blxt 141215 SY [CIC].dta`, and `ID829 azcitidine AML wgtanalaealt 141215 SY [CICC].dta`.

See separate Excel file "Azacitidine AML trial data dictionary.xlsx"

Literature searching

A2. Please clarify the host platform through which EMBASE was searched? If it was not OVID, please separate out the MEDLINE searches from the EMBASE search, thereby providing MEDLINE OVID searches in one annex and the EMBASE search in another.

All searches were executed through OVID.

A3. **Priority Question:** The literature searches exclude studies reporting meta-analyses or systematic reviews. Please provide the rationale for this decision**.**

The purpose of the systematic literature review was to identify all relevant RCT data that can be used to estimate comparative efficacy and safety of the treatments of interest. Although systematic reviews and meta-analyses can provide valuable data, these are not original (primary) data. Further, these reviews should only include studies already identified by the search strategy. As such, there was not a need to include meta-analyses or systematic reviews.

A4. Page 41 of the company submission states that '*three materials were added from a manual search of literature databases and conference proceedings*.'

a. Please provide the complete citations for the materials that were added.

Table 1: List of studies added through manual searches

Study name	Title
Dohner et al 2015[1]	Overall survival and clinical outcomes in older patients with acute myeloid leukemia treated with azacitidine or intensive chemotherapy in the AZA-AML-001 study
Dombret et al 2015[2]	International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts
Kadia et al 2015[3]	Decitabine improves outcomes in older patients with acute myeloid leukemia and higher blast counts

b. Please clarify which literature databases were searched manually.

These materials were obtained through manual searches of the following sources: conference proceedings from the European Hematology Association (EHA) Annual Congress between January 2013 and April 2015, conference proceedings from the American Society of Hematology (ASH) Annual Conference between January 2013 and April 2015, conference proceedings from the British Society for Haematology (BSH) Annual Scientific Meeting between January 2013 and April 2015, clinicaltrials.gov, and bibliographies of systematic literature reviews, meta-analyses, and other included studies.

A5. Page 85 of the company submission states that *'no further studies that report additional adverse reactions… and that are of relevance to the decision problem are available.'*

a. Please clarify if separate literature searches been undertaken to identify studies reporting adverse effects.

No separate literature searches were undertaken to identify studies reporting adverse effects.

b. If a separate literature search has been undertaken, please provide the search strategies and a table of studies excluded.

NA

c. If no separate searches were undertaken, please provide further commentary to support the statement that 'no further studies that report additional adverse events …that are of relevance to the decision problem are available.'

Literature searches are designed to ensure that they are sensitive enough to identify all relevant material, yet specific enough to be feasible for a systematic literature review. Search terms are typically developed to target population, interventions/comparators, and study design. No searches are designed with outcomes in mind as this specification may produce search results that are too narrow relative to the scope of the project. As

such, we are very confident that there are no other relevant studies with adverse effects of interest that were not identified.

A6. Page 98 of the company submission states that *'there are no completed or ongoing company-sponsored studies from which new evidence will become available in the next 12 months.*' Please confirm whether there are any such studies from which new evidence will become available beyond 12 months.

Correct; no new data will become available beyond 12 months.

A7. Please provide full citations for the 15 studies excluded as they were published pre-2000 (Appendix 2.4, Table 1).

The 15 RCTs excluded due to publication year are presented in below.

Table 2: List of RCTs excluded due to publication year

Study name	Title	Full reference
Archimbaud et al 1999	Multicenter randomized phase II trial of idarubicin vs mitoxantrone, combined with VP-16 and cytarabine for induction/consolidation therapy, followed by a feasibility study of autologous peripheral blood stem cell transplantation in elderly patients with acute myeloid leukemia	Archimbaud E, Jehn U, Thomas X, et al. Multicenter randomized phase II trial of idarubicin vs mitoxantrone, combined with VP-16 and cytarabine for induction/consolidation therapy, followed by a feasibility study of autologous peripheral blood stem cell transplantation in elderly patients with acute myeloid leukemia. *Leukemia.* 1999;13(6):843-849
Arlin et al 1990	Randomized multicenter trial of cytosine arabinoside with mitoxantrone or daunorubicin in previously untreated adult patients with acute nonlymphocytic leukemia (ANLL). Lederle Cooperative Group	Arlin Z, Case DC, Jr., Moore J, et al. Randomized multicenter trial of cytosine arabinoside with mitoxantrone or daunorubicin in previously untreated adult patients with acute nonlymphocytic leukemia (ANLL). Lederle Cooperative Group. *Leukemia.* 1990;4(3):177-183
Godwin et al 1998	A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest oncology group study (9031)	Godwin JE, Kopecky KJ, Head DR, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest oncology group study (9031). *Blood.* 1998;91(10):3607-3615
Linkesch et al 1989	Amsacrine, cytarabine and thioguanine (AAT) versus daunorubicin, cytarabine,	Linkesch W, Michlmayr G, Gerhartz H, et al. Amsacrine, cytarabine and thioguanine (AAT) versus

	thioguanine (DAT) in adults with untreated acute non-lymphoblastic leukemia (ANLL). Austrian-German results	daunorubicin, cytarabine, thioguanine (DAT) in adults with untreated acute non-lymphoblastic leukemia (ANLL). Austrian-German results. *Onkologie.* 1989;12(1):8-10
Lowenberg et al 1997	Use of recombinant GM-CSF during and after remission induction chemotherapy in patients aged 61 years and older with acute myeloid leukemia: final report of AML-11, a phase III randomized study of the Leukemia Cooperative Group of European Organisation for the Research and Treatment of Cancer and the Dutch Belgian Hemato-Oncology Cooperative Group	Lowenberg B, Suciu S, Archimbaud E, et al. Use of recombinant GM-CSF during and after remission induction chemotherapy in patients aged 61 years and older with acute myeloid leukemia: final report of AML-11, a phase III randomized study of the Leukemia Cooperative Group of European Organisation for the Research and Treatment of Cancer and the Dutch Belgian Hemato-Oncology Cooperative Group. *Blood.* 1997;90(8):2952-2961
Lowenberg et al 1989	On the value of intensive remission-induction chemotherapy in elderly patients of 65+ years with acute myeloid leukemia: a randomized phase III study of the European Organization for Research and Treatment of Cancer Leukemia Group	Lowenberg B, Zittoun R, Kerkhofs H, et al. On the value of intensive remission-induction chemotherapy in elderly patients of 65+ years with acute myeloid leukemia: a randomized phase III study of the European Organization for Research and Treatment of Cancer Leukemia Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1989;7(9):1268-1274
Rees et al 1996	Dose intensification in acute myeloid leukaemia: greater effectiveness at lower cost. Principal report of the Medical Research Council's AML9 study. MRC Leukaemia in Adults Working Party	Rees JK, Gray RG, Wheatley K. Dose intensification in acute myeloid leukaemia: greater effectiveness at lower cost. Principal report of the Medical Research Council's AML9 study. MRC Leukaemia in Adults Working Party. *British journal of haematology.* 1996;94(1):89-98
Ruutu et al 1994	Oral induction and consolidation of acute myeloid leukemia with etoposide, 6-thioguanine, and idarubicin (ETI) in elderly patients: a randomized comparison with 5-day TAD. Finnish Leukemia Group	Ruutu T, Almqvist A, Hallman H, et al. Oral induction and consolidation of acute myeloid leukemia with etoposide, 6-thioguanine, and idarubicin (ETI) in elderly patients: a randomized comparison with 5-day TAD. Finnish Leukemia Group. *Leukemia.* 1994;8(1):11-15
Schiller et al 1992	A randomized study of intermediate versus conventional-dose cytarabine	Schiller G, Gajewski J, Nimer S, et al. A randomized study of intermediate

	as intensive induction for acute myelogenous leukaemia	versus conventional-dose cytarabine as intensive induction for acute myelogenous leukaemia. *British journal of haematology.* 1992;81(2):170-177
Stone et al 1995	Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. Cancer and Leukemia Group B	Stone RM, Berg DT, George SL, et al. Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. Cancer and Leukemia Group B. *The New England journal of medicine.* 1995;332(25):1671-1677
Tilly et al 1990	Low-dose cytarabine versus intensive chemotherapy in the treatment of acute nonlymphocytic leukemia in the elderly	Tilly H, Castaigne S, Bordessoule D, et al. Low-dose cytarabine versus intensive chemotherapy in the treatment of acute nonlymphocytic leukemia in the elderly. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1990;8(2):272-279
Uyl-de Groot et al 1998	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	Uyl-de Groot CA, Lowenberg B, Vellenga E, Suciu S, Willemze R, Rutten FF. 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. *British journal of haematology.* 1998;100(4):629-636
Vogler et al 1992	A phase III trial comparing idarubicin and daunorubicin in combination with cytarabine in acute myelogenous leukemia: a Southeastern Cancer Study Group Study	Vogler WR, Velez-Garcia E, Weiner RS, et al. A phase III trial comparing idarubicin and daunorubicin in combination with cytarabine in acute myelogenous leukemia: a Southeastern Cancer Study Group Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1992;10(7):1103-1111
Wiernik et al 1979	A comparative trial of daunorubicin, cytosine arabinoside, and thioguanine, and a combination of the three agents for the treatment of acute myelocytic leukemia	Wiernik PH, Glidewell OJ, Hoagland HC, et al. A comparative trial of daunorubicin, cytosine arabinoside, and thioguanine, and a combination of the three agents for the treatment of acute myelocytic leukemia. *Medical and pediatric oncology.* 1979;6(3):261-277

Witz et al 1998	A placebo-controlled study of recombinant human granulocyte-macrophage colony-stimulating factor administered during and after induction treatment for de novo acute myelogenous leukemia in elderly patients. Groupe Ouest Est Leucemies Aigues Myeloblastiques (GOELAM)	Witz F, Sadoun A, Perrin MC, et al. A placebo-controlled study of recombinant human granulocyte-macrophage colony-stimulating factor administered during and after induction treatment for de novo acute myelogenous leukemia in elderly patients. Groupe Ouest Est Leucemies Aigues Myeloblastiques (GOELAM). *Blood.* 1998;91(8):2722-2730

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AZA-AML-001 trial

Methods

A8. Page 54 of the company's submission: Please clarify why the sample size calculations assumed a split of 50:30:20 for intensive chemotherapy: low-dose cytarabine: best supportive care.

At the time of study design, there was little real-world data to inform the split between intensive chemotherapy (IC), low-dose cytarabine (LDAC) and best supportive care (BSC) alone usage in routine clinical practice. Therefore, AZA-AML-001 study investigators assumed that across the world, approximately 50%, 30% and 20% of acute myeloid leukaemia (AML) patients receive IC, LDAC and BSC alone, respectively and this assumption was used as part of the sample size calculation. In reality, the pre-selection within AZA-AML-001 to IC, LDAC and BSC alone was 18%, 64% and 18%, respectively.

A9. Please confirm whether loss to follow-up was treated as an event rather than censored for relapse-free survival, event- free survival (Table 11, page 50 of the company's submission) and progression-free survival (page 112 of the company's submission).Please provide justification as to why loss to follow-up was treated as an event if applicable.

Specific definitions for event free survival (EFS) and relapse free survival (RFS) outcomes are provided below.

- Loss to follow-up was treated as an event for EFS outcomes when such loss occurred without documented treatment failure, progression or relapse from complete remission (CR)/complete remission with incomplete blood count recovery (Cri) and alive at last contact.
- Loss to follow-up was treated as an event for RFS outcomes when such loss occurred after documented CR/CRi without relapse from CR/CRi and alive at last contact.
- Loss to follow-up was treated as an event for progression free survival (PFS) outcomes when such loss occurred and the variable PDFLAG = 1 (progressive disease (PD) being the best IRC assessed response).

This was a conservative approach, as the worst case scenario (e.g. progression, relapse or death) is assumed for subjects who are lost to follow up in the context of such a serious disease that requires ongoing medical attention.

Source Document: AML-001 Statistical Analysis Plan Dated Jan 31, 2014

10.4.2 Event-free Survival (EFS)

Event-free survival is defined as the interval from the date of randomization to the date of treatment failure, progressive disease, relapse after CR or CRi, death from any cause, or lost to follow-up, whichever occurs first. Subjects who are still alive without any of these

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events will be censored at the date of their last response assessment. See Appendix 15.6 and Table 5 (Section 10.4.3) for definitions of response categories and associated date of the response. Details of the EFS definition are given in Table 3 below.

Table 3: Censoring Rules for Event-free Survival

Situation	Date of Event or Censoring	Outcome
Withdrawal and no post-baseline response assessments and alive at date of last contact	Date of randomization	Censored
Death without any adequate response assessment	Date of death	Event
Treatment failure, disease progression, relapse after CR/CRi, or death	Earliest of: Date of treatment failure Date of disease progression Date of relapse from CR or CRi Date of death	Event
Lost to follow-up without documented treatment failure, progression, or relapse from CR/CRi and alive at last contact	Date of last response assessment	Event
No treatment failure, progression, or relapse from CR/CRi and not lost to follow-up	Date of last response assessment of CR, CRi, PR, or SD	Censored

Abbreviations: CR=complete remission; Cri=complete remission with incomplete blood count recovery; PR=partial remission; SD=stable disease

Relapse-free Survival (RFS)

Relapse-free survival is defined only for subjects who achieve CR or CRi and is measured as the interval from the date of first documented CR or CRi to the date of relapse, death from any cause, or lost to follow-up, whichever occurs first. Subjects who are still alive and in continuous CR or CRi will be censored at the date of their last response assessment. See Appendix 15.6 and Table 5 (Section 10.4.3) for definitions of response categories and associated date of the response. Details of the RFS definition are given in Table 4 below.

Table 4: Censoring Rules for Relapse-free

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Survival

Situation	Date of Event or Censoring	Outcome
Relapse or death after CR/CRi	Earliest of: Date of relapse from CR or CRi Date of death	Event
Lost to follow-up after documented CR/CRi without relapse from CR/CRi and alive at last contact	Date of last response assessment	Event
CR/CRi without documented relapse and not lost to follow-up and alive at last contact	Date of last response assessment	Censored

Abbreviations: CR=complete remission; Cri=complete remission with incomplete blood count recovery;

A10. Please clarify why event-free survival, relapse-free survival and progression-free survival were not adjusted for treatment switching.

This was due to sample size primarily. The instances in which switching preceded the clinical event of interest were few, and the impact of this on the results would be very small.

A11. Last row of Table 17, (page 64 of the company's submission) '*Did the analysis include an intention-to-treat analysis*? *If so, was this appropriate and were appropriate methods used to account for missing data*?' In response to the question, it is stated that '*the ITT population was the most appropriate population as it included all randomised patients*.' Please clarify how missing data were dealt with in the analysis of primary and secondary outcomes, including the post-hoc analysis to adjust for treatment switching.

Source Document: AML-001 Statistical Analysis Plan Dated Jan 31, 2014

11.4.2.2 Handling of Dropouts or Missing Data

All subjects who discontinued from protocol-prescribed therapy (azacitidine or conventional care regimens) for any reason were to undergo End-of-Study procedures. Additionally, all discontinued subjects were followed for a period of 28 days following the last dose of study treatment or until the date of the last study visit (whichever was longer) for the collection of AEs. Discontinued subjects were not replaced.

Missing individual data were treated as missing and no values were imputed. Calculations were based on available data. The number of missing observations was indicated for categorical data.

Key missing dates were imputed; the rules for imputing are detailed in the SAP (Appendix 16.1.9).

A12. Section 4.7.4, pages 69-71 of the company's submission:

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a. Please clarify how covariates were selected for the analyses.

Covariates were prospectively identified for the crossover analysis in the trial data and confirmed with a UK-based clinician who is actively treating patients in this indication. Following their feedback, covariates were appropriately included in the analysis according to whether or not they were also time-varying in the trial data.

b. Please clarify why no time-varying covariates (e.g. bone marrow or peripheral blood blast count) were included in the propensity score for the Inverse probability of censoring weighted method.

In line with question B7 below: Table 14 of Appendix 11 captures covariates ultimately included in the model, based on tests of statistically significant differences in covariates between the treatment and also with a view to targeting parsimony in the model.

A13. Section 4.7.4.1, pages 65-66 of the company's submission: Please provide a description of the methods used to perform the regression-based imputation analysis adjusting for subsequent therapy.

The following text from the statistical analysis plan for post-hoc analyses of primary efficacy endpoints describes the approach taken.

2.3 Regression based imputation method

A regression based imputation procedure has been proposed by Luo et al (ref 4 in SAP) that allows for inferences about the treatment effect in the presence of confounding due to additional therapy received subsequent to the randomized study treatment. This method provides an accurate estimate of the treatment effect by removing the confounding effects of additional subsequent therapy. This method provides adjusted estimates of the Kaplan Meier (KM) survival curves, which allows for comparisons using log-rank test and the calculation of an adjusted HR and associated confidence intervals.

A more detailed description of the methodology followed to perform the regression-based imputation are discussed in Appendix 5.1 of the Statistical Methods Addendum (provided separately).

A14. Section 4.7.5.8, Health-related quality of life, page 77 of the company's submission: states that '*A mixed model analysis failed to reveal any statistically significant differences in the impact of treatment on all domains between treatment arms.'* Please clarify what statistical distribution was used for this analysis, any if there were any stratification and fixed and time-varying covariate adjustment and adjustment for differential drop-out across treatment arms.

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- A mixed effect model repeat measurement (MMRM) model was developed for the EORTC QLQ-C30 Fatigue domain with the inclusion of a fixed-effect covariate indicating whether a transfusion had taken place up to 5 days before health related quality of life (HRQL) assessment. This analysis was undertaken because blood transfusions are likely to affect fatigue, but this relationship would not have been explored by previous analyses.
- Additional MMRM models were developed for the secondary HRQL domains (Dyspnea, Physical Functioning and Global Health Status/ quality of life (QoL)) that included RBC or platelet transfusion up to 5 days before the HRQL assessment as a factor.

The statement 'A mixed model analysis failed to reveal any statistically significant differences in the impact of treatment on all domains between treatment arms' references the post-hoc MMRM analysis controlling for the impact of red blood cell (RBC) or platelet transfusion received up to 5 days before HRQoL assessment. It was hypothesized by the clinical study team that transfusions administered shortly before HRQoL assessment may have an effect on fatigue. and this effect would not have been captured in the initial model. The results of the MMRM analysis for the Fatigue domain without this additional covariate were significant in favour of CCR. No significant differences were observed for the secondary domains. Full presentation of both results can be located in the CSR section 11.4.1.2.10.7.

All MMRM analyses were based on the assumption that data are missing at random. A post-hoc sensitivity analysis utilizing a pattern-mixture model was conducted to explore the impact of the missing-at-random assumption. Results of this analysis aligned with the MMRM results for Physical Functioning, Dyspnea and Global Health Status/QoL, with no differences between treatment groups at $p<0.05$, while results favoured CCR for the Fatigue domain (P=0.025).

A15. Please provide a table giving the counts and incidence rates for each treatment arm of the AZA-AML-001 trial (azacitidine, intensive chemotherapy, low-dose cytarabine, best supportive care) of the grade ≥3 treatment related adverse events that occurred in >10% of patients in any treatment arm.

Table 5: Incidence rates for each treatment arm of the AZA-AML-001 trial

			Individual CCR arms					
	Azacitidine (n=236)		BSC only (n=40)		LDAC (n=153)		IC (n=42)	
Preferred term	No.	%	No.	%	No.	%	No.	%
Febrile neutropenia	66	28.0	11	27.5	46	30.1	13	31.0
Neutropenia	62	26.3	2	5.0	38	24.8	14	33.3
Thrombocytopenia	56	23.7	2	5.0	42	27.5	9	21.4
Pneumonia	45	19.1	2	5.0	29	19.0	2	4.8
Anaemia	37	15.7	2	5.0	35	22.9	6	14.3
Leukopenia	16	6.8	0	0	13	8.5	6	14.3

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Hypokalemia	12	5.1	1	2.5	10	6.5	7	16.7

Results

A16. Please state the number of UK patients (26 in total) randomised to azacitidine, intensive chemotherapy, low-dose cytarabine, and best supportive care.

Table 6: Randomisation of UK patients

	RNDTRTC		
RANDPR	Azacitidine	CCR	Total
BEST SUPPORTIVE CARE	2	3	5
INTENSIVE CHEMOTHERAPY	1	0	1
LOW-DOSE CYTARABINE	12	8	20
Total	15	11	26

A17. Table 16, page 61 of the company submission: Please provide a corrected version of Table 16 (The numbers in 'Cytogenetic risk status – local/central' do not appear to sum to the number of patients randomised [unless 'Normal' patients are excluded – perhaps these should be indicated as a subset of 'Intermediate'?]). There also appears to be some inaccuracies in the 'Prior history of MDS' when compared with Dombret et al. 2015 and the AZA-AML-001 clinical study report.

For the prior history of myelodysplastic syndrome (MDS) and cytogenetics, a corrected version of Table 16 is provided below with corrected typographical errors highlighted in red.

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Table 7: Corrected version of table 16

Parameter	Azacitidine (N=241)	CCR			Total (N=488)
		BSC only (N=45)	LDAC (N=158)	IC (N=44)	
Prior history of MDS, n (%)					
Yes	49 (20.3)	11 (24.4)	23 (14.6)	4 (9.1)	87 (17.8)
Primary	46 (19.1)	11 (24.4)	20 (12.7)	4 (9.1)	81 (16.6)
Secondary	3 (1.2)	0 (0.0)	3 (1.9)	0 (0.0)	6 (1.2)
No	192 (79.7)	34 (75.6)	135 (85.4)	40 (90.9)	401 (82.2)
Cytogenetic risk status – local, n (%)‡					
Intermediate	159 (66.0)	28 (62.2)	102 (64.6)	29 (65.9)	318 (65.2)
Normal	118 (49.0)	22 (48.9)	65 (41.1)	18 (40.9)	223 (45.7)
Poor§	82 (34.0)	17 (37.8)	56 (35.4)	15 (34.1)	170 (34.8)
Cytogenetic risk status – central, n (%)‡					
Intermediate	155 (64.3)	29 (64.4)	104 (65.8)	27 (61.4)	315 (64.5)
Normal	113 (46.9)	23 (51.1)	65 (41.1)	17 (38.6)	218 (44.7)
Poor¶	44 (18.3)	6 (13.3)	29 (18.4)	9 (20.5)	88 (18.0)
Very poor††	41 17.0)	10 (22.2)	25 (15.8)	6 (13.6)	82 (16.8)

For cytogenetic risk, we can confirm that in NCCN guidelines, 'cytogenetic normal' is a subgroup of 'intermediate risk' and therefore should not be included when summing the numbers of patients

Table 8: Risk status based on validated cytogenetics. Modified from NCCN AML guidelines

Risk Status	Cytogenetics
Better-risk	Inv(16) or t(16;16) t(8;21) t(15;17)
Intermediate-risk	Normal cytogenetics +8 alone T(9;11) Other non defined
Poor-risk	Complex (≥3 clonal chromosomal abnormalities) -5, 5q-, -7, 7q- 11q23 – non t(9;11)

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	Inv(3), t(3 ;3) t(6;9) t(9;22)

A18. Table 22, page 72 of the company's submission: Please confirm whether the proportion of patients randomised to azacitidine experiencing relapse after complete remission or complete remission with incomplete blood count recovery is 63.2% or 64.2% (as per Dombret et al. 2015 and the AZA-AML-001 clinical study report).

64.2% is correct. (63.2% was a typographical error).

A19. Please confirm whether the age range of patients randomised to low-dose cytarabine is 65–89 years (as per page 59 of the company submission) or 65–88 years (as per Dombret et al. 2015 and the AZA-AML-001 clinical study report).

65-88 years is correct. (65-89 was a typographical error).

A20. Please complete the table below for event-free survival and relapse-free survival.. For each treatment arm (azacitidine [AZA], intensive chemotherapy [IC], low-dose cytarabine [LDAC], best supportive care [BSC]). Please provide a tabulation of the count of each event type (at the latest snapshot), for example for relapse-free survival.

Arm	**AZA**	**CCR**		
		IC	**LDAC**	**BSC**
Relapse	XX	XX	XX	XX
Death from any cause	XX	XX	XX	XX
Loss to follow-up	XX	XX	XX	XX
Total	**53**	**XX**	**XX**	**XX**

These data are provided below.

The numbers in the tables below represent the first event for a patient.

Table 9: Outcomes for relapse-free survival

Arm	**AZA**	**CCR**		
		IC	**LDAC**	**BSC**
Relapse	43	9	25	na
Death from any cause	10	8	5	na
Loss to follow-	0	0	0	na

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up				
Total	**53**	**17**	**30**	na

Table 10: Outcomes for event-free survival

Arm	**AZA**	**CCR**		
		IC	**LDAC**	**BSC**
Progression	34	1	19	6
Relapse	42	9	25	0
Death from any cause	135	26	93	36
Loss to follow-up	1	1	0	0
Total	**212**	**37**	**137**	**42**

Section B: Clarification on cost-effectiveness data

Literature searches

B1. Please provide further details summarising the company's approach to identifying studies reporting health-related quality of life. If separate literature searches were undertaken, please provide the search strategies.

A systematic literature search was not undertaken for health-related quality of life (HRQoL). Instead, a targeted search was performed. As the HRQoL was recorded for all treatments in the trial, this was used in the model as it best reflects the quality of life seen in the target population. The search terms used are detailed below.

Table 11: Search terms for Pubmed search on HRQL data:

1	acute myeloid leukemia OR acute myeloid leukaemia OR acute myelogenous leukemia OR acute myelogenous leukaemia (title/abstract)
2	QALY OR utilit* OR EQ-5D OR EORTC OR QLQ-C30 OR European Organisation for Research and Treatment of Cancer (all fields)
3	1 and 2
Total 224 hits, 6 studies selected in first round including 5 that overlap with CRD and HEED search results	

Table 12: Search terms for HERC database of HRQL mapping studies:

1	EORTC Quality of Life Questionnaire (QLQ-C30) OR EORTC QLQ-C30 OR EORTC QLQ-C30 and EORTC QLQ-B23 (Quality of life measures, From)
2	EQ-5D (Quality of life measures, To)
3	1 and 2
Total 8 hits, 2 studies selected in first round	

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Studies were then excluded based on being:

Paediatric studies, studies comparing different types of stem cell transplantation, studies comparing interventions for prophylaxis of infection.

Methods

B2. Please confirm that event free survival was used directly (without any further adjustment) for relapse-free survival (in patients achieving complete remission or complete remission with incomplete blood count recovery) and progression-free survival (in patients not achieving complete remission or complete remission with incomplete blood count recovery), that is, if relapse-free survival and progression-free survival were recombined, event-free survival would be obtained for the full population.

Event free survival was used directly for relapse-free survival by including only the patients achieving CR or CRi. Progression-free survival was generated by using event free survival for non-responders, and a flag for disease progression (i.e., to measure progression or death as the events of interest, thereby constructing PFS).

PFS and RFS were calculated using the below code:

PFS:

```
gen cens_pd = pdflag

drop if ircresp == 1 | ircresp == 2 | ircresp == 7 | ircresp == 8

gen cycle = tte_efsm*13/12

qui stset cycle, failure(cens_pd)
```

RFS:

```
keep if ircresp < 3

gen cycle = tte_efsm*13/12

qui stset cycle, failure(cens_pd)
```

B3. Please confirm that the following methods were used to calculate different survival curves in the model, and if so whether the curves for relapse-free survival and progression-free survival were fitted to azacitidine (AZA) and conventional care

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regimen (CCR) patients with a proportional-hazards azacitidine treatment variable, or if these were fitted only to CCR patients. Please see the table below.

The following methods were used to calculate different survival curves. The curves for RFS and PFS were fitted only to CCR patients.

Table 13: Methods used to calculate survival curves

Arm	AZA	CCR
Overall survival		
Underlying data	OS from AZA	OS from AZA
Curve fitting	Exponential	Exponential
Adjustments	—	HR of [redacted] from IPCW method (inverse HR)
Relapse-free survival		
Underlying data	EFS for CCR patients achieving CR or CRi	EFS for CCR patients achieving CR or CRi
Curve fitting	Weibull	Weibull
Adjustments	HR of 0.84 from curve fitting	—
Progression-free survival		
Underlying data	EFS for CCR patients not achieving CR or CRi	EFS for CCR patients not achieving CR or CRi
Curve fitting	Gompertz	Gompertz
Adjustments	HR of 0.85 from curve fitting	—

B4. Page 112 of the company's submission: Please clarify whether the results using the Iterative Parameter Estimation (IPE) method are correct, as there appears to be some disparity between these results and the results in Appendix 11 and other sources.

We believe this question is a reference to the p-value, which is incorrectly listed as 0.083, and should 0.060.

B5. **Priority question:** Please provide a copy of the Statistical Analysis Plan cited in Appendix 11 of the company's submission.

Provided separately.

B6. Page 123 of the company's submission states that '*subgroup adjustment was not feasible because of limited data on switching; however, a clinical expert consulted during this analysis stated that questions can be raised about the clinical generalizability of the results in subgroups, because clinicians can identify potential switching candidates based on observed performance, and recommended focusing on the adjusted data for overall patients*.'

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a. Please clarify what baseline patient characteristics were used to define the subgroups and why particular baseline characteristics were chosen.

This refers to controlling/adjusting for the three treatment groups within CCR, as well as for cytogenetic risk or MDS subgroups; these were the subgroups or disaggregated treatment otherwise considered in the modelling.

b. Please provide further details on the reasons why the results of the subgroup analysis were not considered to be clinically generalizable.

The choice of the word "generalizable" was based on discussion with clinicians as well as internal discussion. Because allocation to IC, LDAC, and BSC are at the discretion of the clinicians, the allocation to the CCR components is not blinded and so there is potential for selection bias between these three groups.

c. Please provide details of the number of patients who switched treatments and the number who did not.

Table 14: Number of patients who switched treatments and the number who did not

Patient subgroup	Number of patients who received subsequent AML therapy	Number of patients who did not receive subsequent AML therapy
All patients	[redacted]	[redacted]
Comparator: IC	[redacted]	[redacted]
Comparator: LDAC	[redacted]	[redacted]
Comparator: BSC	[redacted]	[redacted]
Subgroup: Intermediate cytogenetic risk	[redacted]	[redacted]
Subgroup: Poor cytogenetic risk	[redacted]	[redacted]
Subgroup: With MDS-related changes	[redacted]	[redacted]
Subgroup: Without MDS-related changes	[redacted]	[redacted]

B7. Table 37, page 125 of the company's submission. Please clarify whether the information about covariates used in the Inverse probability of censoring weighted

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analysis in Table 37 is correct as there appears to be discrepancies between Table 37 and Table 14 of Appendix 11.

Table 37 has all covariates that were considered for the Inverse probability of censoring weighted (IPCW). Then whether there were any statistically significant differences between CCR patients who switch and CCR patients who do not switch were used to narrow this to the list of covariates to be included in the model, seen in Table 14.

B8. Page 130 of the company's submission: Please explain why the adverse events which are costed on page 130 of the company's submission appear to differ from the adverse events for which disutilities are measured (page 129 of the company's submission).

HRQL analysis from the trial was more restricted in terms of measuring and mapping from EORTC QLQ-C30 scores during an AE in the trial; costing on the other hand used rates of AEs, disaggregated by type, from the main clinical study report, and hence were more detailed.

Thus, in the model, AE disutilities are a single figure that are aggregated at the trial-analysis level; AE costs on the other hand are aggregated within the model itself, calculated from rates and unit costs for AEs.

B9. Please explain what the 'Acute myeloid leukaemia' adverse event refers to, and what the cost represents.

The AE preferred term (PT) "acute myeloid leukaemia" includes the verbatim term "worsening AML" reported by the investigator. If a subject's disease worsened during the study treatment period but did not meet the protocol-defined criteria for progressive disease (PD), the PI reported an AE of "worsening AML." Specific to the intensive chemotherapy treatment group, if a subject did not achieve CR, CRi, or PR after induction therapy, the subject was to be discontinued from the treatment period, per protocol. If intensive chemotherapy subjects achieved a response following treatment, they were to remain in the treatment period until they met the criteria for relapse after CR/CRi or were removed for some other reason. Therefore, there was little opportunity to have an AE or worsening AML in the intensive chemotherapy group. However a subject could have achieved a response of CR/CRi and then worsened, without meeting the relapse definition and then had an AE of worsening AML reported.

AML AE cost is directly from National Schedule of Reference Costs 2013-14, CL. The currency Code: SA25M - Acute Myeloid Leukaemia with CC Score 0-1. The cost represents "Unit day case".

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B10. **Priority question:** Please explain how mean treatment duration for azacitidine from the AZA-AML-001 trial was applied in the model. Please confirm that the model only includes costs for 8 cycles of treatment although 32% of patients were still receiving azacitidine after 12 cycles.

The model uses mean number of cycles per patient (8) to calculate treatment costs. This is on the basis of a time-threshold in terms of cycles based on the mean, but does not account for the distribution around the mean duration and hence the right-hand tail to this distribution, after 8.8 cycles, is not used.

Additional question:
The company has provided the (Stata) dataset used for the final inverse-probability of censoring weights (IPCW) analysis of overall survival (OS), with follow-up divided into 15-day periods. The company has not, however, provided the (SAS) dataset used to estimate the censoring weights used in the analysis. Could the company please provide the dataset (and accompanying data dictionary) used to estimate the IPCW weights. In Appendix 10 of the company submission, these are the datasets required to run the SAS code under '* alternate scenario - reduced periods' (please note that despite the name this is used in their base case analyses).

SAS files are provided separately. The data dictionary provided separately in response to question A1 can be used.

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Patient/carer organisation submission (STA)

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts

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.

We support people affected by leukaemia, lymphoma; Hodgkin lymphoma; non-Hodgkin lymphoma; multiple myeloma; myelodysplastic syndromes;

myeloproliferative neoplasms and aplastic anaemia. 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 throughout the United Kingdom. Support is offered over seven key areas:

- 24-hour CARE Line
- 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 over 25 years ago 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 purely on 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 also 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/code-of-practice

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

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 form of blood cancer, which affects the white blood cells known as myeloid cells. It is a rapidly progressing form of leukaemia. Approximately 2,500 people are diagnosed in England each year. AML, like most forms of cancer, is more common in older people with around three quarters of all patients in the UK with AML are over sixty years old. As such, the majority of AML patients will have co-morbidities that affect their fitness which could make their treatment options more limited.

Patients can be diagnosed with primary AML but it is also possible for myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs) to develop into secondary AML. Patients whose condition has progressed to AML are often associated with resistance to standard chemotherapies and have a poorer overall prognosis. Additionally, poor prognostic factors are

more common in older patients, also making treatment particularly challenging.

The most common signs or symptoms of AML are anaemia (which causes fatigue and breathlessness), low platelet counts (which cause bruising and bleeding) and low white cell count (which causes persistent infections and fever). Less common symptoms include bone pain, enlarged spleen and/or enlarged lymph nodes. Patients can experience some or all of these symptoms and they have a huge impact on their quality of life.

As shown in the recently updated NCIN report “Routes to Diagnosis”, 53% of AML patients are diagnosed following an emergency presentation. This compares to 30.5% for blood cancers and 22% for cancers generally. The acute nature of the disease, which is rapidly progressing and has an extremely poor prognosis, is a key factor in the late diagnosis of this disease. People diagnosed with AML have a 47% chance of surviving for 6 months, 34% chance of surviving for 12 months and only 19% of surviving for 36 months or more.

With most patients diagnosed following emergency presentation and the extremely poor prognosis expected, being diagnosed with AML can be extremely traumatic, shocking and scary. Following diagnosis some patients may experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation and depression.

Due to the extremely poor prognosis of patients with AML, it will not affect patients in isolation but can cause a “ripple”, affecting a patient’s family and friends. As most patients will die within a year of diagnosis, the emotional impact on the family and friends can often be profound. As such, any improvements in patients’ outcomes and quality of life will also have a wider impact on the lives of their family and friends.

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.

Whilst it is difficult to make generalised statements concerning patient's wishes, it must generally be accepted that the most important treatment outcomes are:

- Survival (progression-free and overall)
- Durable responses to treatment
- Quality of Life – including more tolerable side effects and improved symptom control
- Active treatment (rather than Best Supportive Care)

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?

As previously mentioned, around three quarters of all AML patients in the UK are over sixty years old. Due to this many AML patients have co-morbidities that may affect their health and fitness. As such, patients are often unable to tolerate aggressive treatment options which would usually give them the best chance of prolonged survival. For most patients, treatment options are therefore limited.

- In this setting, the treatment usually recommended is a low dose chemotherapy (cytarabine and hydroxyurea). This treatment often offers a limited benefit, but can encourage haematological remissions in a small proportion of patients.
- An additional (or alternative) treatment option for patients in this setting is best supportive care which focuses on treating any symptoms or complications of the disease, keeping the patient as comfortable as possible. Whilst it is currently sometimes the only available option for patients, it is not actively treating the AML.
- For patients who are younger, or have no other health issues, intensive chemotherapy is the recommended treatment option. However for most

patients within the proposed patient group, this is not an appropriate treatment option as it is reserved for patients who are well enough to tolerate the treatment.

AML is an aggressive, fast developing cancer with a poor prognosis. As previously mentioned, the survival rates for patients with AML are very low and have barely improved for over 40 years. Following diagnosis, most patients will die within a year, which demonstrates the desperate need for improvements in treatment for these 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/advantages that patients or carers expect to gain from using the treatment being appraised over other NHS treatments in England.

- During clinical trials azacitidine appears to demonstrate an improved overall survival. Any potential improvement in survival rates in a patient population with such a poor prognosis is extremely welcome.

- Improved quality of life

- Azacitidine appears to be a more tolerable treatment option, demonstrating fewer adverse effects.
- Remains an effective treatment option in hard to treat patients with poor risk cytogenetics and those with myelodysplasia-related changes.
- Azacitidine is superior to best supportive care, which confirms that active treatment should be considered for older AML patients.
- Fewer hospitalisation days
- Transfusion independency
- Patients without a complete response to azacitidine still encountered a significant benefit compared to alternative therapies.
- Additional option following currently available alternative treatments

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.

See above.

Please list any concerns patients or carers have about the treatment being appraised.

- Patients taking azacitidine encountered adverse effects such as nausea, neutropenia and thrombocytopenia (although many of these compare more favourably than the alternative options).

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.

- This treatment may be of particular benefit for less fit or frailer patients who are unable to tolerate the more aggressive treatment options, as there is little option for alternative therapies.

- Potential particular benefit for patients with poor-risk cytogenetics and poor prognostic factors (as their alternatives are limited).

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

N/A

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

✓ Yes ☐ No

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.

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.

9. Other issues

Do you consider the treatment to be innovative?

✓ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

We consider azacitidine to be innovative as it is the only AML treatment that has demonstrated an improved overall survival rate in older patients with poor-risk cytogenetics.

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 fast progressing form of leukaemia that typically affects patients over 65. It can have a fundamental impact on the physical and emotional health of patients and their family and friends.

- Common symptoms of AML are anaemia (which causes fatigue and breathlessness), low platelet counts (which causes bruising and bleeding) and low white cell count (which causes persistent infections and fever). The symptoms can have a profound impact on the quality of life of the patient.

- As 53% of AML diagnoses are in an emergency presentation, when most patients are diagnosed, the condition has already progressed significantly. Patient prognosis following diagnosis is generally very poor, with one year survival rates of only 34%.

- It is a difficult to treat disease, especially when patients are unable to receive more intensive treatment options. For patients within this population, who are often unable to tolerate intensive chemotherapy options, there are very limited treatments available. Currently available options include low-dose chemotherapy and best supportive care, with limited efficacy. There is a clear need for more tolerable, effective treatments for patients in this setting in order to improve overall survival rates.

- Azacitidine seems to be a promising treatment option, in an area where there are fewer options and low overall survival rates. It seems to be especially beneficial for older patients and those with poor prognosis (e.g. poor-risk cytogenetics or myelodysplasia-related changes).

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts

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], submitting on behalf of:

Name of your organisation: NCRI-RCP-ACP

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None to declare

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?
Current therapy of acute myeloid leukaemia (AML) in patients >65 years is chemotherapy-based in most patients. Broadly, younger fitter patients are treated with intensive combination chemotherapy (rarely, but increasingly followed by) stem cell transplantation with the intention of cure or the achievement of short-term improvement in quality of life if complete remission is achieved in the absence of major morbidity. Complete remission is obtained in 50-70% patients selected for intensive chemotherapy. Cure rates in patients >65years treated with intensive chemotherapy are approximately 10-15% and this varies to a small extent by biological subgroup as in younger patients. Median survival (real-world data) is approximately 12-18 months with the majority of long term survivors found in the 60-70y age group.

Older patients, those with significant co-morbidity or refractory forms of AML tend to receive non-intensive/palliative therapy. By definition the goal is not cure but an improvement in overall survival with an acceptable quality of life. Approximately 20% patients treated with low dose Cytarabine will achieve complete remission but survival beyond 2 years is not achievable. Median survival for typical AML patients treated with low dose Cytarabine in the real world setting is 6 months (HMRN audit data). All patients will require best supportive care in addition to chemotherapy (blood product transfusions, antibiotics etc.). Best supportive care alone is offered to patients who prefer this approach, or for whom the practicalities of administering chemotherapy plus supportive care are not feasible typically due to comorbidities.
A substantial proportion of these patients are treated within the current clinical trials evaluating emerging therapies for AML.
In summary the decision making process for individual older AML patients includes a subjective assessment of 'fitness' for intensive chemotherapy, in the context of disease biology, comorbidities and patient preference. Up to age 70-75yrs (and in some clinician's opinion up to 80y) intensive chemotherapy would be offered if patients are relatively fit, their AML lacks adverse biological characteristics and their goal for therapy is achievement of complete remission and hence good quality of life for the duration of that complete remission. If these criteria are not met, or patients prefer, non-intensive therapy is likely to prolong survival compared with best supportive care alone but with a lower chance of quality of life benefit given the lower complete remission rate; such an argument applies both to LDAC and to the new technology azacitidine.
Is there significant geographical variation in current practice?
No

Are there differences of opinion between professionals as to what current practice should be?
There is some variation in the clinician's evaluation of those patients who should be treated intensively and those who shouldn't, given that there are no objective validated tools which assess frailty and comorbidity in the context of outcome that are available to inform this decision.

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What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
The current technology is a non-intensive/palliative approach. The standard here has been low dose cytarabine (ara-C) chemotherapy (LDAC). Probable advantages for azacitidine over LDAC include greater efficacy in AML with adverse biological characteristics, and higher frequency of haematological improvement, with reduced risk for transfusion dependence and infections. LDAC produces profound myelosuppression during the first 1-2 cycles, greater than with azacitidine hence an increased risk for transfusional support and infection with LDAC. Both drugs are less myelosuppressive in patients who have achieved remission. LDAC is often administered in the community and although there are sporadic examples of community administration of azacitidine this is currently not widely available. As such in the current models, patients treated with azacitidine will visit hospital more frequently for drug administration. Blood product support is comparable for both technologies and diminishes / ceases in patients that achieve remission.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
AML can be biologically subdivided by cytogenetic risk group and more recently by mutational landscape. Cytogenetic risk group classification is well validated as a prognostic marker and there is rapid evolution in the understanding of the prognostic significance of mutations. To date, the prognostic significance of a handful of mutations only is useful in clinical practice (e.g. FLT3 ITD/TKD, NPM1, CEBP α).

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
AML patients with proliferative disease (white blood cell count >15 x 10^9/l)were not eligible for the trial and therefore have not be adequately evaluated. Similar to all such trials, patients with significant co-morbidity have not be fully evaluated. In the context of the new technology, the adverse risk cytogenetic group, which has a poor prognosis, appears to respond better to azacitidine than to LDAC as evidenced by a small but statistically significant survival advantage in this (relatively small) subgroup of patients, although the standard arm (LDAC) may have been undertreated as the trial was unblinded

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?
Secondary care- generally a haematology day unit, although models of ambulatory home delivery have been undertaken.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
This is comparable to the current standard for treatment of AML. Similarly azacitidine is already widely used (and NICE approved) for high risk myelodysplasia (MDS) and AML (with less than 30% blasts).

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Single Technology Appraisal (STA)

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts

If the technology is already available, is there variation in how it is being used in the NHS?
Yes- due to clinician preference.

Is it always used within its licensed indications? If not, under what circumstances does this occur?
Azacitidine has been used for low risk MDS (was previously funded on CDF).

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 British Committee for Standards in Haematology (BCSH) guidelines in the management of AML and MDS predate the publication of the recent AML-001 study so do not currently consider this. A similar situation applies to the European Leukaemia Network (ELN) guidelines.

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?

As described above it's already in regular use for MDS and AML (with less than 30% blasts) reasonably comparable in administration and supportive care requirements to the current most comparable standard (LDAC)(see above)

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.

No additional diagnostic or prognostic testing is required prior to initiation of azacitidine. Clinical trial experience and guidelines for use of azacitidine in high-risk MDS require regular bone marrow assessments (every 3-6 cycles of therapy) to evaluate response. Post-hoc trial analysis and retrospective cohort studies ata in MDS and AML (with less than 30% blasts) suggests a survival benefit even for those patients not achieving a complete remission (CR) and as such continuation of therapy in stable patients is standard practice. Progression on therapy is a clear stopping criterion. As azacitidine is well tolerated, stopping therapy for adverse drug reactions is uncommon.

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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.

Broadly yes- with the caveat as with all such clinical trials that the exclusion/inclusion criteria inevitably does not wholly represent the patient population.

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?

They do and UK sites participated in the study. One significant variation is however that administration of azacitidine within the trial consisted of 7 consecutive days of administration- in reality few day units are open at weekends so on a worldwide basis this has led to the adoption of a '5+2+2' schedule- where it is administered mon-fri then again on mon/tue to complete the seven days- there is less data here, but responses appear to be comparable.

What, in your view, are the most important outcomes, and were they measured in the trials?

Overall survival, response rate, safety assessments and quality of life. Yes but as is often the case, compliance with PRO completion reduced precipitously with time. As such it is difficult to interpret these data and of some interest that the only clinically significant benefits for QoL (with many caveats) were seen in the CCR arm. No decrement in QoL was apparently observed in the azacitidine arm.

If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

N/A

What is the relative significance of any side effects or adverse reactions?

Generally well tolerated, with fewer adverse events compared to current standard therapies.

In what ways do these affect the management of the condition and the patient's quality of life?

Ongoing supportive care requirements- potentially reduced from from current standard (LDAC).
QoL - see above.

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Not at a significant rate to my knowledge.

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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.

The audits and registries I'm aware of have been published.

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)?

Could be implemented with limited impact. This is a relatively rare disease and the technology would largely be replacing an alternative in units who are already very experienced in azacitidine therapy. This would require a non-licensed dosing schedule to be used as outlined above (5+2+2) In view of the short half-life many units require patients to attend their day units for daily administration- a home administration service is available in some areas of England and can provide much greater convenience for patients.

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;

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- 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.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

I don’t believe there would be such impact.

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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 [redacted]

Your name:

Name of your organisation: RCPath

Are you (tick all that apply):

a specialist in the treatment of people with the condition for which NICE is considering this technology?

-
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
-

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

AML in the majority of patients aged 60-70 yrs is treated with intensive chemotherapy with the aim of achieving a complete remission, many of these patients will be considered for BMT. Allo transplant has been shown to improve survival in patients aged 60 – 70 years. Patients over 70 are also frequently treated with intensive therapy if considered fit but older frailer patients may be offered non-intensive therapies such as LDAC or if elderly and v frail with supportive care of transfusions and prophylactic antibiotics (BSC). This is the group of patients where the technology may benefit. The judgement of whether a patient is fit for intensive therapy is clinically based and there may be some variation in practice. There are useful ELN guidelines on the treatment of AML.
A substantial proportion of these patients are treated within the current clinical trials evaluating emerging therapies for AML.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

The current technology is a non-intensive/palliative approach for older patients not fit for intensive therapy. The standard here has been low dose cytarabine (ara-C) chemotherapy (LDAC). Azacitidine is comparable in tolerability and response rates in terms of remission induction. Azacitidine (AZA) may have a greater response rate in the sub group of patients who have an adverse cytogenetic karyotype

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)?

Secondary Care though some patients may receive home delivered care

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?

Yes it is available and widely used for patients with MDS and selected low blast count AML. It has been also used in the relapsed setting as many older AML patients relapse as an MDS

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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.

Mentioned above. The UK guidelines in this area are older and do not mention this technology

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?

As described above it's already in regular use for MDS and AML (with less than 20% blasts) Its use is reasonably comparable in administration and supportive care requirements to the current most comparable standard (LDAC)

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.*

Most patients are assessed after 4 cycles of therapy with a bone marrow to assess their response and a decision made as to whether continue therapy or not.

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? 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?

Certain patients with AML were excluded from the trial if they had a high WCC. There is little evidence that this proliferative type of AML responds well to this technology. Overall the benefit from Azacytidine seemed strongest against BSC rather than LDAC and subgroups with AML with MDS like features and adverse risk cytogenetics seemed to benefit most

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?

These are manageable

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.

Implementation issues

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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)?

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Equality
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- 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.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

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Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by National Cancer Research Institute (NCRI), Royal College of Physicians, Royal College of Radiologists (RCR) and Association of Cancer Physicians and consequently I will not be submitting a personal statement.

Name: [redacted]

Signed: [redacted]

Date: 14.Dec.2015

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts

A Single Technology Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter St Luke's Campus, Heavitree Road, Exeter, EX1 2LU
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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.
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Contributions of authors

Ruben Mujica Mota	Led the critique of the review of economic evaluation studies, the critique of the economic model and subsequent treatment adjustment. Wrote the respective sections of these contributions.
Jo Varley-Campbell	Led the critique of the company's decision problem and clinical effectiveness evidence. Wrote the Decision problem and Clinical effectiveness chapters. Contributed to the writing and editing of the report.
Irina Tikhonova	Contributed to the critique of the company's economic model and to the writing and editing of the Cost-effectiveness chapter.
Chris Cooper	Led the critique of the company's literature searching for this submission. Wrote the review of the literature searches for the report. Contributed to the writing and editing of the report.
Martin Hoyle	Provided occasional advice on the critique of the economic evaluation, commented on drafts of the report and is the guarantor of the report.
Claudius Rudin	Provided clinical advice on acute myeloid leukaemia and its management within the NHS. Reviewed and revised a draft version of the report.
Tristan Snowsill	Contributed to the critique of the company's clinical and cost-effectiveness evidence. Wrote the Summary, Background, End of Life and Overall conclusions sections. Compiled the report. Provided overall project management.

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Abbreviations

AE	Adverse event
AIC	Akaike information criterion
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
AZA	Azacitidine
BIC	Bayesian information criterion
BM	Bone marrow
BNF	British National Formulary
BSC	Best supportive care
CCR	Conventional care regimens
CI	Confidence interval
CMML	Chronic myelomonocytic leukaemia
CNS	Clinical nurse specialist
CR	Complete remission
CRc	Cytogenetic complete remission
CRi	Complete remission with incomplete blood count recovery
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EORTC	European Organization for Research and Treatment on Cancer
EQ-5D	EuroQol five dimensions questionnaire
ERG	Evidence Review Group
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio

HRQoL	Health-related quality of life
HCRU	Healthcare resource utilisation
HSCT	Haematopoietic stem cell transplantation
IC	Intensive chemotherapy
ICER	Incremental cost-effectiveness ratio
IPCW	Inverse probability of censoring weighting
IPE	Iterative parameter estimation
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWG	International Working Group
KM	Kaplan Meier
LDAC	Low-dose cytarabine
LYG	Life years gained
MDS	Myelodysplastic syndromes
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazards
PR	Partial remission
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcomes
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit

QALY	Quality-adjusted life year
QLQ	Quality of life questionnaire
RBC	Red blood cell
RCT	Randomised controlled trial
RFS	Relapse-free survival
RPSFTM	Rank preserving structural failure time model
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Stable disease
SF-12	Short-form 12 questionnaire
WBC	White blood cell
WHO	World Health Organization

1 Summary

1.1 Critique of the decision problem in the company submission

The company narrowed the population from adults with acute myeloid leukaemia (AML) and bone marrow blasts more than 30% (as per the NICE Scope) to adults aged ≥65 years who are not eligible for haematopoietic stem cell transplantation with AML and bone marrow blasts more than 30% to adults. This change was to coincide with the European Medicines Agency marketing authorisation for azacitidine and was deemed a reasonable change by the ERG.

The intervention in the decision problem was azacitidine, as in the NICE Scope.

The comparator(s) in the decision problem were different from the NICE Scope. The company replaced three individual comparators (intensive chemotherapy [IC], non-intensive chemotherapy with low dose cytarabine [LDAC] and best supportive care [BSC]) with one composite comparator (conventional care regimen; CCR) on the basis that there are no established criteria for selecting one CCR. As a result, the company has not assessed whether azacitidine demonstrated clinical and/or cost-effectiveness versus each of the CCR comparators. The ERG considered this to be a weakness of the submission.

The company reported the same outcomes to that of the NICE Scope.

The NICE Scope asked for evidence, if available, on the following subgroups: people with AML secondary to myelodysplastic syndrome (MDS) and people with adverse-risk cytogenetics. The company reported that these subgroups were assessed. Although the submission looked at the subgroup of AML with MDS-related changes (which is a broader subgroup than AML secondary to MDS), these other considerations were deemed acceptable by the ERG.

1.2 Summary of clinical effectiveness evidence submitted by the company

The primary focus of the company's submission was the RCT AZA-AML-001. Patients were randomised to azacitidine (N=241) or to a conventional care regimen (N=247; BSC=45, LDAC=158, IC=44). Baseline characteristics were reported as being balanced between arms. Outcome results were as follows:

Overall survival

Azacitidine was numerically superior to CCR in prolonging survival of adults ≥65 years with AML with >30% bone marrow blasts but statistical significance was not reached. Median duration of follow up was 24.5 months. By the study end, there were 193 deaths (80.7%) following treatment with azacitidine and 201 deaths (81.4%) following CCR treatment.

Secondary endpoints

1-year survival rates were 46.5% for azacitidine compared to 34.3% in the CCR arm (difference 12.3 %; 95% CI: 3.5, 21.0).

Measures of haematologic response, duration of remission and remission free survival were similar between treatment arms when CCR was combined. When CCR was not combined, it

appeared that IC was numerically superior to azacitidine for these outcomes, although the study was not powered to detect any such differences.

No statistical analyses were presented for the health-related quality of life (HRQoL) data. Appearances from the figures suggest that CCR was favourable to azacitidine.

Adverse events

Treatment related AEs were common for both azacitidine, LDAC and IC. Unsurprisingly, AEs were less common for BSC.

1.3 Summary of the ERG's critique of the clinical effectiveness evidence submitted

The company presented a poorly constructed systematic review of the literature. Their searches were weak and their inclusion criteria were both over- and under-exclusive. Ultimately however, the ERG concluded that the company did not miss any evidence.

The primary focus of the company's submission was the RCT AZA-AML-001. This was generally an appropriately-designed RCT, although it was underpowered for comparisons of azacitidine to each of the CCR arms. It is not clear whether the proportion of patients pre-selected to each CCR therapy in the RCT (18% IC, 64% LDAC and 18% BSC) are representative of NHS clinical practice; data from a registry in Yorkshire suggests more patients may receive BSC [redacted] and fewer LDAC [redacted], while clinical expert advice is that more patients would be expected to receive IC. The use of subsequent therapies following treatment assignment was permitted, and this was a limitation to the study design as it resulted in confounded estimates for the primary efficacy endpoint and other endpoints.

The open-label design of the trial, although unavoidable as the treatments generally require different levels of medical intervention, increases the risk of bias.

Statistical analyses of time-to-event outcomes relied on the proportional hazards assumption, which transpired not to be justified.

1.4 Summary of cost-effectiveness evidence submitted by the company

1.4.1 Company's systematic review of economic evaluations

The company conducted a systematic review of economic evaluations, which did not find any pre-existing studies adequately addressing the decision problem.

1.4.2 Company's submitted economic evaluation

1.4.2.1 Methods

The company presented a model-based economic evaluation to address the decision problem.

A semi-Markov (survival partition) model was used with four health states: Remission, Stable disease, Relapse/Post-progression and Death. Patients achieving remission started the model in the Remission state, while patients not achieving remission started in the Stable disease state. A model cycle length of four weeks was used, and a time horizon of ten years

was used. Outputs of the model (costs, life years and quality-adjusted life years [QALYs]) were discounted at 3.5% per annum.

Two treatment arms were modelled. The azacitidine (AZA) arm modelled treatment with azacitidine until discontinued, followed by BSC. The CCR arm modelled a mixture of conventional treatments (IC, LDAC and BSC), with IC and LDAC followed by BSC after discontinuation.

Overall survival, relapse-free survival and progression-free survival curves were constructed by fitting parametric survival models to data from the AZA-AML-001 trial. The treatment effect was modelled using proportional hazards for all survival curves. A model selection process was followed, which resulted in the selection of an exponential survival model for overall survival, a Weibull model for relapse-free survival and a Gompertz model for progression-free survival. Hazard ratios of 0.84 and 0.85 were used for relapse-free and progression-free survival respectively, while a hazard ratio of [redacted] was used for overall survival based on an analysis adjusting for subsequent treatment with azacitidine in patients randomised to CCR.

Health state utility values were estimated by mapping EORTC QLQ-30 data collected in the AZA-AML-001 trial to EQ-5D utility values, and were not modelled as varying according to treatment given. The impact of adverse events on health-related quality of life was also directly modelled by treatment.

Costs were modelled from the NHS and personal social services perspective. Drug acquisition costs were estimated using the average daily dose in AZA-AML-001 and list prices (British National Formulary; BNF), with a confidential patient access scheme (PAS) discount of [redacted] applied to the cost of azacitidine. In the base case full wastage was assumed (i.e., no vial sharing across days or across patients). Patients were assumed to receive the relevant first-line treatment until relapse or progression. Drug administration, medical management, diagnostic test and transfusion resource use were estimated through a survey of clinicians conducted by the company. The PSSRU Unit cost of health and social care and the NHS reference costs were used to estimate unit costs. Costs of adverse events were also modelled.

Univariate and probabilistic sensitivity analyses were conducted to explore uncertainty in the incremental cost-effectiveness ratio (ICER) and to identify parameters to which the model was sensitive. Scenario analyses were also conducted.

1.4.2.2 Results

In the company's base case analysis, treatment with CCR resulted in 0.6365 QALYs and £40,608 cost, while treatment with azacitidine resulted in [redacted] QALYs [redacted] and [redacted] cost [redacted], with a corresponding ICER of £20,648 per QALY.

Azacitidine was predicted to provide QALY gains across all health states, and was predicted to result in increased costs in the Remission and in Relapse/Progressive disease health states, partially compensated for by savings in the Stable disease health state.

Drug acquisition costs were the largest cost component in the AZA arm [redacted] more costly than in the CCR arm), while drug administration costs were the largest cost component in the CCR arm [redacted] more costly than in the AZA arm). Other costs were largely similar between the two arms.

In their probabilistic sensitivity analysis, incremental QALYs were similar to the deterministic analysis, while incremental costs were marginally lower. The resulting ICER for azacitidine was £17,423 per QALY. At cost-effectiveness thresholds of £20,000, £30,000 and £50,000 per QALY, azacitidine was cost-effective versus CCR in 69.9%, 90.8% and 99.6% of iterations respectively.

Univariate sensitivity analyses identified that the results were sensitive to a number of parameters, with administration costs in the CCR arm, the hazard ratio for overall survival, the remission rates in the CCR arm and the acquisition and administration costs in the AZA arm as the five parameters to which the model was most sensitive.

One notable scenario analysis showed that when overall survival in the CCR arm was not adjusted for subsequent treatment, this resulted in improved cost-effectiveness of azacitidine (£11,537 per QALY).

1.5 Summary of the ERG's critique of the cost-effectiveness evidence submitted

The ERG identified several issues with the company's submitted economic evaluation.

The model assumed that no patients would receive active treatment following discontinuation of first-line treatment. However, in the AZA-AML-001 trial underpinning the analysis, 29% of participants received active second-line treatment. Advice from clinical experts suggests that active second-line treatment is considered for some patients in the NHS.

The model assumed proportional hazards for all time-to-event outcomes, even though this was not supported for overall survival and relapse-free survival by results from the AZA-AML-001 trial.

Overall survival in the AZA arm was not adjusted for subsequent active treatment, resulting in an inconsistency between the modelled health outcomes and costs, since only the costs of best supportive care were modelled following azacitidine.

Implementation issues were identified in the model. The most significant of these was an error in the calculation of the duration of first-line treatment which resulted in an underestimate of the drug acquisition and administration costs in both arms.

The ERG also identified that there were significant differences in the cost associated with the Relapse/progressive disease state between the AZA and CCR arm, even though all patients (in both arms) are expected to be receiving BSC at this point.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company's submission was based on a recent and relevant RCT (AZA-AML-001) with the following strengths:

- Multicentre RCT conducted across multiple countries, including countries in Western Europe;

- Sufficient follow-up for mature estimates of survival outcomes, including overall survival;
- Appropriate dosing in the intervention and comparator arms;
- Appropriate randomisation, including concealment of allocation prior to randomisation and stratified blocking on key prognostic variables;
- Appropriate and relevant outcomes measured.

The company's submitted economic evaluation had the following strengths:

- Simple and transparent overall model structure;
- Inclusion of relevant costs from an NHS and personal social services perspective;
- Suitable cycle length and time horizon;
- Transparent process for fitting survival models;
- Utility values suitably mapped from health-related quality of life measurements from AZA-AML-001;
- Probabilistic sensitivity analysis to estimate the importance of parameter uncertainty in the decision problem.

1.6.2 Weaknesses and areas of uncertainty

The decision problem addressed by the company's submission had a key weakness that instead of individual conventional care regimens as comparators (as in the NICE Scope), a combined comparator was used.

The company's systematic review of clinical effectiveness evidence was hampered by poorly designed and reported searches.

The pivotal trial (AZA-AML-001) had the following weaknesses:

- Underpowered for comparisons between azacitidine and individual conventional care regimens;
- Significant proportion of patients used subsequent active treatments, including treatments not currently used in the NHS, and these were not balanced between treatment arms;
- Limited proportion of patients allocated intensive chemotherapy as their conventional care regimen compared to expectation of routine clinical practice according to clinical experts;
- Open-label design increases the risk of bias;
- Statistical analyses relying on proportional hazards assumption which is not justified.

The company's submitted economic evaluation had the following weaknesses:

- Inconsistency between the treatments costed post-discontinuation (BSC only) and the subsequent treatments reflected in overall survival estimates (AZA: active treatments; CCR, active treatments except azacitidine);

- Inappropriate proportional hazards assumption for overall survival and relapse-free survival outcomes;
- Implementation errors, including a significant underestimate of treatment duration in both arms;
- Inadequate exploration of structural uncertainty;
- Significantly greater costs after relapse/progression in the CCR arm despite patients in both arms receiving BSC only in this state.

The following areas of uncertainty remain:

- The overall survival benefit demonstrated in AZA-AML-001 did not reach statistical significance in pre-planned analyses, yet it is interpreted nevertheless as a positive result;
- It is not clear to what extent azacitidine is a clinically effective and cost-effective alternative to IC, LDAC and BSC as individual comparators.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG preferred base case ICER is £169,606 per QALY, compared to the company's base case ICER of £20,648 per QALY. The reasons for the increased ICER are:

- Corrections to errors in model formulae (increases ICER from £20,648 to £62,518 per QALY);
- Increased costs in the AZA and CCR arms due to correcting the implementation of treatment duration in the model (increases ICER from £62,518 to £131,698 per QALY);
- Equalised costs in the Relapse/progressive disease health state across the model (increases ICER from £131,698 to £238,674 per QALY);
- Overall survival in both arms adjusted for subsequent active treatment (reduces ICER from £238,674 to £171,511 per QALY);
- Relapse-free survival Kaplan-Meier curves used for AZA and CCR arms (increases ICER from £171,511 to £174,205 per QALY);
- Progression-free survival Kaplan-Meier curves used for AZA and CCR arms (increases ICER from £174,205 to £246,488 per QALY);
- Adjusting overall survival for baseline covariates (reduces ICER from £246,488 to £169,606 per QALY).

2 Background

2.1 Critique of company's description of underlying health problem

Celgene describe acute myeloid leukaemia (AML) as *'an aggressive, clonal myeloid neoplasm with maturation arrest of myelopoiesis, leading to an accumulation of myeloblasts in the [bone marrow (BM)] and/or blood.'* (Source: Celgene submission, Section 3.1, p. 31).

AML is a haematological cancer affecting the myeloid line of blood cells. In AML, myeloid stem cells in the bone marrow produce immature blood cells (usually myeloblasts) which do not develop fully and build up in the bone marrow. These immature blood cells are not able to function properly and they reduce the ability of the bone marrow to produce other cells the body needs.

AML can develop following myelodysplastic syndrome (MDS), or can develop as a result of therapy (e.g., cytotoxic therapy), or can arise without previous associated disease or treatment (primary AML).

The World Health Organisation (WHO) system requires involvement of at least 20% of blood and/or bone marrow by myeloblasts for AML diagnosis, and is also used to classify AML into subtypes to aid clinical decision making and prognosis.

Celgene describe the following signs and symptoms of AML (Source: Celgene submission, Section 3.1, p. 31):

> *The clinical signs and symptoms of AML are diverse and non-specific, but they are usually directly attributable to the leukaemic infiltration of the [bone marrow], with resultant cytopenias (reduction in blood cell counts). Typically, patients present with signs and symptoms of fatigue, haemorrhage, and/or infections and fever due to reductions in [red blood cells], platelets, and [white blood cells].[1] The corresponding impact on physical and psychological aspects of quality of life is significant and increases over the course of the condition.[2]*

The ERG believes the description given is appropriate.

2.1.1 Epidemiology

Celgene give the following estimates of the incidence of AML (Source: Celgene submission, Section 3.1, p. 31):

> *AML is the most frequent form of leukaemia, accounting for approximately 25% of all leukaemia cases in adults in the Western world.[3] […] In the UK between 2009 and 2011, an average of 40% of cases were diagnosed in men and women aged 75 years and over, and almost three quarters of cases (73%) were diagnosed in those aged 60 and over.[4] The median age of diagnosis is between 65 and 72 years for the entire population, and 78 years when evaluating the population who are aged over 65 years.[5-10]*
>
> *The annual incidence rate of AML in England has been estimated to be 4.1 per 100,000.[11] The incidence increases dramatically with older age, rising to 18.35 per*

> *100,000 in people aged 65 years and over,[11] equating to approximately 1,777 new cases of AML in this patient group in England annually.[11-13]*

The incidence statistics provided by Celgene appear to be well-sourced, but we estimate a marginally lower number of new cases in adults aged over 65 per year in England (1,610 versus 1,777) using the same datasets but a different method (applying the different age-specific rates to the relevant population estimates and aggregating afterwards rather than applying an aggregated rate to an aggregate population estimate). This also corresponds to a marginally lower incidence rate for the over-65s of 16.88 per 100,000 (rather than 18.35).

2.1.2 Diagnosis

Diagnostic criteria are given by Celgene (Source: Celgene submission, Section 3.1, p. 31):

> *Diagnosis of AML requires the examination of peripheral blood and BM specimens, using morphology, cytochemistry, immunophenotyping, cytogenetics, and molecular genetics. According to the WHO classification of myeloid neoplasms, a myeloid neoplasm with ≥20% blasts in the peripheral blood or BM is considered to be AML when occurring de novo, evolution to AML when it occurs with previous diagnosis of MDS or myelodysplastic/myeloproliferative neoplasm.[14]*

An abnormal result on a complete blood count is a typical finding prior to a diagnosis of AML. An excess of white blood cells is commonly seen, and counts for platelets and/or red blood cells may be reduced.

2.1.3 Prognostic markers and risk factors

Celgene have provided general information on survival in AML (Source: Celgene submission, Section 3.4, p. 34):

> *AML is a heterogeneous disease in terms of response to treatment and OS. Prognostic factors that contribute to this heterogeneity can be patient-related (such as increased age, reduced performance status, comorbidities, vulnerability, or frailty) or disease-related (such as genetic factors, adverse cytogenetics, somatic mutations, or whether the patient has MDS-related changes).[15-17]*
>
> *Survival is highly age dependent with survival rates being significantly lower in older patients.[5] The median [overall survival (OS)] of elderly patients with AML in population-based studies has remained unchanged since 1995 at 1.5 to 3 months.[18, 19] Furthermore, a recent analysis of the [Haematological Malignancy Research Network] HMRN registry highlights the current poor outcomes in UK routine practice, with a median OS of [redacted] months for non-transplant-eligible AML patients 65 years or older treated with [conventional care regimens (CCR)].[20] There is also a clear disparity in 5-year survival rates between AML patients of different ages. Between 2003 and 2009, 5-year survival rates for patients <65 years of age was 41.6%, but just 5.4% in patients ≥65 years of age.[21] In contrast, the life expectancy of people in the general population once they have reached 75 years of age is a further 10.6 years (males) and 12.9 years (females).[22] Therefore, AML represents a challenging disease to treat, and results in a significant reduction in patient's life expectancy.*

Age and cytogenetics appear to be the most important prognostic factors. The NICE Scope identified two subgroups to be considered if evidence allowed, these were: people with AML secondary to myelodysplastic syndrome, and people with adverse-risk cytogenetics.

AML secondary to myelodysplastic syndrome is associated with reduced likelihood of treatment response and therefore with worse prognosis.[9]

Cytogenetics are generally classified as being favourable, intermediate or poor, with survival differing markedly between these groups. In a recent analysis of patients enrolled in the Cancer and Leukaemia Group B first-line trials, median (overall) survival for patients aged over 60 was 1.6 years for individuals in the favourable group (based on cytogenetics and molecular genetics), 0.9 years for individuals in the intermediate groups, and 0.5 years for individuals in the adverse groups.[23]

2.1.4 Burden and impact on quality of life

Celgene note the following in relation to the impact on the quality of life of the patient (Source: Celgene submission, Section 3.2, p. 32):

> *When compared with the general population, patients with AML experience a significant reduction in physical functioning (as determined via the physical component domain of quality of life assessments), and experience a higher incidence of depression.[2] Furthermore, quality of life deteriorates over time, with a significant reduction observed as early as 2 weeks after AML diagnosis.[2] Patients with AML can also experience appetite loss and fatigue; both having a negative impact on overall measures of quality of life.[24] The burden of the disease continues until death, with patients frequently suffering from open bleeding, infection, and pain during the final stages of the disease.[25]*

The ERG note that the study by Sekeres et al.[2] found similar SF-12 mental component scores for AML patients as population norms, which should be considered alongside the finding of a higher incidence of depression. Other than this the description is appropriate and relevant.

Celgene also note the potential impact on caregivers (Source: Celgene submission, Section 3.2, p. 32):

> *The impact is far reaching with caregivers, including family or friends, often having to deal with numerous and concurrent stressful events, and often suffering negative psychological, behavioural and physiological effects on their daily lives and their health.[26]*

The ERG note that the publication by Bevans and Sternberg[26] cited by the company is a case study of a single individual with AML secondary to MDS, who also received HSCT. The ERG considers that this does not constitute high-quality evidence of an impact on caregivers, although the ERG does not dispute that such impacts may exist.

2.2 Critique of company's overview of current service provision

The company gives the following overview of the clinical pathway of care for *elderly* patients with AML – the company's decision problem focuses on elderly patients as opposed to all adults, *see Section 3 (p. 23)* – (Source: Celgene submission, Section 3.3, p. 33):

> *Due to the heterogeneity of disease, there is no standard of care for elderly patients with AML, resulting in complex treatment guidelines.[27-30] Despite differences between published treatment guidelines, there is a general consensus that treatment decisions should be based on a number of patient- and disease-related prognostic factors. Patients with favourable prognostic factors are more likely to be assessed as "fit" to receive treatment with IC while patients with unfavourable prognostic factors, such as increased age, poor performance and/or cytogenetic risk status, and increased comorbidities are typically deemed unfit for treatment with IC. As such, these patients are usually offered less intensive chemotherapy options, such as LDAC and those unable to tolerate chemotherapy or who chose not to receive LDAC should receive BSC only.*
>
> *Despite this general guidance there is no widely accepted risk algorithm which clinicians use in the UK when deciding which patients are most likely to benefit from intensive or non-intensive treatment options. A recent review further demonstrated the lack of structure when making treatment decisions, concluding that decisions remain complex and selection is subjective based on the clinician's judgement.[31] Patient choice was also found to be a confounding factor, accounting for approximately 8% of treatment decisions, irrespective of the clinicians' recommendation.[32]*

The company also provide the following information in relation to current service provision (Source: Celgene submission, Section 3.7, p. 37):

> *Treatment options for elderly patients with >30% BM blasts AML include HSCT, IC, low-dose chemotherapy (LDAC), or BSC alone.[28] However, HSCT is rarely used in patients older than 65 years.[33] Decitabine is also licenced in the EU for the treatment of elderly WHO-defined AML but it is not reimbursed (NICE TA270[34]) and so is not used in UK routine clinical practice. Treatment with IC is typically contraindicated for patients aged ≥65 years with an adverse performance status, organ damage, and comorbidities.[28] Treatment with IC can however be successfully used in older patients, if restricted to patients with a favourable performance status, minimal organ dysfunction and/or comorbidity, and favourable cytogenetics, but is associated with an increased risk of treatment-related mortality.[5, 28] In this patient population, treatment options usually consist of LDAC or BSC and patients suffer from low survival rates, with a 26% 30-day mortality reported in patients receiving low-intensity treatment.[21, 28]*

The ERG note that a Swedish registry study covering 98% of Swedish patients diagnosed with AML by the French-American-British criteria (requiring at least 30% bone marrow blasts) found that 55% of patients aged at least 65 years with ECOG PS 0–2 were reported

fit for intensive chemotherapy, and 45% of patients aged at least 65 years of any ECOG PS.[22]

Our clinical expert (CR) advised that IC is administered in an inpatient setting, while LDAC may be self-administered at home. Azacitidine would most likely be administered as a regular day case in the NHS, which presents the problem of administering azacitidine on seven consecutive days since many day case units do not currently operate over the weekend. Patients treated with azacitidine would normally attend for five consecutive days (Monday to Friday) and then two consecutive days after a weekend break (Monday and Tuesday). Prevailing clinical opinion is that this schedule is non-inferior to administration over seven consecutive days. Patients treated with best supportive care may be admitted at times to treat certain complications (e.g., infection). A UK study recently found that of patients with one of three haematological malignancies (AML, diffuse large B-cell lymphoma and myeloma), 74% died in hospital, 15% at home, and the remainder in a hospice or nursing home.[35]

The ERG believes that these descriptions are appropriate and relevant to the company's chosen decision problem (*see Section 3, p. 23*).

3 Critique of company's definition of the decision problem

The company presented their decision problem within the Executive Summary chapter, under the subheading 'statement of the decision problem' (Celgene submission, Section 1.1, p. 12–16). A summary table of the NICE Scope,[36] the company's decision problem and the ERG's critique is presented below (*Table 1*). Further comments to the decision problem follow the table.

Table 1: Summary table of decision problem critique

Decision problem	NICE Scope	Company's decision problem	ERG notes
Population	Adults with acute myeloid leukaemia with bone marrow blasts more than 30%	Adults aged ≥65 years who are not eligible for HSCT with AML with >30% marrow blasts	The changes in population by the company brought the population in line with the EMA marketing authorisation for azacitidine. The ERG is satisfied this is a reasonable change.
Intervention	Azacitidine	As per Scope	No comments.
Comparator	• Intensive chemotherapy with an anthracycline in combination with cytarabine • Non-intensive chemotherapy with low dose cytarabine • Best supportive care which may include blood product replacement, antibiotics, antifungals and intermittent low dose chemotherapy with hydroxycarbamide	• Conventional care regimen (CCR; consisting of IC, LDAC and BSC)	The company have replaced three individual comparators with one composite comparator on the basis that there are no established criteria for selecting one CCR. As a result the company have not assessed whether azacitidine demonstrates clinical and cost effectiveness compared to each CCR (in patients for whom that CCR would be appropriate). The ERG considers this to be a weakness of the submission.
Outcome	The outcome measures to be considered include: • Overall survival • PFS • Time to disease progression • Response rates, including haematologic response and improvement • Blood-transfusion independence • Infections • Adverse effects of treatment • Health-related quality of life • Cost per quality-adjusted life year.	The outcomes measured include: • Overall Survival • PFS – estimated from EFS and RFS for the purpose of economic modelling • Time to disease progression • Response rates, including CR, CRc, and PR • Blood-transfusion independence • Infections • Adverse effects of treatment • Health-related quality of life • Cost per quality-adjusted life year.	Two outcomes (PFS and response rate) reported by the company do not match exactly to the Scope. Differences are either terminology or added detail for clarification. These differences are deemed acceptable.
Other considerations	If the evidence allows the following subgroups will be considered. These include: • People with AML secondary to myelodysplastic syndrome • People with adverse-risk cytogenetics	A number of pre-defined patient- and disease-related subgroups were assessed during the pivotal trial, AZA-AML-001 and included those with MDS-related changes, and poor cytogenetic risk status, as per Scope	AML secondary to MDS is a subgroup of AML with MDS-related changes (constituting just over half), but outcomes are expected to be similar.

Key: AML, acute myeloid leukaemia; BM, bone marrow; BSC, best supportive care; CCR, conventional care regimens; CR, complete remissions; CRc, cytogenetic complete remission; EFS, event-free survival; EMA; European Medicines Agency; HSCT; haematopoietic stem cell transplantation; IC, intensive chemotherapy; IV, intravenous; LDAC, low-dose cytarabine; MDS, myelodysplastic syndromes; OS, overall survival; PFS, progression-free survival; PR, partial remission; RFS, relapse-free survival; SC, subcutaneous.

Source: NICE Scope [36] and Celgene submission, Table 1, p. 12–16

3.1 Population

The population in the company's submission did not match for age and eligibility (adults aged ≥65 years who are not eligible for haematopoietic stem cell transplantation), to the population specified in the NICE Scope (adults).[36] Celgene justify this inconsistency by stating that:

> *This submission specifically evaluates the efficacy and tolerability of azacitidine in patients aged ≥65 years and who are not eligible for HSCT in line with the new indication approved by the EMA.*

The European Medicines Agency (EMA) indication for azacitidine has been expanded, and now includes: "Treatment of adult patients aged 65 years or older who are not eligible for HSCT with AML with >30% marrow blasts according to the WHO classification." Therefore, the population reported by the company matches the EMA marketing authorisation for azacitidine but does not match the NICE Scope. Overall we agree that the population considered by the company's submission is appropriate based on it matching the EMA indication.

3.1.1 Subgroups to be considered

The NICE Scope states that if evidence allows, the following subgroups should be considered:

- People with AML secondary to myelodysplastic syndrome;
- People with adverse-risk cytogenetics.

The company's decision problem suggests that pre-defined subgroups were assessed in the pivotal trial, including those with MDS-related changes and those with poor cytogenetic risk status. The ERG note that AML with MDS-related changes is a broader category including AML secondary to MDS, and that in the pivotal trial there were 158 patients with MDS-related changes but only 87 patients with prior MDS.[37] Nevertheless, the prognosis of AML with MDS-related changes is likely to be similar to the prognosis of AML secondary to MDS.

3.2 Intervention

The company's decision problem specified the intervention as 'azacitidine', which matches the NICE Scope.[36]

The NICE Scope describes azacitidine as follows; 'Azacitidine (Vidaza, Celgene) is an analogue of nucleotide cytidine that reduces DNA methylation by inhibition of DNA methyltransferase. Azacitidine is administered subcutaneously.'

The EMA recommend the following for administering azacitidine:

> *The recommended starting dose of Vidaza is 75 mg per square metre body surface area (calculated using the patient's height and weight). It is given as an injection under the skin… …every day for one week, followed by three weeks with no treatment. This four-week period is one 'cycle'. Treatment continues for at least six cycles and then for as long as it benefits the patient. The liver, kidneys and blood should be checked before each cycle. If the blood counts fall too low or if the patient*

> *develops kidney problems, the next treatment cycle should be delayed or a lower dose should be used. Patients who have severe liver problems should be carefully monitored for side effects, but Vidaza must not be used in patients with advanced liver cancer.*

Our clinical advisor (CR) commented that they would typically administer azacitidine for five days (Monday to Friday), and then administer the remaining two days on Monday and Tuesday of the following week, as this is more convenient for the patients and the day case setup at the hospital.

3.3 Comparators

The comparators in the submission do not match those in the Scope.[36] There is more detail given by the Scope, regarding component treatments, than by the company who just report the overarching term for the comparator. The company also refer to decitabine, a treatment that was included in the NICE Draft Scope as a form of non-intensive chemotherapy. Decitabine has marketing authorisation in the UK but has not received a positive NICE recommendation following termination of NICE technology appraisal 270.[34] The company note that decitabine was removed for the Final Scope and do not include it in their decision problem.

The comparator in the company submission is a composite comparator, containing the comparators as identified in the Scope. This comparator is referred to as Conventional Care Regimen (CCR). Further details on dosing schedules for the CCR are as follows:

- Intensive Chemotherapy (IC): generally consists of cytarabine 100-200 mg/m^2 per day by continuous intravenous infusion for 7 days, plus three days of either daunorubicin 45-60 mg/m^2 per day or idarubicin 9-12 mg/m^2 per day for one cycle, followed by up to two consolidation cycles.[28] Our clinical expert commented that there are various different schedules for the administration of the IC treatment; however these differing combinations are unlikely to alter the clinical effectiveness of the drugs.
- LDAC: subcutaneously, 20 mg twice per day for 10 days.[28] This dosing practice was considered routine by our clinical expert.
- BSC: typically BSC will consist of prophylactic anti-infectious treatment (including fungal and antibiotic prophylaxis) and transfusion support (platelet, red blood cell and granulocyte transfusion).[28] This dosing practice was considered routine by our clinical expert.

Our clinical advisor (CR) commented that most patients are offered IC even if they ultimately receive an alternative treatment.

The ERG considers it a weakness to use a combined comparator in the decision problem, since it is possible that azacitidine could be effective and cost-effective (at a chosen cost-effectiveness threshold) versus some individual comparators but not others, but this would be obscured. This could result in either: azacitidine being used in patients when it would have been better for them and/or a better use of limited NHS resources for an alternative treatment to be used; or, azacitidine not being used in patients when it would have been better for the patient and/or a better use of limited NHS resources.

3.4 Outcomes

The outcomes in the company submission match those in the Scope. However, they have made the following amendments to progression free survival and response rate:

> *Progression free survival (PFS) - estimated from event-free survival (EFS) and relapse-free survival (RFS) for the purpose of economic modelling.*
>
> *Response rate – including complete remission, cytogenetic complete remission and partial remission.*

The company justify the alterations to PFS, by suggesting that PFS is not a standard endpoint for AML. Our clinical advisor (CR) believes that estimating PFS from EFS and RFS would be an appropriate alternative measure.

For the measure of response rate, the Scope specified response rate, including haematologic response and improvement, whereas the company reports that the outcome response rate included complete remission, cytogenetic complete remission and partial remission. These are only terminological differences.

3.5 Other relevant factors

In response to special considerations relating to equity and equality, the company make the following statement within their decision problem. The ERG has no comments on their statement.

> *AML presents primarily in the elderly population, with 64% of newly diagnosed cases in the UK in patients aged ≥65 years.[4] Equity of treatment of the elderly is a concern, as evident from a report published by the National Audit Office in January 2015.[38] AML is also an orphan disease.[39] The Cancer Patient Experience Survey in 2010 found that people with rarer forms of cancer reported a poorer experience of their treatment and care than people with more common forms of cancer.[40] Therefore, access where appropriate to a treatment such as azacitidine should help to promote equality for both elderly patients and those with rarer forms of cancer.*

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

Celgene presented a literature search protocol to support its review of clinical effectiveness. This protocol included systematic searches of key biomedical databases using a literature search strategy, hand-searching of conference abstracts, and a search of ClinicalTrials.gov. The literature search was last updated in November 2015.

The bibliographic database searching used a search strategy that took the following form:

1. (controlled index terms for acute granulocytic, acute myeloblastic, acute myelomonocytic, acute monocytic or acute megakaryocytic leukemia or erythroleukemia or promyelocytic) *and*
2. (controlled index terms for Azacitidine, cytarabine, gemcitabine, deoxycytidine, etoposide, etopofos, fludarabine, anthracycline, mitoxantrone, daunorubicin or tioguanine or best supported care) *and*
3. (a range of search terms for study design (RCTs and observational), limits to remove studies conducted on animals and studies published in languages other than English. Systematic reviews and meta-analysis were also excluded from identification. The searches were date limited 2000 to current).

The search strategy was applied in the following bibliographic databases: MEDLINE (OVID), EMBASE (OVID) and Cochrane CENTRAL (OVID).

The following conference proceedings were hand-searched: European Haematology Association (EHA) Annual Congress, American Society of Haematology (ASH) Annual Conference, and the British Society for Haematology (BSH) Annual Scientific Meeting between January 2013 and April 2015. Finally, ClinicalTrials.gov was searched for relevant, unpublished studies.

The ERG believes the literature searching for clinical effectiveness studies was poorly conducted and reported.

The literature search strategies provided rely entirely on controlled indexing search terms. Free-text search terms for acute myeloid leuk(a)emia or AML (as used in the submission of cost-effectiveness literature searching) have been omitted. This is inappropriate for two reasons:

1. The searches (as presented) will only return studies that have been indexed. Newly published studies (or additional trial outcome data), or relevant studies published ahead of print, will likely be excluded from these searches as, whilst studies are uploaded to bibliographic databases on receipt, there is a delay between a study being published and then indexed. This point affects the currency of the literature searches and introduces bias into the identification of studies.
2. Any studies that have been incorrectly indexed but are of relevance to the decision problem would be missed by these searches. The inclusion of free-text terms for

AML, for example, would address this risk. This point affects the sensitivity of the literature search, which is poor.

The search strategy excludes the identification of systematic reviews and meta-analyses. In clarification, the manufacturer stated that the bibliographies of systematic literature reviews, meta-analyses and other included studies were used as a search strategy to identify further studies. As systematic reviews and meta-analyses were excluded from bibliographic searching it is not clear how they were identified and therefore how this particular search was actually conducted. This affects the replicability of the literature searching.

The literature searching is difficult to validate and it has been poorly reported.

The literature search strategies for MEDLINE and EMBASE have been combined and reported as if one search. This makes it difficult to validate and repeat the literature search used in MEDLINE as the EMBASE search strategy has been used and presented as the base search. Furthermore, the combination, and practicable use of study design literature search filters, is poorly considered when balanced against the decision problem of the review. This affects the transparency of the literature searching.

In view of these points, the ERG has undertaken its own scoping searches to ensure that no phase III RCTs have been missed by this review. Whilst basic scoping searches have not identified any additional studies, the ERG has been unable to validate aspects of this search, and the overall quality of the approach to literature searching is sufficiently poor, that it raises questions if it is truly fit for purpose.

4.1.1.1 Adverse events

Celgene did not undertake separate literature searches to identify studies reporting adverse events. In their submission, Celgene stated that (Source: Celgene submission, Section 4.12, p. 85):

> *No further studies that report additional adverse events …that are of relevance to the decision problem are available*

In clarification, Celgene confirmed that no separate literature searches to identify studies reporting adverse events were undertaken, stating that their literature searches were not limited by adverse event outcomes. Whilst it is true that Celgene's literature searches were not limited by outcomes, Celgene's literature searches were limited by study design. It is therefore possible that studies reporting adverse events may have been missed.

4.1.2 Inclusion criteria

Celgene's inclusion criteria are given below (*Table 2*) with an additional column added to the right of the table, taken from the Scope[36] for reference and comparison. Comments about the differences in inclusion criteria are outlined below the table.

Table 2: Scope of the literature review: PICOS criteria for study inclusion

Criteria	From Celgene	From Scope
	Definition	
Population	Older adult AML patients[a] with peripheral blood or BM leukaemic myeloblasts >20%, who either: • Are newly diagnosed with AML • Have developed AML secondary to "preleukaemic" blood disorders such as MDS or myeloproliferative disease • Have developed AML secondary to exposure to leukaemogenic therapy or agents with primary malignancy in remission for at least 2 years	Adults with acute myeloid leukaemia with bone marrow blasts more than 30%

Interventions/ comparators	• Azacitidine 75 mg/m^2
	• LDAC (20 mg SC once or twice a day for 10-14 days)
	• Decitabine 20 mg/m^2
	• Other high dose chemotherapy:
	  ○ Combination of etoposide or fludarabine (plus granulocyte-colony stimulating factor aka "G-CSF") with cytarabine (preferred for patients with cardiac disease)
	  ○ 7+3: continuous IV infusion of cytarabine for 7 days followed by 3 days of IV anthracycline push
	  ○ Combination of IV mitoxantrone, etoposide IV, and cytarabine
	  ○ Combination of IV daunorubicin, cytarabine, and etoposide
	  ○ Combination of IV cytarabine, daunorubicin, and oral thioguanine
	  ○ Combination of IV cytarabine and daunorubicin: 3+10 for cycle 1 followed by DA 3+8 for cycle 2 (standard for UK)
	• Best supportive care[b]
		Intervention: Azacitidine
		
		Comparators:
		• Intensive chemotherapy with an anthracycline in combination with cytarabine
		• Non-intensive chemotherapy with low dose cytarabine
		• Best supportive care which may include blood product replacement, antibiotics, antifungals and intermittent low dose chemotherapy with hydroxycarbamide

Outcomes	Studies are eligible if at least one of the following outcomes are included:[c]
	• Efficacy outcomes
	  ○ Overall survival
	  ○ Event-free survival
	  ○ Progression-free survival
	  ○ Relapse-free survival
	  ○ Complete response
	• Safety outcomes
	  ○ Treatment-related mortality
	  ○ Hospitalisation due to AE
	  ○ Grade 3 or 4 haematologic AEs
	  ○ Discontinuations due to AEs
	  ○ Discontinuations due to reasons other than disease progression
		The outcome measures to be considered include:
		• Overall survival
		• Progression free survival
		• Time to disease progression
		• Response rates, including haematologic response and improvement
		• Blood-transfusion independence
		• Infections
		• Adverse effects of treatment
		• Health-related quality of life

Criteria	From Celgene	From Scope
	Definition	
Study Design	• Randomised controlled trials and comparative non-randomised studies (prospective and retrospective observational studies) • Studies must compare two unique treatment classes (e.g. IC vs. IC or dose-ranging studies not eligible)	
Other	• English language only • Published in or after the year 2000 (Selected on the advice of a panel of haematologists who advised that there would be limited evidence of relevance pre the year 2000).	

Key: AE, adverse event; AML, acute myeloid leukaemia; BM, bone marrow; CR, complete response; EFS, event-free survival; IC, intensive chemotherapy; IV, intravenous; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; SC, subcutaneous.

Notes: a, Note that although the primary population of interest is those 65 years of age and older, this criteria was relaxed (e.g. 55 years of age and older) to ensure sufficient evidence was available; b, It was expected that definitions in best supportive care would vary; c, Note that additional outcomes were of interest, but only those identified in the table above were used to guide the selection of studies; safety outcomes were extracted only for those studies providing efficacy data.

Source: Celgene submission, Table 7, pp. 39–40 and NICE Scope[36]

4.1.2.1 Population

Celgene's population was broader (bone marrow blasts more than 20%) than the Scope (bone marrow blasts more than 30%).[36] The company explained that this was to capture studies on bone marrow blasts over 20% that had included sub-analysis on the 30% bone marrow blast population.

Conversely, Celgene's population was narrower (older adult AML patients) than the Scope (adults with AML).[36] Older adults were defined by Celgene for their systematic review as a population over 55 years. In order to check if any studies were excluded based on population; the ERG checked the reasons given in table of excluded studies (Celgene appendices to submission, Appendix 2, Table 1, pp. 10–11) and found none. However, we cannot exclude the possibility studies may have been excluded from title/abstract screening.

4.1.2.2 Interventions/comparators

The intervention/comparators for inclusion broadly match the Scope.[36] However, there are some key differences. For the intervention azacitidine and two of the comparators (LDAC and decitabine) drug doses were included. It is not clear whether studies were excluded based on the drug administration dose, nevertheless drug administration doses are not specified within the Scope.

The comparators for inclusion reported by the company include all of those reported in the Scope and also decitabine.[36] The company also include specific drug combinations to be given alongside intensive chemotherapy rather than, 'with an anthracycline in combination with cytarabine' as per the Scope. This may have resulted in relevant studies being excluded.

4.1.2.3 Outcomes

The outcomes overall survival, progression-free survival match the Scope.[36] However, event-free survival, relapse-free survival and complete response are not within the Scope. Other outcomes within the Scope, but not in the inclusion table submitted by the company include: time to disease progression; response rates, including haematologic response and improvement; blood transfusion independence; infections; adverse effects of treatment and health related quality of life. In order to check if any studies were excluded based on outcomes; the ERG checked the reasons given in table of excluded studies (Celgene appendices to submission, Appendix 2, Table 1, p. 10–11) and found none. However, we cannot exclude the possibility studies may have been excluded from title/abstract screening.

4.1.2.4 Study Design

The Scope did not restrict study design. However, the NICE reference case guide to the methods of technology appraisal 2013 (Chapter 5.2.3)[41] recommends studies should be restricted to RCTs and when they are not available, non RCTs. Studies included in the company submission were RCTs, observational studies and information from registries. We are satisfied the study designs meet the reference case.

4.1.2.5 Other

Celgene applied an English language restriction to their systematic review. Language was not given as a reason for exclusion from full-text screening (Celgene appendices to submission, Appendix 2, Table 1, p. 10–11). However, we cannot exclude the possibility studies may have been excluded from title/abstract screening.

Another restriction was to exclude studies published before 2000. The decision to restrict the studies to only include studies post-2000 was (Source: Celgene submission, Section 4.1.2, p. 40):

> *Selected on the advice of a panel of haematologists who advised that there would be limited evidence of relevance pre the year 2000*

The ERG notes that azacitidine was used for primarily haematologic malignancies in the 1960s-1980s.[42-44] Consequently, studies excluded based on date limitation could add relevant information for the use of azacitidine in treating AML. Reference citations for the 15 RCT studies reported as excluded based on publication date (Celgene appendices to submission, Appendix 2, Table 1, p. 10–11) were requested and subsequently examined. None of the 15 studies would have been eligible for inclusion in this submission.

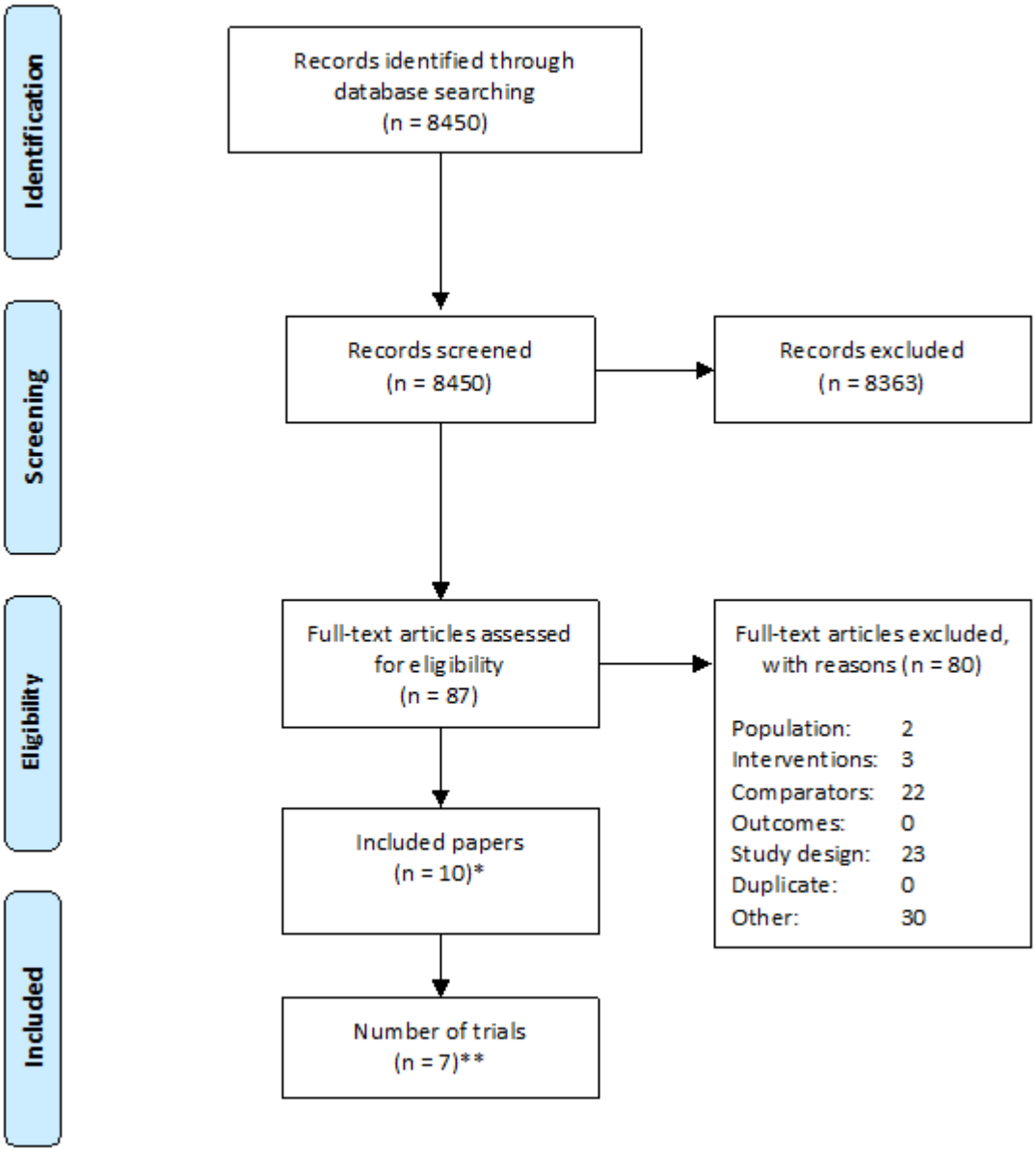
4.1.2.6 Study selection

Celgene's submission explains the process used in study selection (i.e., that two researchers independently reviewed the abstracts and the full-texts of studies, that discrepancies between investigators were resolved by involving a third investigator and coming to a consensus). These are standard procedures for systematic reviews.[41]

From the 8,450 citations the company identified from their searches, 8,363 citations were excluded and 87 were taken to full-text screening at the abstract screening stage. From the full-text screening, 80 citations were excluded with reasons for exclusion provided (Celgene appendices to submission, Appendix 2, Table 1, pp. 10–11). The company go on to explain

that three further materials were added from manual searches of literature databases and conference proceedings. One of the three additional materials identified from the manual searches was the pivotal trial AZA-AML-001. The company included ten citations from seven trials. The PRISMA diagram reported in Celgene's submission is copied below (*Figure 1*).

Figure 1: PRISMA study flow diagram



Notes: * 3 materials added; ** 4 RCTs and 3 observational studies.
Source: Celgene submission, Figure 4, p. 42

From the seven included studies, the company go on to exclude a further five studies. The exclusion of these five studies is justified by the company on the basis that their inclusion criteria were over-inclusive. Four studies were excluded as the population was those with bone marrow blasts over 20% and not 30% as per the Scope. The fifth study was excluded as the comparator treatment was decitabine, a comparator not included in the decision problem.

The remaining two studies were an RCT by Dombret et al. 2015.[45] and an observational study by Lao et al. 2015.[46] The main focus of the submission was the RCT study by Dombret et al. (AZA-AML-001). The company also refer to registry data from three countries (Austria, Spain and France) within their submission.

4.1.3 Data extraction

The submission explains the process of data extraction used, which is in line with the standard review process (Source: Celgene submission, Section 4.1.2, p. 40)

> *Two investigators independently extracted data on study characteristics, interventions, patient characteristics at baseline, and outcomes for the study populations of interest for the final list of selected eligible studies. Any discrepancies found between the data extracted by the two data extractors were resolved by involving a third reviewer and coming to a consensus.*

The ERG notes that in relation to the pivotal RCT by Dombret et al.,[45] all the typical data (including but not limited to: participant inclusion criteria, baseline characteristics, methods, primary and secondary study outcomes and adverse events) has been extracted from the paper, but that there were several typographic errors in the extracted data reported in their submission. The ERG has referred to the original publication and the clinical study report for AZA-AML-001[37] to resolve discrepancies where they have been identified.

4.1.4 Quality assessment

Details of the company's critical appraisal of the RCT AZA-AML-001,[45] alongside our critique, can be seen below in *Table 3*. The critical appraisal appears (since no reference is given to the tool used) to have been performed by the company using the CRD assessment criteria for risk of bias in RCTs. However, they have slightly adjusted the wording of the questions, as they do not match exactly. The meanings behind the questions remain the same.

Table 3: Critical appraisal of AZA-AML-001

Critical appraisal criterion	Celgene's Assessment	ERG Comment
Was randomisation carried out appropriately?	Yes Patients were randomised in a 1:1 ratio. Randomisation was performed using an IVRS. Patients were stratified at randomisation by: • CCR selection (IC, LDAC or BSC), • ECOG performance status at baseline (0–1 versus 2) • Cytogenetics (intermediate-risk versus poor-risk)	Further information on the randomisation process from the paper reports that: a central, stratified, and permuted block randomisation method and IVRS were used to randomly assign 1:1 to received azacitidine or CCR. This is an acceptable system for randomisation.
Was the concealment of treatment allocation adequate?	Open-label study. Blinding of study treatment was not feasible due to multiple comparators and routes of administration. However, all central reviewers were blinded to subject treatment assignment.	Celgene have not answered this question. Allocation sequence concealment obtains strict implementation of an allocation sequence without prior knowledge of the intervention assignments. Methods for allocation concealment refer to techniques used to implement the sequence, not to generate it. For this trial, central randomisation ensured allocation sequencing was adequately concealed.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Patient demographics in the azacitidine and combined CCR groups were well balanced in terms of age, age distribution, sex, geographic location, race, weight and BSA. The azacitidine and combined CCR groups were also comparable for all baseline disease characteristics (including AML classification, prior history of MDS, time since AML diagnosis, ECOG performance status and cytogenetic status), with the exception of prior anticancer systemic therapies.	As Celgene have written, demographics between azacitidine and combine CCR are well balanced and we are satisfied with this assessment. More meaningfully perhaps, baseline characteristics for the three individual CCR arms could have been compared to the azacitidine arm split by the CCR assignment prior to randomisation. However, this data was not available. Confusingly, Celgene contradict themselves by reporting (p. 26) that they provided evidence to the CHMP that outcome failures were due to an imbalance of patients' baseline characteristics/prognostic factors.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Although the trial was open-label, all central reviewers were blinded to subject treatment assignment. Evaluations by central review were used for the statistical efficacy analyses. The independent review committee which reviewed and confirmed the haematologic responses and durations was blinded to treatment, investigative site, and subject identifier.	Since the study was open labelled, the care providers and participants could not be blinded to treatment allocation. Awareness of treatment allocation will have introduced the potential for bias within the study, particularly with reporting of adverse events. All central reviewers were however, blinded to treatment assignment.

Critical appraisal criterion	Celgene's Assessment	ERG Comment
Were there any unexpected imbalances in drop-outs between groups?	No. The most common reasons for discontinuation from the treatment phase in both the azacitidine and CCR groups were occurrence of an AE (36.9% and 26.7%, respectively) or death (22.0% and 23.5%, respectively). Discontinuations due to occurrence of an AE or study closure were more common in the azacitidine group whereas discontinuations due to withdrawal of consent were more common in the CCR group, with the highest percentage in the BSC group. The percentages of subjects who were discontinued from treatment because of death or disease progression were comparable between the azacitidine and the CCR treatment groups. No subject discontinued due to loss of follow-up or protocol violation in the azacitidine group. One subject discontinued due to loss of follow-up in the IC group and one subject discontinued due to protocol violation in the LDAC treatment group.	The drop-outs provided by Celgene represent the figures reported in the RCT. However, neither Celgene nor the RCT report the drop outs for the three CCR treatments separately, therefore it is unknown whether the actual treatments that make up the CCR are comparatively different to azacitidine. The dropout rates due to an AE look imbalanced for azacitidine (36.9%) compared to the CCR group (26.7%).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. All treatment outcomes were reported other than those that are not currently available for analysis (exploratory molecular markers).	The ERG agrees with Celgene's response to this question.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The ITT population was used for the analysis of the primary and secondary efficacy endpoints. The ITT population was the most appropriate population as it included all randomised patients.	Yes – the main analysis adopts 'intention to treat' principles.

Key: AE, adverse event; AML, acute myeloid leukaemia; BSA, body surface area; BSC, best supportive care; CHMP, Committee for Medicinal Products for Human Use; CCR, conventional care regimens; ERG; evidence review group; IC, intensive chemotherapy; ITT, intent-to-treat; IVRS, interactive voice response system; LDAC, low-dose cytarabine; MDS, myelodysplastic syndromes. Clinical effectiveness results of the relevant randomised controlled trials.

Source: Celgene submission, Table 17, p. 64

4.1.5 Evidence synthesis

From the searches, one RCT was identified. Therefore synthesis of the evidence was not required.

4.2 Critique of the trials of the technology of interest, their analysis and interpretation

4.2.1 Methods

The single RCT (study name AZA-AML-001; main publication by Dombret et al. 2015[45]) identified was presented in detail within the submission.

4.2.1.1 Study objectives

The company submission reports the study objectives as follows (Source: Celgene submission, Section 4.3.1, p. 43):

> *The primary objective of the study was to demonstrate superiority in OS of azacitidine compared with combined CCRs in subjects aged 65 years or over who had newly diagnosed AML with more than 30% BM blasts according to the WHO criteria,[14, 47] and who were not eligible for haematopoietic stem cell transplantation. Overall survival was defined as time from randomisation to death from any cause.*

Secondary objectives included 1-year OS rate, EFS, RFS, overall remission rate, cytogenetic complete remission (CRc) rate, safety and toxicity assessments, HRQoL and health resource utilisation.

The primary objective concurs with the primary outcome; an outcome specified within the NICE Scope.[36] The secondary objectives correspond in parts to the outcomes from the Scope. The differences are the same as those already discussed in *Section 4.1.2.3 (page 32)*.

4.2.1.2 Study design and treatment

The study AZA-AML-001 was a multicentre (over 18 countries), randomised, open-label, parallel-group study.

Before randomisation, the most appropriate CCR (IC, LDAC or BSC) was determined by investigators on the basis of age, Eastern Cooperative Oncology Group Performance Status (ECOG PS), comorbidities and regional guidelines and/or institutional practice. Once the CCR had been chosen, a central, stratified, and permuted block randomisation method and interactive voice response system was used to randomly assign 1:1 to receive azacitidine with BSC or the pre-selected CCR. The random treatment assignment was concealed so that investigators and subjects did not know in advance the next treatment assignment. Following randomisation and drug administration, follow-up appointments were scheduled once per week during the first two treatment cycles, then every other week thereafter. The frequency of safety and efficacy measures ranged from weekly to every 12 weeks, depending on the procedure. Drug administration and data collection protocols are outlined in *Table 4*.

By design, there is awareness of the treatment allocated for both the patient and primary care givers from an open-labelled study. Awareness of treatment allocation will have introduced the potential for bias within the study, particularly with reporting of adverse events. Based on the treatments administered within the study, an open-label study design was the most appropriate study design to be utilised. Treatment protocols for administration were confirmed as appropriate by our clinical advisor (CR) and follow-ups were similar and appropriate in time.

Table 4: Treatment protocol

Treatment	Administration	Data collection[a]
Azacitidine & Best Supportive Care	75 mg/m^2/day, subcutaneously for 7 consecutive days per 28-day treatment cycle for at least 6 cycles. Dosing could be reduced or delayed as needed until the blood count recovered. BSC: as for BSC and including transient use of hydroxyurea (hydroxyurea was not allowed within 72 hours before or after azacitidine administration).	Within 7 days before initiation of every second cycle beginning at cycle 3
Best supportive care	Included, but was not limited to, treatment with red blood cell or whole blood transfusions, fresh frozen plasma transfusions, platelet transfusions, antibiotic and/or antifungal therapy, and nutritional support. Hydroxyurea use was permitted under certain conditions	On day 1 of every third cycle (a BSC cycle was defined as 28 days), beginning at cycle 4.
LDAC and BSC	20 mg of cytarabine twice per day, subcutaneously for 10 days per 28-day treatment cycle for at least 4 cycles). Dosing could be reduced or delayed as needed until the blood count recovered. BSC: as for BSC and including transient use of hydroxyurea	Within 7 days before initiation of every second cycle beginning at cycle 3
IC and BSC	Cytarabine 100-200 mg/m^2/day by continuous intravenous infusion for 7 days, plus on days 1-3 if cytarabine an anthracycline (either daunorubicin 45-60 mg/m^2/day or idarubicin 9-12 mg/m^2/day) for 1 cycle. Followed by up to 2 consolidation cycles (i.e., the same anthracycline regimen as used at induction and the same cytarabine dose used for induction but administered for 3 to 7 days) for those achieving complete response or partial response. Re-induction was not allowed. BSC: as for BSC and including transient use of hydroxyurea	At screening and within 7 days before each treatment cycle

Key: BSC, best supportive care; IC, intensive chemotherapy; LDAC, low-dose cytarabine
Notes: a, consisting of cytogenetic testing and pathological samples (BM aspirates, BM biopsies, and peripheral blood smears) to confirm diagnosis.

Concomitant medications were kept to a minimum, but where necessary and where unlikely to interfere with trial drugs, were given at the discretion of the investigator. Concomitant medications included and excluded were as described in *Table 5*.

Table 5: Concomitant medications in/excluded

Included	Excluded
• Hydroxyurea • Serotonin • Blood product support (red blood cells and platelets) • Myeloid growth factors (only for the treatment of neutropenic infections, prophylactically during IC treatment, or in subjects with two or more previous episodes of neutropenic infection who were at risk of subsequent neutropenic infection. For subjects who developed an absolute neutrophil count (ANC) <0.5 x 10^9/L, administration of prophylactic fluoroquinolone was permitted.) • Erythropoietic agent.	• Clofarabine • Decitabine • Targeted agents (e.g. FLT-3 antagonists) • Systemic anticancer therapy (excluded hydroxyurea) • Oral retinoids (topical retinoids were permitted) • Use of any other investigation drug or therapy

Key: ANC, absolute neutrophil count; FLT-3, FMS-like tyrosine kinase 3

Subjects had follow-up visit for the collection of AEs up to 28 days after the last dose of trial drug or up to the end-of-study visit, whichever period was longer. After this visit, subjects were followed for survival on a monthly basis until death, lost to follow-up, withdrawal of consent, or end of the study. Considering the short survival duration for people with AML, perhaps assessing AEs on a monthly basis was not frequent enough to capture all the changes over time for AEs.

4.2.1.3 Study duration

Celgene report the following for the planned study duration (Source: Celgene submission, Section 4.3.2.1, p. 46):

> *The expected duration of the study was 31 months. This time frame consisted of a 19-month subject enrolment period, followed by 12 months of subject treatment and observation. The study was planned to conclude 12 months after the last subject was randomised.*

Study duration was suitable, enabling adequate assessment of the outcomes following treatment for AML.

4.2.1.4 Blinding

The treatment of AML within AZA-AML-001 necessitated an open-labelled design due differing routes of administration (subcutaneous injection / intravenous infusion) and time periods of treatment. Open-label design creates an opportunity for bias, particularly for reporting of AEs. Central review of peripheral blood, BM samples and cytogenetics was conducted by a pathologist and cytogeneticist blinded to treatment. AML classification for each person was determined by local investigators at study entry. The Independent Review Committee which reviewed and confirmed the International Working Group responses and durations was blinded to treatment, investigative site, and subject identifier. Blinding of the central reviewers was appropriate.

4.2.1.5 Inclusion/exclusion

Table 6 gives the inclusion/exclusion criteria from the trial.[45] Critique of these follows the table.

Table 6: Eligibility Criteria

Key inclusion criteria	Key exclusion criteria
• Newly diagnosed, histologically confirmed de novo or secondary AML • BM blasts >30% • Adults aged ≥65 years • Not considered eligible for hematopoietic stem cell transplantation, • Intermediate- or poor-risk cytogenetics (NCCN 2009 criteria) • ECOG performance status of ≤2 • White blood cell count ≤15 × 10^9/L	• Acute promyelocytic leukaemia with t(15;17)(q22;q12) • AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22), t(8;21)(q22;q22), or t(9;22)(q34;q11.2) • AML arising from previous hematologic disorders other than myelodysplastic syndrome (e.g., myeloproliferative neoplasms) • Other malignancies • Uncontrolled systemic infection • Prior recipient of decitabine, azacitidine, or cytarabine treatment • Prior AML therapy (except hydroxyurea, which was allowed up to 2 weeks before the screening haematology sample was taken) • Any experimental drug within 4 weeks of starting study treatment

Key: AML, acute myeloid leukaemia; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group
Source: Dombret et al. 2015[45]

Additional exclusion criteria provided in the company submission but not specified in the RCT paper include: Prior BM or stem cell transplantation, proven central nervous system leukaemia, inaspirable BM, unstable angina, significant cardiac arrhythmia, or New York Heart Association class 3 or 4 chronic heart failure, pregnant or lactating women, active viral infection with known HIV or viral hepatitis B or C, known or suspected hypersensitivity to azacitidine or mannitol, use of any experimental drug or therapy within 28 days prior to day 1 of cycle 1, unwilling or unable to complete PRO assessments without assistance or minimal assistance, any condition, including laboratory abnormalities, which would place the subject at an unacceptable risk, any significant medical condition, including the presence of laboratory abnormalities, or psychiatric illness which would interfere with subject participation, any condition that confounded the ability to interpret data from the study.

Of note, the exclusion criteria related to cytogenetics are all primarily *favourable* characteristics (in line with the inclusion criteria of intermediate- or poor-risk cytogenetics), except for t(9;22) which is classed as poor-risk and is managed as the blast crisis phase in chronic myeloid leukaemia with the addition of tyrosine kinase inhibitors.

4.2.1.6 Location

The location of investigation sites were reported to be as follows (Source: Celgene submission, Section 4.3.4, p. 48):

> *Screening was conducted in 107 investigational sites, of which, 98 sites randomised at least one patient across 18 countries in different geographic regions. Locations included: Asia (12 sites); Australia (6 sites); the US/Canada (12 sites); Eastern Europe (12 sites); and Western Europe and Israel (56 sites). These included 5 sites in the UK which in total randomised 26 patients: Oxford (n=4), Bournemouth (n=1), St Bartholomew's (n=13), King's College (n=4) and Wolverhampton (n=4).*

In terms of the 26 people recruited from the UK, these people made up 5.3% of the total patient population from the trial. Fifteen UK people we randomised to receive azacitidine and 11 people received CCR (three to BSC and eight to LDAC). People recruited from Western Europe/Israel made up 48.8% of the total patient population.

4.2.1.7 Study endpoints

The study endpoints and definitions are presented in *Table 7*.

Table 7: Study endpoints

End point	Definition
Primary end point	
Overall survival (OS)	Defined as the time from randomisation to death as a result of any cause
Secondary end points	
1-year OS rate	No definition provided in either submission or Dombret et al 2015. Presumed to mean the number (or percentage) of people still alive 1 year post randomisation.
Event free survival (EFS; not in Scope)	Defined as the interval from the date of randomisation to the date of treatment failure,[a] progressive disease, relapse after complete response (CR) or complete response with incomplete blood count recovery (CRi), death from any cause, or loss to follow-up, whichever occurred first
Relapse free survival (RFS; not in Scope)	Defined only for subjects who achieved CR or CRi and was measured as the interval from the date of first documented CR or CRi to the date of relapse, death from any cause, or loss to follow-up, whichever occurred first. Relapse defined as either the recurrence of >5% blasts in the peripheral blood following Cr or CRi, (the percentage of peripheral blood blasts must have been ≤5% at the time of CR or CRi or a single finding of >15% blasts in the BM following a CR or CRi
Overall remission rate (CR+CRi)	Conditions for CR include: the BM should contain fewer than 5% blast cells; ANC ≥1,000/μL and Platelet count ≥100,000/μL. No RBC, platelet, or whole blood transfusions for 1-week prior to the haematology assessment used for the response evaluation. CRi was defined as a morphologic complete remission but the ANC count may be <1,000/μL and/or the platelet count may be <100,000/μL.
Duration of remission (CR + CRi)	Defined as the time from the date of CR or CRi until the date of relapse from Cr or CRi
Cytogenetic complete remission rate (CRc)	Defined as morphologic CR with a return to a normal karyotype at the time of CR (based on ≥10 metaphases)

End point	Definition
Progressive disease (PD)	Defined as either: 1) a >50% increase in BM blast count from baseline that persists for at least 2 BM assessments separated by at least 1 month, or if the baseline BM blast count is >70% and persists for 2 post-baseline BM assessments separated by at least 1 month, or 2) a doubling of the baseline absolute peripheral blood blast count that persists for at least 7 days and the final absolute peripheral blood blast count is >10 x 10^9/L. The date of PD is defined as the first date that there was either a >50% increase in BM blast count from baseline, a persistence of BM blasts >70% in subjects with a baseline BM blast count of >70%, or a doubling of the peripheral blood blast count.
Partial remission (PR)	Defined as an ANC ≥1,000/μL and platelet count ≥100,000/μL with a >50% decrease in the percentage of BM blasts to 5–25%
Stable disease (not in Scope)	Defined as any evaluable time point where criteria for all other response categories (i.e., CR, CRi, PR, progressive disease, treatment failure, not assessable) are not met
Safety/tolerability	Covering type, frequency, severity, and relationship of AEs to study treatments; physical examinations, vital signs; clinical laboratory evaluations; and concomitant medication/therapy
Patient-reported quality of life	Using the European organisation for research and treatment on cancer, quality of life questionnaire C-30 (EORTC QLQ-C30) Completed on day 1 of cycle 1 (baseline), every other cycle thereafter, and at the end-of-study visit
Measures of healthcare resource utilisation (HCRU)	Any consumption of healthcare resources directly or indirectly related to the treatment of the subject. Five items of HCRU were collected: inpatient hospitalisations, transfusions, procedures or surgeries, and concomitant medications
Additional endpoints	
Transfusion status (RBC and platelet transfusion status [dependence or independence])	On-treatment RBC/platelet transfusion independence was defined as the absence of any RBC/platelet transfusions for 28 or 56 consecutive days during the treatment period
Peripheral blood counts	To include platelets, absolute neutrophil count, haemoglobin, white blood cell, and blasts

Key: AE, adverse event; AML, acute myeloid leukaemia; ANC, absolute neutrophil count; BM, bone marrow; CR, complete response; CRi, complete response with incomplete blood count recovery; DNA, deoxyribonucleic acid; EFS, event-free survival; EORTC, European Organization for Research and Treatment on Cancer; Hgb, haemoglobin; IWG, international Working Group; MDS, myelodysplastic syndrome; PR, partial remission; QLQ, quality of life questionnaire; RBC, red blood cell; RFS, relapse-free survival; WBC, white blood cell.

Notes: a, Treatment failure defined as death during cycle 1 or within 28 days of the last dose and prior to day 1 of cycle 2

These endpoints are common and reasonable for a study investigating AML. A similar AML study[48] investigating a different drug to that of AZA-AML-001, report fewer endpoints than AZA-AML-001. However, the endpoints that they do report, match those of AZA-AML-001.

4.2.1.8 Statistical methods

4.2.1.8.1 Analysis population

The different populations reported within Celgene's submission for their analyses, along with their definitions are presented in *Table 8*. Celgene also included analysis of a modified ITT population and an evaluable population. These analyses were deemed not relevant to the question asked from this STA by the ERG.

Table 8: Analysis Population

Analysis Population	Definition
Intent-to-treat population (ITT)	All subjects who were randomised, independent of whether or not they received study treatment. The ITT population was used for the analysis of the primary and secondary efficacy endpoints. Subjects in the ITT population were analysed as randomised.
HRQoL evaluable population	All randomised subjects who completed the baseline HRQoL assessment (day 1) and had at least one follow-up assessment.
Safety population	All randomised subjects who had received at least one dose of trial drug and had at least one post-dose safety assessment. Subjects who were randomised to BSC within the CCR group were considered to be included in the safety population is that had at least one post-randomised safety assessment. Drug exposure and all safety analyses were based on the safety population. All subjects were analysed according to the initial treatment they received.

Key: BSC, best supportive care; CCR, conventional care regimen; ITT, intention-to-treat; HRQoL, health-related quality of life

The ITT population is the most appropriate population to use for analysis and the definition of the ITT population is correct. There is a risk of bias for the HRQoL population, as this population represents those who were well enough to complete the questionnaire and provide data. The safety population is defined appropriately.

4.2.1.8.2 Determination of sample size

Celgene report in their submission the determination of sample size to have been as follows (Source: Celgene submission, Section 4.4.3., p. 54):

> *The equality of OS curves was to be compared between the azacitidine and combined CCR groups using a stratified log-rank test. The planned sample size was approximately 480 subjects (240 per treatment arm), calculated on the assumption of a median OS of 10.5 months in the azacitidine arm and 7.5 months in the combined CCR arm (40% improvement), with a dropout rate of 1% from both treatment groups. The investigator selection of CCR was anticipated to be 50%, 30%, and 20% of subjects to the IC, LDAC, and BSC groups, respectively. This design required 374 deaths to allow the demonstration of a statistically significant difference in OS at a one-sided significance level of 0.025 with at least 90% power to detect a constant HR of 0.71.*

The study was powered for azacitidine compared to combined CCR. The results would have been more meaningful if the study had been powered to each of the CCR treatments

individually. Celgene anticipated the selection of CCR to be 50:30:20 for IC:LDAC:BSC. The actual study recruitment to CCR has the ratio 18:64:18. Celgene were asked to comment on the difference in anticipated selection of CCR and actual selection on CCR. Their anticipated selection for CCR was based on an educated guess since there was little real-world data to inform the prospective split.

4.2.1.8.3 Primary and secondary efficacy analysis

The company report the following for their primary efficacy analysis (Source: Celgene submission, Section 4.4.4, p. 54):

> *The primary efficacy analysis was performed using the ITT population. The analysis of the primary efficacy endpoint was conducted using an unstratified log-rank [test] and a stratified log-rank test (stratified by CCR selection, ECOG performance status, and cytogenetic risk status). The Kaplan Meier (KM) method was used to estimate the survival distribution functions for each treatment group. KM estimates for median OS, 25th and 75th percentiles, and associated two-sided 95% CIs were summarised for each treatment group (both unadjusted for the stratification variables and within strata). Additionally, the numerical difference and associated 95% CI in the median, and the 25th and 75th percentiles between the two treatment groups (azacitidine vs. CCR) were presented for the unstratified KM estimates.*
>
> *Cox proportional hazards models (unstratified and stratified) were used to estimate the hazard rate ratio and the corresponding 95% CI for azacitidine vs CCR.*
>
> *Surviving subjects were censored upon study discontinuation (loss to follow-up, withdrawal of consent) or at the end of the post-study follow-up.*

The company report the following for their secondary efficacy analysis (Source: Celgene submission, Section 4.4.5, p. 55):

> *All secondary endpoints were analysed using the ITT population, except for HRQoL and healthcare resource utilisation (HCRU). Analyses for both HRQoL and HCRU were conducted using a HRQoL evaluable population, defined as all randomised subjects who completed the baseline HRQoL assessment (day 1) and had at least one follow-up assessment.*
>
> *Kaplan-Meier methods were used to estimate the 1-year survival probabilities for time to death from any cause and death probabilities at 30 and 60 days.*
>
> *Time-to-event endpoints (EFS and RFS) were analysed using the same methods as the primary efficacy analysis, but without stratification. For EFS, subjects who were alive and event-free were censored at the date of their last response assessment, and for RFS, subjects who were in continuous CR or CRi were censored at the date of their last response assessment.*
>
> *Haematologic status was explored by examining the percentage of responders, defined as CR and CRi, and the duration of remission, CRc, peripheral blood counts, and transfusion requirements. All responses were based on the modified International Working Group (IWG) response criteria for AML.*

> *For duration of remission, subjects who were lost to follow-up or were alive at follow-up without documented relapse were censored at the date of their last response assessment. Summary statistics included KM estimates of median duration of remission, and 1-year cumulative incidence of relapse for each treatment group.*
>
> *For transfusion status, subjects who maintained red blood cell/platelet transfusion independence to the end of the treatment period were censored at the date of treatment discontinuation or death, whichever was sooner. Duration of transfusion independence was estimated and summarised using KM methods.*
>
> *For HRQoL analyses, the mean change from baseline for each domain at each time point was compared with the minimal important difference to determine whether the change was clinically meaningful. A mean change of at least 10 points on the standardised domain scores was required to be considered meaningful.*[49]
>
> *All reported log-rank or Fisher's exact test p values for secondary endpoints are nominal.*

The majority of the statistical methods used in the trial to analyse time-to-event data (and in particular, the primary efficacy outcome, overall survival) assume proportional hazards or have reduced efficiency in the presence of non-proportional hazards. There is no justification given for expecting this assumption to hold, and considering the results (e.g., *Figure 2, page 47*) this assumption was not reasonable.

In the presence of non-proportional hazards, appropriate alternatives to the log-rank test employed in the trial would be the Wilcoxon–Breslow–Gehan and Peto–Peto–Prentice tests (the choice between these based on the assessment of there being any differences in censoring patterns). In the presence of non-proportional hazards, there is no simple alternative to using a hazard ratio, but statistics such as the difference in restricted mean survival could be meaningful.

Using both stratified and unstratified tests is not directly justified. Overstratification can lead to loss of information, but unstratified tests are not appropriate when there is heterogeneity between strata.[50] Given the variables used for stratification are considered prognostic indicators, this suggests that the stratified analyses are more appropriate. Furthermore, the set of variables used for stratification was reduced in the event that stratification with the full set of variables would lead to individual strata with fewer than 16 patients, which should have reduced the risk of overstratification.

The ERG considers the censoring events loss to follow-up and withdrawal of consent may be informative for overall survival (which would violate the necessary assumptions for Kaplan–Meier analyses) but the most common reason for censoring was the patient being alive at the time of study closure,[37] so this is unlikely to have significantly impacted on results.

4.2.2 Results

4.2.2.1 Population distribution

In total, 488 people were randomised. Of these, 241 subjects were randomised to receive azacitidine, and 247 people were randomised to receive conventional care treatment. The

number of participants evaluable for each of the different population (ITT, safety, evaluable, HRQoL evaluable), are presented in *Table 9*. *Table 9* also presents the distribution of pre-selected CCR within the 247 people randomised to the azacitidine arm.

Table 9: Population distribution for analysis

Analysis population	Azacitidine[a]				CCR			
	BSC only (N=44)	LDAC (N=154)	IC (N=43)	Total (N=241)	BSC only (N=45)	LDAC (N=158)	IC (N=44)	Total (N=247)
ITT	44	154	43	241	45	158	44	247
Safety	42	151	43	236	40	153	42	235
Evaluable	35	114	30	179	25	132	34	191
HRQoL evaluable	—	—	—	157	—	—	—	134

Key: AZA, azacitidine; BSC, best supportive care; CCR, conventional care regimens; HRQoL, health related quality of life; IC, intensive chemotherapy; ITT, intent-to-treat; LDAC, low-dose cytarabine.
Notes: a, Number of patients randomised to azacitidine for each prespecified CCR
Source: Celgene submission, Table 14, p. 59

4.2.2.2 Baseline characteristics and demographics

Baseline characteristics of the ITT population are summarised in *Table A1* (*Appendix 1*) and baseline disease characteristics are presented in *Table A2* (*Appendix 1*). The demographic characteristics are well balanced between those randomised to azacitidine and the combined CCR. Those in the IC group were slightly younger than any of the other treatment groups. Conversely, those in the BSC group were slightly older than other treatment groups. These age differences are to be expected based on the participant demographic typically assigned to these types of CCR treatments. The azacitidine and combined CCR treatment groups were comparable for baseline disease characteristics.

4.2.2.3 Treatment exposure

Median treatment cycles were as follows:

- Azacitidine treatment cycles received 6 (range, 1-28 cycles);
- IC treatment cycles received 2 (range, 1-3 cycles);
- LDAC treatment cycles received 4 (range, 1-25 cycles);
- BSC treatment cycles received 65 days (range, 6-535 days).

From the azacitidine group, 52.5% received 6 or more treatment cycles and 32.2% received 12 or more treatment cycles. From the LDAC group, 35.9% received 6 or more treatment cycles and 17.6% received 12 or more treatment cycles. Cumulative patient-years of study drug exposure were 174.9 for azacitidine, 82.9 for LDAC, 14.1 for IC, and 9.6 (i.e., time on study) for BSC.[45]

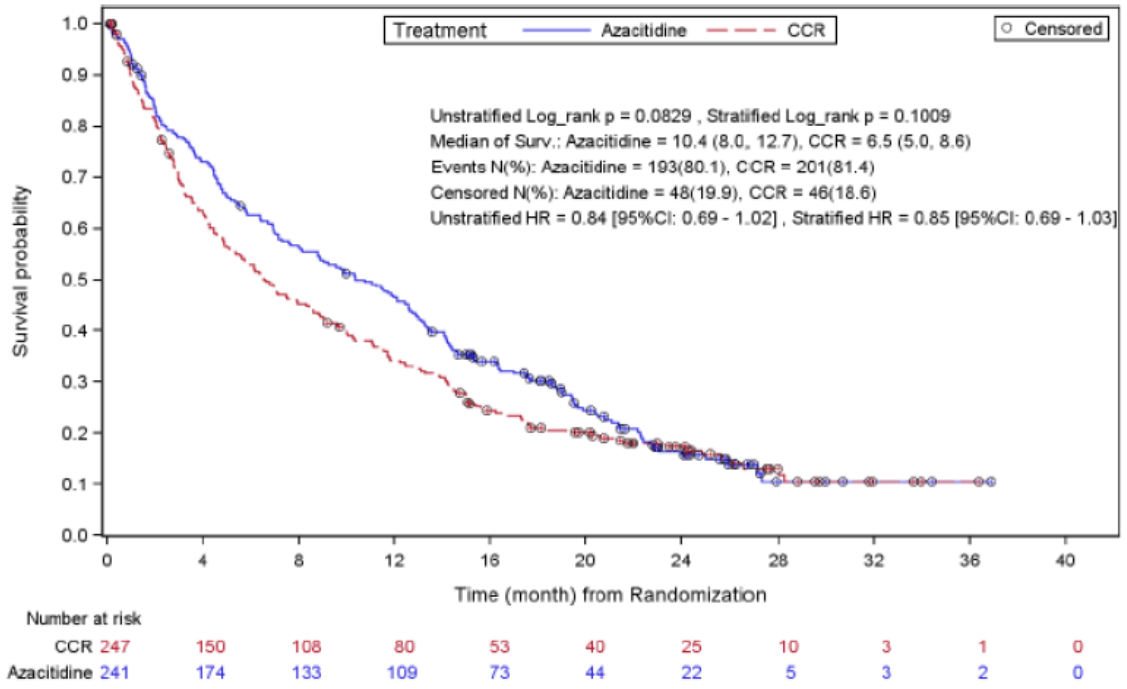
4.2.2.4 Clinical effectiveness results

4.2.2.4.1 Primary efficacy analysis – overall survival

The median duration of follow up was 24.4 months. By study end, 394 deaths (80.7%) had occurred; 193 (80.1%) in the azacitidine group and 201 (81.4%) in the CCR group. The Kaplan-Meier plot of time to death from any cause is presented in *Figure 2* and a summary of OS is presented in *Table 10* (both taken from the submission). The primary OS analysis was performed with and without stratification. Stratification minimises the potential for bias by restricting comparisons to more homogeneous groups. Pre-specified stratification factors were: preselected CCR (IC versus LDAC or BSC); ECOG performance status (0–1 versus 2); and cytogenetic risk (intermediate versus poor).

Reporting mean OS may have offered superior understanding for the efficacy of treatments in comparison to what the median offers. It would have been better if Celgene had presented both the mean and median for OS.

Figure 2: Kaplan-Meier plot of overall survival



Key: CCR, conventional care regimens; CI, confidence interval; HR, hazard ratio.
Source: Celgene submission, Figure 8, p. 66

Table 10: Summary of overall survival in the ITT population

Outcome	Azacitidine (N=241)	CCR (N=247)
Event, n (%)	193 (80.1)	201 (81.4)
Censored, n (%)	48 (19.9)	46 (18.6)
Median OS (95% CI), months[a]	10.4 (8.0, 12.7)	6.5 (5.0, 8.6)
Difference (95% CI), months[a]	3.8 (1.0, 6.5)	
HR [AZA:CCR] (95% CI)[b]	0.85 (0.69, 1.03)	
Stratified log-rank test: p-value[c]	0.1009	
HR [AZA:CCR] (95% CI)[d]	0.84 (0.69, 1.02)	
Unstratified log-rank test: p-value[e]	0.0829	
1-year survival, % (95% CI)	46.5 (40.1, 52.7)	34.3 (28.3, 40.3)
Difference, % (95% CI)[f]	12.3 (3.5, 21.0)	

Key: AZA, azacitidine; CCR, conventional care regimens; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intent-to-treat; KM, Kaplan Meier; OS, overall survival; PH, proportional hazards.

Notes: a, Median, 25th, and 75th percentile estimates of OS are from an unstratified KM analysis. Differences were calculated as AZA:CCR. The CIs for the differences were derived using Kosorok's method; b, The HR is from a Cox PH model stratified by ECOG performance status and cytogenetic risk status; c, p-value is two-sided from a log-rank test stratified by ECOG performance status, and cytogenetic risk status; d, the HR is from an unstratified Cox PH model; e, p-value is two-sided from an unstratified log-rank test; f, CI for the difference in the 1-year survival probabilities was derived using Greenwood's variance estimate.

Source: Celgene submission, Table 18, p. 66

4.2.2.4.2 Secondary efficacy endpoints

A summary of secondary endpoints for azacitidine versus CCR is presented in *Table 11*. The ERG used the data reported by Celgene to produce Kaplan-Meier figures for event-free survival (*Figure 3*), relapse-free survival (*Figure 4*) and progression-free survival (*Figure 5*). *Table 12* and *Table 13* present outcomes based on pre-selection prior to randomisation.

Table 11: Secondary endpoints: azacitidine versus CCR

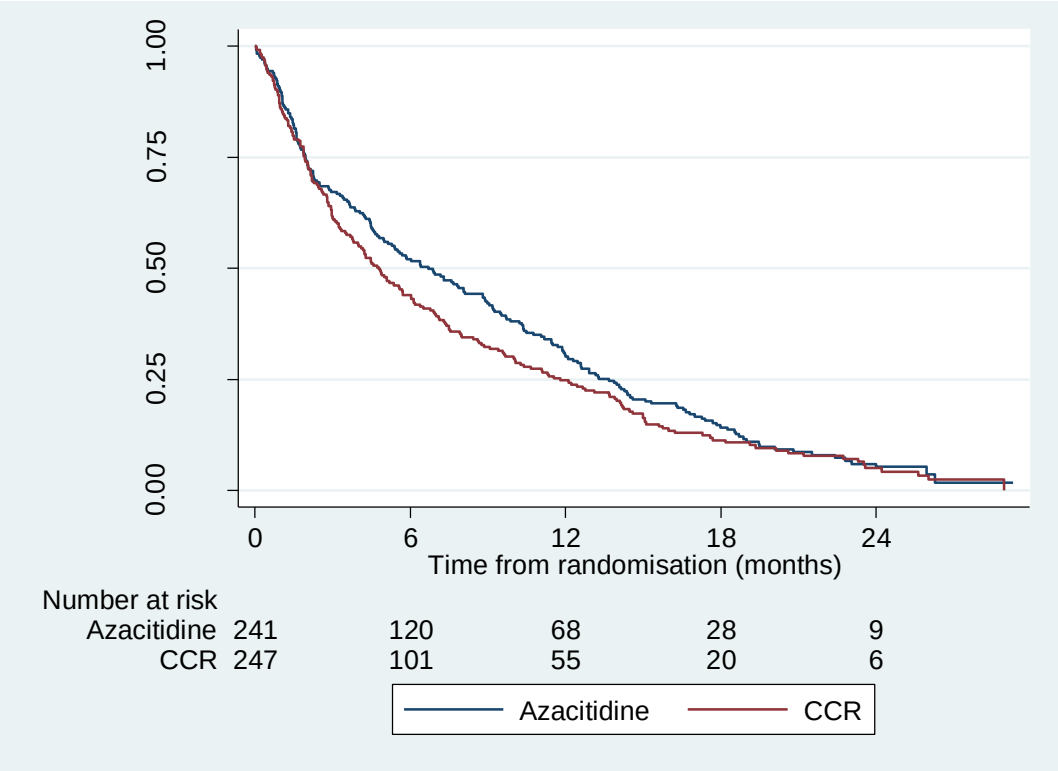
	Azacitidine (N=241)		CCR (N=247)		HR	95% CI	p value
	N	%	N	%			
Death estimates							
30-day	16	6.6	25	10.1	–	–	–
60-day	39	16.2	45	18.2	–	–	–
Haematologic response[a]							
CR + CRi	67	27.8	62	25.1	–	–	0.5384
CR	47	19.5	54	21.9	–	–	0.5766
CRc-20	5	2.1	14	5.7	–	–	0.0589
PR	3	1.2	3	1.2	–	–	1.0
Progressive disease	20	8.3	20	8.1	–	–	1.0
Stable disease	71	29.5	59	23.9	–	–	0.1833
Other secondary endpoints							
EFS[b]							
Median, months		6.7		4.8	0.87	0.72, 1.05	0.1495
RFS							
Median, months		9.3		10.5	1.11	0.75, 1.66	0.5832
Relapse after CR or CRi	43	63.2	35	56.5	–	–	0.4712
Duration of remission							
Median, months		10.4		12.3	–	–	–
Transfusion independence[c]							
RBC	65	38.5	45	27.6	–	–	–
Platelets	41	40.6	24	29.3	–	–	–

Key: CCR, conventional care regimens; CI, confidence interval; CR, complete response; CRc-20, complete cytogenetic remission in at least 20 metaphases; CRi, complete remission with incomplete blood count recovery; EFS, event-free survival; PR, partial remission; RBC, red blood cell; RFS, relapse-free survival.

Notes: a, Defined by International Working Group criteria and was adjusted by an independent review committee; b, Events included treatment failure, progressive disease, relapse after CR or CRi, or death; c, Defined as no transfusions for 56 consecutive days on study for patients who were transfusion dependent at baseline.

Source: Celgene submission, Table 22, p. 72

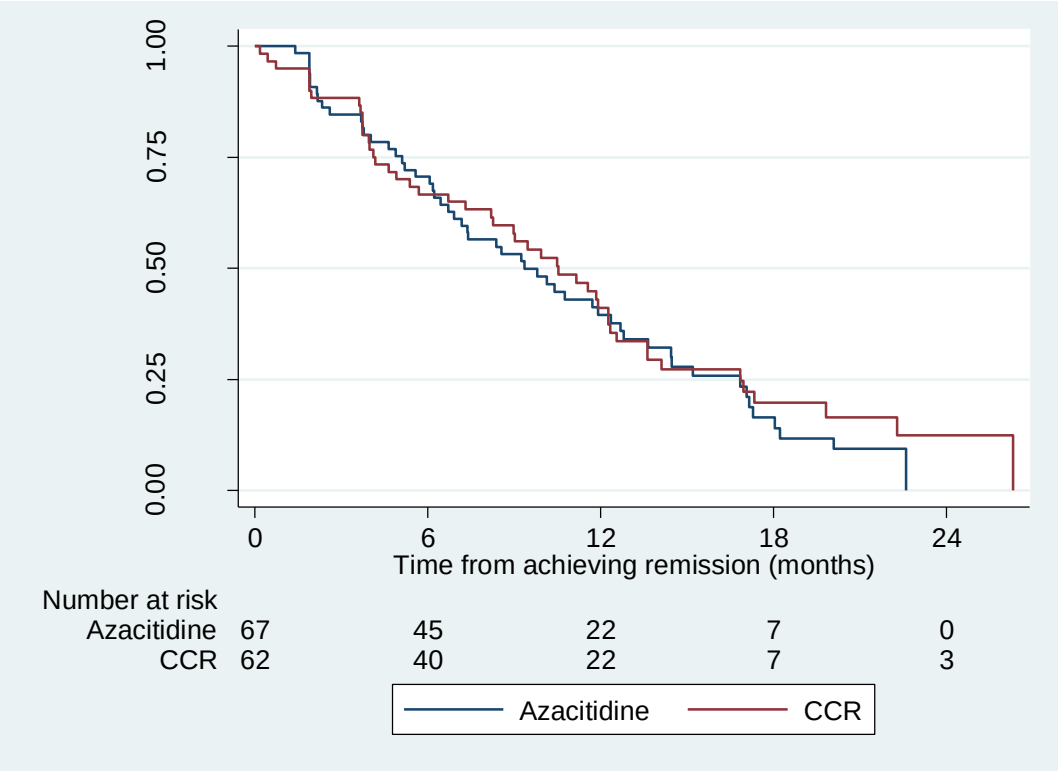
Figure 3: Kaplan-Meier plot of event-free survival



Key: CCR, conventional care regimens; CR, complete remission; CRi, complete remission with incomplete blood count recovery

Notes: Event-free survival, defined for all patients as the time from randomisation to treatment failure, disease progression, relapse after CR or CRi, death from any cause, or loss to follow-up

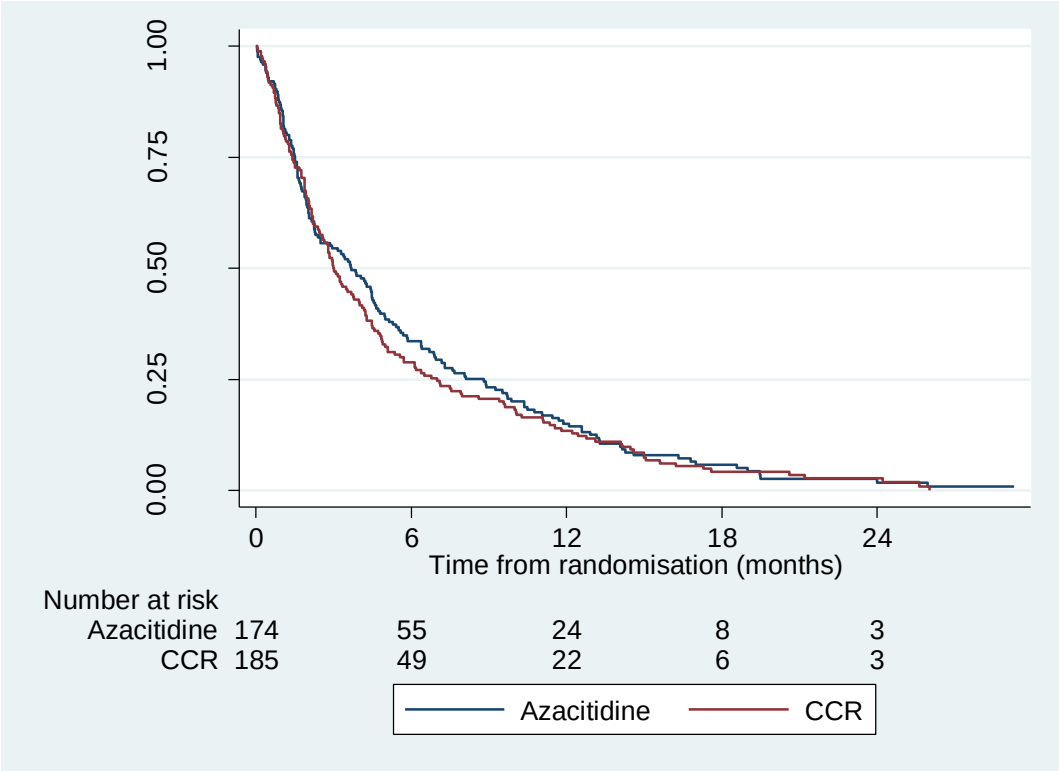
Figure 4: Kaplan-Meier plot of relapse-free survival



Key: CCR, conventional care regimens; CR, complete remission; CRi, complete remission with incomplete blood count recovery

Notes: Relapse-free survival, defined for patients achieving CR or CRi as the time from first documented CR or CRi to relapse, death from any cause, or loss to follow-up

Figure 5: Kaplan-Meier plot of progression-free survival



Key: CCR, conventional care regimens; CR, complete remission; CRi, complete remission with incomplete blood count recovery
Notes: Progression-free survival, defined as for event-free survival but for patients achieving neither CR nor CRi

Table 12: Secondary endpoints – according to investigator pre-selection: haematologic response

Investigator pre-selection	BSC		LDAC		IC	
	AZA (N=44)	CCR (N=45)	AZA (N=154)	CCR (N=158)	AZA (N=43)	CCR (N=44)
Haematologic response, n (%)[a]						
CR + CRi	7 (15.9)	0 (0.0)	42 (27.3)	41(25.9)	18 (41.9)	21 (47.7)
CR	6 (13.6)	0 (0.0)	28 (18.2)	38 (24.1)	13 (30.2)	16 (36.4)
CRc-20	1 (2.3)	0 (0.0)	3 (1.9)	8 (5.1)	1 (2.3)	6 (13.6)
PR	0 (0.0)	0 (0.0)	3 (1.9)	1 (0.6)	0 (0.0)	2 (4.5)
Progressive disease	4 (9.1)	5 (11.1)	10 (6.5)	14 (8.9)	6 (14.0)	1 (2.3)
Stable disease	14 (31.8)	6 (13.3)	47 (30.5)	46 (29.1)	10 (23.3)	7 (15.9)

Key: AZA, azacitidine; CCR, conventional care regimens; CR, complete response; CRc-20, complete cytogenetic remission in at least 20 metaphases; CRi, complete remission with incomplete blood count recovery; PR, partial remission.
Notes: a, Defined by International Working Group criteria and was adjusted by an independent review committee.
Source: Celgene submission, Table 23, p. 73; AZA-AML-001 Clinical Study Report[37]

Table 13: Secondary endpoints – according to investigator pre-selection: other secondary outcomes

Investigator pre-selection	BSC		LDAC		IC	
	AZA (N=44)	CCR (N=45)	AZA (N=154)	CCR (N=158)	AZA (N=44)	CCR (N=45)
Event-free survival						
Median, months	4.5	3.1	7.3	4.8	8.1	9.7
Hazard ratio (95% CI)	0.67 (0.43, 1.04)		0.89 (0.70, 1.13)		1.02 (0.64, 1.63)	
p-value	0.0756		0.3563		0.9196	
Relapse-free survival						
Median, months			8.6	9.9	10.8	12.1
Hazard ratio (95% CI)			1.11 (0.68, 1.81)		1.21 (0.58, 2.51)	
p-value			0.6638		0.6135	
Relapse after CR or CRi, n (%)	2 (28.6)	NA	31 (73.8)	25 (61.0)	10 (55.6)	10 (47.6)
Duration of remission						
Median, months			9.2	11.2	17.3	19.8

Key: AZA, azacitidine; CCR, conventional care regimens; CI, confidence interval; CR, complete response; CRi, complete remission with incomplete blood count recovery.
Sources: Celgene submission, Table 23, p. 73-74; AZA-AML-001 Clinical Study Report[37]

Similarly to the primary outcome, OS, reporting the mean for the secondary outcomes may have offered superior understanding for the efficacy of treatments in comparison to what the median offers. There is also limited reporting of time-to-event reporting for the secondary outcomes.

One-year survival

Comments on one year survival from Celgene were as follows (Source: Celgene submission, Section 4.7.5.1, p. 75):

> *Azacitidine improved 1-year survival compared with CCR (46.5% vs. 34.3%, respectively), resulting in a clinically meaningful difference of 12.3% in favour of azacitidine (95% CI: 3.5, 21.0).*
>
> *1-year survival was also improved for azacitidine when compared with each of the CCR therapies (within investigator pre-selection) (BSC only: 30.3% vs. 18.6%, LDAC: 48.5% vs. 34.0%, and IC: 55.8% vs. 50.9%, respectively), and in a post-hoc analysis, when compared with BSC plus LDAC (within investigator pre-selection) (44.5% vs. 30.6%, respectively).*

None of these improvements reported by Celgene were significantly different.

Event-free survival

Additional information about event-free survival from Celgene was given (Source: Celgene submission, Section 4.7.5.3, p. 75):

> *Overall, 212 (88.0%) events (defined as treatment failure, progressive disease, relapse after CR or CRi, death from any cause, or loss to follow-up) were reported in subjects treated with azacitidine and 216 (87.4%) events in subjects treated with CCR.*

4.2.2.4.3 Health-related quality of life

The European organisation for research treatment of cancer (EORTC) QLQ-C-30 was used to assess HRQoL. The questionnaire was completed at baseline, on day 1 of every other cycle and at the end-of-study visit. To be evaluable as the HRQoL population, baseline assessment and at least one other post-baseline assessment was required. The HRQoL population comprised of initially of a total of n=291 (n=157 azacitidine and n=134 CCR). The size of the HRQoL population decreased in size over time in both groups. *Table 14* presents the evaluable HRQoL population throughout treatment up to cycle 9.

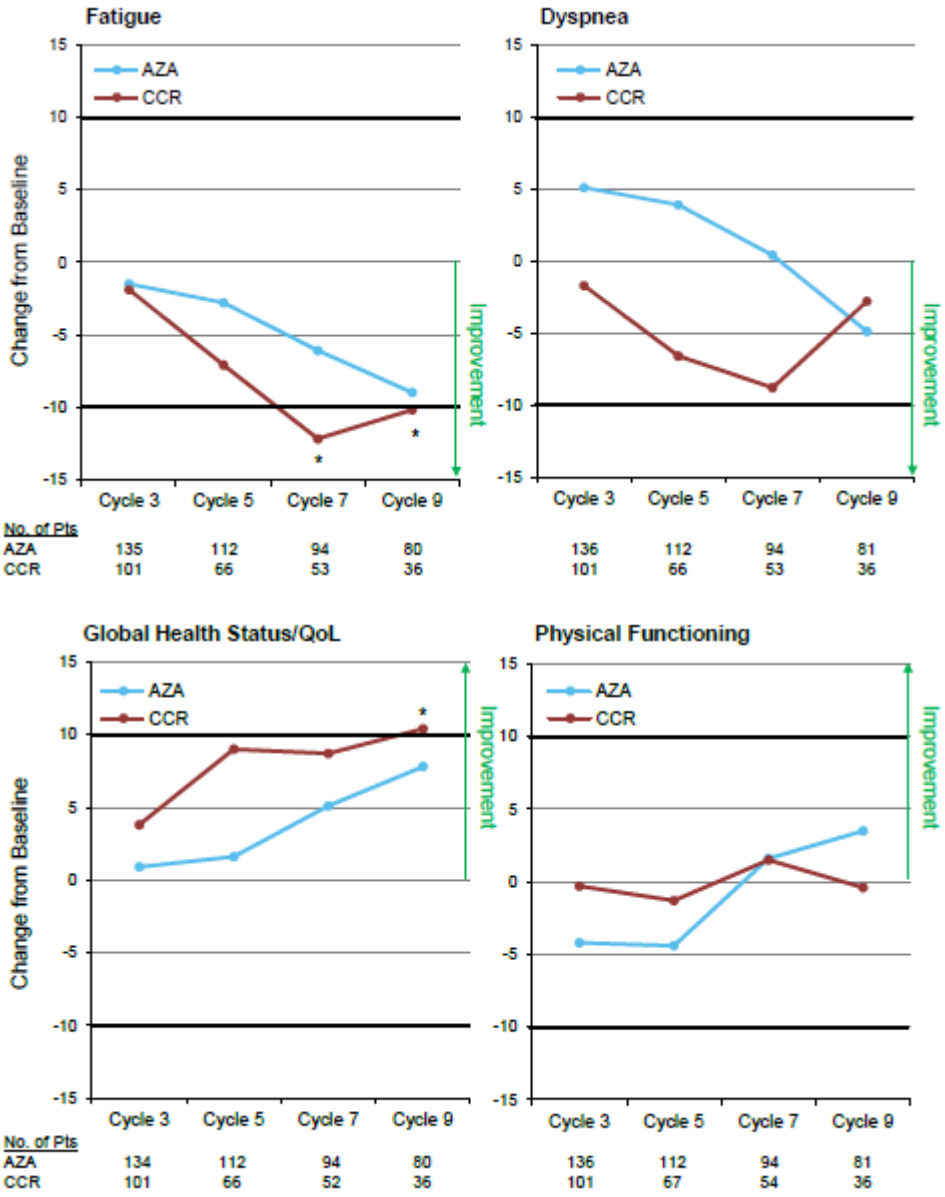
Primary HRQoL endpoints reported include fatigue score, dyspnoea, physical functioning and global health status. Changes over time for these four endpoints are depicted in *Figure 6*.

Table 14: HRQoL assessment rates

HRQoL assessment	AZA (n=241)			CCR (n=247)		
	Treated	Assessed n (%)	Evaluable n (%)	Treated n	Assessed n (%)	Evaluable n (%)
Cycle 1 (Baseline)	237	210 (89)	157 (66)	236	210 (89)	134 (57)
Cycle 3	174	152 (87)	137 (79)	131	113 (86)	102 (78)
Cycle 5	146	127 (87)	112 (77)	86	72 (84)	67 (78)
Cycle 7	118	105 (89)	94 (80)	67	58 (87)	54 (81)
Cycle 9	98	89 (91)	81 (83)	49	38 (78)	36 (73)

Key: AZA, azacitidine; CCR, conventional care regimens; CI, confidence interval; HR, hazard ratio.
Notes: HRQOL assessment rates = number of patients with an EORTC QLQ-C30 assessment ÷ the total number of patients receiving treatment at the scheduled cycle visit. Numbers reported in this table represent all HRQOL assessments at each cycle; some patients may not be included in HRQL analyses due to missing baseline HRQOL assessments. Evaluable patients completed an HRQL assessment at baseline and had ≥ 1 post-baseline assessment.
Source: Celgene submission, Table 24, p. 77

Figure 6: Mean absolute score change from baseline for primary and secondary HRQoL endpoints (HRQoL evaluable population)



Key: AZA, azacitidine; CCR, conventional care regimens.
Notes: Decreasing scores indicate improvement in the Fatigue and Dyspnoea domains of the QLQ-C30, and increasing scores indicate improvement in the Physical Function and Global Health Status/QoL domains.
The minimally important difference, defined as a mean change of at least 10 points from baseline and representing a clinically meaningful effect is denoted by bold black lines at 10 and -10 on the y-axis.
*Met the threshold for minimally important difference.
Source: Celgene Submission, Figure 10, p. 78

Statistical tests were not reported between treatment arms for HRQoL. From Figure 6, the CCR arm appears to be favourable in comparison to azacitidine for cycle three, five and seven the four HRQoL measures reported (fatigue, dyspnoea, global health status and physical functioning). For the final cycle reported (cycle nine), CCR is favourable for fatigue and global health status, whilst azacitidine is favourable for physical functioning and dyspnoea.

There are two significant critiques of the HRQoL analyses by Celgene:

- Assessments are made at the start of each cycle, after a significant recovery period for patients after treatment;
- A significant number of patients (197 patients, 40%) are not represented in the HRQoL assessment at any time point as they did not have a baseline assessment (14%) and/or lacked a post-baseline assessment; these patients are likely to have been more ill (lower HRQoL) than the patients who were assessed and evaluable.

4.2.2.4.4 Adverse events

AML-AZA-001 included 471 subjects in the safety population who had newly diagnosed AML with >30% blasts and were randomised to receive azacitidine or CCR. The median age of the safety population was 75.0 years with 53.3% of subjects ≥75 years of age, 32.7% of subjects had AML with MDS-related changes, 18.0% had a prior history of MDS, 35.7% had a poor or very poor cytogenetic risk status, and 22.9% had ECOG performance status of 2. Median baseline BM blast count was 71.5%.

A summary for adverse events (AEs) is presented in *Table 15*. *Table 16* reports the incidences of AEs for > 10 % of people in any treatment arm. *Tables A3*, *A4* and *A5* (*Appendix 1*) presents AEs for both treatment arms, based on the number of events occurring in ≥10% of people in the azacitidine group.

Table 15: Summary of adverse events

Adverse events	AZA, n (%) (N=236)	CCR		
		BSC, n (%) (N=40)	LDAC, n (%) (N=153)	IC, n (%) (N=42)
≥1 AE	234 (99.2)	36 (90.0)	153 (100.0)	42 (100.0)
≥1 treatment-related AE	188 (79.7)	0 (0.0)	124 (81.0)	39 (92.9)
≥1 Grade 3 or 4 AE	207 (87.7)	26 (65.0)	141 (92.2)	37 (88.1)
≥1 Grade 3 or 4 treatment-related AE	125 (53.0)	0 (0.0)	90 (58.8)	29 (69.0)
≥1 Grade 5 (leading to death) AE	56 (23.7)	23 (57.5)	38 (24.8)	9 (21.4)
≥1 Grade 5 (leading to death) treatment-related AE	12 (5.1)	0 (0.0)	10 (6.5)	4 (9.5)
≥1 SAE	188 (79.7)	30 (75.0)	118 (77.1)	27 (64.3)
≥1 treatment-related SAE	87 (36.9)	0 (0.0)	56 (36.6)	14 (33.3)
≥1 AE leading to discontinuation	110 (46.6)	0 (0.0)	68 (44.4)	11 (26.2)
≥1 treatment-related AE leading to discontinuation	22 (9.3)	0 (0.0)	20 (13.1)	5 (11.9)
≥1 AE leading to dose reduction only	8 (3.4)	0 (0.0)	2 (1.3)	2 (4.8)
≥1 AE leading to study drug dose interruption only	116 (49.2)	0 (0.0)	61 (39.9)	4 (9.5)
≥1 AE leading to study drug dose reduction and interruption	13 (5.5)	0 (0.0)	7 (4.6)	0 (0.0)

Key: AE, adverse event; AML, acute myeloid leukaemia; AZA, azacitidine; BSC, best supportive care; CCR, conventional care regimens; CI, confidence interval; IC, intensive chemotherapy; LDAC, low-dose cytarabine; SAE, serious adverse event.

Notes: AE refers to treatment-emergent adverse events. Adverse events included events that started (1) between the date of first dose of study drug and 28 days after the date of last dose of study drug for azacitidine and LDAC (2) between the date of first dose of study drug and 70 days after the date of last dose of study drug for IC (3) between the date of randomisation and the date of discontinuation from the treatment period for BSC only. Adverse events that started outside the treatment-emergent period and assessed as related to study drug was considered treatment-emergent.

Source: Celgene Submission, Table 26, p. 86

Table 16: Grade 3 to 4 Treatment emergent adverse events occurring in ≥10% of patients in any treatment group

Adverse events	Azacitidine (n=236)		CCR					
			BSC only (n=40)		LDAC (n=153)		IC (n=42)	
Preferred term	No.	%	No.	%	No.	%	No.	%
Febrile neutropenia	66	28.0	11	27.5	46	30.1	13	31.0
Neutropenia	62	26.3	2	5.0	38	24.8	14	33.3
Thrombocytopenia	56	23.7	2	5.0	42	27.5	9	21.4
Pneumonia	45	19.1	2	5.0	29	19.0	2	4.8
Anaemia	37	15.7	2	5.0	35	22.9	6	14.3
Leukopenia	16	6.8	0	0	13	8.5	6	14.3
Hypokalaemia	12	5.1	1	2.5	10	6.5	7	16.7

Key: BSC, best supportive care; CCR, conventional care regimens; IC, intensive chemotherapy; LDAC, low-dose cytarabine.
Source: Dombret et al. 2015[45]

4.2.3 Interpretation

Key efficacy findings from the RCT reported from the submission were as follows:

Overall survival

Azacitidine was not significantly superior to CCR in prolonging survival of adults ≥65 years with AML with >30% bone marrow blasts.

Secondary endpoints

1-year survival rates were 46.5% for azacitidine compared to 34.3% in the CCR arm (difference 12.3 %; 95% CI: 3.5, 21.0).

Measures of haematologic response, duration of remission and remission free survival were similar between treatment arms when CCR was combined. When CCR was not combined, it appeared (although limited statistical analysis was reported) that IC was superior to azacitidine. Participant numbers for the IC arm compared to those originally assigned to IC were small (n=44 and n=43 respectively).

No statistical analyses were presented for the HRQoL data. Appearances from the figures suggest that CCR was favourable to azacitidine.

Adverse events

Treatment related AEs were common for both azacitidine, LDAC and IC. Unsurprisingly, AEs were less common for BSC.

4.2.3.1 Strengths and limitations

Strengths

- Multicentre, appropriately randomised design of the RCT AZA-AML-001

- The population recruited to AZA-AML-001 was representative of the typical UK patient population
- The appropriate CCR regimes used as a comparator in AZA-AML-001 compared to UK standard practices

Limitations

- Underpowered for individual CCR arms
- The open-label design introduces the risk of bias
- The use of subsequent therapies following treatment assignment, some of which are not used in routine NHS practice, and which were not balanced across treatment arms
- Limited reporting of time-to-treat outcomes (except for OS)
- Use of statistical analyses which have reduced efficiency when proportional hazard assumptions are not met

4.3 Adjustments of overall survival estimates for subsequent therapy

In order to address confounding effects of subsequent therapy on overall survival (OS), the company's submission presents post-hoc analyses that adjust for subsequent therapy use. Among these, the analyses that censored data at the start of subsequent therapy and weighted the remaining data by the inverse of the probability of not being censored, i.e., the inverse probability of censoring weights (IPCW) method, play the most prominent role in the submission. Other methods of adjustment of OS treatment effects were considered elsewhere in the submission (Celgene submission, Section 5.3.5, p. 122), such as the Rank Preserving Structural Failure Time Model (RPSFTM) and the Iterative Parameter Estimation (IPE), but these were considered inferior to the IPCW.

The company presented estimates of relative effects for two sets of IPCW analyses. In the first set of analyses, adjustment for subsequent treatment was applied to both trial arms (i.e., azacitidine and CCR). In the second set of analyses, adjustment for subsequent treatment with azacitidine was applied to the CCR arm.

Celgene adopted the results of the second set for its health economic base case analysis. The company justified this choice on the basis of methodological guidelines (Source: Celgene submission, Section 4.4.4.3, p. 55):

> *For regulatory purposes, an initial IPCW analysis was undertaken in which both treatment arms were adjusted. A further IPCW analysis was conducted in line with the NICE DSU TSD16 in which adjustments were only made to the comparator treatment arm (CCR).*[51]

This reasoning led Celgene to devote little space in its submission to describe the first set of IPCW analyses, which adjusted for subsequent therapy in both arms, and to focus on detailing the second IPCW analysis, which only adjusted for subsequent azacitidine use in the CCR arm.

The ERG believes the first set of analyses, which adjust for subsequent AML treatment in both trial arms, should have been used for the base case economic analysis instead of the IPCW analysis adjusting for azacitidine use in CCR. The ERG believes the company are mistaken in their interpretation of the methodological guidelines. The NICE DSU TSD16 illustrates the application of IPCW to estimate treatment effects in a hypothetical context where a policy choice needs to be made among two states of the world, one where a new, experimental treatment is available to patients and the alternative state where such treatment is not available, and the evidence comes from an RCT where some control patients switch to the experimental treatment after randomisation. IPCW adjustment (or indeed adjustment by any other suitable method for that matter) of outcome data in the control arm would then be warranted. In this example no IPCW adjustment was made in the experimental arm because it was assumed that the mix of subsequent therapies used by patients in that arm is representative of patterns of care in the state of the world where the experimental treatment is made available. In contrast, as acknowledged in the NICE DSU TSD16, if the mix of subsequent therapies in any trial arm (whether is the experimental or control) is not representative of patterns of care in the state of the world of interest to the decision problem, then adjustment for those subsequent treatments is needed.

Therefore, in the case where, as the cost-effectiveness model submitted by Celgene for this appraisal implies (see *Section 5*), the decision problem involves the evaluation of two alternative states of the world where no subsequent active treatment is available, then adjustment of outcomes for active treatment switching in both trial arms is warranted. Whether the premise that no subsequent active treatment would be available to UK patients in routine practice is correct may of course be questioned (see *Section 5* for clinical expert opinion on this issue obtained by the ERG for this appraisal), but the point here is that applying IPCW adjustment for subsequent treatment to the outcome data of the CCR but not the azacitidine arm in the AZA-AML-001 trial is inconsistent with the economic model which the OS IPCW analysis was designed to inform.

Since OS differences between the two arms in AZA-AML-001 narrowed over time and the statistically insignificant ITT findings in OS were reversed when data were censored at subsequent AML treatment initiation (Celgene submission, Section 4.7.2.3, pp. 67–68), Celgene undertook further post-hoc analyses to adjust for imbalance in the use of subsequent treatment and baseline covariates across trial arms. The following methods were explored.

4.3.1 Cox proportional hazards models

Three post-hoc Cox proportional hazards models of survival were considered in the clinical effectiveness submission, although were not part of scenarios investigated in the economic submission:

- Model 1 was a function of a time varying indicator of subsequent treatment (as a main effect and interacted with treatment allocation);
- Model 2 was a function of baseline covariates alone;
- Model 3 included covariates in Models 1 and 2.

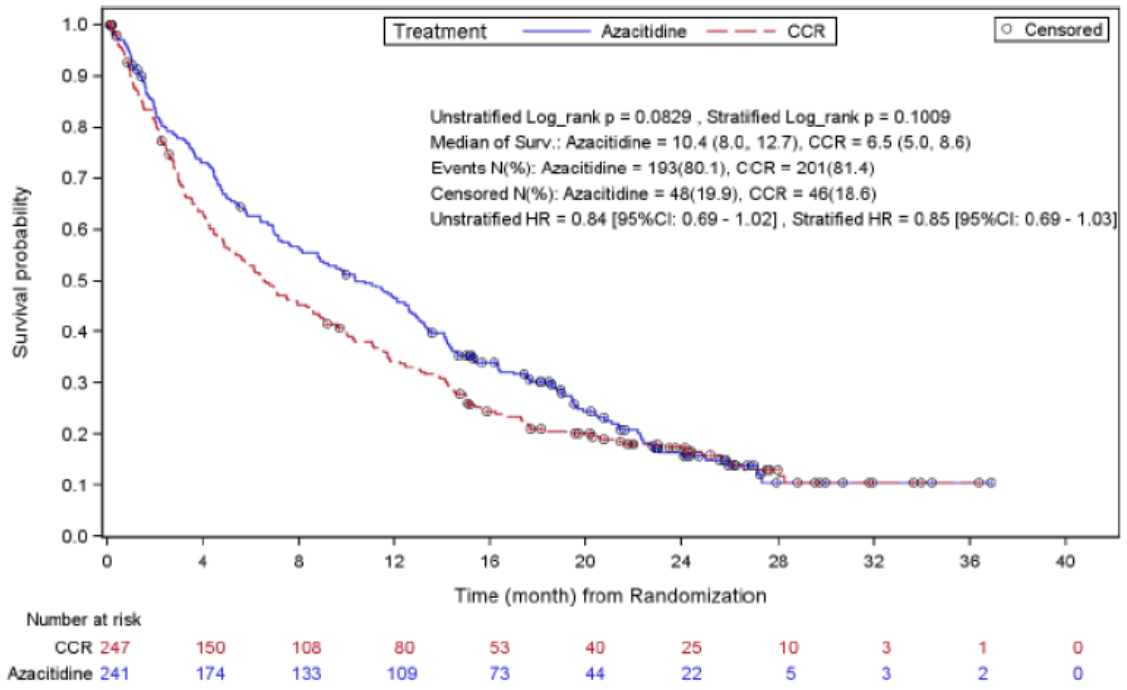
Model 3 produced a large treatment effect estimate (HR 0.69, 95% CI: 0.54, 0.88; p=0.0027). However, this estimate and those from the other two post-hoc Cox proportional hazards models are susceptible to bias.

The treatment effect of azacitidine in Model 2 is likely confounded by treatment switching, whilst the adjustment for treatment switching in Model 1 and Model 3 implausibly implies the following two assumptions: (a) either those who switch have the same prognosis as those that do not switch or their prognoses differ but they are evenly distributed across arms; and (b) subsequent treatments have the same average effect across arms conditional on prognosis. The different mix of subsequent therapies used across azacitidine and CCR arms (*see Table 48, page 105*) and noticeable differences in results between Model 3 and the respective IPCW analysis (*see Section 4.3.2*) suggests that neither assumption (a) nor (b) are likely to be borne out by the data.

4.3.2 Inverse probability of censoring weights (IPCW) method

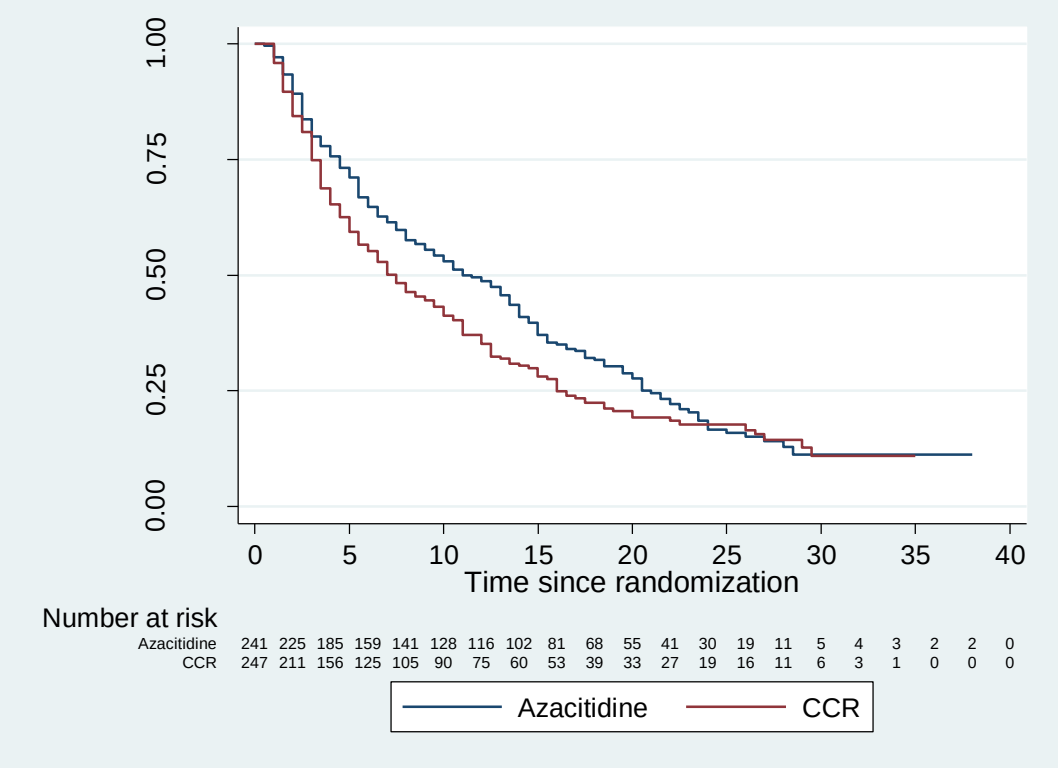
The IPCW method was used, adjusting for treatment switching in the CCR arm only. This approach sought to account for the possibility that subsequent treatment use did not occur at random. Results were presented for a Cox proportional hazards model unadjusted for differences in baseline characteristics across treatment arms (unadjusted IPCW Cox proportional hazards model; HR AZA versus CCR [redacted], 95% CI: [redacted], and another Cox proportional hazards model that included covariates for those baseline characteristics (adjusted IPCW Cox proportional hazards model; [redacted], [redacted]. The adjusted IPCW Cox proportional hazards estimate was used in the base case economic analysis by Celgene (*see Section 5.2.5, page 73*). This estimate only adjusts outcomes in the CCR arm for subsequent azacitidine use, which accounted for 32 out of the 74 (43.2%) control subjects with subsequent treatment (Source: Celgene submission, Section 4.7.2.3, p. 67). *Figure 7* and *Figure 8* show the Kaplan-Meier curves for the ITT and IPCW data, measured in days and 15-day periods respectively (Celgene did not provide the figure in days or the individual patient data to produce this graph to ERG). The azacitidine curve is the same in the two figures, whereas the CCR curve with IPCW lies above that of ITT.

Figure 7: Overall survival in AZA-AML-001 based on intention-to-treat population



Key: CCR, conventional care regimen; HR, hazard ratio
Source: Celgene submission, Figure 8, p. 66

Figure 8: Overall survival in AZA-AML-001 following adjustment of the CCR arm for subsequent treatment with azacitidine using the IPCW method



Key: CCR, conventional care regimen; IPCW, inverse probability of censoring weight
Note: Based on discrete (15-day period) time-to-event data
Source: Patient-level data supplied to ERG by Celgene

The company also reported that "For regulatory purposes, an initial IPCW analysis was undertaken in which both treatment arms were adjusted." (Source: Celgene Submission, Section 4.4.4.3., p. 55). Two sets of results for these IPCW Cox proportional hazards models of treatment switching in both AZA and CCR treatment arms were presented, one set for a model that adjusted for baseline prognostic covariates and another for a model unadjusted for those covariates (Source: Celgene submission, Table 21, p. 70). The baseline covariate-unadjusted IPCW Cox proportional hazards model HR estimate was 0.77 (95% CI, 0.61–0.98), and the adjusted estimate was 0.71 (95% CI, 0.56–0.90) (Celgene submission: Table 21, p. 70).

Although the respective methods are not clearly reported, it appears that these estimates adjust for any subsequent treatment in both arms, as opposed to adjusting only for azacitidine in the CCR arm as in the IPCW Cox proportional hazards method previously described and used by Celgene for its base case economic analysis. As explained in *Section 5,* if IPCW methods were indeed used to adjust for any subsequent treatment in both arms, the associated results may be the most suitable of those submitted by Celgene to populate the model with for the company's base case economic analysis. However, the submission is unclear about what treatments these analyses adjusted for (Source: Celgene, Appendices to submission, Appendix 11, Section 3.3.1):

[redacted]

[redacted]

In AZA-AML-001, azacitidine was not the only subsequent treatment for AML used in the CCR arm, and there were also active treatments after azacitidine in the azacitidine arm (*see Table 48, page 105*).

4.3.3 Other analyses

Other analyses submitted by the company separately analysed patients who did and did not receive any subsequent therapy. These analyses are by their nature of limited use in informing assessments of relative effectiveness, because the differences in outcomes between those two groups of patients are likely to confound the effect of treatment with individual variation in the propensity to receive treatment, and are not reviewed further.

Another set of treatment effect estimates were reported for an analysis that censored subsequent cytarabine-based therapy in the azacitidine group and subsequent azacitidine in the CCR group (HR [redacted]; 95% CI: [redacted]). These results are more in line with the assumptions of Celgene's economic model, which assumes no subsequent active treatment after treatment failure is used in the azacitidine and CCR groups. However, as reported by the Celgene submission, cytarabine accounted only for 40 (59.7%) of the 67 subjects who received subsequent treatment in the azacitidine group (Celgene submission, Section 4.7.2.3, p. 67).

Another analysis used an imputation method to adjust for treatment switching (Celgene Post hoc statistical methods addendum AZA-AML-001), but since little information was provided on the methods and the results of this analysis played no subsequent role in the submission, we do not discuss these further.

4.3.4 Summary and additional issues

Comparing HR estimates between the baseline covariate-unadjusted IPCW PH, 0.77 (95% CI: 0.61–0.98) (Celgene submission, Table 21, p. 70), and the unstratified HR (ITT) censoring at switch to AML therapy, 0.75 (95% CI: 0.59–0.95) (Celgene submission, Table 19, p. 68), suggests sophisticated methods of adjustment for subsequent treatment use that account for censoring not-at-random (e.g., IPCW) make little difference versus simple methods that assume censoring at random.

Further, similar HR estimates were found with IPCW Cox proportional hazards versus simply estimating Cox proportional hazards treatment effects without subsequent therapy-related censoring and a time-varying covariate indicator of subsequent therapy interacted with randomly allocated therapy (0.71 versus 0.69).

Adjusting versus not adjusting for baseline covariates appears to be the single structural factor to which estimates of relative effectiveness are most sensitive, as evidenced by the difference in HR estimates between Cox proportional hazards Model 1 versus Model 3 (0.75 versus 0.69) and the corresponding estimates with IPCW applied to both trial arms (0.77 versus 0.71).

The wide range of HR estimates reported by the company relies on the assumption of constant proportional hazards, which was statistically tested for the Cox but not for the IPCW approaches. No reasons for the absence of tests of the proportional hazards assumption in the IPCW analyses were presented in the submission. The methods description presented in the cost-effectiveness section of the Celgene submission suggests these tests were not performed and does not provide reasons for this omission (*see Section 5.3* for our critique of methods presented in the cost-effectiveness section of the Celgene submission).

In *Figure A1* (*Appendix 2*) we present log-log plots for the IPCW analysis adjusting for azacitidine use in the CCR arm only (the corresponding data for the IPCW analysis adjusting both the azacitidine and CCR arm for subsequent AML therapy use were not provided by the company). This suggests that the proportional hazards assumption (i.e., curves being parallel) is unlikely to hold after month 20. Statistical test of this assumption using Schoenfeld residuals also rejects the assumption (X^2=5.82; p=0.016).

As explained in *Section 5.3.6.2* (*page 111*), the IPCW method applied by Celgene consisted of two parts, first a regression analysis to predict the probability of a CCR patient not receiving subsequent treatment at each follow-up point (every 15-days), as a function of fixed baseline covariates and time-varying covariates that affect both the likelihood of treatment switching and overall survival outcomes. In a second step the survival time of CCR individuals who switched to azacitidine are censored at the time of switching and the inverse of the predicted probability of switching corresponding to uncensored CCR individuals at a given follow-up point is used as sampling weight to account for the unobserved outcomes of censored individuals in the counterfactual situation that they had not switched treatment. This method thus intends to estimate the outcomes that would have been observed in the CCR sample had no patients switched to azacitidine, and does so by adjusting for non-random censoring (i.e., treatment switching) using a predictive model for subsequent treatment.

The validity of overall survival IPCW estimates (and resulting hazard ratios) depends on the AZA-AML-001 data conforming to two key assumptions.

The first key assumption (referred to as the exchangeability assumption) dictates that after controlling for the measured predictors common to survival and subsequent azacitidine use, subsequent azacitidine users have the same survival prognosis as those who remain in CCR. As discussed elsewhere, this assumption only holds under the following three conditions:

- All common predictors are appropriately measured and accounted for in the analysis;
- The sample of patients available at all follow-up times is sufficiently large to ensure that the probability of not switching is positive for every combination of values observed for the common predictors over the whole sequence of follow-up points (i.e., the positivity condition, Cole and Hernan 2008[52]);

- The common predictors cannot perfectly or nearly perfectly predict survival or switching to azacitidine.

Thus, small sample size or perfect common predictors violate the exchangeability assumption because the survival outcomes of uncensored CCR patients would not be representative of censored individuals, who switched to azacitidine, even if all common confounders were appropriately measured and included in the analysis.[53] This problem is thus aggravated by small sample sizes, highly stratified data due to a large set of predictors used to estimate weights, and continuous predictors can generate random non-positivity.

The second assumption is that the functional forms in which the common predictors enter the switching prediction model is correctly specified, so that exchangeability is maximised by controlling for selection bias while maintaining positivity.[52]

While the ERG could replicate the IPCW hazard ratio estimates reported by Celgene using individual patient data provided by the company, it was not provided the data to replicate the estimation of IPCW weights, which were estimated in SAS (Celgene appendices to submission, Appendix 10). This limited the ability to assess whether the assumptions implied by the IPCW method are consistent with the data from AZA-AML-001. Further details are provided in *Section 5.3.6.2* (*page 111*).

Celgene notes that besides the limitations inherent in the IPCW, there was an additional limitation (Source: Celgene Post hoc statistical methods addendum AZA-AML-001, pp. 6–7):

> *An additional limitation of the post-randomization data in the current study was that for subjects who did not receive subsequent therapy, the last visit interval extended from the last assessment done at the time of discontinuation from the treatment phase of the study to the time of censoring (study closure or lost to follow-up) or death. If the subject was alive and in the survival follow-up phase for a long period of time then the gap between treatment discontinuation and death or censoring could be quite long and represents a time interval during which no additional clinical information was collected or available.*

This issue is a potentially important one for the company's IPCW analyses, because it suggests that an unknown proportion of patients might have received unrecorded subsequent therapy, for which survival outcomes remained unadjusted for. For the IPCW analysis that adjusted only outcomes of CCR arm, this implies that the benefit of azacitidine may be underestimated. In contrast, in the IPCW analysis that adjusted survival outcomes of both trial arms, if patients with improved survival prognosis were to be more likely to have received subsequent therapy during the period of unrecorded clinical management activity it is possible that unrecorded treatment switching may have produced a larger omitted variable bias in overall survival outcomes of azacitidine than CCR, and that the survival benefits of azacitidine may be overestimated.

The implications of these issues are covered further in *Section 5* that discusses the cost-effectiveness analysis submitted by Celgene.

4.4 Critique of trials identified and included and of the indirect comparison and/or multiple treatment comparison

As one RCT was identified from the searches and screening,[45] indirect comparisons and/or multiple treatment comparisons could not be made and were not presented by the company.

4.5 Critique of other evidence sources

Celgene provided four further sources (one non-RCT and three trial registries) of evidence within their submission.

4.5.1 Non-randomised evidence

The single non-RCT relevant to the decision problem identified by Celgene was by Lao et al.[46] This was a study which included a broader population of >20% blasts, however they provided sub-analysis for the population with >30% blasts. Celgene do not report any of the findings from this study as they claim the number of people with >30% blasts was small (n=12 for azacitidine group versus n=8 for the IC group versus n=22 for BSC group). From exploring the Lao et al. study, there is no evidence reported that compares any outcomes between the azacitidine group and either IC or BSC for those with >30% blasts. There is evidence comparing <30% and 30% or higher BM blasts in the azacitidine arm.

4.5.2 Registry data

The company report registry data from three countries: Austria, Spain and France. They hoped to conduct matched-adjusted indirect comparison using single-arm data. None of the published registry data (Austrian azacitidine registry (NCT01595295); Spanish AMLA registry and French compassionate patient named programme) provided information on the population with >30% bone marrow blasts, a population requirements for the Scope for this report.

4.6 Conclusions of the clinical effectiveness section

In spite of poorly designed and reported searches, the company submission identified a single RCT trial (AZA-AML-001) that matched the decision problem. Information from this study was reported in detail. The RCT was well conducted, although underpowered for each of the CCR arms.

The primary efficacy endpoint for the RCT was an ITT comparison of overall survival for patients randomised to azacitidine versus patients randomised to CCR. An improvement was demonstrated but it did not reach statistical significance. Statistical significance was also not reached for other outcomes assessed and reported. There was some evidence, though not statistically significant due to underpowering, that azacitidine was inferior to LDAC and IC on a number of outcomes, including response rate and relapse-free survival, although azacitidine appeared to be superior in relation to overall survival.

Post-hoc analyses were presented where overall survival outcomes were adjusted for subsequent treatment in CCR, where a significant improvement with azacitidine was found. However, these analyses were hampered by the fact that they relied on the assumption that treatment effects displayed a proportional hazards pattern, which was not statistically tested in the analysis sample.

5 Cost-effectiveness

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 Objective

The company conducted a systematic review to identify cost-effectiveness studies from the published literature relevant to the decision problem (*see Section 3, page 23*).

5.1.2 Search strategies

5.1.2.1 Economic evaluations

The company presented a literature search protocol to support its review of cost effectiveness. This protocol included systematic searches of key biomedical databases using a literature search strategy combined with hand-searching of conference abstracts and included studies. The literature searching was last updated in October 2015.

The bibliographic database searching used a search strategy that took the following form:

1. (search terms for acute myeloid leukaemia/leukaemia); *and*
2. (search terms for Azacitidine, cytarabine, clofarabine, daunorubicin, etoposide, fludarabine, idarubicin, mitoxantrone, mercaptopurine, amsacrine, cytotoxic or anthracycline or supportive or conventional care or chemotherapy or antineoplastic agent); *and*
3. (search terms to identify cost analysis, studies reporting economic evaluations or cost parameters).

This search strategy was applied in: MEDLINE and EMBASE (both via OVID), NHS EEDs and the HTA library (via the Cochrane Library: OVID interface) and Econlit (OVID).

The following conference proceedings were hand-searched between 2013 and 2015 inclusive:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) - European, International, Asia-Pac, and Latin American
- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- Tufts Cost-effectiveness Analysis (CEA) registry
- WHO International Clinical Trials Registry Platform (ICTRP)
- HTA Database of the International Network of Agencies for Health Technology Assessment (INAHTA)
- NIHR HTA website
- Research Papers in Economics (RePEc) website
- NICE website.

The ERG accepts that these literature searches were fit for purpose.

5.1.2.2 Health-related quality of life

Celgene did not record a systematic search for studies reporting HRQoL in their original submission. In response to a question for clarification, Celgene confirmed that they had undertaken a targeted systematic search. This literature search was undertaken in PubMed and the HERC database and takes population search terms combined with search terms for: QALY or utlilit* (search term is truncated) or EQ-5D. The ERG has been able to replicate and validate this search.

Celgene noted further that HRQoL was recorded for all treatments in the trial that supports their submission. Celgene have therefore used this data to parameterise their model arguing that it best reflects the quality of life seen in the target population. Given the inherent difficulty of measuring HRQoL outcomes in oncology trials and in particular in this clinical area, ERG believes that Celgene is likely to have identified the best available source of evidence on these outcomes relevant to this assessment.

5.1.3 Inclusion criteria

The review included cost-utility studies in the English language, or English abstracts of studies from studies written in other languages, relating to adults (>18 years) with AML with >30% blasts. In terms of treatments, included studies had to investigate azacitidine (intervention) and comparators of including intensive or non-intensive low-dose chemotherapy, including:

- Cytarabine (Ara C)
- Clofarabine (Evoltra®)
- Daunorubicin (daunomycin)
- Etoposide (Etopophos®, Vepesid®)
- Fludarabine (Fludara®)
- Idarubucin (Zavedos®)
- Mercaptopurine (Xaluprine®)
- Mitoxantrone
- Amsacrine
- Hydroxycarbamide (Hydrea)

or best supportive care (BSC).

All of these criteria were within the NICE Scope.

5.1.4 Results

Of 334 titles identified by the company's searches, forty eight studies were candidates for inclusion based on abstract and title content and its full text screened for possible inclusion. Forty studies were excluded after screening their full text, mostly due to the patient population investigated; six studies were excluded due to the study design being limited to

costs only rather than cost-effectiveness analysis. The remaining eight studies were included in the review.

Of the eight reviewed studies four were published abstracts and the remaining four were full journal article publications. Two of the full publications reported studies in populations within the NICE score of AML with >30% blasts, one was a study conducted in France,[54] and another was a study conducted in China.[55] The company performed quality assessment of the four full publications only, since abstract publication reported insufficient information to be assessed.

Although Celgene did not discuss the results of their quality assessment of the four included full publications, the quality checklist (Celgene appendices to submission, Appendix 8) makes clear that the studies were of very poor quality in terms of design, since no study was designed as an incremental cost-utility analysis, details of modelling methods required to extrapolate outcomes from short term efficacy studies to capture all important costs and benefits were not provided, and the degree of uncertainty in estimates was not measured. None of the studies were conducted in the UK and the one European study identified did not provide adequate methodological evidence to be of use to this assessment.

Only one of the reviewed studies evaluated azacitidine (versus LDAC). This was a study conducted in Russia that reported that azacitidine resulted in RUB 909,573 ($32,261 at 2012 PPP; source: OECD http://www.oecd-ilibrary.org/economics/purchasing-power-parities-for-gdp-2013-1_ppp-gdp-table-2013-1-en) extra costs and 0.76 additional life years per patient than LDAC, for an incremental cost per life year gained of RUB 1,196,808 (£42,449), but since it was published as an abstract[56] it provided limited information (ICER calculations made by ERG from information reported in the publication). Further, its relevance to the NICE decision problem is ambiguous since it is not clear whether patients had >30% blasts, and it included MDS patients. Moreover, these results did not take account of HRQoL outcomes and the costs results may not be transferable due to differences in relative prices between UK and Russia.

5.1.5 Conclusions

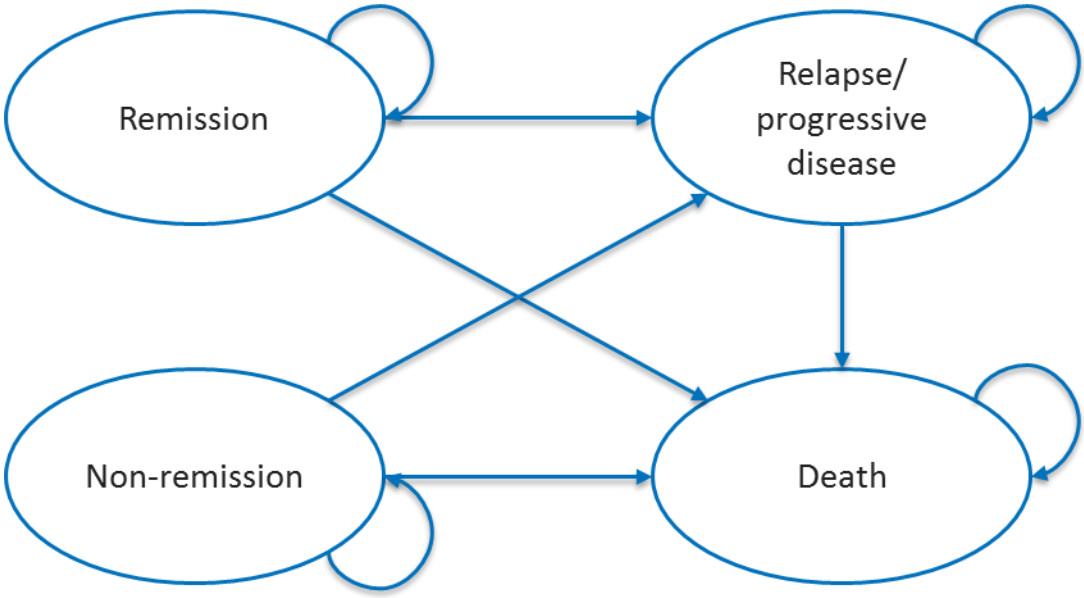
Although no conclusions were provided by the submitted review, ERG concludes that the quality of the evidence is poor and in any case unlikely to be relevant to the present assessment.

5.2 Summary of company's submitted economic evaluation

5.2.1 Model structure

A semi-Markov model, proposed by Celgene, is based on AZA-AML-001 study, a literature review of clinical guidelines and economic models for AML, and advice from two UK clinical oncologists. The structure of the model is described in the submission (Celgene submission, Section 5.5.5, pp. 106–108) and shown in *Figure 9* below.

Figure 9: Structure of the model submitted by Celgene



Source: Celgene submission, Figure 14, p. 107

The model simulates remission, non-remission, relapse/progressive disease and death in AML patients.

The model starts after patients have completed the first cycle of either AZA or CCR (i.e., 4 weeks after the start of treatment). Those patients, who have responded to the treatment by the end of the first cycle and have complete remission (CR) or complete remission with incomplete blood count recovery (CRi), enter the model in “Remission” state; patients with partial remission (PR) or stable disease are placed in “Non-remission” state.

Disease pathways in the subsequent treatment cycles are as follows:

- Patients in the remission state may continue in remission, relapse or die.
- Those in the non-remission state may remain in this state, progress to “Relapse/Progressive disease” state or die.
- Patients in the “Relapse/Progressive disease” state may remain in this state or die.

For every model cycle, the proportion of patients in each health state is estimated using RFS, PFS and OS curves in the following way:

- The proportion of patients in the remission state is based on RFS from AZA-AML-001 study. In the trial, RFS was estimated from the date of first documented CR or CRi to the date of relapse, while OS and PFS were measured from randomisation to event. Therefore, in the model, RFS was adjusted to ensure consistency with OS and PFS.
- The proportion of patients in the non-remission state was estimated from PFS curve for patients who have achieved partial response (PR) or stable disease (SD).
- The proportion of patients in the relapse/progressive disease (PD) state was the difference between the proportions in OS state, and RFS and PFS states.
- The proportion in the “Death” state was a complement of the OS curve.

The model cycle length is 4 weeks which corresponds to one treatment cycle of azacitidine, and is in line with AZA-AML-001 study.

The other key structural assumptions are presented in *Table 17*.

Table 17: Key assumptions in Celgene's economic model

Assumption	Justification
Patients are not eligible for HSCT at any point	The marketing authorisation extension for azacitidine excludes those patients who are eligible for HSCT. Patients in AZA-AML-001 were ineligible for HSCT.
Patients who do not achieve remission in the treatment phase do not subsequently achieve remission	Clinical expert advice. Once off treatment and not in remission, a patient will not achieve remission.
Once in the PD state, patients either remain in PD or die	Clinical expert opinion and previous TAs in similar end-of-life cancers.
There is no treatment switching	Clinical expert opinion. Only a very small percentage of patients at this stage of disease would be fit for a second treatment after failing their first.
In any cycle, patients can only be in one of the health states	Markov model Structure

Key: HSCT, haematopoietic stem cell transplantation; BSC, best supportive care; TAs, technology appraisals; PD, progressive disease.
Source: Celgene submission, Table 54, p. 141

5.2.2 Population

The model population, parameterised from the AZA-AML-001 trial, represents older patients with de-novo or secondary AML with more than 30% bone marrow blasts who were not eligible for hematopoietic stem cell transplantation (HSCT), with intermediate- or poor-risk cytogenetics (NCCN 2009 criteria), Eastern Cooperative Oncology Group performance status (ECOG PS) scores 0–2, and white blood cell count not more than 15×10^9/L.

The starting age of the model population was 75 years and the patient's body surface area (BSA) was 1.8 m², based on the mean age and BSA of AML patients from the AZA-AML-001 trial.

The model allows cross-over adjusted, cross-over unadjusted and censor-at-switch analyses performed for the whole population, IC, LDAC, or BSC patient subpopulations, subpopulations with different cytogenetic risk (intermediate and poor), with and without myelodysplasia-related changes. The following rationale was given for these subgroups (Source: Celgene submission, Section 5.2.1, p. 106):

> *Subgroups on cytogenetic risk and myelodysplasia-related changes were chosen based upon a current unmet need for an effective option for patients presenting with these characteristics and the observed significant (P-values < 0.05) OS benefit of azacitidine over CCR in the AZA-AML-001 trial in these subgroups.*

The results from alternative and subgroup analysis are reported in Section 5.8 of Celgene's submission.

Celgene presented cost-effectiveness results for two subgroups: patients with poor-risk cytogenetics and patients with MDS related changes:

> *Since subsequent-treatment adjustment was not possible for these subgroups, analysis was performed without adjustment.*

5.2.3 Interventions and comparators

The model, proposed by Celgene, estimates cost-effectiveness of AZA compared to conventional care regimens (CCR) comprised of IC+BSC, LDAC+BSC and BSC alone.

Further details regarding the interventions and comparators were given (Source: Celgene submission, Section 5.2.3, pp. 108–109):

> *IC:*
>
> - *Induction therapy – Cytarabine was administered at a dose of 100–200 mg/m²/day via continuous IV infusion for a total of 7 days. Anthracycline was given in combination with cytarabine for 7 days.*
> - *Consolidation - Two consolidation cycles for those who responded to the treatment, followed by BSC. Those who do not respond to induction therapy receive BSC.*
>
> *LDAC: Cytarabine at a dose of 20 mg SC [twice daily] for 10 days, every 28 days, until disease progression or unacceptable toxicity; patients then receive BSC.*
>
> *BSC: Including but is not limited to red cell or whole blood transfusions, fresh frozen plasma transfusions, platelet transfusions, antibiotic and/or antifungal therapy, and nutritional support). This is continued until death.*
>
> *The same BSC is assumed to apply to all patients who have stopped active treatment on AZA, IC or LDAC.*
>
> *Azacitidine is incorporated at a dose of 75 mg/m²/day SC for 7 days every 28 days. In the base case wastage is assumed and vials used are rounded up to the cost of the nearest full vial. Vial sharing is tested in the sensitivity analysis (this also applies to CCR regimens).*

The distribution of patients over IC, LDAC and BSC treatments (18%, 64% and 18%, respectively), modelled in the base case, was derived from the pivotal RCT. It differed substantially from the distribution observed in UK clinical practice and reported in the HMRN registry ([redacted] of patients were treated with IC, [redacted] with LDAC and [redacted] with BSC). To assess the effect of this assumption on the outcome, the manufacturer performed a scenario analysis (Celgene submission, Section 5.8.3, pp.154-156) by calculating a weighted average ICER from individual CCR and AZA arms, with weights equal to the proportions of patients in individual CCR from the HMRN registry.

5.2.4 Perspective, time horizon and discounting

In the model, the perspective on costs was NHS and personal social services perspectives, and the perspective on health effects was direct health effects on patients, in accordance with the NICE reference case.

The model time horizon was 10-years, which was considered the life-time horizon of the patient population in question.

For utilities and costs, the manufacturer used the discount rate of 3.5%, in line with the NICE reference case. In addition, the model allows analyses with the discount rates of 1.5% and 6%.

5.2.5 Treatment effectiveness and extrapolation

Treatment effectiveness was estimated from the AZA-AML-001 trial and post-hoc analyses conducted on the data collected.

The economic model used the following clinical endpoints:

- Overall survival (OS), defined as the time from randomization to death from any cause;
- Relapse-free survival (RFS), the time from first documented CR or CRi to relapse, death from any cause, or loss to follow-up (for the model this was adjusted to time from randomization until relapse or death);
- Progression-free survival (PFS), defined as the time from randomization to death or disease progression (PD) for patients who did not achieve remission (CR or CRi);
- Event-free survival (EFS), defined as the time from randomization to treatment failure, disease progression, relapse after CR or CRi, death from any cause, or loss to follow-up).

EFS was employed to estimate both RFS and PFS, which were obtained (Source: Celgene submission, Section 5.3.1., p. 109):

> *[…] by disaggregating the data into those who did or did not achieve CR or CRi; then, patients with CR or CRi were assessed for death or relapse (i.e., RFS); patients with no CR or CRi were instead assessed for death or disease progression (i.e., PFS).*
>
> *Response status was also used to allocate utilities and disease management costs; in particular, costs for consolidation IC were attributed to patients with CR, CRi, and PR. The cost of BSC was allocated to patients with PD after stopping active treatment.*

In response to an ERG question for clarification regarding the treatment of loss to follow-up, Celgene provided further information:

> *Specific definitions for event free survival (EFS) and relapse free survival (RFS) outcomes are provided below:*
>
> - *Loss to follow-up was treated as an event for EFS outcomes when such loss occurred without documented treatment failure, progression or relapse from*

complete remission (CR)/complete remission with incomplete blood count recovery (Cri) and alive at last contact.

- *Loss to follow-up was treated as an event for RFS outcomes when such loss occurred after documented CR/CRi without relapse from CR/CRi and alive at last contact.*
- *Loss to follow-up was treated as an event for progression free survival (PFS) outcomes when such loss occurred and the variable PDFLAG = 1 (progressive disease (PD) being the best IRC assessed response).*

This was a conservative approach, as the worst case scenario (e.g. progression, relapse or death) is assumed for subjects who are lost to follow up in the context of such a serious disease that requires ongoing medical attention.

The company also referred to definitions in *Table 18* and *Table 19* reproduced from the AML-001 Statistical Analysis Plan document.

Table 18: Censoring rules for event-free survival

Situation	Date of Event or Censoring	Outcome
Withdrawal and no post-baseline response assessments and alive at date of last contact	Date of randomization	Censored
Death without any adequate response assessment	Date of death	Event
Treatment failure, disease progression, relapse after CR/CRi, or death	Earliest of:	Event
	Date of treatment failure	
	Date of disease progression	
	Date of relapse from CR or CRi	
	Date of death	
Lost to follow-up without documented treatment failure, progression, or relapse from CR/CRi and alive at last contact	Date of last response assessment	Event
No treatment failure, progression, or relapse from CR/CRi and not lost to follow-up	Date of last response assessment of CR, CRi, PR, or SD	Censored

Key: CR, complete remission; CRi, complete remission with incomplete blood count recovery; PR, partial remission; SD, stable disease
Source: AML-001 Statistical Analysis Plan Dated Jan 31, 2014

Table 19: Censoring rules for relapse-free survival

Situation	Date of Event or Censoring	Outcome
Relapse or death after CR/CRi	Earliest of:	Event
	Date of relapse from CR or CRi	
	Date of death	
Lost to follow-up after documented CR/CRi without relapse from CR/CRi and alive at last contact	Date of last response assessment	Event
CR/CRi without documented relapse and not lost to follow-up and alive at last contact	Date of last response assessment	Censored

Key: CR, complete remission; CRi, complete remission with incomplete blood count recovery
Source: AML-001 Statistical Analysis Plan Dated Jan 31, 2014

Response rates from the trial (after excluding non-confirmable or non-assessable subjects) used in the model are shown in *Table 20*.

Table 20: Response rates in the AZA-AML-001 trial

Response	Azacitidine response rate	CCR response rate
Remission (CR, CRi)	0.28	0.25
Non-response (PR, SD, PD, TF)	0.72	0.75

Key: CR, complete remission; CRi, morphologic complete remission with incomplete blood count recovery; PD, progressive disease; PR, partial remission' SD, stable disease; TF, treatment failure
Source: Celgene submission, Table 31, p. 109

Several models were fitted to extrapolate overall survival, progression-free survival and relapse-free survival data for each RCT arm:

- Exponential;
- Weibull;
- Gompertz;
- Log-logistic;
- Log-normal.

For each of these models and outcomes treatment effects were also estimated in the form of constant hazard ratios from the coefficient of a binary covariate treatment group indicator included in time to event regressions. Because the log-logistic and log-normal are accelerated failure time models they do not have associated constant hazard ratios, although in the submission (Section 5.3.3, pp. 111, 114, 116, Tables 32–24) the company presents a HR estimate from a Cox proportional hazards model as if it was applicable to the log-logistic and log-normal extrapolation models.

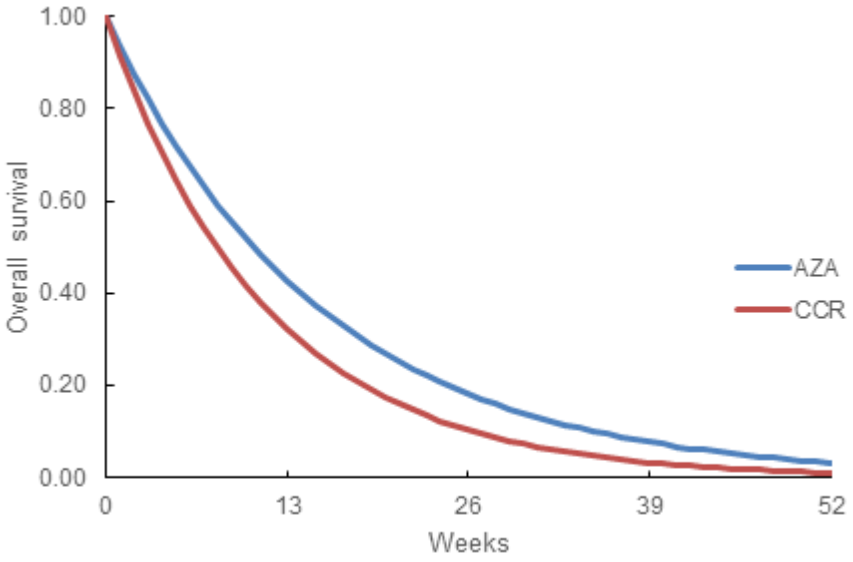
The survival model selection process algorithm recommended by the NICE DSU TSD14 was employed to identify the best fitting curves (Source: Celgene submission, Section 5.3.2, p. 110), with a detailed account on curve fitting also given by the company (Source: Celgene submission, Section 5.3.3, p. 110-116).

For the base case, the manufacturer selected the exponential model for OS, Weibull for RFS and Gompertz for PFS. The company adjusted OS outcomes for treatment switching using a range of different methodological options. PFS and RFS were not adjusted for treatment switching, and Celgene stated that all progression and relapse events in the trial occurred before other censoring events (Celgene submission, Section 5.3.3, p. 116), among which Celgene does not mention treatment switching. In response to the questions for clarification from ERG on why RFS and PFS had not been adjusted for subsequent treatment, the company stated that:

> *This was due to sample size primarily. The instances in which switching preceded the clinical event of interest were few, and the impact of this on the results would be very small.*

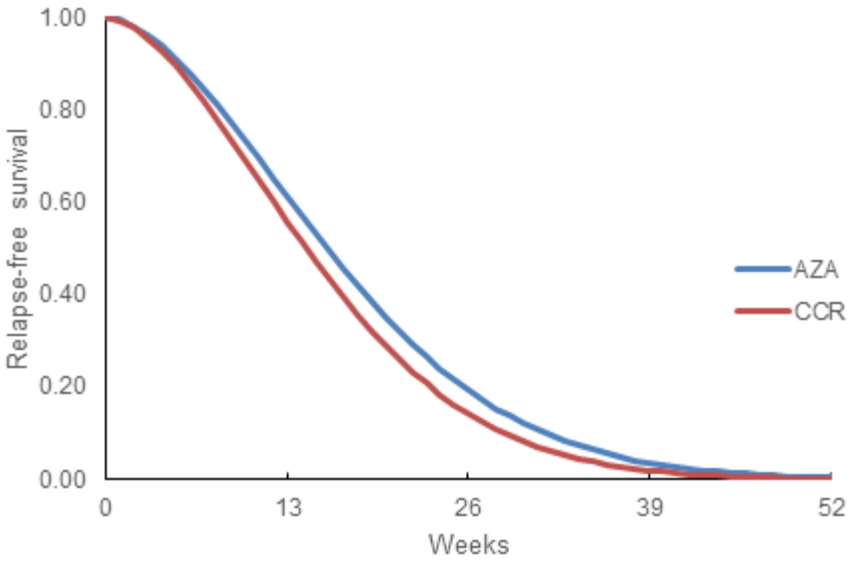
The overall survival, relapse-free survival and progression-free survival used in the model are given in *Figure 10*, *Figure 11* and *Figure 12* respectively.

Figure 10: Overall survival used in the company's submitted model



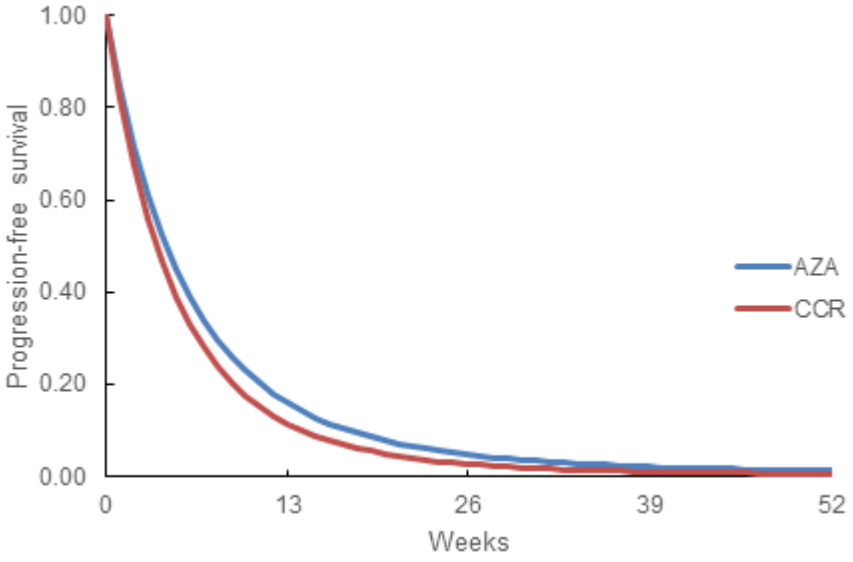
Key: AZA, azacitidine; CCR, conventional care regimens

Figure 11: Relapse-free survival used in the company's submitted model



Key: AZA, azacitidine; CCR, conventional care regimens

Figure 12: Progression-free survival used in the company's submitted model



Key: AZA, azacitidine; CCR, conventional care regimens

5.2.5.1 Treatment switching

The base case OS estimates were based on an adjustment for subsequent treatment use in the CCR arm that censored the data at the time of subsequent treatment initiation and weighted the remaining data by the inverse of the probability of not starting subsequent therapy, which was separately estimated using a logistic regression model. This method is referred to as the inverse probability of censoring weights (IPCW), and was originally developed for the analysis of observational data, applying a similar logic to that used to estimate population statistics from survey data.[57]

The validity of this method hinges on the untestable assumption that information on all determinants of the probability of not using subsequent treatment that are also correlated with OS outcomes is measured in the trial and available to include in the logistic model. This is unlikely to be the case in any practical application, and the question is therefore to what extent any omitted variable bias is likely to be significant. Also, the method may be unstable if few individuals remain uncensored in some patient subgroups as defined by the covariates in the logistic regression (i.e. low effective sample size).

The IPCW method was summarised as follows (Source: Celgene submission, Section 5.3.5, pp. 124–125):

> *Patients who switch treatments are artificially censored at the time of switching, and observations for the remaining patients are weighted to adjust for censored patients. A pooled logistic model is constructed to predict the probabilities of remaining uncensored-by informative censoring (crossover) at each measurement point and must include all baseline or post-randomization variables that predict both treatment switching and outcome. Briefly, the procedure for estimation using IPCW is as follows[52, 57]:*
>
> *1. Panel data are created for the pooled logistic models. The follow-up period is partitioned into intervals based on follow-up measurement points (visit dates). At each measurement point, time-dependent variables that could predict treatment discontinuation, switching, and OS are assessed for all patients.*
>
> *2. The probability of remaining uncensored is calculated. A logistic regression model is fitted to predict participation at each measurement (remaining uncensored) for each subject. The probability of remaining uncensored using baseline risk factors of interest (E) is estimated, as is the probability P of remaining uncensored using both baseline risk factors of interest (E) and time-dependent covariates (Z). The results of this modelling process are summarized to describe the factors associated with participation at each procedure.*
>
> *3. IPCWs are calculated: the inverse probability weight for remaining uncensored (1/P) will consist of the probability for remaining uncensored estimated in step 2, using both covariates E and Z. This inverse probability is stabilized by multiplying it by the probability for remaining uncensored using covariates.*
>
> *4. A standard Cox regression (i.e., in accordance with estimation with no crossover) is fitted for the current outcome using 1/P as weights. The set of covariates E and any other appropriate adjustment covariates for that outcome may also be included in a parametric regression approach. The weighted Cox regression is fitted using stabilized weights (S/P). Standard errors are corrected using sandwich estimation or bootstrapping methods.*
>
> *5. An unweighted version of the Cox regression is fitted for comparison. The same models are fitted as in step 3 but without any sampling weights.*
>
> *Preliminary reviews of the data suggested that subsequent use of azacitidine often closely followed relapse or progression. The model constructed had relatively short time periods (15 days) in order to capture this association. This model was constructed using the status of patients at 15 day time points. The last time period for each study subject usually contained less than 15 days.*

The "numerator" model in the pooled logistic model consisted of baseline factors and the "denominator" model consisted of baseline factors and time-varying covariates. This method provides an estimate of the adjusted HR of survival for the CCR arm in relation to the azacitidine arm but does not generate an estimate of the survival distribution (i.e., does not produce a KM curve). However, a crude estimate of the survival distribution can be obtained by applying the estimated HR to the azacitidine KM curve; this will result in an estimated CCR survival curve with a similar profile (shape) to the azacitidine curve. Similarly, the converse of the HR can be used as an estimate of the median of the adjusted survival distribution for CCR – the actual estimated values are indicative only and will reflect the estimated distribution based on the distribution of the azacitidine KM curve.[58]

Baseline characteristics and time-varying variables were captured during the trial and were used in step 2 of the IPCW method in order to estimate the probabilities of remaining uncensored or having no subsequent use of azacitidine. These variables were assessed by a clinician to establish which factors would be considered relevant and appropriate for use in the crossover analysis models, and whether any of the laboratory variables collected at each visit were relevant for analysis of survival data, either as factors that influence the change in treatment or as factors that could affect the estimate of survival.

Statistical tests were then conducted to assess whether there were any statistically significant differences between CCR patients who switch and CCR patients who do not switch for the list of potential covariates to be included in the model. Means and standard deviations were calculated for numerical variables and counts and percentages for categorical variables for all patients, but also separately for patients who were censored or died. P values were determined using chi-square test for categorical variables and Student's t-test for numerical variables.

The covariates included initially in the model, are presented in [Table 21]. These were summarized by basic summary statistics (number and percentages for categorical variables and means and standard deviations for numerical variables).

Table 21: Covariates used in the company's IPCW analysis

Type of variable	Variable
Non time-varying covariates	
Demographic characteristics	Age at informed consent (continuous)
	Age (<75 years, ≥75 years)
	Sex (male or female)
	Geographic region (North America/Australia, Western Europe/Israel, Eastern Europe, or Asia)
	Race (Asian, Black or African American, White, Native Hawaiian or other Pacific islander, other, n/a)
Clinical characteristics	ECOG performance status at randomization (0–1, 2)
	AML classification (newly diagnosed, histologically confirmed de novo AML; AML secondary to prior myelodysplastic disease not treated with azacitidine, decitabine, or cytarabine; AML secondary to exposure to potentially leukemogenic therapies or agents with the primary malignancy in remission for at least 2 years)
	Time since initial AML diagnosis to randomization (< median; ≥ median) (derived from time since initial diagnosis and date of signed informed consent)
	Baseline comorbidity score
	Prior history of myelodysplastic syndromes (yes or no)
	Cytogenetic risk status (intermediate risk, poor risk)
Study design	Pre-randomization CCR assignment (BSC, low-dose cytarabine, intensive chemotherapy)
	International working group response assessment
Laboratory variables	Percentage bone marrow blasts (continuous) according to central review
Time-varying covariates	
Laboratory variables	WBC count
	Haemoglobin
	Platelet count
	ANC
	RBC transfusion status (independent or dependent)
	Platelet transfusion status (independent or dependent)
Adverse events	Occurrence of a grade 3/4 adverse event since last visit (yes/no)
Other	Time since last visit (in months; included at each visit)

Key: ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group; RBC, red blood cell; WBC, white blood cell

Source: Celgene submission, Table 37, p. 125

In relation to the statement that "this method provides an estimate of the adjusted HR of survival for the CCR arm in relation to the azacitidine arm but does not generate an estimate of the survival distribution (i.e., does not produce a KM curve)," the ERG notes that this statement is incorrect, because survival curves for both trials arm may be generated from the IPCW analysis. The respective figure is produced by ERG in *Figure 8* (*page 62*) using individual patient data provided by Celgene.

ERG also consulted clinical experts on whether there were any variables missing from *Table 21* that may be considered to predict or explain the use of subsequent therapy and at the same time be associated with survival prognosis. The clinical experts did not suggest any additional variables.

In arriving at their preferred base case method the company also considered other approaches, including not adjusting for treatment switching, censoring at switch, and the Rank Preserving Structural Failure Time Model (RPSFTM) and the Iterative Parameter Estimation (IPE). Celgene considered the RPSTFM and IPE approaches as involving a fundamental assumption (i.e., that the treatment effect of azacitidine is the same for patients who received it as initially randomly allocated therapy as for patients who received it as subsequent treatment) that is unlikely to be valid. The company stated (Source: Celgene submission, Section 5.3.5, p. 123):

> *These limits notwithstanding, the IPCW method and results are stronger than the alternatives. The use of RPSFT and IPE methods has an underlying assumption of a common treatment effect for patients who started treatment with azacitidine and for those who switched to azacitidine. This assumption does not hold in this case: differences in prognosis between the two groups are likely to lead to a different benefit from delayed versus immediate treatment; CCR itself, particularly LDAC and IC, is also an active treatment, so the prognosis of a patient switching from CCR will not be the same as for a patient receiving azacitidine from the start of the study.*
>
> *The similarity of the results for the IPE and RPSFT analyses is likely because of violation of the key assumption, that treatment benefit in terms of OS is the same regardless of whether a patient began on azacitidine or switched; this assumption is hard to justify given the prognosis for with AML in the trial.*

In addition, Celgene reported the attempt to use of two-stage methods,[51] which could not be implemented due to insufficient numbers of subsequent treatment users in the CCR arm and recorded data (Source: Celgene appendices to submission, Appendix 11, Section 4.7).

Similarly to the IPCW method, the censor-at-switch method dropped the data after the start of azacitidine in the CCR trial arm, but unlike IPCW it did not apply any adjustment to the remaining data for the differences in probability of censoring (azacitidine) across CCR arm patients. Thus, to the extent that the estimates from the two methods differ (provided IPCW is validly in this application), would suggest that azacitidine was not given to CCR patients at random (as one would expect). As it transpires, Celgene reported hazard ratio estimates from Cox proportional hazards models of [redacted] for both the IPCW and censor-at-switch methods, suggesting that adjusting for non-random subsequent therapy use is not important in this case (see also the critique of treatment switching in the clinical effectiveness *Section 4.3*).

5.2.5.2 Summary of methods of effectiveness estimation and extrapolation

In response to ERG's request to confirm the methods used to calculate different survival curves in the model, and whether the curves for relapse-free survival and progression-free survival were fitted to azacitidine (AZA) and conventional care regimen (CCR) patients with a proportional-hazards azacitidine treatment variable, or if these were fitted only to CCR patients, Celgene provided the following information:

> *The following methods were used to calculate different survival curves. The curves for RFS and PFS were fitted only to CCR patients.*

Table 22: Methods used to calculate survival curves in the model submitted by Celgene

Arm	AZA	CCR
Overall survival		
Underlying data	OS from AZA	OS from AZA
Curve fitting	Exponential	Exponential
Adjustments	—	HR of [redacted] from IPCW method (inverse HR)
Relapse-free survival		
Underlying data	EFS for CCR patients achieving CR or CRi	EFS for CCR patients achieving CR or CRi
Curve fitting	Weibull	Weibull
Adjustments	HR of 0.84 from curve fitting	—
Progression-free survival		
Underlying data	EFS for CCR patients not achieving CR or CRi	EFS for CCR patients not achieving CR or CRi
Curve fitting	Gompertz	Gompertz
Adjustments	HR of 0.85 from curve fitting	—

Key: AZA, azacitidine; CCR, conventional care regimen; CR, complete remission; CRi, complete remission with incomplete blood count recovery; EFS, event-free survival; HR, hazard ratio; IPCW, inverse probability of censoring weights

5.2.6 Health-related quality of life

Health effects were measured in QALYs in accordance with the NICE reference case.

Utilities were estimated from response status. They were mapped from trial-based EORTC QLQ-C30 data using published algorithms (Source: Celgene submission, Section 5.4, p. 127). Two mapping algorithms were incorporated in the model, one reported by Proskorovsky et al. 2014,[59] which was used for the base case, and the other by McKenzie and Van der Pol, 2009,[60] used for a scenario analysis. The algorithms are presented in Celgene's Submission, Table 40 (p. 128) and the corresponding utility values are shown in *Table 23*.

Table 23: Summary of utility values for Celgene's economic evaluation

Health state	Calculation method	
	Proskorovsky et al. 2014[59] *(base case)*	*McKenzie and Van der Pol 2009*[60] *(scenario analysis)*
Remission (CR/CRi)	0.7707	0.7400
Non-remission (PR, SD)	0.7160	0.6574
Post-progression/relapse (PD)	0.6233	0.5680
Grade 3+ AEs	−0.0240	−0.0207

Key: AE, adverse event; CR, complete remission; CRi, morphologic complete remission with incomplete blood count recovery; PD, progressive disease; PR, partial remission' SD, stable disease
Source: Celgene submission, Table 41, p. 129

The model accounts for disutility associated with overall grade 3 or above treatment-emergent adverse events (TEAEs) (Source: Celgene submission, Table 41, p. 129). The EORTC QLQ-C30 data used to map the EQ-5D utility for TEAEs are from patients who were hospitalised with and without grade 3 or higher TEAEs in the AZA-AML-001 trial.

Adverse event-related QALYs were calculated by (Source: Celgene submission, Section 5.4.3, p. 129):

> *[Multiplying the probability of at least one TEAE occurring] by its duration in days, then multiplying the result by the day equivalent of the HSUV.*

5.2.7 Resources and costs

5.2.7.1 Drug acquisition

Drug utilization was estimated directly from the AZA-AML-001 trial.

Total drug use per cycle per patient (*Table 24*) was calculated by multiplying the number of vials per day per patient, the cost of one vial (*Table 25*) and the mean number of treatment days per cycle (*Table 26*).

The number of vials per day per patient was based on the average daily dose (*Table 24*) and the assumption on vial sharing, i.e., no wastage, full wastage or wastage with 30% tolerance.

For azacitidine, IC and LDAC treatments, the average daily dose was estimated from the average daily dose in mg/m² (*Table 24*) and the average body surface area (BSA) of 1.80 m². However, according to the CSR, the daily dose for LDAC treatment should have been estimated in mg/day (further details are provided in *Section 5.3.8*, *page 122*).

Table 24: Drug utilisation per cycle (4 weeks) for no wastage scenario

Treatment	Medications	Daily dose (mg/m^2)	Days per cycle	Total Dose (mg) per cycle
Azacitidine	Azacitidine	[redacted]	[redacted]	[redacted]
IC, induction	Cytarabine	122.20	7.10	1,561.72
	Daunorubicin[a]	49.70	3.00	268.38
	Idarubicin[a]	11.00	3.00	59.40
IC, consolidation	Cytarabine	120.20	5.00	1,081.80
	Daunorubicin[a]	49.40	2.00	177.84
	Idarubicin[a]	10.70	2.00	38.52
LDAC	Cytarabine	84.05	10.22	696.65

Key: IC, intensive chemotherapy; LDAC, low-dose cytarabine
Notes: a, Use of anthracycline in the trial comprised 50% idarubicin and 50% daunorubicin
Source: Celgene submission, Table 42, p. 131

Full wastage (i.e., no vial sharing) was assumed in the base case, and alternative scenarios of no wastage and wastage with 30% tolerance (i.e., vial sharing assumed in 30% of cases) were explored in sensitivity analyses.

For drugs with several vial or pack sizes, vial size selection was on the basis of the largest available size, rather than smaller vials as required to minimize vial wastage. The number of vials for each drug was not reported in the company's submission, but was available from their executable model.

Drug acquisition unit costs, presented in *Table 25*, were estimated from British National Formulary (BNF).[61]

Table 25: Drug acquisition unit costs

Drug name	Vial or pack	mg per vial or pack	Price (£) per vial/pack
Azacitidine	100 mg vial	100	[redacted]
Cytarabine (non-proprietary)	20 mg/mL; 5 mL vial or 100 mg/mL; 1 mL vial	100	4.95[a]
	20 mg/mL; 25 mL vial or 100 mg/mL; 5 mL vial	500	19.75[a]
	100 mg/mL; 10 mL vial	1000	39
	100 mg/mL; 20 mL vial	2000	77.5
Daunorubicin (non-proprietary)	20 mg vial	20	55
Idarubicin (Zavedos®)	5 mg vial	5	87.36
	10 mg vial	10	174.72

Notes: a, Average of two prices
Sources: Celgene submission, Table 43, p. 132; BNF 2015

Table 26: Drug acquisition cost per cycle

Treatment		Total drug cost per cycle per patient (£)		
		No wastage	*Wastage*	*Wastage with 30% tolerance*
Azacitidine		[redacted]	[redacted]	[redacted]
IC, induction	Cytarabine	£77	£105	£77
	Daunorubicin[a]	£738	£825	£738
	Idarubicin[a]	£1,038	£1,048	£1,038
IC, consolidation	Cytarabine	£54	£75	£54
	Daunorubicin[a]	£550	£489	£489
	Idarubicin[a]	£673	£699	£673
LDAC	Cytarabine	£34	£48	£34

Key: IC, intensive chemotherapy; LDAC, low-dose cytarabine
Notes: a, Average of two prices
Source: Celgene submission, Table 44, p. 132

The total cost of drug acquisition was estimated from the per-cycle cost of drugs and setting the maximum number of treatment cycles equal to the average number of treatment cycles shown in *Table 27*.

Table 27: Mean number of treatment cycles in the AZA-AML-001 trial

Treatment		Mean number of cycles per patient
Azacitidine		8.80
IC, induction	Cytarabine	1.00
	Daunorubicin[a]	1.00
	Idarubicin[a]	1.00
IC, consolidation	Cytarabine	1.00
	Daunorubicin[a]	1.00
	Idarubicin[a]	1.00
LDAC	Cytarabine	5.21
BSC		3.60

Key: BSC, best supportive care; IC, intensive chemotherapy; LDAC, low-dose cytarabine
Notes: a, 1:1 ratio was assumed for patients on daunorubicin and idarubicin
Source: Celgene submission, Table 45, p. 133

5.2.7.2 Drug administration

Health-care resource use (HCRU) for each model state is reported in Celgene's submission, Section 5.5.3 (p. 133).

Unit costs for health professionals, used in the model, are from Personal Social Service Research Unit (PSSRU) and NHS reference costs (*Table 28*).

Table 28: Unit costs for each item of healthcare resource use

Staff type	Unit costs available 2013/2014 (costs including qualifications given in brackets)	Cost per minute (per day for inpatient stay)
CNS Haematologist	Nurse advanced (includes lead specialist, clinical nurse specialist, senior specialist). £51 (£58) per hour; £80 (£90) per hour client contact cost	£1.33
Consultant	Consultant: medical, £101 (£140) per contract hour	£1.68
Day Care Nurse	Nurse, day ward (includes staff nurse, registered nurse, registered practitioner), £34 (£41) per hour; £84 (£100) per hour of patient contact	£1.40
Day Care Specialist registrar	Registrar group, £40 (£60) per hour (48 hour week); £34 (£51) per hour (56 hour week); £48 (£71) per hour (40 hour week)	£0.80
District Nurse	Community nurse (includes district nursing sister, district nurse), £43 (£50) per hour; £57 (£66) per hour of patient-related work.	£0.95
Doctor	Associate specialist, £97 (£124) per hour (40 hour week). An associate specialist is a doctor who has trained and gained experience in a medical or surgical specialty but has not become a consultant.	£1.62
Jnr. Doctor	Foundation house officer 2, £29 (£41) per hour (48 hour week); £25 (£35) per hour (56 hour week); £35 (£49) per hour (40 hour week)	£0.58
Pharmacist	Hospital pharmacist, £42 (£48) per hour; £84 (£96) per cost of direct clinical patient time (includes travel); £60 (£68) per cost of patient-related activities.	£1.40
Oncology nurse	Nurse team leader (includes deputy ward/unit manager, ward team leader, senior staff nurse), £42 (£48) per hour; £104 (£120) per hour of patient contact	£1.73
Inpatient stay for IC (cost/day)	Average of "Elective Inpatients - Excess Bed Days", "Non-Elective Inpatients - (Long Stay) Excess Bed Days", "Day Case", "Non-elective Inpatients - Short Stay", "Regular Day or Night Admissions"	£714.64

Key: CNS, clinical nurse specialist; SpR, specialist registrar; PSSRU, Personal Social Services Research Unit; IC, intensive chemotherapy

Sources: Celgene submission, Table 48, p. 136; PSSRU Unit costs of health and social care 2014[62]; NHS Reference costs

The frequency (*Table 29*) and mean time in minutes of health professionals involved during different health states (*Table 30*) were estimated from a healthcare resource use questionnaire developed by Celgene (Celgene's appendices to submission, Appendix 12).

Table 29: Healthcare resource use (frequency per cycle) for each health state

Healthcare resouce	Induction/pre-response		Remission		Stable disease		Progressive disease	
	AZA	*CCR*	*AZA*	*CCR*	*AZA*	*CCR*	*AZA*	*CCR*
CNS Haematologist	2.77	2.38	1.66	0.87	2.08	2.37	2.03	2.62
Consultant	2.58	3.52	0.92	1.13	1.29	1.66	2.03	1.60
Day Care Nurse	7.75	2.35	5.54	0.95	6.00	3.41	3.69	3.47
Day Care SpR	1.66	5.16	1.11	2.07	1.66	2.85	2.95	2.95
District Nurse	0.62	5.39	0.31	5.61	0.62	6.33	0.62	0.59
Doctor	0.85	4.95	1.23	2.21	1.54	3.04	0.92	0.88
Jnr. Doctor	0.23	17.11	0.62	21.75	2.54	17.31	2.77	2.64
Pharmacist	2.77	3.09	2.77	1.78	2.95	1.37	0.31	0.42
Oncology nurse	0.62	2.17	0.31	0.05	0.62	0.50	0.62	0.59
Inpatient day	3.16	13.91	0.25	0.90	2.30	9.20	1.73	2.61

Key: AZA, azacitidine; CCR, conventional care regimens; CNS, clinical nurse specialist; SpR, specialist registrar
Source: Celgene submission, Table 46, p. 134

Table 30: Healthcare resource use (mean time in minutes per frequency) for each health state

Healthcare resource	Induction/pre-response		Remission		Stable disease		Progressive disease	
	AZA	*CCR*	*AZA*	*CCR*	*AZA*	*CCR*	*AZA*	*CCR*
CNS Haematologist	34.20	25.51	26.40	25.85	33.00	37.23	24.40	34.20
Consultant	25.60	20.33	20.80	16.29	24.00	16.97	20.80	25.60
Day Care Nurse	40.72	22.99	18.40	3.91	26.83	27.55	33.00	40.72
Day Care SpR	22.00	19.82	22.00	17.79	22.00	19.08	22.00	22.00
District Nurse	15.00	13.87	15.00	4.26	15.00	17.31	15.00	15.00
Doctor	12.67	13.00	12.67	9.79	12.67	12.10	9.00	12.67
Jnr. Doctor	9.00	16.01	15.00	0.94	20.00	10.76	12.67	9.00
Pharmacist	13.50	25.64	13.50	0.71	13.50	19.68	6.00	13.50
Oncology nurse	6.00	11.68	4.00	0.00	6.00	4.55	6.00	6.00
Inpatient day	1,440	1,440	1,440	1,440	1,440	1,440	1,440	1,440

Key: AZA, azacitidine; CCR, conventional care regimens; CNS, clinical nurse specialist; SpR, specialist registrar
Source: Celgene submission, Table 47, p. 135

Monitoring and testing requirements for different disease states are captured in the same questionnaire (Celgene appendices to submission, Appendix 12). The number of drug monitoring tests per cycle is shown in *Table 31*, and the unit costs in *Table 32*.

Table 31: Healthcare resource use (number of tests per cycle) for drug monitoring tests

Monitoring test	Induction/pre-response		Remission		Stable disease		Progressive disease	
	AZA	*CCR*	*AZA*	*CCR*	*AZA*	*CCR*	*AZA*	*CCR*
Bone marrow aspirates	0.92	1.25	0.15	0.21	0.42	0.35	0.15	0.16
Bone marrow biopsies	0.50	0.41	0.00	0.00	0.04	0.08	0.00	0.03
Peripheral blood smears	1.08	1.01	0.77	0.59	0.77	0.83	0.77	0.74
Blood tests	9.23	13.29	1.85	3.53	6.54	7.82	7.23	8.33
DNA and RNA extractions for molecular testing	0.92	1.24	0.15	0.15	0.15	0.20	0.15	0.15
Extractions for cytogenetic testing	0.92	0.80	0.15	0.16	0.15	0.19	0.15	0.13
Serum blood chemistry	8.46	12.00	1.69	3.53	6.38	7.72	6.92	7.74

Key: AZA, azacitidine; CCR, conventional care regimens; DNA, deoxyribonucleic acid; RNA, ribonucleic acid
Source: Celgene submission, Table 49, p. 137

Table 32: Unit costs for drug monitoring tests

Laboratory and disease monitoring tests	HRG (Description)	Cost per test
Bone marrow aspirates	DAPS04 (Clinical Biochemistry, National average cost)	£1.18
Bone marrow biopsies	DAPS04 (Clinical Biochemistry, National average cost)	£1.18
Peripheral blood smears	DAPS05 (Haematology, National average cost)	£3.00
Blood tests	DAPS05 (Haematology, National average cost)	£3.00
DNA and RNA extractions for molecular testing	DAPS04 (Clinical Biochemistry, National average cost)	£1.18
Extractions for cytogenetic testing	DAPS01 (Cytology, National average cost)	£7.77
Serum blood chemistry	DAPS04 (Clinical Biochemistry, National average cost)	£1.18

Key: DNA, deoxyribonucleic acid; HRG, healthcare resource group; RNA, ribonucleic acid
Source: Celgene submission, Table 50, p. 137; NHS reference costs 2013–14

Red blood cell and platelet transfusions were also included in the model (*Table 33*).

Table 33: Unit cost and resource use (number of transfusions per cycle) of transfusions

Transfusion type	Induction/pre-response		Remission		Stable disease		Progressive disease		Unit cost (per transfusion)
	AZA	*CCR*	*AZA*	*CCR*	*AZA*	*CCR*	*AZA*	*CCR*	
Red blood cells	3.62	3.40	0.15	0.72	3.00	3.05	4.55	4.78	£121.85[63]
Platelets	4.54	3.63	0.15	0.48	3.92	3.46	5.70	5.85	£193.15[64]

Key: AZA, azacitidine; CCR, conventional care regimens
Source: Celgene submission, Table 51, p. 138

5.2.7.3 Adverse events

The cost of managing AEs was calculated as a cost per patient, based on the arithmetic average cost for managing grade 3 or 4 TEAEs in the AZA-AML-001 trial such as anaemia, neutropenia, febrile neutropenia, thrombocytopenia, pneumonia, and worsening AML (not qualifying as a progression or relapse event); the cost are shown in *Table 34*.

Table 34: Costs of managing adverse events (≥ grade 3)

Adverse Event	Cost per inpatient episode	Source
Anaemia Neutropenia Febrile neutropenia	£341.69	SA08J (Other Haematological or Splenic Disorders, with CC Score 0-2)[a]
Thrombocytopenia	£316.46	SA12K (Thrombocytopenia with CC Score 0-1)[a]
Pneumonia	£143.64	WF01A Service Code 300 (Consultant-led outpatient attendance, General Medicine, Non-Admitted Face to Face Attendance, Follow-up)[b]
Acute myeloid leukaemia	£377.01	SA25M (Acute Myeloid Leukaemia with CC Score 0-1)[a]
Grade ≥ 3 TEAEs	£310.36	Average

Key: CC, complications and comorbidities; TEAE, treatment-emergent adverse event
Notes: a, Unit day case cost; b, National unit cost
Sources: Celgene submission, Table 52, p. 139; National schedule of reference costs 2013-14

5.2.8 Cost-effectiveness results

Base-case results are shown in *Table 35*. Estimated cost per QALY reported by Celgene is £20,648.

Table 35: Base case results of the company's model

Arm	Total			Incremental			ICER (cost per QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
CCR	£40,608	0.9041	0.6365	—	—	—	—
Azacitidine	[redacted]	1.1820	[redacted]	[redacted]	0.2779	[redacted]	£20,648

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CCR; conventional care regimens

Disaggregated results are shown in *Table 36*, *Table 37* and *Table 38*.

Table 36: Health outcomes (QALYs) by health state in the company's model

Health state	Azacitidine	CCR	Incremental QALYs	Contribution to total incremental QALYs
RFS	[redacted]	0.2312	[redacted]	[redacted]
PFS	[redacted]	0.2725	[redacted]	[redacted]
PD	[redacted]	0.1328	[redacted]	[redacted]
Total	[redacted]	0.6365	[redacted]	[redacted]

Key: CCR, conventional care regimens; PD, progressive disease; PFS, progression-free survival; QALY, quality-adjusted life year; RFS, relapse-free survival
Notes: Figures may not add due to rounding

Table 37: Costs by health state in the company's model

Health state	Azacitidine	CCR	Incremental costs	Contribution to total incremental costs
RFS	[redacted]	£6,503	[redacted]	[redacted]
PFS	[redacted]	£22,235	[redacted]	[redacted]
PD	[redacted]	£6,260	[redacted]	[redacted]
Terminal care	[redacted]	£5,609	[redacted]	[redacted]
Total	[redacted]	£40,608	[redacted]	[redacted]

Key: CCR, conventional care regimens; PD, progressive disease; PFS, progression-free survival; RFS, relapse-free survival
Notes: Figures may not add due to rounding

Table 38: Costs by component in the company's model

Cost component	Azacitidine	CCR	Incremental costs	Contribution to total incremental costs
Drug acquisition	[redacted]	£370	[redacted]	[redacted]
Drug administration	[redacted]	£23,316	[redacted]	[redacted]
Tests to monitor disease	[redacted]	£157	[redacted]	[redacted]
Transfusion	[redacted]	£4,624	[redacted]	[redacted]
Management of AEs	[redacted]	£269	[redacted]	[redacted]
BSC/Monitoring costs	[redacted]	£6,260	[redacted]	[redacted]
Terminal care	[redacted]	£5,609	[redacted]	[redacted]
Total	[redacted]	£40,608	[redacted]	[redacted]

Key: AEs, adverse events; BSC, best supportive care; CCR, conventional care regimens; PD, progressive disease; PFS, progression-free survival; RFS, relapse-free survival
Notes: Figures may not add due to rounding

5.2.8.1 Subgroup analyses

Celgene presented cost-effectiveness results for two subgroups: patients with poor-risk cytogenetics (*Table 39*) and patients with MDS related changes (*Table 40*). For these subgroups, analysis was performed without adjustment for subsequent active treatment.

Table 39: Results for patients with poor-risk cytogenetics

Arm	Total			Incremental			ICER (cost per QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
CCR	£46,683	0.6607	0.4567	—	—	—	—
Azacitidine	[redacted]	1.1855	[redacted]	[redacted]	0.5248	[redacted]	£20,227

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CCR; conventional care regimens
Source: Celgene submission, Table 63, p. 158

Table 40: Results for patients with MDS related changes

Arm	Total			Incremental			ICER (cost per QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
CCR	£50,098	0.9459	0.6583	—	—	—	—
Azacitidine	[redacted]	1.4050	[redacted]	[redacted]	0.4591	[redacted]	£19,175

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CCR; conventional care regimens
Source: Celgene submission, Table 64, p. 158

5.2.9 Sensitivity analyses

Celgene performed deterministic and probabilistic sensitivity analyses to estimate the effect of uncertainty in model parameters on the ICER.

5.2.9.1 Univariate sensitivity analyses

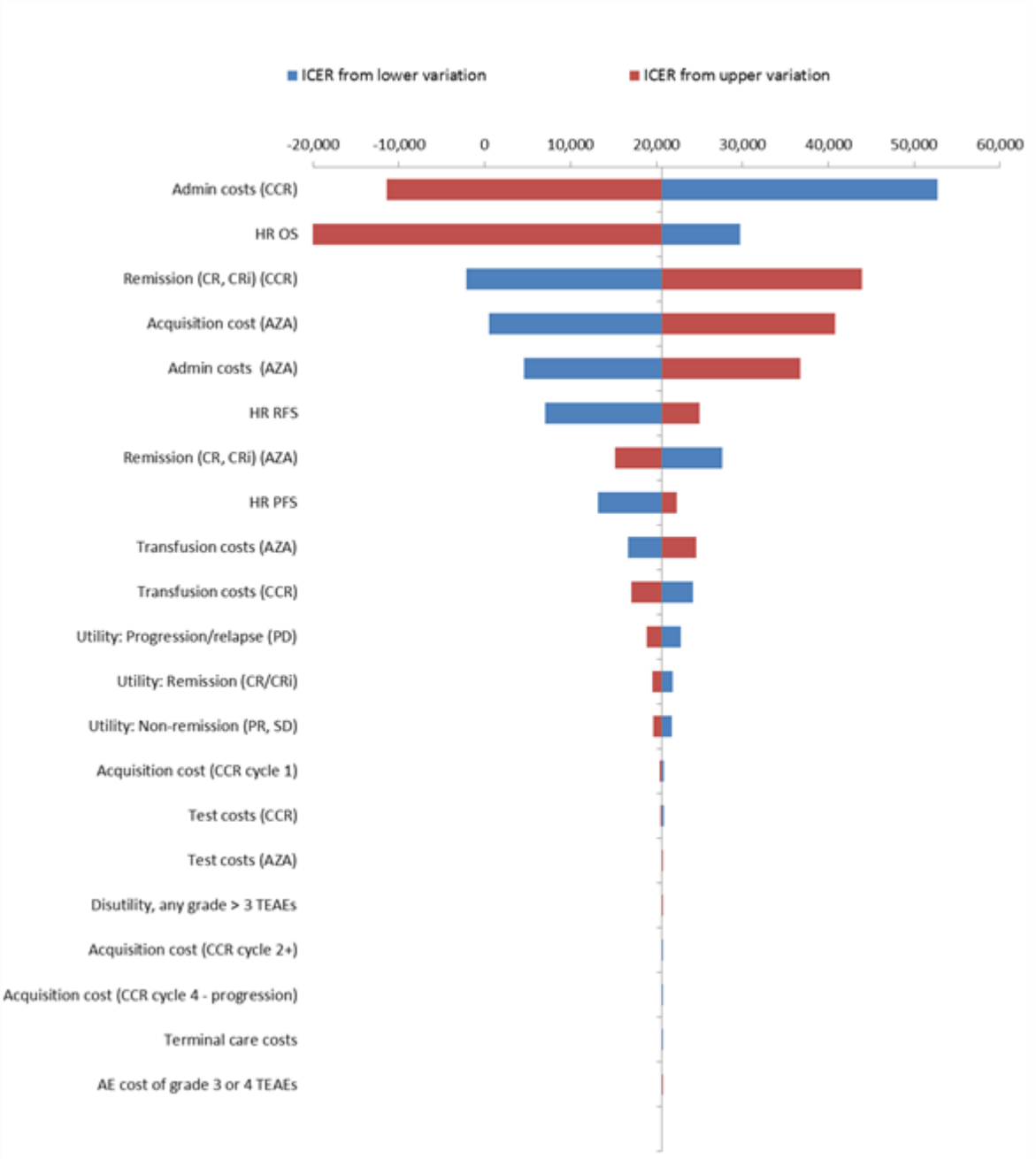
One-way SA is a form of deterministic sensitivity analysis in which one parameter value is varied while keeping all other parameter values constant, to investigate the impact of individual parameters on the base case ICER.

In the model, the base case values of the following parameters were varied by ±20% or around a confidence interval (for HRs) to evaluate this impact:

- Drug utilization costs;
- Drug administration costs;
- Drug monitoring cost (transfusion and tests);
- BSC/palliative care costs;
- HRs;
- Safety;
- Response rate;
- Health state utility values.

A tornado diagram demonstrating the results of the univariate sensitivity analyses is shown in *Figure 13*.

Figure 13: Tornado diagram of company's deterministic sensitivity analyses



Key: AZA, azacitidine; CCR, conventional care regimens; CR, complete remission; CRi, complete remission with incomplete blood count recovery; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PD, progressive disease; RFS, relapse-free survival; SD, stable disease; TEAE, treatment-emergent adverse events

Source: Celgene submission, Figure 34, p. 152

5.2.9.2 Probabilistic sensitivity analysis

The manufacturer performed second-order Monte Carlo simulations by randomly drawing from all predefined parameter distributions simultaneously and computed incremental costs and health outcomes for the random variates. The results were plotted as X-Y scatter plot and cost-effectiveness acceptability curves where the "willingness to pay" is plotted against the proportion of runs that resulted in incremental cost-effectiveness ratios below this

willingness to pay. The parameter distributions used for the probabilistic sensitivity analysis are reported in *Table 41*.

Table 41: Distributions used in the company's probabilistic sensitivity analysis

Beta distribution	Gamma distribution
• Response rate • HSUVs • HSUVs for adverse events • Incidence of adverse events	• Patients' weights and heights • Drug usage and number of treatment cycles • Healthcare resource use

Key: HSUV, health state utility value
Source: Celgene submission, Table 59, p. 148

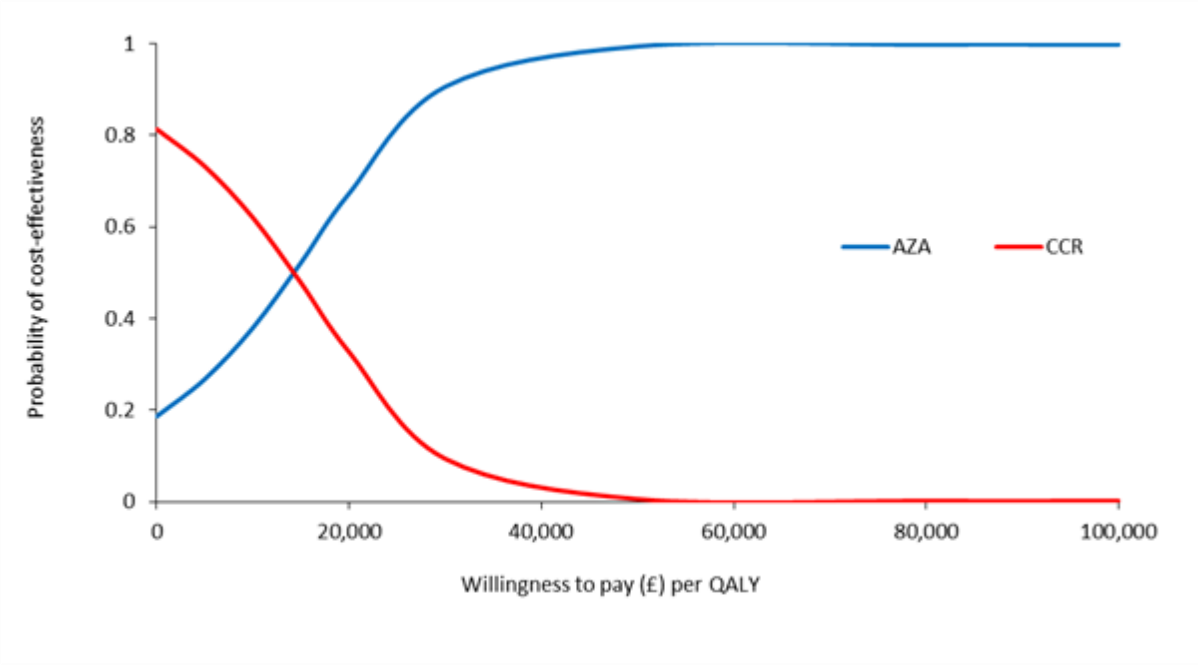
Point estimates and 95% uncertainty intervals from PSA are reported in *Table 42*. Cost-effectiveness acceptability curves are shown in Figure 14, and show that at cost-effectiveness thresholds of £20,000, £30,000 and £50,000 per QALY, azacitidine was cost-effective versus CCR in 69.9%, 90.8% and 99.6% of iterations respectively.

Table 42: Results of the company's submitted probabilistic sensitivity analysis

Arm	Total (95% CI)			Incremental			ICER (cost per QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
CCR	£41,429 (£34,562, £49,698)	0.9073 (0.6970, 1.1358)	0.6386 (0.5047, 0.7924)	—	—	—	—
AZA	[redacted]	1.1824 (1.0337, 1.3468)	[redacted]	[redacted]	0.2751	[redacted]	£17,423

Key: AZA, azacitidine; CCR, conventional care regimens; CI, confidence interval; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life year
Source: Celgene submission, Table 60, p. 149

Figure 14: Cost-effectiveness acceptability curves in the company's probabilistic sensitivity analysis



Key: AZA, azacitidine; CCR, conventional care regimens; QALY, quality-adjusted life year
Source: Celgene submission, Figure 33, p. 151

5.2.9.3 Scenario analyses

Celgene presented the results of the following scenario analyses (Source: Celgene submission, section 5.8.3, p. 154):

> *KM curves for RFS, PFS and OS*
>
> *OS data unadjusted for treatment-switching*
>
> *OS using the censor at switch population*
>
> *EQ-5D based on the mapping algorithm from McKenzie et al*
>
> *Vial Sharing*
>
> *Vial sharing in 30% of cases*
>
> *1 year and 5 year time horizons*
>
> *Discount rate at 1.5% and 6%*
>
> *Individual treatment arms with adjustment for subsequent therapies*
>
> *Individual treatment arms without adjustment for subsequent therapies*

Celgene also conducted a scenario analysis in which the proportion of patients assigned to each CCR arm was estimated from HMRN registry data (IC, [redacted]; LDAC, [redacted]; BSC, [redacted]). A weighted average ICER was calculated by multiplying the total costs and QALYs from the individual CCR and azacitidine arms (azacitidine results from individual arms not CCR population) by these proportions and then summing the resulting totals.

The results of the scenario analyses are shown in *Table 43*.

Table 43: Results of the company's scenario analyses

Scenario		Incremental			ICER (cost per QALY)[a]
		Costs	LYG	QALYs	
Base case		[redacted]	0.2779	[redacted]	£20,648
KM curves for RFS, PFS and OS		[redacted]	0.1485	[redacted]	£32,393
OS data unadjusted for treatment-switching		[redacted]	0.3630	[redacted]	£11,537
OS using the censor at switch population		[redacted]	0.8309	[redacted]	£10,397
EQ-5D based on the mapping algorithm from McKenzie et al.[60]		[redacted]	0.2779	[redacted]	£22,243
Vial sharing		[redacted]	0.2779	[redacted]	-£13,300
Vial sharing in 30% of cases		[redacted]	0.2779	[redacted]	-£9,323
Time Horizon	1 year	[redacted]	0.0791	[redacted]	£30,305
	5 year	[redacted]	0.2673	[redacted]	£20,860
Discount Rate	1.50%	[redacted]	0.2861	[redacted]	£20,604
	6%	[redacted]	0.2685	[redacted]	£20,704
Individual treatment arms with adjustment for subsequent therapies	IC	[redacted]	0.3759	[redacted]	-£52,184
	LDAC	[redacted]	0.2729	[redacted]	£25,136
	BSC	[redacted]	0.2095	[redacted]	-£169,672
Individual treatment arms without adjustment for subsequent therapies	IC	[redacted]	0.2449	[redacted]	-£85,266
	LDAC	[redacted]	0.2600	[redacted]	£41,671
	BSC	[redacted]	0.3386	[redacted]	-£50,300
Use of individual treatment arm proportions from the HMRN registry with adjustment for subsequent therapies		[redacted]	0.2665	[redacted]	-£57,756
Use of individual treatment arm proportions from the HMRN registry without adjustment for subsequent therapies		[redacted]	0.2874	[redacted]	-£20,218

Key: BSC, best supportive care; EQ-5D, EuroQol Five Dimensions; HMRN, Haematological Malignancy Research Network; IC, intensive chemotherapy; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LDAC, low dose cytarabine; LYG, life years gained; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; RFS, relapse-free survival
Note: a, Negative ICER indicates that azacitidine is dominant
Source: Celgene submission, Table 62, p. 156

5.2.10 Model validation and face validity check

The manufacturer performed the following model validation and verification.

Model structure and assumptions were assessed at four levels (Source: Celgene submission, Section 5.9.1, p. 159):

> *An internal clinical validation was performed by PRMA Consulting's Senior Medical Director, Professor Deborah Saltman.*

> *PRMA Consulting's senior management and expert health economists performed an internal validation.*
>
> *The validity of the model was confirmed by Professor Stephen Palmer, an external technical advisor with extensive experience of NICE HTAs.*
>
> *Externally, two UK clinical oncologists validated the model structure and key assumptions; one of them also validated HCRU inputs (types of HCRU involved) and model outputs on effectiveness.*
>
> *The model was also reviewed by the Celgene team.*

Technical validity was ensured by performing model checks reported in *Table 44*.

Table 44: Checklist used to check the model inputs and results

Check	Purpose
Set discount rate to 0	To confirm that discounted and non-discounted results are equal
Set main HSUVs to 0	To confirm that QALYs are zero, or can be explained by utility decrements associated with adverse events
Set all HSUVs to 1	To confirm that LYs are equal to QALYs, or that any difference can be explained by utility decrements associated with adverse events
Set drug costs to 0	To confirm that drug costs are zero
Set admin costs to 0	To confirm that administration costs are zero
Set all non-drug costs to 0	To confirm that non-drug costs are zero
Manually confirm tornado diagram calculations by changing user-altered cells	To confirm that that tornado diagram calculations are correct

Key: HSUV, health state utility value; LY, life-year; QALY, quality-adjusted life-year
Source: Celgene submission, Table 65, p. 159

The OS for patients in CCR arm, predicted by the model, has been compared to UK real world data from the HMRN registry. *Figure 15* provides a comparison for all patients and *Figure 16* for those patients with poor-risk cytogenetics. Celgene's submission states (Source: Celgene Submission, Section 5.9.3., p.160-161):

> *It can be seen that the model predicts slightly better outcomes than have been seen for patients treated with CCR in UK clinical practice. When adjustment is made for subsequent therapies, the survival curves move closer to that seen in the real world. This further emphasises that CCR survival in AZA-AML-001 could have benefited from patients switching treatment to receive azacitidine which they currently cannot do in clinical practice in the UK. The similar curve shapes suggest the model is replicating real life experience plausibly and that the results of AZA-AML-001 can be interpreted with a degree of comfort once adjustments have been made for subsequent treatments.*

Figure 15: Comparison of CCR overall survival predictions to Haematological Malignancy Research Network data

Key: CCR, conventional care regimens; HMRN, Haematological Malignancy Research Network
Source: Celgene submission, Figure 35, p. 160

Figure 16: Comparison of CCR overall survival predictions for patients with poor-risk cytogenetics to Haematological Malignancy Research Network data

Key: CCR, conventional care regimens; HMRN, Haematological Malignancy Research Network
Source: Celgene submission, Figure 36, p. 161

5.3 Critique of company's submitted economic evaluation by the ERG

5.3.1 Critical appraisal checklists

Table 45: NICE reference case

NICE reference case requirement		Meets criteria?	Reviewer comment
Defining the decision problem	The Scope developed by NICE	Y	
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	U	The ERG believe that subsequent treatments after initial treatment with azacitidine, IC and LDAC should have been allowed in the model, which assumed that the no subsequent AML treatment was given and patients were managed by BSC instead.
Perspective on outcomes	All health effects on individuals	Y	
Perspective on costs	NHS and PSS	Y	
Type of economic evaluation	Incremental Cost-utility analysis	Y	
Time horizon	Lifetime	Y	At the mean age, 75, of patients at the start of the effectiveness study and economic model the 10-year horizon used in the analysis covers most patients' remaining lifetime.
Synthesis of evidence on health effects	Based on a single study	U	Based on evidence from a single trial (AZA-AML-001) since systematic review of clinical effectiveness found no relevant studies. The searches for the systematic review were judged to be poorly designed and reported.
Measuring and valuing health effects	QALYs	Y	
Source of data for measurement of HRQL	Reported directly by patients and/or carers	Y	Based on data collected with a disease specific questionnaire (EORTC-Q30) from a single trial (AZA-AML-001)
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Y	EQ-5D survey mapped from disease specific single trial data using a published mapping algorithm

NICE reference case requirement		Meets criteria?	Reviewer comment
Evidence on resource use and costs		Y	Unit costs reflect the perspective adopted. However, resource use was based on experts' opinion on expected quantities of resource utilisation by disease state and initial treatment; it is unclear why those quantities are different across initial arms in the progressive disease state when all patients are assumed to receive best supportive care only.
Discount rate	3.5% p.a. for costs and health effects	Y	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Y	

Key: BSC, best supportive care; HRQL, health-related quality of life; IC, intensive chemotherapy; LDAC, low-dose cytarabine; N, no; p.a., per annum; QALY, quality-adjusted life year; U, unclear; Y, yes

Table 46: Drummond checklist[65]

Item	Critical appraisal	Reviewer comment
Has the correct patient group/population of interest been clearly stated?	Y	
Is the correct comparator used?	N	The ERG believes that subsequent therapy after azacitidine and CCR (IC and LDAC) is likely to be used in the UK, but the model assumed only BSC was given after the initial treatments being compared.
Is the study type reasonable?	Y	
Is the perspective of the analysis clearly stated?	Y	UK NHS PSS
Is the perspective employed appropriate?	Y	NHS Reference Costs
Is the effectiveness of the intervention established?	Y	The trial on which the model is based, AZA-AML-001 establishes the effectiveness of azacitidine relative to CCR in general and the subgroup of people eligible only to BSC in particular.
Has a lifetime horizon been used for analysis, if not has a shorter time horizon been justified?	Y	The model ran for 10 years. Although this is shorter than lifetime given the average patient starting age of 75, most people would be expected to die by the end of the modelled time horizon.
Are the costs and consequences consistent with the perspective employed?	Y	All costs are presented from the UK NHS & PSS perspective
Is differential timing considered?	Y	All future costs and benefits are discounted with a 3.5% rate.
Is incremental analysis performed?	Y	
Is sensitivity analysis undertaken and presented clearly?	N	Probabilistic sensitivity analyses is reported, although it inadequately assesses variations in structural uncertainty due to clinical effectiveness outcomes not adhering to the maintained assumption of the base case relative treatment effects (i.e., proportional hazards).

Key: BSC, best supportive care; CCR, conventional care regimen; HRQL, health-related quality of life; IC, intensive chemotherapy; LDAC, low-dose cytarabine; N, no; Y, yes

Table 47: Philips checklist[66]

Dimension of quality		Critical appraisal	Comments
Structure			
S1	Statement of decision problem/objective	Y	To evaluate the cost-effectiveness of azacitidine in older patients with de-novo or secondary AML with > 30% bone marrow blasts who were not eligible for hematopoietic stem cell transplantation (HSCT), with intermediate- or poor-risk cytogenetics, Eastern Cooperative Oncology Group performance status (ECOG PS) scores 0–2, and white blood cell count ≤ 15×10^9/L
S2	Statement of scope/perspective	Y	NHS & PSS perspective was implemented. Cost and benefit inputs were consistent with this. Scope of the model stated.
S3	Rationale for structure	U	Unclear; see next comment
S4	Structural assumptions	N	Generally, the ERG is not convinced by some of the structural assumptions. These are explored in Section 5 of this report. The model structure is not consistent with routine practice in relation to use of subsequent treatments nor with the adjustment for treatment switching methodology used to derive the hazard ratios that populated the model (i.e., adjustment was only made of CCR arm -and only for subsequent azacitidine treatment-; subsequent treatment use in the azacitidine arm in AZA-AML-001 was not adjusted).
S5	Strategies / comparators	Y	Azacitidine was compared with CCR, which itself was a composite of different preselected treatments according to patient health status and patient and physician preference
S6	Model type	Y	A semi-Markov model. The choice of model type is adequate.
S7	Time horizon	Y	The model ran for 10 years. At the average typical age of this patient population, 75 years, by the end of this period most patients are expected to have died.
S8	Disease states / pathways	Y	Four disease states were modelled two depending on the initial response: Remission (CR/CRi) or Non-remission (PR, SD), Post-Progressive disease/relapse and Death.
S9	Cycle length	Y	Cycle length is 4 months. Clinical opinion sought by the ERG indicated that this cycle length should be appropriate to capture the events and outcomes most influential on costs and quality of life.
Data			

Dimension of quality		Critical appraisal	Comments
D1	Data identification	U	The evidence on relative effectiveness was sourced from AZA-AML-001, which is likely to provide the best available evidence. However, it is possible that other complementary sources of relevant effectiveness evidence may have been missed due to poor quality of methods used for systematically searching bibliographic databases. Searches of costs and cost-effectiveness studies were appropriate.
D2	Pre-model data analysis	U	No information given
D2a	Baseline data	Y	Baseline data used in the model presented similar characteristics to those from the source of effectiveness data, the AZA-AML-001 study, which includes 3.9% of patients with < 30% blasts.
D2b	Treatment effects	N	The ERG feel that the treatment effects may be biased, since a) they are based on overall survival outcomes in the azacitidine arm that are unadjusted for treatment switching, unlike OS outcomes in the comparator arm, and b) the untested and implausible assumption of constant proportional hazards.
D2c	Quality of life weights (utilities)	N	HRQoL was recorded in AZA-AML-001 using a validated disease specific questionnaire (EORTC QLQ30). These outcomes were measured every two cycles; clinical experts consulted by ERG advised that this is unlikely to miss the effects of important acute health events on quality of life. EQ-5D utilities were derived from these disease specific measures using published mapping algorithms. The model grouped together the effect of adverse events and may have thus failed to account for the effects of repeated adverse events. However, this limitation is likely to have limited effect on results.
D3	Data incorporation	N	Parameter values in the submission are well referenced. A number of errors in cell referencing and formulas were found. An error was found in the way parameter values for the number of treatment cycles was inputted in the model, which resulted in a large underestimation in costs of drug administration, monitoring tests, transfusions and the company's drug ICER
D4	Assessment of uncertainty	N	A range of sensitivity analyses was presented, but important sources of uncertainty were left unexplored or unaccounted for.
D4a	Methodological	N	The main analysis (based on IPCW approach) of overall survival outcomes was not informed by specification tests. The analysis of Progression Free Survival was based on the Cox proportional hazards assumption, which was tested and found to be inconsistent but nevertheless used by the company in their base case analysis.
D4b	Structural	N	Structural uncertainty associated with the untested assumption of proportional hazards (PH) in the effect on overall survival was not assessed. Neither the effect of using non-PH to estimate the effect on relapse free survival was investigated.

Dimension of quality		Critical appraisal	Comments
D4c	Heterogeneity	Y	Subgroup analysis was undertaken in the model.
D4d	Parameter	Y	Univariate deterministic and multi-way probabilistic sensitivity analyses were performed.
Consistency			
C1	Internal consistency	N	Even though Celgene claim to have sought validation for the Excel model, the model did not match the number of treatment cycles observed in the single trial that was the source for the relative effectiveness estimates in the model. The model is in any case inconsistent by design with the same source, since the former assumed no subsequent therapy use in the azacitidine treatment group whereas the latter allowed active subsequent treatments in the respective arm.
C2	External consistency	U	Only expert opinion was sought for external validation.

Key: BSC, best supportive care; CCR, conventional care regimen; CR, complete remission; CRi, complete remission with incomplete blood count recovery; HRQL, health-related quality of life; IC, intensive chemotherapy; IPCW, inverse probability of censoring weights method; LDAC, low-dose cytarabine; N, no; PH, proportional hazards; PR, partial remission; PSS, personal social services; SD, stable disease; Y, yes

5.3.2 Model structure

This four-state model structure has the advantage of being simple and transparent. One possible drawback of the model simplicity is that some states are too broadly defined to capture important differences in costs and quality of life between the treatments being compared. For example, it is questionable whether using the same health state to measure costs and health related quality of life for patients who experience relapse or disease progression after initial remission and patients with disease progression after initial non-remission may mask important differences in outcomes between treatments. However, clinical experts consulted by the ERG suggested that combining the Post-Progressive Disease and the Relapsed states into a single health state in the model had clinical face validity.

The main limitation of the model structure was the assumption that no subsequent active treatment was given after the initial azacitidine or CCR treatment. The model assumption that only BSC would be given following initial treatment is questionable since, as advised by clinical expert opinion, patients treated under azacitidine would be likely to receive LDAC (IC as subsequent therapy would not be likely). Similarly, patients under CCR, specifically IC, could be eligible to receive and able to benefit from LDAC.

The absence of all subsequent treatment in the model is also inconsistent with the AZA-AML-001 trial, from which the clinical effectiveness data used in the model was derived. As seen in *Table 48*, a number of subsequent treatments were used in the trial after azacitidine and the CCR treatments.

Table 48: Subsequent therapies used in AZA-AML-001 by randomly allocated therapy

Azacitidine treatment group			CCR treatment group, Best supportive care only			CCR treatment group, Intensive chemotherapy			CCR treatment group, Low dose cytarabine		
Subsequent treatment	**Freq.**	**%**	**Subsequent treatment**	**Freq.**	**%**	**Subsequent treatment**	**Freq.**	**%**	**Subsequent treatment**	**Freq.**	**%**
Azacitidine[a]	9	13.43	Azacitidine	4	66.67	Azacitidine	5	27.78	Azacitidine	22	43.14
Cytarabine	37	55.22	Cytarabine	1	16.67	Cytarabine	9	50.00	Cytarabine	12	23.53
Decitabine	2	2.99	Etoposide	1	16.67	Other[c]	4	22.22	Hydroxycarbamide	6	11.76
Hydroxycarbamide	10	14.93							Mercaptopurine	5	9.80
Mercaptopurine	5	7.46							Other[d]	6	11.76
Other[b]	4	5.96									
Total	67	100.00	Total	6	100.00	Total	18	100.00	Total	51	100.00

Notes: a, The ERG believes this may be a coding error in the company data; b, Includes one instance each of: 'Chemotherapeutics','Erismodegib', 'Gemtuzumab ozogamicin' and 'investigational drug'; c, Includes one instance each of: 'Decitabine', 'Hydroxycarbamide', 'Mercaptopurine', and 'Tioguanine'; d, Includes one instance each of: 'Clofarabine', 'Decitabine', 'Etoposide', Gemtuzumab ozogamicin', 'investigational drug' and 'Tioguanine'

5.3.3 Population

The model considered in the base case a cohort of patients with mean age 75, 59% of whom are male, weighing 71 kg and with a Body Surface Area of 1.80 m². In terms of the pre-selected CCR treatments, the distribution used was that of AZA-AML-001 (BSC, 18%; LDAC, 64%; IC, 18%) but results from sensitivity analyses using the alternative distribution in the HMRN registry (BSC, [redacted]; LDAC, [redacted]; IC, [redacted]) were also submitted for this assessment. The clinical experts consulted by the ERG advised that the distribution of patients amongst CCR treatments in these registry data was different to their local practice but they thought it plausible that the registry data reflected routine UK practice and they had no alternative data.

A footnote to Table 1 of the study report by Dombret et al. 2015,[45] states that "Patients were randomly assigned on the basis of local pathology assessment of baseline BM blast count, which was subsequently reviewed by the central pathologist; in a small number of cases, baseline blast count was <30% upon central review." In the data provided by Celgene, baseline blast count data were grouped in bands, 0 to 5%, 5 to <25%, 25 to <50%, and 50-100%, and 3.9% (19/488) of the sample had baseline blast count <25%.

5.3.4 Interventions and comparators

The specification of evaluated treatments was consistent with randomly allocated treatments specified in AZA-AML-001. The number of cycles of treatment and the doses were intended to mirror those in the trial. However, the way parameter values for the number of treatment cycles were implemented in the model was incorrect, resulting in a mean number of treatment cycles in the azacitidine group of 5.6 instead of the intended 8.8, in the CCR group IC of 1.86 instead of 2 (initiation and consolidation) and 4.4 when estimating drug acquisition costs and 5.3 when calculating the costs of drug administration, tests and transfusion instead of 6.10 in the CCR group LDAC.

In addition, the description of the CCR IC regimen in the economic section of the submission (*Section 5.2.3, p. 72*), states that one-cycle of induction with IC was followed by "two consolidation cycles for those who responded to the treatment, followed by BSC. Those who do not respond to induction therapy receive BSC". In effect, the model applied costs for up to two consolidation cycles to the group of patients who achieved CR/CRi after induction and did not relapse (i.e., were in Remission) and to the group of those who did not achieve CR/CRi after induction but whose disease did not progress (i.e. were in non-Remission).

As discussed before, subsequent therapies were not allowed in the model, despite their use in AZA-AML-001. It is possible that the use of subsequent treatments in the trial may have resulted in a number of treatment cycles that may not correspond with the number of treatment cycles that would be expected in a situation such as that modelled by Celgene, where subsequent therapy is unavailable.

In any case it is questionable that the sequence of treatments studied in the model (i.e., AZA followed by BSC and CCR followed by BSC) is realistic and the relative effectiveness parameter values used in the model themselves reflect a treatment pathway different to that of the model, especially for the azacitidine intervention, whose estimated relative survival effectiveness was not adjusted for the effects of subsequent treatments in the RCT data source as discussed in *Section 5.3.6.*

5.3.5 Perspective, time horizon and discounting

The NHS and PSS perspective was used, in line with the NICE reference case. Given the mean age of the modelled cohort and the limited life expectancy of its patient population, the 10-year time horizon is likely to capture practically all important differences in costs and health benefits as almost all patients would have died within such period. Discounting was also applied to costs and QALYs as in the NICE reference case.

5.3.6 Treatment effectiveness and extrapolation

5.3.6.1 Extrapolation of overall, progression-free and relapse-free survival and effectiveness estimates of progression-free and relapse-free survival

The choice of parametric curves for extrapolation of OS, PFS and RFS, was based on a comparison of goodness of fit statistics associated with the candidate parametric models. However, only models that implied proportional hazards treatment effects were considered (i.e., exponential, Weibull and Gompertz). Other parametric models, in particular log-logistic and log-normal models, i.e., accelerated failure time models, which allow increasing event rates over time at the start of follow-up and decreasing event rates at later times, were not considered.

According to the submission, Celgene's decision only to consider PH models found support in the statistical tests of the assumption for the OS and PFS, but not in the tests results of RFS data. The company states that (Source: Celgene submission, Section 5.3.3, p. 112):

> *Figure 17 [of the company's submission] shows the log-log plot for RFS hazards; unlike OS and PFS, these indicate that the PH assumption is weak, and a Cox regression run with an interaction between treatment group and ln(time) showed a statistically significant effect of the interaction (p-value of 0.011); however, the PH assumption overall has been retained for consistency.*

It is unclear what consistency means in this statement, but it appears the PH assumption was imposed in the extrapolation and estimation of treatment effects on relapse because PH was not rejected in the analysis of OS and PFS, which is a methodology that is likely to be flawed.

The submission elaborates on the company's methodological practice stating that "HRs are also used still for RFS in the model because the shape of the RFS curves, both overall and for treatment groups and subgroups, are not well suited for independent regression models (for illustration of this: there is no indication visually that independent regression models would better characterise observed RFS for extrapolation)". It is unclear what this statement tries to convey. In any case, Celgene had better options to their chosen biased approach. The company could have fitted a separate curve to the RFS data of each trial arm, instead of forcing a common parametric shape on those curves. Also more flexible models could have been estimated than those supporting the proportional hazard assumption, which although convenient was not indispensable in this or any similar analysis.

The analysis of OS in the submission is also flawed. Although the company reported results of a statistical test (for statistically significant interaction of the treatment group variable and the logarithm of time) and visual inspection of log-log plots that supported the PH assumption, these diagnostic checks were only applied to data that was unadjusted for

treatment switching, i.e., had no IPCW weights applied. The company did not perform diagnostic tests on the data underlying the IPCW Cox PH estimates that were ultimately used for the base case economic analysis. We elaborate on this problem below.

Unlike OS and RFS, PFS was the only time-to-event outcome where tests for the proportional hazard assumption supported the PH assumption. These included statistical tests on the interaction of the treatment group indicator and the logarithm of time ($p<0.187$, Source: Celgene submission, Section 5.3.3, p. 114), as well as visual inspection of log-log plots. Celgene also documented the goodness of fit statistics in support of their choice of parametric curve (i.e., Gompertz).

The set of statistics used to inform Celgene's choice of time-to-event curves for the base case analysis (Celgene submission, Section 5.3.4, pp. 120–121), are reproduced below in *Table 49* and *Table 50*. These are goodness of fit statistics for candidate parametric models fitted to each arm for each of the three effectiveness outcomes (OS, PFS and RF). *Table 49* refers to ITT data whereas *Table 50* refers to results of analyses that censor-at-switch to AML therapy data in both arms. The Weibull provides the best, most parsimonious parametric fit to the RFS data (i.e., lowest AIC and BIC statistics). The best fit to the PFS data was the exponential for the azacitidine arm and Gompertz for the CCR, although differences in goodness of fit between models were smaller than those for RFS or OS data. The best parametric fit to the OS data is not that clear for azacitidine, but for the CCR Gompertz appears best for ITT and censor-at-switch data.

Table 49: Goodness of fit for OS, RFS, and PFS parametric functions (ITT data)

Parametric model	OS				RFS				PFS			
	Azacitidine (n = 241)		CCR (n = 247)		Azacitidine (n = 67)		CCR (n = 62)		Azacitidine (n = 112)		CCR (n = 111)	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	752	759	799	806	**100**	**104**	**133**	**138**	353	359	373	378
Gompertz	752	759	**793**	**800**	108	113	137	141	353	359	**372**	378
Exponential	**750**	**754**	802	806	149	151	149	151	**351**	**354**	374	**376**

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CCR, conventional care regimens; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival
Note: Figures in bold indicate best fitting model according to criteria referred to by the column heading
Source: Celgene submission, Table 35, p. 120

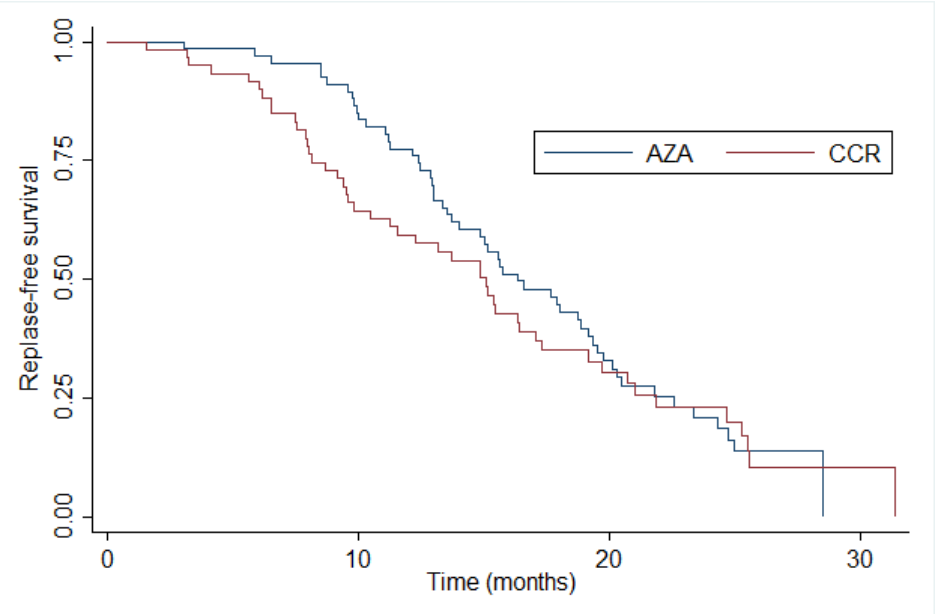
Table 50: Goodness of fit for OS, RFS, and PFS parametric functions (censor-at-switch data)

Parametric model	OS				RFS				PFS			
	Azacitidine (n = 241)		CCR (n = 247)		Azacitidine (n = 67)		CCR (n = 62)		Azacitidine (n = 112)		CCR (n = 111)	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	**674**	681	694	701	**103**	**108**	**137**	**141**	344	349	344	349
Gompertz	674	681	**684**	**691**	113	117	141	145	342	348	**342**	**347**
Exponential	676	**680**	700	704	150	152	150	152	**342**	**345**	344	347

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CCR, conventional care regimens; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival
Note: Figures in bold indicate best fitting model according to criteria referred to by the column heading
Source: Celgene submission, Table 36, p. 121

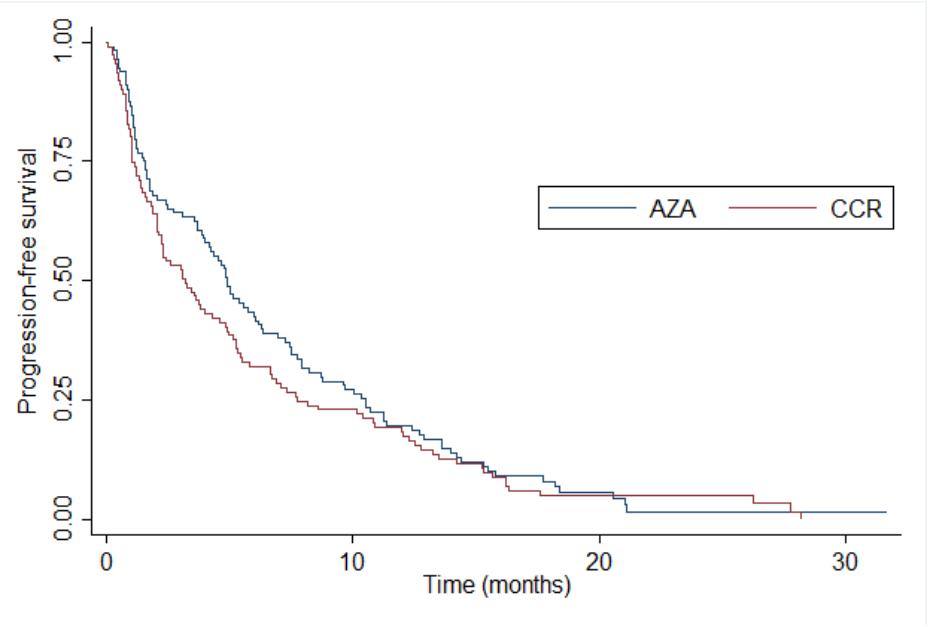
The range of models evaluated by Celgene was too restrictive, as these are all models with constant or monotonic hazards that are assumed to be proportional between the two treatments. Since, as discussed above and in the submission, RFS failed the proportional hazards test, fitting separate Weibull curves, as the company did for its base case analysis and ERG verified in the Excel model files, is still likely to bias the extrapolation of RFS outcomes. In fact, seeking to fit a rigid statistical model to limited RFS data (n=67 in azacitidine and n=62 CCR at randomisation) and PFS (n=112, and n=111, respectively) lacks justification because during the observed trial period most people relapse and progressed (*Figure 17* and *Figure 18* respectively).

Figure 17: Kaplan-Meier estimate of relapse-free survival in AZA-AML-001



Key: AZA, azacitidine; CCR, conventional care regimens
Source: Celgene submission, Figure 16, p. 113

Figure 18: Kaplan-Meier estimate of progression-free survival in AZA-AML-001

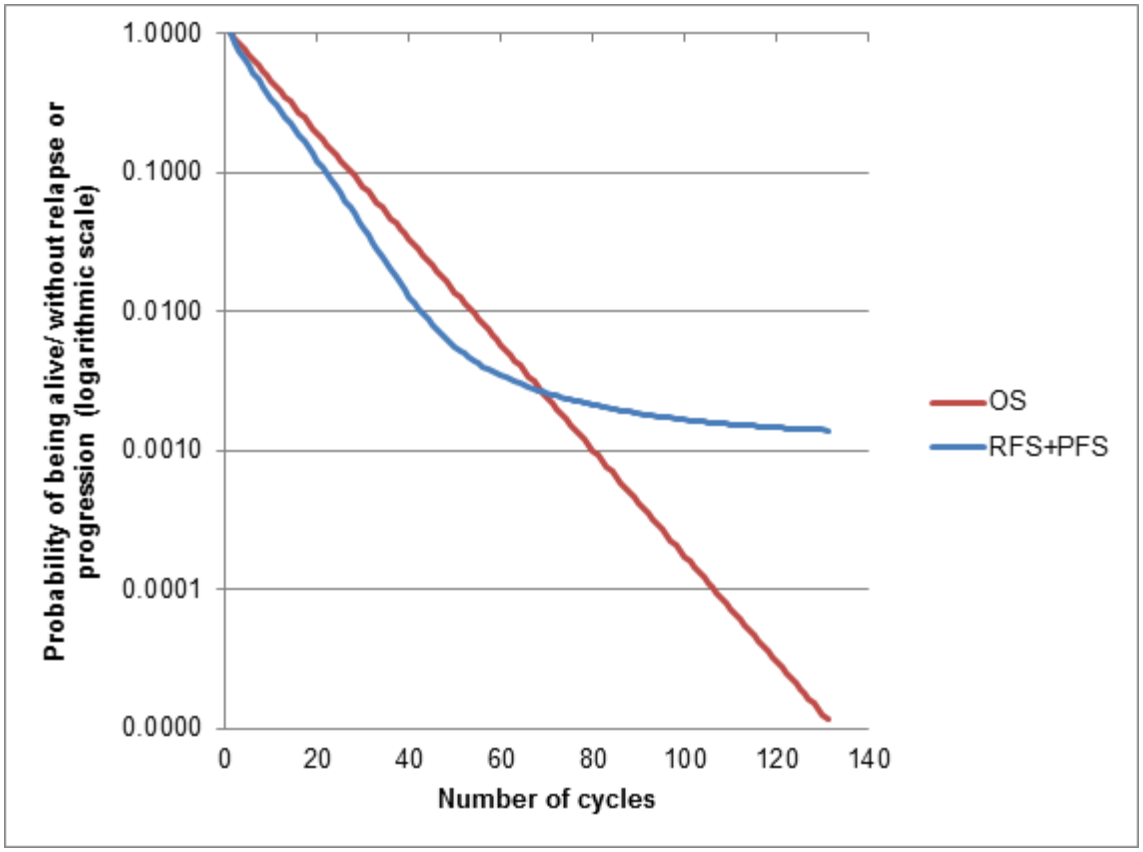


Key: AZA, azacitidine
Source: Celgene submission, Figure 18, p. 115

The inadequacy of the statistical analysis may be illustrated by comparing the estimated time to event curves used by Celgene in their base case analysis, combining PFS with RFS and contrasting it with OS. *Figure 19* below illustrates the problem for the CCR arm. By cycle 69, that is, just after the start of the sixth year after first receiving treatment the estimated curves imply that there are more patients in the treated cohort who are either in Remission or non-remission (stable disease) than there are patients alive. Ironically, Celgene's consistent choice of parametric extrapolation curves that implied PH (possibly including their choice of overall survival curve) led them to use survival models that are mutually incompatible.

It is tempting to disregard the problem depicted in *Figure 19* by thinking that the crossing of curves occurs only when less than 1% of patients are still alive. However, the crossing itself is a sign that the estimated time spent by patients in the different states of the model (and the associated base case results) may be severely biased. In fact, it is easy to see why the two curves in *Figure 19* have incompatible shapes: the OS curve assumes a constant hazard (which appears as a straight line in the figure due to log scale metric used for the Y axis), whilst the RFS was modelled using a Weibull function with a shape parameter estimate of 1.7 (Celgene Excel model sheet 'CCR parameters' cell HF42), which implies an increasing hazard; the shape of these two curves would be mutually compatible as time passes, but not accompanied by the Gompertz function used for PFS since its estimated negative parameter of -0.03 (Celgene Excel model 'CCR parameters' cell HF30) implies a (small) proportion of people never die, which is what ultimately drives the crossing of the curves.

Figure 19: Survival curves used in Celgene's base case (Y-axis in logarithmic scale)



Key: OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival
Source: Produced by the ERG using Celgene's decision model

As a consequence the ERG believes that using Kaplan-Meier nonparametric curves as observed in the AZA-AML-001 trial provide the best source data with which to populate PFS and RFS model parameters, while minimising the structural uncertainty of the cost-effectiveness results.

As for OS, it is not clear to the ERG whether the data underlying these assessments of parametric curves are censored at switch to some or all subsequent treatment use, and to CCR only or both arms. Analyses based on censoring for switching in both arms, possibly adjusting for non-random treatment switching may be required to obtain valid estimates of survival benefits, and the choice of parametric extrapolation need not restrict to proportional hazards functions without statistically testing for such assumption in the data. Therefore, the ERG undertook further analyses of individual patient data provided by the company; these analyses are presented in the next section, where the justification for extrapolating using parametric curves is also considered.

5.3.6.2 Critique of adjustment of overall survival for subsequent treatments

This section is focused on the IPCW method used by Celgene to derive its primary estimates of relative effectiveness. The other methods explored in the submission either faced problems of face-validity (the RPSFTM and IPE methods), were not feasible (the two-stage method, which required a second baseline), or appeared only as an appendix (Celgene Post hoc statistical methods addendum AZA-AML-001) without details of their application to the present assessment or results.

As discussed in *Section 5.2.5.1* (*page 77*), the validity of the IPCW method, which originated in the literature of causal effects estimation using observational data, is limited by its requirement that data for all relevant confounders related to treatment switching and mortality are included in the analysis, and tends to perform poorly in small samples or applications with rare events. In an RCT context where the method could take advantage of high quality prognostic information to adjust for observed confounding in treatment switching, the IPCW method is hampered by the small size of available samples of patient data. Consequently, IPCW was not used by Celgene to estimate OS effectiveness by CCR preselected therapy.

Indeed, the company stated (Source: Celgene submission, Section 5.3.5, p. 123):

> *subgroup adjustment was not feasible because of limited data on switching; however, a clinical expert consulted during this analysis stated that questions can be raised about the clinical generalizability of the results in subgroups [This refers to controlling/adjusting for the three treatment groups within CCR, as well as for cytogenetic risk or MDS subgroups, as clarified by Celgene in response to questions by ERG], because clinicians can identify potential switching candidates based on observed performance, and recommended focusing on the adjusted data for overall patients.*

Similarly, in response to the request by ERG to clarify the reason for not adjusting event-free survival, relapse-free survival and progression-free survival for treatment switching, the company answered that "This was due to sample size primarily. The instances in which switching preceded the clinical event of interest were few, and the impact of this on the results would be very small."

Celgene provided the ERG with the individual patient data for replicating the IPCW estimation of the Cox proportional hazard ratios used in the company's base case cost-effectiveness analysis. ERG was able to replicate those results (*Table 51*). The ERG was unable, however, to replicate the estimation of IPCW weights, which were provided by the company but without the dataset used to estimate them. Thus the ERG can only comment on the quality of the analyses of OS with the IPCW weights as given, without being able to assess whether the statistical model used to estimate these weights is of good quality. This is a relevant issue given the relatively small sample available for analysis and the large number of groups of patients as defined by the covariates used in the IPCW model, which according to the SAS code (Celgene appendices to submission, Appendix 10) and *Table 52*, included four binary and one three-level fixed baseline variables, three binary time-varying covariates, and one variable indicating the 76 15-day periods of observation, for a total of $2^4 \times 3^1 \times 2^2 = 192$ possible subgroups at each of the 76 follow-up times. It is unlikely that the validating condition (see *Section 4.3.2, p. 61*) of there being a positive probability of not being censored at each and every follow-up point and for every combination of values observed for the covariates in the IPCW model, might have been met in this sample, and this became less likely as time passed in the trial.

Table 51: Results of the IPCW models

Model	HR (95% CI)	P value[a]
Unadjusted	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]

Key: HR, hazard ratio; IPCW, inverse probability of censoring weight
Notes: a, P value calculated using a log-rank test
Source: Celgene submission, Table 38, p. 126

Table 52: List of covariates used for calculating stabilised weights in the IPCW model

Non time-varying covariates	Time-varying covariates
• [redacted]	• [redacted]

Key: AML, acute myeloid leukaemia; CR, complete remission; CRi, complete remission with incomplete blood count recovery; ECOG, Eastern Cooperative Oncology Group
Source: Celgene appendices to submission, Appendix 11, Table 14

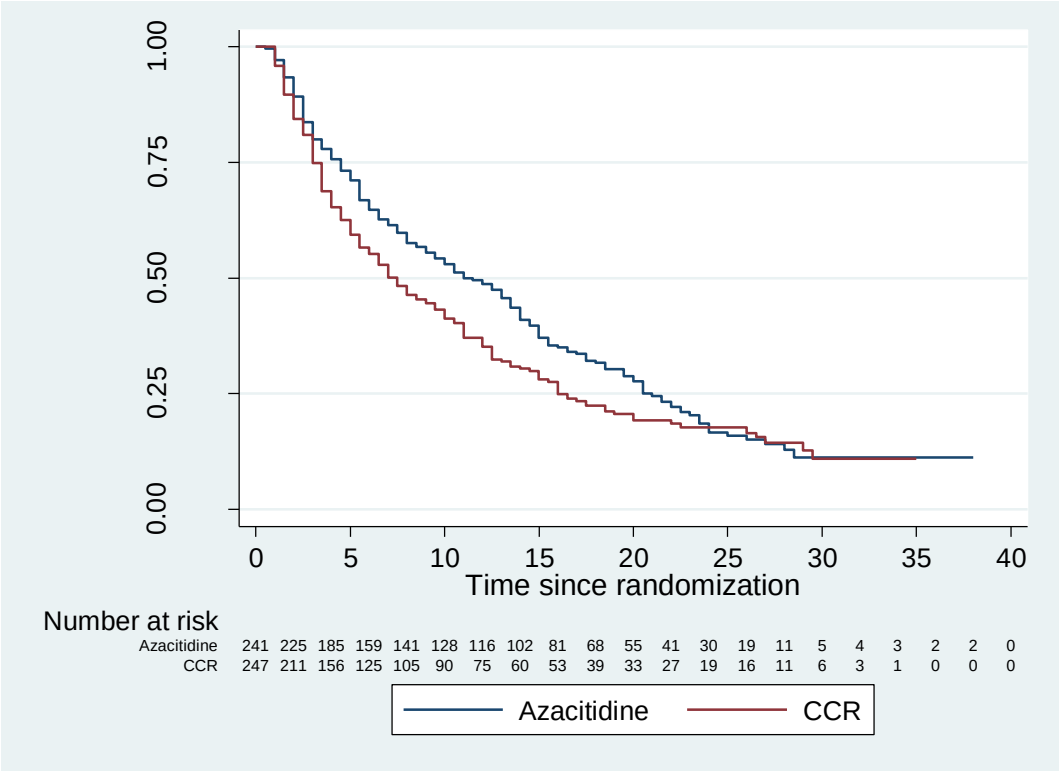
The IPCW estimate of OS effect, which was selected for the company's base case cost-effectiveness analysis, is based on the assumption of proportional hazards. Celgene acknowledge this limitation (Source: Celgene Submission, Section 5.3.5., p. 122):

> *A further limitation of the IPCW approach is that it does not produce counterfactual survival data directly; in order to use adjusted CCR data in subsequent survival analysis and economic modelling, counterfactual data are required. The survivor function approach, in which the CCR hazard function is calculated using the observed azacitidine hazard function and using the inverse of the IPCW-adjusted HR, changed the shape of the CCR survival curve relative to the observed data. On the face of it, this is problematic – as well as altering the shape of the CCR survival curve, the method forces hazards to be proportional – but it must be acknowledged that the purpose of the analyses is to produce counterfactual data, which may result in counterfactual hazard functions (i.e., different KM curve shapes) and not just counterfactual hazards from curves whose shapes do not change.*

It is not clear, however, why Celgene did not test for the proportional hazard assumption using the IPCW adjusted data. In their OS analysis, they overlooked the possibility of graphically and statistically testing for the constant proportional hazards assumption. They seemed to ignore the fact that the survival curve of the CCR arm under the IPCW adjustment is observed; in *Figure 20*, we plot the CCR OS Kaplan-Meier curve for the CCR arm after adjustment for IPCW. In contrast, *Figure 21* depicts the curve used by Celgene in

their base case analysis. The Kaplan-Meier curve for the azacitidine arm is one and the same since it was not subject to adjustment for treatment switching by the company. This suggests that forcing the proportional hazards assumption on the OS curves is likely to result in different estimates of survival benefits from those obtained by fitting separate parametric curves, of possibly different shapes, to the OS data from each of the two trial arms. For the base case, Celgene used a hazard ratio estimated from a Cox proportional hazards analysis adjusted for baseline covariates. The ERG undertook diagnostic tests of the proportional hazards assumption on the adjusted Cox PH OS curves by comparing the cumulative log-log plot of the azacitidine and CCR arms directly as well as testing for time and treatment effect interactions and Schoenfeld residuals (see details in *Appendix 2*). The results of these tests suggest the constant proportional hazards assumption is not supported by the data.

Figure 20: Overall survival curves in AZA-AML-001 following adjustment of the CCR arm for subsequent treatment with azacitidine using the IPCW method



Key: CCR, conventional care regimens; IPCW, inverse probability of censoring weight; ITT, intention-to-treat
Note: Based on discrete (15-day period) time-to-event data
Source: Produced by the ERG using individual patient data provided by Celgene

Figure 21: Overall survival from AZA-AML-001 adjusted using hazard ratio from the IPCW method

Key: CCR, conventional care regimens; HR, hazard ratio; IPCW, inverse probability of censoring weight
Source: Celgene submission, Figure 25, p. 127

Celgene stated that progression and relapse events in the trial occurred before other censoring events and few cases of progression and relapse occurred after subsequent therapy use in CCR (Source: Celgene responses to NICE questions for clarification). This suggests that adjustment of PFS and RFS using the IPCW method would not have been practicable due to very small numbers, but the company could have applied simple censoring at switch adjustments on curves to verify that indeed subsequent therapy use was not important for the results, as the company suggests.

In any case, these adjustments for treatment switching are inconsistent with the economic model for which they were intended. The Celgene model assumes no subsequent therapy use was available after either azacitidine or CCR (Celgene submission, Section 5.6.2, p. 161). In contrast, the clinical effectiveness analyses conducted by Celgene only adjusted for subsequent treatment with azacitidine in CCR arm, thus ignoring the use of subsequent treatments in the azacitidine arm of AZA-AML-001 (the source of the clinical effectiveness data), as well as any active subsequent treatments other than azacitidine used in the CCR arm.

In defence of their methodology, Celgene referred to the methodological recommendations in the NICE DSU TSD16[51] as indicating that the NICE preferred approach is to adjust treatment switching in the comparator (CCR arm) but not the intervention (azacitidine arm). As discussed in *Section 4.3* (*page 59*), this is an incorrect interpretation of NICE DSU TSD16, which clearly recommends that in situations where, as in the present case, the decision problem involves the evaluation of two alternative states of the world where no subsequent active treatment is available, then adjustment of outcomes for active treatment switching in both trial arms is warranted. Whether the assumption that no subsequent active treatment would be available to UK patients in routine practice is plausible may of course be questioned, but the point here is that applying IPCW adjustment for subsequent treatment to

the outcome data of the CCR but not the azacitidine arm in the AZA-AML-001 trial is inconsistent with the economic model which the overall survival IPCW analysis was designed to inform.

To remedy the contradiction between the model structure, on the one hand, and the methodology underlying the OS treatment effect estimates, on the other, two options were available to the ERG. One was to correct the model to include the costs of subsequent treatments used in the AZA-AML-001 and left unadjusted for in the statistical analysis that produced the base case OS treatment effect estimates. This option was not feasible because the required data on the dates of start and end of subsequent treatments as well as treatment dosages and frequencies of administration were not available to ERG. The alternative of adjusting the estimates of relative effectiveness for subsequent AML treatment use in both arms of AZA-AML-001 was feasible, since the company provided results of such analysis using IPCW (Celgene submission, Table 21, p. 70). A limitation of this option was that statistical tests to validate these analyses were not reported, and the Kaplan-Meier or individual patient data required to perform them were not available to ERG either (not all the required data were available in the individual patient data that Celgene provided for ERG use). Ideally, testing for the Cox PH assumption would be performed and, if rejected, treatment effects estimated using a different model.

The only option available to ERG was to base the test of the proportional hazards assumption on OS data censored-at-switch, which had similar Kaplan-Meier plots as the OS IPCW weighted data in the CCR arm, and resulted in small differences in hazard ratio estimates (Celgene appendices to submission, Appendix 11). The data provided by Celgene did not allow ERG to extend the IPCW analysis to adjust for subsequent AML therapy to both treatment groups. However, the company provided the data to perform censor-at-switch analysis for any subsequent AML therapy use in both trial arms, as well as testing for the proportional hazards assumption in the data. Fitting a range of parametric curves including proportional (exponential, Weibull, Gompertz, Bathtub) and non-proportional hazard parametric models (log-normal and log-logistic) to OS data from each trial arm separately resulted in the following goodness of fit statistics and test statistics for nested models (i.e., whether the simple exponential model could be supported by the results of more complex proportional hazards models).

Table 53: Goodness of fit and test statistics for OS parametric functions (patients censored at switch for any subsequent therapy in both arms)

Parametric model	Unadjusted for baseline covariates						Adjusted for baseline covariates[a]					
	Azacitidine (n=241)			CCR (n=247)			Azacitidine (n=241)			CCR (n=247)		
	AIC	BIC	p^b	AIC	BIC	p^b	AIC	BIC	p^b	AIC	BIC	p^b
Weibull	**676**	687	0.050	696	707	0.008	638	708	0.858	642	713	0.708
Gompertz	**676**	687	0.057	686	697	<0.001	638	708	0.810	641	711	0.202
Exponential	678	**685**		702	709		**636**	**702**		**641**	**707**	
Bathtub	678	689		706	716		640			645		
Log-logistic	676	686		684	694		637	707		643	714	
Log-normal	678	688		**678**	**689**		641	711		644	714	

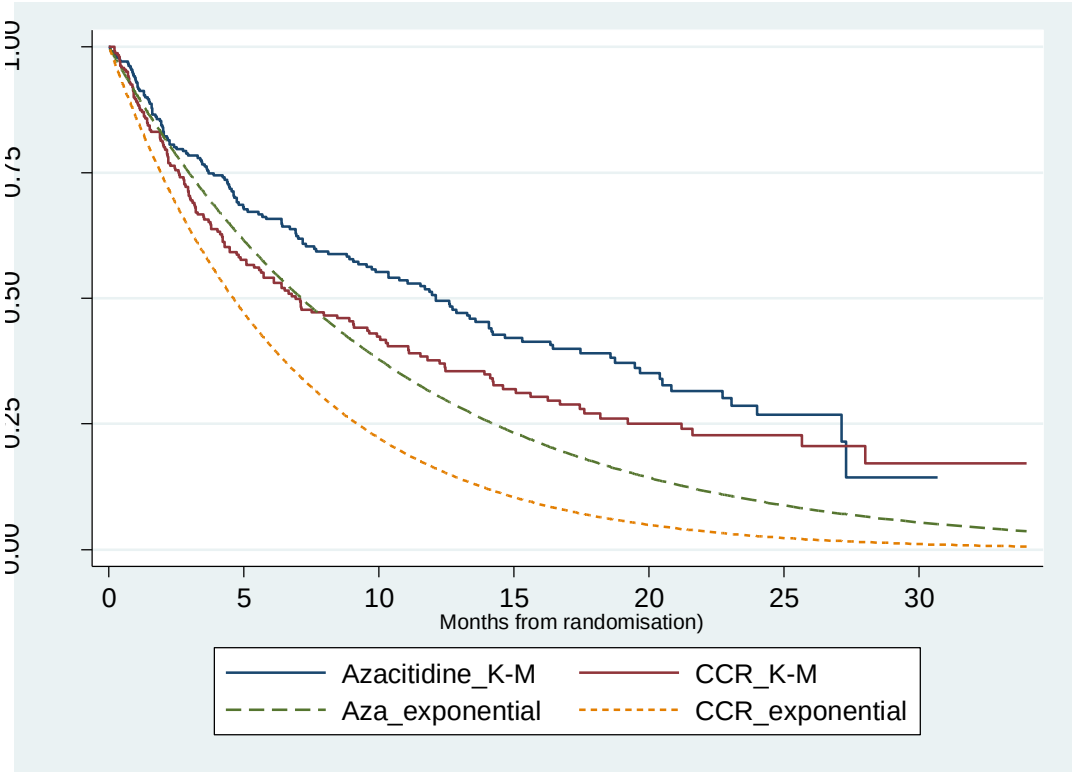
Key: AIC, Akaike information criterion; AML, acute myeloid leukaemia; CCR, conventional care regimens; ECOG, Eastern Cooperative Oncology Group; OS, overall survival

Notes: a, Covariates included in adjustment: age, sex, ECOG, cytogenetic risk, % blast group, CCR therapy preselect group, comorbidities, AML days, platelet transfusion status, geographical region; b, p-value from Z-test on shape coefficient (versus null hypothesis of exponential distribution); Figures in bold indicate best fitting model according to criteria referred to by the column heading

According to AIC, there is no difference in performance between unadjusted models of azacitidine, since all lie within a 2-unit difference of one another.[67] For unadjusted analyses of CCR, the models consistent with PH are not supported by the data, except for the Gompertz, because they perform worse than the model with the minimum AIC, the log normal, by more than 10 units.[67] BIC rewards parsimonious models relative to AIC, since the former penalises the inclusion of each additional covariate in the model by 5.5 points whereas the latter does it by 2. Thus, the exponential, which uses one fewer parameter than the other models, moves up the BIC performance ranking to be the best unadjusted model fit to azacitidine OS data, but still 'strongly' underperforms the unadjusted model that best fits the CCR data, the log-normal model, since it has more than 10 additional points.[68] The best performing unadjusted model for the CCR arm that is consistent with the PH assumption is the Gompertz, but its 8 additional points over the log normal model may be considered 'strong' evidence against it and in favour of the log-normal model.[68] Although the accelerated failure time models (the log normal and log-logistic) perform better than other models they imply implausible predictions as detailed in *Appendix 2*. In contrast, an exponential unadjusted model fitted separately to each arm produces life expectancy estimates of 17.09 versus 12.36 months for azacitidine and CCR, respectively.

As for models that adjusted for baseline covariates, the exponential is the optimal model for both azacitidine and CCR arms, although all other models except the log-normal show comparable AIC and BIC performance. The adjusted exponential model fitted to both arms results in a HR of 0.64 and has a predicted difference in OS of 3.64 months, in favour of azacitidine; details are presented in the *Appendix 2*. *Figure 22* presents the ITT Kaplan-Meier data and the fitted adjusted exponential OS model to data censored at switch to subsequent AML therapy in both trial arms.

Figure 22: Overall survival in AZA-AML-001 – ITT Kaplan-Meier data and adjusted exponential model fitted to censor-at-switch (any AML therapy) data



Key: AML, acute myeloid leukaemia; Aza, azacitidine; CCR, conventional care regimens; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; K-M, Kaplan-Meier

Note: Adjusting covariates: age, sex, ECOG, cytogenetic risk, CCR therapy preselect group, comorbidities, AML days, platelet transfusion status, geographical region were effects-coded so that baseline is an estimated overall mean in the sample; % blast group <25% adjusted using 1 vs. 0 indicator (see *Appendix 2*)

Source: ERG analysis using censored-at-switch to subsequent AML therapy (in both trial arms) individual patient AZA-AML-001 data provided by Celgene

Although the frequency of subsequent therapy use was similar in both groups, overall (azacitidine 28% versus CCR 30%), and by subgroups (see *Table 54*, Source: Celgene's response to questions for clarification), patients who used subsequent treatments did so earlier in CCR than azacitidine (273 versus 322 days post-randomisation; Source: ERG extraction from individual patient data provided by Celgene). The [redacted] difference between unadjusted censor-at switch (HR 0.72, Source: ERG analysis using individual patient data provided by Celgene) and unadjusted IPCW (HR [redacted], Celgene submission, p. 70, Table 21) for subsequent AML treatment in both arms, suggests the censor-at-switch estimate is biased in favour of azacitidine, and thus may be considered a conservative choice of estimates given the effect on results of other changes adopted by the preferred ERG base case analysis. *Figure 22* depicts the adjusted fitted exponential survival curves alongside the ITT Kaplan-Meier curves.

Table 54: Number of patients who switched treatments in AZA-AML-001

Patient subgroup	Number of patients who did not receive subsequent AML therapy	Number of patients who received subsequent AML therapy
All patients	[redacted]	[redacted]
	[redacted]	[redacted]
Comparator: IC	[redacted]	[redacted]
	[redacted]	[redacted]
Comparator: LDAC	[redacted]	[redacted]
	[redacted]	[redacted]
Comparator: BSC	[redacted]	[redacted]
	[redacted]	[redacted]
Subgroup: Intermediate cytogenetic risk	[redacted]	[redacted]
	[redacted]	[redacted]
Subgroup: Poor cytogenetic risk	[redacted]	[redacted]
	[redacted]	[redacted]
Subgroup: With MDS-related changes	[redacted]	[redacted]
	[redacted]	[redacted]
Subgroup: Without MDS-related changes	[redacted]	[redacted]
	[redacted]	[redacted]

Key: AML, acute myeloid leukaemia; AZA, azacitidine; BSC, best supportive care; CCR, conventional care regimen; IC, intensive chemotherapy; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome

The ERG believe that baseline covariate-adjusted censor-at-switch methods coupled with parametric curves fitted to each arm offer a practical, transparent alternative to IPCW with similar performance in this application. While the censor-at-switch assumption that subsequent treatment occurs at random is likely biased, in the current case the alternative of adjusting for non-random treatment switching with the IPCW was not feasible due to the the ERG lacking the data required to assess or replicate the model used to estimate the IPCW weights. In any case, given the relative magnitudes of costs and QALYs presented in *Section 6* (*page 130*), the degree of uncertainty in effectiveness parameters is unlikely to matter for the economic results.

As a conservative approach, the ERG's preferred base case analysis adopted the exponential OS HR estimates adjusted for baseline covariates used by the IPCW method, including sex, age, ECOG status, preselected CCR treatment, time since initial AML diagnosis, comorbidity score, in data censored at switch to any subsequent AML treatment from both trial arms in the dataset provided by Celgene to ERG. The resulting HR estimate, 0.64, is more favourable to azacitidine than the respective estimates from applying IPCW to subsequent azacitidine use in CCR only, [redacted] and [redacted] (Celgene's base case), IPCW to any AML in both arms arms, 0.77 and 0.71, and the ITT value of 0.85.[45]

It must be noted that the adjusted censored at switch analysis performed by the ERG in obtaining its preferred estimate of OS effectiveness was not extended to subgroup analyses, since the small sample is likely to lead to bias due to overfitting when adjusting for baseline covariates. The subgroup analyses were thus based on the original censor-at switch exponential OS curves estimates used by the company in their model.

5.3.7 Health-related quality of life

A number of problems were found with the assessment of health related quality of life in the economic analysis. However, based on univariate sensitivity analyses presented by Celgene and conducted by ERG, the bias originating from this element of the model has an insignificant influence on the ICER.

In line with RCT studies in this field, health related quality of life was measured at the start of every other cycle in AZA-AML-001 using a disease specific HRQoL measure, the EORTC QLQ-C30. Since EQ-5D outcomes were not measured in the trial, peer-reviewed mapping algorithms were identified and used by Celgene in accordance with NICE methodological guidance.[41]

Three potential limitations of this analysis were identified by ERG. One related to the possibility that because HRQoL was measured every 56 days in AZA-AML-001, the effects of some important acute adverse clinical events, especially treatment-related ones, may have been missed by the data collection. Advice sought from clinical experts suggests that no obvious important events would have been expected to be missed by the quality of life study supporting the Celgene submission.

Another potential issue was missing data. Celgene reported that longitudinal statistical analysis using mixed methods were employed to assess HRQoL (Celgene Submission, Section 4.7.5.8, p. 77), and in response to clarification questions by ERG, the company stated that:

> *A mixed effect model repeat measurement (MMRM) model was developed for the EORTC QLQ-C30 Fatigue domain with the inclusion of a fixed-effect covariate indicating whether a transfusion had taken place up to 5 days before health related quality of life (HRQL) assessment. This analysis was undertaken because blood transfusions are likely to affect fatigue, but this relationship would not have been explored by previous analyses.*
>
> *Additional MMRM models were developed for the secondary HRQL domains (Dyspnoea, Physical Functioning and Global Health Status/ quality of life (QoL)) that included RBC or platelet transfusion up to 5 days before the HRQL assessment as a factor.*
>
> *The statement 'A mixed model analysis failed to reveal any statistically significant differences in the impact of treatment on all domains between treatment arms' references the post-hoc MMRM analysis controlling for the impact of red blood cell (RBC) or platelet transfusion received up to 5 days before HRQoL assessment. It was hypothesized by the clinical study team that transfusions administered shortly before HRQoL assessment may have an effect on fatigue, and this effect would not have been captured in the initial model. The results of the MMRM analysis for the Fatigue domain without this additional covariate were significant in favour of CCR.*

> *No significant differences were observed for the secondary domains. Full presentation of both results can be located in the CSR section 11.4.1.2.10.7.*
>
> *All MMRM analyses were based on the assumption that data are missing at random. A post-hoc sensitivity analysis utilizing a pattern-mixture model was conducted to explore the impact of the missing-at-random assumption. Results of this analysis aligned with the MMRM results for Physical Functioning, Dyspnoea and Global Health Status/QoL, with no differences between treatment groups at p<0.05, while results favoured CCR for the Fatigue domain (P=0.025).*

The ERG is satisfied that the statistical analyses of HRQoL conducted by Celgene were thorough and conducted following best methodological practice. As is typical with patient reported outcome studies conducted alongside RCT in this clinical area, missing data is a problem due to the high drop-out rates and item non-response, and analytical methods employed by Celgene have tried to address it. However, the results of this analysis were crudely applied in the cost-effectiveness model, as explained next.

The third limitation was the way the effect of adverse events was implemented in the model, which treated disutility effects of adverse events differently from their cost impacts. The ERG asked the company to explain why the adverse events which are costed on page 130 of the company's submission appear to differ from the adverse events for which disutilities are measured (page 129 of the company's submission). The company replied:

> *HRQL analysis from the trial was more restricted in terms of measuring and mapping from EORTC QLQ-C30 scores during an AE in the trial; costing on the other hand used rates of AEs, disaggregated by type, from the main clinical study report, and hence were more detailed.*
>
> *Thus, in the model, AE disutilities are a single figure that are aggregated at the trial-analysis level; AE costs on the other hand are aggregated within the model itself, calculated from rates and unit costs for AEs.*

The QALY impact of AEs was modelled as the probability of at least one TEAE of Grade > 3 per 100 person-years multiplied by the utility of grade > 3 TEAEs. In the model, the effect of AEs on QALYs in azacitidine have been modelled for a maximum of 8.8 treatment cycles, which is effectively less than the mean 8.8 in the trial, while for CCR as a whole they were counted for a maximum number of cycles of 5.1 which is more than the mean number of 2 cycles with IC. These calculations are likely to overestimate the additional costs of CCR relative to azacitidine but this bias had a small effect on the results given other issues identified by the ERG in the model.

These features of the model are likely to lead to bias in estimating the costs and QALYs differences between the azacitidine and CCR treatment groups, as they conflated different types of adverse events and inaccurately measured repeated or continued episodes of AEs.

5.3.8 Resources and costs

5.3.8.1 Drug costs

The ERG identified some errors in the calculation of drug costs. The most important error was that the model incorrectly applied the mean number of cycles reported in the trial.[45] In order to obtain the mean 8.8 number of azacitidine cycles, a maximum number of 19 cycles needs to be set given the distribution of the modelled cohort between the Remission and Non-remission states (the proportion of cohort members in the relapse/PD state and Death states do not consume azacitidine medication). Instead Celgene applied a maximum of 8.8 (rounded down to the closest integer, 8) number of treatment cycles effectively accounting for a mean number of azacitidine cycles in the model less than 6 as opposed to the intended 8.8. Likewise the correct maximum number of cycles for LDAC in CCR is 10 cycles (the 1.6 cycles used for IC in CCR modelled by Celgene is practically correct). In correcting the probabilistic sensitivity analysis ERG chose SE 3 for azacitidine, 1 LDAC and (0.06 for IC as used by Celgene's base case is correct), to calibrate the respective model outputs to the reported figures for mean minus one standard error in the number of cycles reported by Dombret et al. 2015.[45] As documented below, correcting this error of implementation to calibrate the model outputs with the summary statistic reported by the trial increases the ICER from a level around £20,000 to £84,000 per QALY gained.

A mistake was also found in the calculation of dosing. Celgene incorrectly estimated daily dose of cytarabine ('HRU_costs'!C115:C117) assuming mg/m² instead of using mg/day as in the CSR. However, this error does not affect acquisition costs, since the inflated dose is still less than the size of a vial, but has a small effect on ICERs for the 'no wastage' analyses.

More importantly, the costs of drug acquisition and administration, monitoring tests, and transfusions in CCR were based on a formula with reference to the azacitidine number of cycles (8.8) instead of the number of cycles of CCR treatments (2 cycles, 1 initiation and 1 consolidation cycle in IC, and 6.1 in LDAC).

The ERG also corrected an error in how the model calculated the costs of drug administration, monitoring tests and transfusions in the first (induction/pre-response) cycle for both azacitidine (Model AZA sheet AB23:AD23 and Model CCR sheet AB23:AD23). In the first cycle, the model accounts for costs of two cycles for these costs, unlike for drug acquisition costs (AA23 in Model CCR and Model AZA sheets), which only accounts for the initial cycle. This has the effect of loading the costs of two cycles of treatment to all patients, since the survival curves in the model assume all are alive and under treatment while awaiting the initial evaluation of response. For IC this implies one induction cycle and one consolidating cycle thus overestimating the mean number of consolidation cycles reported in the trial of 1.[45]

5.3.8.2 Health resource utilisation and unit costs

The quantities of resource use for medical staff costs, drug monitoring tests and outpatient procedures (including transfusions), and inpatient hospitalisations by health state and initial treatment (azacitidine, IC, LDAC or BSC) were derived from expert opinion. Apart from drug monitoring testing and outpatient procedures during Remission and Non-remission phases (i.e., while the initial treatments are being administered or when treatment has recently been withdrawn or concluded), it is not clear the rationale for having different resource use quantities within the same health state for the different treatments being compared. Models

of health state transitions that use generic health states, where health status entirely determines health related quality of life and costs and where treatment is irrelevant (apart from explicit treatment-related events), are more transparent and arguably robust to bias. In terms of resource use none of the health states are generic, and only adverse events-related costs are independent of initial treatment.

Without a clear clinical rationale, asking expert opinion about costs in the Relapse/progressive disease phase contingent on initial treatment, despite the model assumption that all patients in this phase are managed under BSC only, is susceptible to framing bias in surveyed responses. This issue is apparent in the health resource use questionnaire used by Celgene and presented in its submission Appendix 12. Furthermore, in this model, variation of costs in Relapse/progressive disease across initial treatments are not accompanied by a corresponding variation in utilities, which implies resources are being used without noticeable effects on quality of life.

Most notably in the differences in resource use quantities is the amount of inpatient days per 4-week cycle of 1.73 in azacitidine versus 2.61 in CCR (Celgene Submission, Table 46, p. 134). At the Intensive Care per inpatient day cost used by Celgene of £714, inpatient costs differences between groups accumulate at a rate of £628 per month per patient in Relapse/PD. The CCR per cycle inpatient days figure breakdown by treatment is, as presented in the Excel model file, 1.66, 0.95 and 0.00, for IC, LDAC and BSC (sheet 'Default values' cells I283, M283, Q283). While heterogeneity by pre-selected CCR therapy is to be expected it is unclear why the weighted average across subgroups should differ between azacitidine and CCR in Relapse/PD managed with BSC.

The ERG believes that costs in the Relapse/PD phase should be equal across treatment arms and pre-selected therapy arms, which significantly increases the ICER for azacitidine versus CCR. *Appendix 3* presents the costs per cycle in PD/Relapse under BSC, which were applied to the PD/Relapse state across all arms and therapies within CCR to reflect the assumption that all patients are in the same health state and managed equally.

Another limitation was that the costs of managing AEs in patients from azacitidine and CCR groups were estimated as the product of the probability of at least one TEAE of Grade > 3 per 100 person-years and the average cost of managing grade 3 or 4 TEAEs observed in the AZA-AML-001 trial. The average cost was calculated as arithmetic average of the treatment costs of anaemia, neutropenia, febrile neutropenia, thrombocytopenia, pneumonia and worsening AML. Furthermore, it was assumed that the most frequent TEAEs of grade 3 or 4 and their incidence rates in azacitidine and CCR groups are the same.

In the executable model, the costs of managing AEs in azacitidine and CCR patients have only been accounted as a one-off initial cost, which is at odds with the way the associated quality of life effects were implemented in the model (see *Section 5.3.7*).

5.3.9 Cost-effectiveness results

The deterministic base case ICER presented by Celgene is £20,648 per QALY. Comparison of Tables 56 on QALYs and 57 on Costs results in the submission, (Celgene Submission, Tables 56 and 57, p. 146-147), reproduced below, points to RFS and Relapse/PD as the phases in the model where the largest outcome differences between treatment groups appear. While in the RFS phase azacitidine is associated with a [redacted] increase in utilities over CCR that is accompanied by a [redacted] increment in costs. As for the Relapse/PD phase these

figures are [redacted] and [redacted]. Consistent with our critique in *Section 5.3.6.1* these results may be biased as they are derived from extrapolations of RFS data based on parametric functions that invalidly imply proportional hazards, and which determine the length of Relapse/PD phase given that OS duration was determined separately from PFS and RFS duration. Further, as discussed in the previous section and in *Sections 5.3.8.1* and *5.3.8.2*, the estimation of costs in RFS is incorrect due to invalid account for the number of treatment cycles and counting two cycles instead of one in the first model cycle.

Table 55: Summary of QALYs by health state in company base case

Health state	QALY azacitidine	QALY CCR	Increment	Absolute increment	% absolute increment
RFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: QALY, quality-adjusted life-year, CCR; conventional chemotherapy regimens, RFS; relapse free survival, PFS; progression free survival PD, progressive disease
Source: Celgene Submission, Table 56, p.146

Table 56: Summary of costs by health state in company base case

Health state	Cost azacitidine	Cost CCR	Increment	Absolute increment	% absolute increment
RFS	[redacted]	£6,503	[redacted]	[redacted]	[redacted]
PFS	[redacted]	£22,235	[redacted]	[redacted]	[redacted]
PD	[redacted]	£6,260	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	£5,609	[redacted]	[redacted]	[redacted]
Total	[redacted]	£40,608	[redacted]	[redacted]	[redacted]

Key: CCR; conventional chemotherapy regimens, RFS; relapse free survival, PFS; progression free survival PD, progressive disease
Source: Celgene Submission, Table 57, p.147

In addition, the PD costs assume healthcare resource utilisation associated with BSC, whereas, as discussed in *Section 5.3.6.2*, estimates of relative overall survival effectiveness and thus duration of the PD phase were estimated on AML-AZA-001 study data that were affected by the use of subsequent AML active therapy, to a larger extent in the azacitidine than the CCR arm.

5.3.10 Sensitivity analyses

When sampling uncertainty in the parameter values used in the base case were accounted for, the probabilistic sensitivity analysis resulted in an ICER of £17,423 per QALY, which is lower than the base case deterministic ICER of £20,648 per QALY. Taken at face value these different results between the deterministic and PSA results would suggests that there are important nonlinearities in the model that make PSA results more adequate estimates of cost-effectiveness than the deterministic values. However, the ERG found a number of problems as discussed before in this critique, which invalidate both the deterministic and PSA results. The ERG has corrected some errors in the implementation of the model and estimates of some parameter values populating it, as presented below in *Table 57*.

Despite the limitations identified in the model from which Celgene derived their base case cost-effectiveness results, its analysis of the most influential individual parameter values provides guidance as to which elements may need special consideration in assessing the validity of results. As described in *Section 5.2.9.1* (*page 92*), ICER results are most sensitive to variation in the costs of drug administration in CCR, followed by the hazard ratio of OS, with acquisition costs of AZA, administration costs of AZA and the HR of RFS being the fourth, fifth and sixth most influential parameters. In these parameters ERG found flaws either in model implementation or parameter estimation, as discussed above. To illustrate the importance of this, Celgene reports that a 20% increase in the value of these parameters is associated with an increase of their base case results of 155%, 44%, 113%, 98% and 78% (Celgene submission, Table 61, p. 153).

Of particular interest is the subgroup analysis of patients who would be candidates for LDAC under the control situation. In this group Celgene's scenario analysis is reported to result in an ICER of £25,136 per QALY with IPCW adjustment for treatment switching in the control arm. However, some 28% of the azacitidine arm subjects received subsequent active treatment but their health outcomes and costs were not adjusted for the effect of subsequent lines of treatment. This caveat is also relevant for the comparison of patients pre-selected for BSC and for IC controls, where according to results presented by Celgene, azacitidine generates more QALYs and has lower costs relative to BSC and IC. However, as explained next, the results of this subgroup analyses did not collectively pass a fundamental validation test.

Celgene provides the results of a scenario where the distribution of patients by pre-selected CCR treatment is that observed in clinical practice from HMRN registry data ([redacted] IC, [redacted] LDAC, [redacted] BSC) instead of the original trial case mix (18%, 64% and 18%, respectively). The ICERs change from £20,648 to -£57,756 per QALY, i.e., to the result that azacitidine is both more effective and less costly than CCR. Although an improvement in cost-effectiveness of azacitidine is to be expected when applying a distribution of the patient population with a larger proportion of patients in poorer health condition and thus eligible to receive BSC under CCR, as in AZA-AML-001 the largest detectable difference was found precisely in those patients, these are unexpectedly large results. ERG replicated these results to a small degree of discrepancy (-£57,968 versus -£57,656 per QALY), using the weighted average method described by Celgene in its submission (Celgene submission, Section 5.8.3, p. 155). However when ERG tried to replicate the base case results using the same method we obtained and ICER of -£17,960 per QALY (azacitidine dominant), quite a different result from the base case model result of £20,648 per QALY. This suggests that the method used by Celgene to calculate an alternative ICER based on HMRN data may not be compared with that used in the base case. It must be noted that this discrepancy is despite both the subgroup analysis by CCR pre-selected treatment and the analysis of the overall sample using the same OS effectiveness estimates, i.e., the exponential extrapolation using the adjusted IPCW HR estimate of [redacted].

The inability to replicate the base case results using the weighted average method described in the Celgene submission poses a severe limitation to ERG's ability to correct the most important flaws of the model submitted by Celgene. This is because the error incurred by the company in implementing the number of treatment cycles described in *Section 5.3.8.1* (*page 122*) may only be corrected, within their model, by separately calculating costs and QALYs for each CCR pre-selected treatment subgroup and combining results using weighted

averages of costs and of QALYs using the patient distributions in AZA-AML-001, in the same way as the company did for their sensitivity analysis of the HMRN patient population. Our corrected results presented in *Section 6* (*page 130*) are subject to this caveat.

5.3.11 Model validation and face validity check

5.3.11.1 Internal validity

We conducted two assessments of internal validity of the model submitted by Celgene. First, we compared the mean number of treatment cycles produced by the model in the azacitidine arm with the reported mean number of cycles in AZA-AML-001.[45] As discussed in *Section 5.3.8.1* we found that the model underestimated the mean number of treatment cycles, and this was due to an error of implementation in that the maximum number of treatment cycles allowed by the model was 8 (after rounding 8.8 to the lowest integer), thus overlooking the fact that a proportion of the modelled cohort would have made a transition to Relapse/PD and therefore be receiving no treatment within those first 8 cycles. Similar but more severe underestimation problems applied to the active treatments in the CCR arm.

The second validity check compared the overall survival outputs from the model with the respective outcome in the original trial report, for the azacitidine arm. In this case the model overestimated the observed data; the median overall survival was approximately 11.5 in the model base case (exponential distribution) versus 10.4 months in the Kaplan-Meier OS curve in AZA-AML-001 (Figure 1A of Dombret et al. 2015[45]). Incidentally, the model output was closer to the median OS obtained by censoring data at switch to subsequent AML therapy, i.e., 12.1 months (Figure 1B of Dombret et al. 2015[45]).

5.3.11.2 Model implementation checks

We conducted a list of model checks, including black-box tests (varying inputs and checking for the anticipated impact on outputs) and checking individual formulae in the model. We highlight below problems identified by this and a subsequent process that sought to replicate model results in the submission.

In calculating the costs of drug administration, monitoring tests and transfusions corresponding to stable disease ("Model CCR" and "Model AZA" columns AB:AD), the company subtracted a portion of these costs equal either to the differences between the proportion of patients in the modelled cohort who were in Non-remission and the proportion of patients who were in remission at each cycle, or to zero, whichever of the two quantities was higher. This was found to have no rational basis and was not explained nor described in the submission.

The model was also subject to verification tests, where individual parameters' values in the model were varied and results compared to *a priori* expectations. Further, the ERG identified an error in the formulae referencing the Kaplan-Meier curves for PFS and RFS in the "KM" worksheet (DD:DI columns). This is correction was important in the light of ERG's preference for using Kaplan-Meier time to event curves to model the evolution in these outcomes, as described in the next section.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

5.4.1 Corrected base case

The ERG identified a number of implementation errors in the model submitted by Celgene and corrected them, as shown in *Table 57*.

Table 57: Corrections to the implementation of Celgene's model

Celgene's model	ERG's corrections
The costs of drug administration, tests and transfusions in LDAC patients were estimated for 8 model cycles, as for azacitidine, instead of 6.1 cycles reported in the submission (AB, AC and AD in 'Model CCR').	Corrected to incorporate changes in the mean number of treatment cycles for LDAC patients
Transfusion costs pre-response in CCR arm were modelled using the corresponding costs for azacitidine group ('Model CCR'!AD23)	Corrected
Transfusion costs in cycles 2+ in CCR arm were modelled incorrectly: the cost of transfusion in remission state was assumed to be equal to the transfusion costs in patients with stable disease ('Model CCR'!AD24:153).	Corrected
Cytarabine daily dose for LDAC assumed mg/m² (resulting in 71.82 mg/day) instead of 39.9 mg/day reported in CSR. However, it has no effect on costs in the base case and has a minimal effect on ICER in scenario analyses for no wastage and wastage with 30% tolerance ('HRU costs'!C115:117).	39.9 mg/day of cytarabine in LDAC patients
Kaplan-Meier OS, PFS and RFS curves for the overall sample were incorrectly referenced to the IC curves in the KM worksheet (DD:DI columns)	Corrected
Costs of tests and transfusions in PD state were not modelled by Celgene	Corrected
Celgene assume the drug administration costs for IC patients after cycle 3	Corrected
"BSC only" patients are assumed to incur drug administration costs	Corrected
Wastage with 30% tolerance was coded incorrectly	Corrected
The number of treatment cycles for which drug administration, monitoring tests and transfusions costs were accounted was two in the first treatment cycle (AB23, AC23 and AD23 in Model AZA and Model CCR), in contrast to drug acquisition costs for which only one cycle was accounted in the first cycle (AA23 in Model AZA and Model CCR sheets).	Corrected

Key: CCR, conventional care regimen; CSR, clinical study report; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LDAC, low-dose cytarabine; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival

5.4.2 ERG preferred base case

The corrections to the implementation were followed by a series of changes made to the model parameter values to reflect what ERG considers the best values to reflect current UK practice and model logic. The results of these changes are presented as a sequence of cumulative changes in *Section 6*.

5.4.2.1 Calibrating the number of treatment cycles

The maximum number of treatment cycles of azacitidine treatment was set to 19, in order to match the 8.80 mean number of cycles in the respective arm of AZA-AML-001.[45] Similarly the maximum number of treatment cycles of LDAC was set to 10 to match the respective mean reported in the trial of 6.1 cycles of treatment. The IC was set to a maximum of two cycles as specified in the trial protocol and reported in the submission.

5.4.2.2 Equalising costs of relapse and progressive disease across treatments

The frequency and amount of use of medical staff, monitoring and outpatient procedures and hospitalisations used by patients managed under BSC in the progressive disease/relapse state as estimated from clinical opinion surveyed by Celgene was applied to IC and LDAC preselected CCR patients and azacitidine patients that were in the progressive disease or relapse health state. *Appendix 3* details the costs used in PD/Relapse by ERG for its preferred base case analysis.

5.4.2.3 Adjusting overall survival in both arms for subsequent active treatment

The ERG set the OS curves to the Censor At Switch analysis mode in Celgene's model, keeping the exponential functional form adopted in Celgene's base-case. This choice was associated with a hazard ratio of 0.72, which corresponded to the analysis that was unadjusted for baseline covariates. Given the high ICERs that were obtained after the preceding revisions in *Sections 5.4.2.1* and *5.4.2.2*, the effect of adopting the smaller hazard that resulted from censored at switch analysis that adjusted for baseline covariates was investigated in exploratory analyses.

5.4.2.4 Fitting separate parametric survival curves to relapse-free survival and progression-free survival in each arm

Since finding the optimal fitting functional form for RFS and PFS is highly uncertain as discussed in this report, the ERG adopted the observed non-parametric Kaplan-Meier curves from the trial for these outcomes. The rationale for this choice is further strengthened by the fact that the Kaplan-Meier curves are almost completely observed by the end of the observation period at 37 months and extrapolation is not necessary. Neither is it obvious that adjusting those survival curves for any observed confounders is practicable or indeed desirable.

5.4.2.5 Adjusting overall survival for baseline covariates

The effect of using the OS hazard ratio estimate of 0.64 from the exponential model adjusted for baseline covariates, which found support in statistical tests conducted by the ERG, was investigated.

5.4.3 Exploratory analyses

The ERG sought to perform some exploratory assessment of the subgroup analysis by preselected CCR treatment, while acknowledging that for PFS and RFS outcomes, the sample sizes make subgroup-specific time to event data highly unreliable. Thus in these analyses subgroup specific differences in OS outcomes were allowed using censor-at-switch data, while keeping common PFS and RFS curves across the three subgroups.

5.5 Conclusions of the cost-effectiveness section

The ERG identified several issues with the company's submitted economic evaluation.

The model assumed that no patients would receive active treatment following discontinuation of first-line treatment. In the AZA-AML-001 trial underpinning the analysis, 29% of participants received active second-line treatment. Advice from clinical experts suggests that active second-line treatment is considered for some patients in the NHS.

The model assumed proportional hazards for all time-to-event outcomes, even though this was not supported for overall survival and relapse-free survival by results from the AZA-AML-001 trial.

Overall survival in the AZA arm was not adjusted for subsequent active treatment, resulting in an inconsistency between the modelled health outcomes and costs, since only the costs of best supportive care were modelled following azacitidine.

Implementation issues were identified in the model. The most significant of these was an error in the calculation of the duration of first-line treatment which resulted in an underestimate of the drug acquisition and administration costs in both arms.

The ERG also identified that there were significant differences in the cost associated with the Relapse/progressive disease state between the AZA and CCR arm, even though all patients (in both arms) are expected to be receiving BSC at this point.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG's preferred base case ICER is £169,606 per QALY (see *Table 58* and *Table 59*).

Corrections to implementation errors in the model increased the ICER from the base case £20,648 to £62,518 per QALY (analysis A).

Analyses B to G are the additional changes made to reach the ERG's preferred base case. Of these, two independently lead to significant increases in the ICER: calibrating the number of treatment cycles to match the mean number of cycles in AZA-AML-001[45] increases the ICER to £131,698 per QALY; setting the costs of relapse/progressive disease equal across the arms increases the ICER to £159,352 per QALY. Two independently lead to reductions in the ICER: adjusting overall survival for treatment switching in both arms reduces the ICER to £47,482 per QALY; adjusting overall survival for baseline covariates reduces the ICER to £39,145 per QALY. Using Kaplan-Meier relapse-free survival has little impact on the ICER (£63,569 per QALY). Using Kaplan-Meier progression-free survival increases the ICER to £75,471 per QALY.

Table 58: Corrected base case and elements of ERG preferred base case

Analysis	Outcome	Azacitidine	CCR	Difference
Celgene base case	Costs	[redacted]	£40,608	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£20,648
A = Corrected base case[a]	Costs	[redacted]	£45,954	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£62,518
A + B = A **and** Calibrating number of treatment cycles[b]	Costs	[redacted]	£50,064	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£131,698
A + C = A **and** Using the same costs of Relapse/PD across treatments[c]	Costs	[redacted]	£68,688	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£159,352
A + D = A **and** Overall survival adjusted for treatment switching in both arms[d]	Costs	[redacted]	£52,225	[redacted]
	QALYs	[redacted]	0.728	[redacted]
	ICER (cost per QALY gained)			£47,482
A + E = A **and** Kaplan-Meier RFS curves for each trial arm[e]	Costs	[redacted]	£46,221	[redacted]
	QALYs	[redacted]	0.636	[redacted]
	ICER (cost per QALY gained)			£63,569
A + F = A **and** Kaplan-Meier PFS curves for each trial arm[e]	Costs	[redacted]	£45,753	[redacted]
	QALYs	[redacted]	0.635	[redacted]
	ICER (cost per QALY gained)			£75,471
A + G = A **and** Relative OS effects from adjusted parametric curves[f]	Costs	[redacted]	£36,028	[redacted]
	QALYs	[redacted]	0.391	[redacted]
	ICER (cost per QALY gained)			£39,145

Key: CCR, conventional care regimen; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PD, progressive disease; PFS, progression-free survival; QALY, quality-adjusted life year; RFS, relapse-free survival

Notes: a, See *Table 57*; b, See *Section 5.4.2.1*; c, See *Section 5.4.2.2*; d, See *Section 5.4.2.3*; e, See *Section 5.4.2.4*; f, See *Section 5.4.2.5*

Table 59: Derivation of the ERG's preferred base case

Analysis[a]	Outcome	Azacitidine	CCR	Difference
Celgene base case	Costs	[redacted]	£40,608	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£20,648
A = Corrected base case	Costs	[redacted]	£45,954	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£62,518
A + B	Costs	[redacted]	£50,064	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£131,698
A + B + C	Costs	[redacted]	£72,798	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£238,674
A + B + C + D	Costs	[redacted]	£91,847	[redacted]
	QALYs	[redacted]	0.728	[redacted]
	ICER (cost per QALY gained)			£171,511
A + B + C + D + E	Costs	[redacted]	£92,676	[redacted]
	QALYs	[redacted]	0.727	[redacted]
	ICER (cost per QALY gained)			£174,205
A + B + C + D + E + F	Costs	[redacted]	£98,046	[redacted]
	QALYs	[redacted]	0.724	[redacted]
	ICER (cost per QALY gained)			£246,488
A + B + C + D + E + F + G = ERG preferred base case	Costs	[redacted]	£41,161	[redacted]
	QALYs	[redacted]	0.390	[redacted]
	ICER (cost per QALY gained)			£169,606

Key: CCR, conventional care regimens; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year
Note: a, See *Table 58*

6.1 Exploratory analyses

Exploratory subgroup analyses by preselected CCR treatment using the changes A–F described in *Table 58* by the ERG produce ICERs above £100,000 per QALY for all subgroups (*Table 60*). An adjustment for baseline covariates, which is not reliable due to the small sample sizes available within each group, would be expected to reduce these figures but they would remain around the £100,000 per QALY value.

Table 60: Scenarios explored for subgroup analysis explored by ERG

Scenario			Pre-selected CCR therapy subgroup	Incremental		ICER (cost per QALY)[b]
Analysis	PFS and RFS	OS		Costs	QALYs	
Celgene	PH Gompertz and PH Weibull	IPCW applied to CCR arm for switching to azacitidine	IC	[redacted]	[redacted]	-£52,184
			LDAC	[redacted]	[redacted]	£25,136
			BSC	[redacted]	[redacted]	-£169,672
Celgene	PH Gompertz and PH Weibull	ITT	IC	[redacted]	[redacted]	-£85,266
			LDAC	[redacted]	[redacted]	£41,671
			BSC	[redacted]	[redacted]	-£50,300
ERG[a]	Kaplan-Meier	Censored at switch for any active AML treatment	IC	[redacted]	[redacted]	£210,767
			LDAC	[redacted]	[redacted]	£276,260
			BSC	[redacted]	[redacted]	£98,715
ERG[a]	Kaplan-Meier	ITT	IC	[redacted]	[redacted]	£122,722
			LDAC	[redacted]	[redacted]	£408,492
			BSC	[redacted]	[redacted]	£80,952

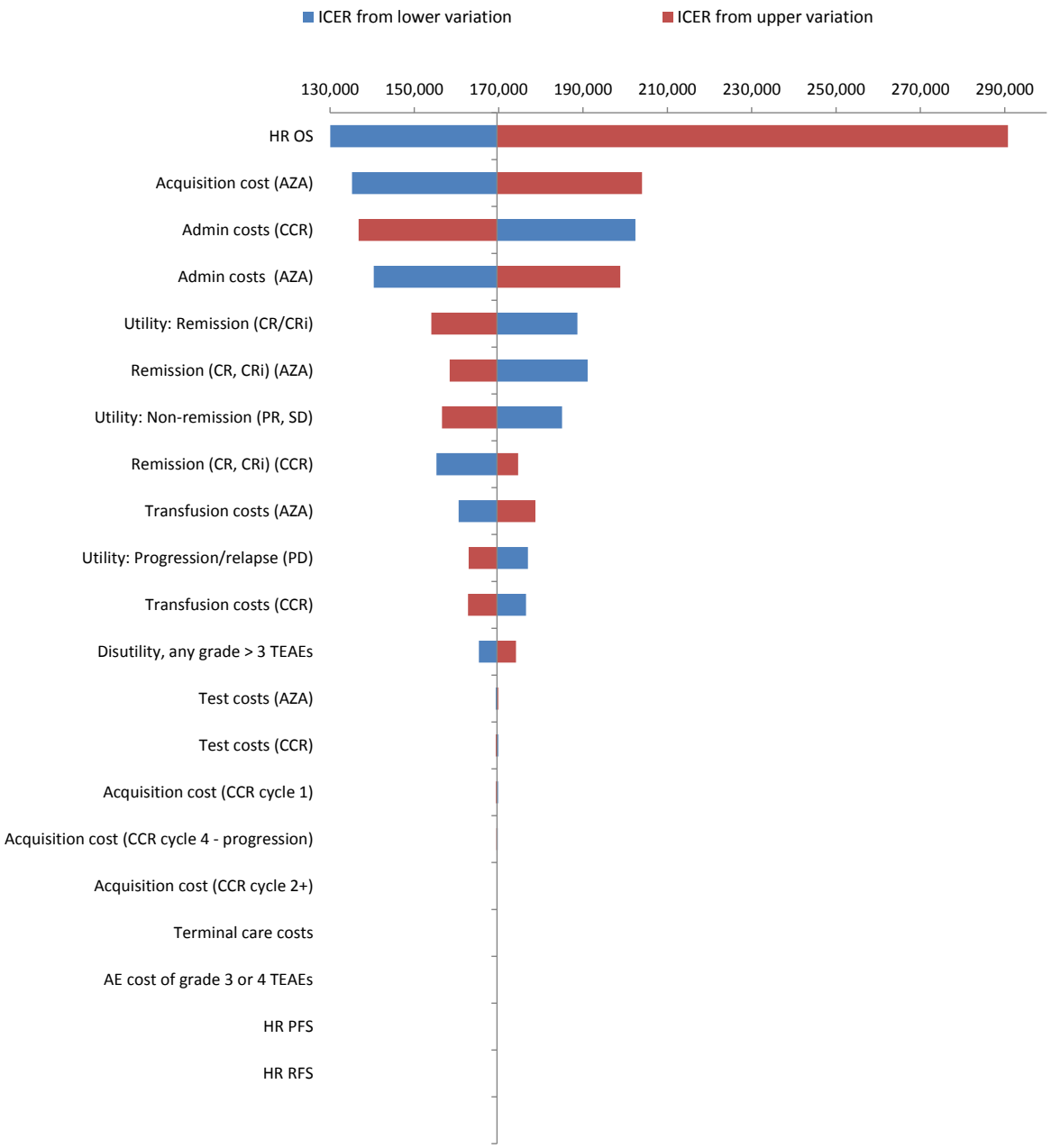
Key: AML, acute myeloid leukaemia; BSC, best supportive care; CCR, conventional care regimens; ERG, Evidence Review Group; IC, intensive chemotherapy; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weight; ITT, intention-to-treat; LDAC, low-dose cytarabine; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; QALY, quality-adjusted life year; RFS, relapse-free survival

Notes: a, Includes corrections and changes as described in *Table 59* except for component 'G' (i.e., not including adjustment for baseline covariates); b, Negative ICERs indicate azacitidine is dominant

6.2 Univariate sensitivity analyses

The univariate sensitivity analysis with the base case preferred by ERG is presented in the tornado analysis of *Figure 23*; plausible variation of parameter values results in ICERs above £130,000 per QALY.

Figure 23: Tornado diagram of ERG's preferred base case deterministic analysis



Key: AZA, azacitidine; CCR, conventional care regimens; CR, complete remission; CRi, complete remission with incomplete blood count recovery; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RFS, relapse-free survival; SD, stable disease; TEAE, treatment emergent adverse event

6.3 Probabilistic sensitivity analysis

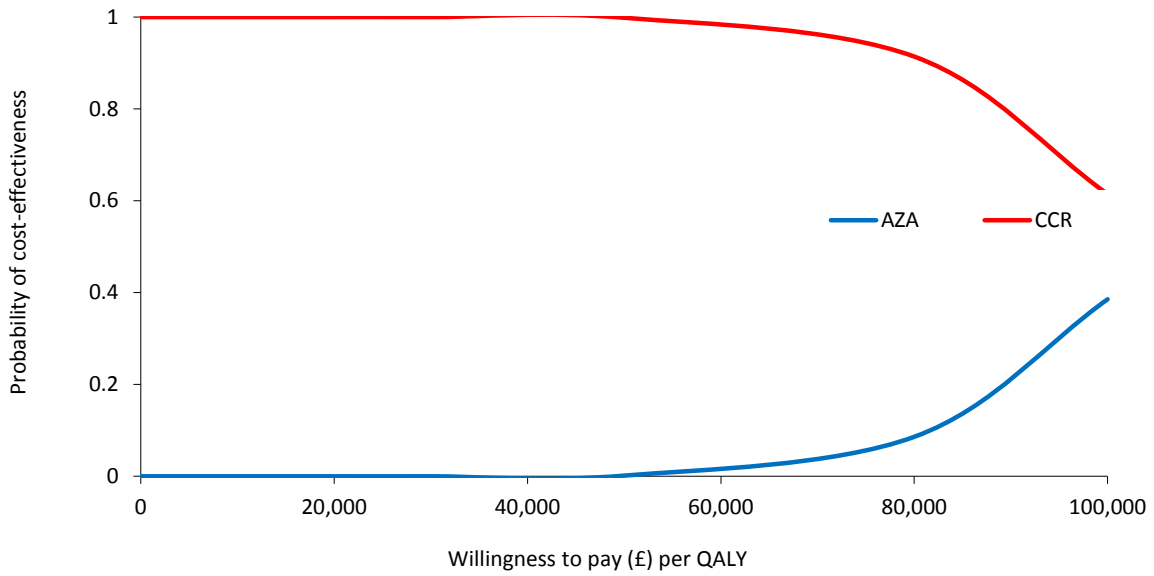
A probabilistic sensitivity analysis was conducted for the ERG's preferred base case (Table *61*). An ICER of £182,151 per QALY was obtained, which is similar to the deterministic ICER of £169,606 per QALY. *Figure 24* presents the cost-effectiveness acceptability curves from the probabilistic sensitivity analysis in the ERG's preferred base case. At a willingness to pay threshold of £100,000 the probability of azacitidine being cost-effective is less than 40%.

Table 61: Cost-effectiveness results for ERG's preferred base case probabilistic sensitivity analysis

Arm	Total			Incremental			ICER (cost per QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
CCR	£41,063	0.5478	0.3911	—	—	—	—
Azacitidine	[redacted]	0.8186	[redacted]	[redacted]	0.2708	[redacted]	£182,151

Key: CCR; conventional care regimens; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 24: Cost-effectiveness acceptability curves from ERG's preferred base case probabilistic sensitivity analysis



Key: AZA, azacitidine; CCR, conventional care regimens; ERG, Evidence Review Group; QALY, quality-adjusted life year

7 End of life

The NICE Guide to the methods of technology appraisal[41] indicates that while in the reference case all QALYs are regarded as being of equal weight, the Appraisal Committee can consider QALY weighting in the case of life-extending treatment at the end of life.

Celgene included an assessment of three criteria (all of which should be met for end of life consideration), and this is reproduced accompanied by ERG comments in *Table 62*.

Table 62: Assessment of end-of-life criteria

Criterion	Data available (Celgene)	ERG comment
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS reported in the literature ranges between 1.5 months (aged >65 years) and 2 months (aged >55 years)[18, 19]	Median OS in AZA-AML-001 trial is 6.5 months without azacitidine treatment. Restricted mean survival at 30 months is estimated to be 10.55 months (*Appendix 4*). Azacitidine is also indicated for intermediate-2 and high-risk myelodysplastic syndromes, CMML with 10–29% marrow blasts without myeloproliferative disorder and AML with 20–30% blasts and multi-lineage dysplasia. The results of the AZA-001 trial in this population suggest median OS of 15.0 months without azacitidine treatment.[69]
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	Median OS based on the primary endpoint was 10.4 months in the azacitidine group and 6.5 months in the CCR group, providing an OS benefit of 3.8 months with azacitidine. As reported in Section 4.7 [of Celgene's submission], various pre-defined analyses demonstrated that treatment with azacitidine provided a statistically significant survival benefit versus CCR	Extension to life should be assessed considering differences in mean overall survival in addition to median OS. ERG analyses based on restricted mean survival at 30 months suggest an extension to life of 1.8–2.5 months (depending on how treatment switching is handled – see *Appendix 4*). The estimated improvement in restricted mean OS is greatest for patients pre-selected to BSC, although comparisons to individual CCR are subject to uncertainty.
The treatment is licensed or otherwise indicated for small patient populations	The estimated total population for all licensed indications in England is 3,354, consisting of 1,026 covered by the proposed new indication and 2,328 for all existing indications. See additional detail provided [in Celgene submission, Section 4.13.2, pp. 97–98]	No comment.

Key: AML, acute myeloid leukaemia; BSC, best supportive care; CCR, conventional care regimen; CMML, chronic myelomonocytic leukaemia; ERG, Evidence Review Group; OS, overall survival; NHS, National Health Service.

Source: Celgene submission, Table 28, p.97

The NICE guide also indicates that the Committee will need to be satisfied that the estimates of the extension to life are robust, and that the assumptions used in the reference case economic modelling are plausible, objective and robust.

The ERG considers that the estimates of extension to life are not robust. The company's estimate based on median overall survival difference is not robust as it is does not reflect the convergence of survival curves seen in AZA-AML-001. Overall survival benefit was also the primary endpoint of AZA-AML-001 and this did not reach statistical significance. Estimates of overall survival are affected by adjustments for baseline imbalances and for subsequent active treatment.

The ERG conducted additional analyses of the restricted mean overall survival at 30 months (see *Appendix 4*) and found that the survival gain was less than three months on average for azacitidine versus CCR.

The ERG also considers that the assumptions used in the company's economic modelling were not plausible or robust. In *Section 6* (*page 130*) the ERG show the results of correcting these assumptions and implementation errors. The ERG's preferred base case ICER is considered to be more plausible, objective and robust.

8 Overall conclusions

The ERG believes that by limiting the comparators in the decision problem to a combined CCR comparator, there is the possibility of azacitidine being recommended or not recommended inappropriately for certain patients (according to the most appropriate CCR for them). Although it is claimed that these patients cannot be reliably and objectively identified, they are at least sufficiently identifiable for CCR regimens to be assigned both in routine clinical practice and in the pivotal RCT. In the absence of high-quality clinical effectiveness data on the clinical value of azacitidine versus individual conventional care regimens, clinical decision making may be made more challenging if azacitidine is recommended for all elderly AML patients with >30% blasts.

Of the key changes made to the economic model by the ERG in arriving at their preferred base case (ICER £169,606 per QALY), the following might be considered to be differences of opinion between the company and the ERG:

- Adjustment of overall survival in the azacitidine and CCR arms for subsequent active treatment – the company only adjusted survival in the CCR arm (for subsequent treatment with azacitidine), while the ERG has adjusted survival in both arms for any active treatment for AML;
- Equalising costs per month spent in the Relapse/progressive disease state – the company assumed significant incremental costs in the CCR arm despite all patients in the model receiving best supportive care only in this state; their assumption is based on a questionnaire-based survey of clinicians, but expert opinion solicited by the ERG does not support this assumption;
- Replacing parametric survival models for relapse-free and progression-free survival with Kaplan-Meier curves to avoid imposing a proportional hazards assumption – the company used a proportional hazards assumption "for consistency" although they acknowledged it was in contradiction of the data.

The ERG considers that the changes made to the modelled treatment duration cannot be considered matters of opinion and are corrections to implementation errors. After correcting solely for these implementation issues, an ICER of £131,698 per QALY was obtained.

The base case analysis preferred by the ERG has the limitation that the sum of the cohort proportions in PFS and RFS exceeds the proportion alive by the third cycle in the model. Celgene included an adjustment in the model to eliminate such anomalies, but nevertheless this remains a deficiency of the model structure. The ERG has not attempted to correct this, due to the difficulties of fitting plausible parametric models to the PFS and RFS data (as discussed in this critique) and adjusting for baseline covariates, given the small samples available for analysis.

8.1 Implications for research

8.1.1 Clinical effectiveness

Further research is needed to establish the effectiveness of azacitidine in elderly AML patients with >30% blasts. This research should be powered to detect clinically meaningful improvements in survival between azacitidine and individual conventional care regimens.

The statistical analyses planned for the research should account for the likelihood of non-proportional hazards and for treatment switching, with adequate data collection to support multiple plausible statistical models.

8.1.2 Health-related quality of life (HRQoL)

This research should also collect HRQoL data measured using a generic (as opposed to condition-specific) and validated instrument, which allow outcomes to be valued using preferences from the general public (preferably EQ-5D) and is preferred for economic analyses. Significant efforts should be made to collect HRQoL data across all patients and across all time points to reflect the full range of quality of life experienced by patients.

8.1.3 Healthcare resource use

Further research (likely separate from the research above) is required to accurately estimate healthcare resource use in elderly AML patients with >30% blasts within the NHS. For conventional care regimens this should be based on routine clinical practice. For azacitidine, this may involve a pilot study, or, if azacitidine receives a positive recommendation from NICE, prospective collection of healthcare resource use data, and collection of data relating to the most clinically appropriate alternative treatment for each patient.

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List of appendices

Appendix 1: Additional clinical effectiveness results from AZA-AML-001

Appendix 2: Statistical analysis of individual patient data for overall survival in AZA-AML-001

Appendix 3: Resource use values applied by ERG to Relapse/PD phase across all arms for calculating their preferred base case analysis

Appendix 4: Estimation of restricted mean overall survival in AZA-AML-001

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts

Addendum

This addendum updates and replaces Section 6 “Impact on the ICER of additional clinical and economic analyses undertaken by the ERG”.

An error was identified in the ERG’s estimate of the baseline overall survival curve adjusted for baseline covariates. This has been corrected and the effect on the results has been reflected in the new Section 6. The ERG has also made certain clarifications within the section and has conducted additional exploratory analyses.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG's preferred base case ICER is £273,308 per QALY (see *Table 58* and *Table 59*).

Corrections to implementation errors in the model increased the ICER from the base case £20,648 to £62,518 per QALY (analysis A).

Analyses B to G are the additional changes made to reach the ERG's preferred base case. Of these, two independently lead to significant increases in the ICER: calibrating the number of treatment cycles to match the mean number of cycles in AZA-AML-001[45] increases the ICER to £131,698 per QALY (analysis B); setting the costs of relapse/progressive disease equal across the arms increases the ICER to £159,352 per QALY (analysis C).

The primary focus of analysis D is to change the way overall survival is modelled by censoring for treatment switching in both arms. As a side effect (due to the model wiring) this also results in changes to the modelling of relapse-free and progression-free survival, again to censor for treatment switching in both arms. The effect of this analysis is to reduce the ICER to £47,482 per QALY.

Analysis E replaces the parametric proportional hazards progression-free survival curves with Kaplan-Meier curves and increases the ICER to £75,471 per QALY.

Using Kaplan-Meier curves for relapse-free survival (analysis F) has little impact on the ICER (£63,569 per QALY).

Adjusting overall survival for treatment switching (censoring at switch in both arms) and baseline covariates (analysis G) increases the ICER to £65,188 per QALY. The reason the ICER for analysis G is higher than the ICER for analysis D is that analysis G does not have the side effects on relapse-free and progression-free survival and so azacitidine patients spend longer in the progressive disease model state with high costs and low utility.

Table 58: Corrected base case and elements of ERG preferred base case

Analysis	Outcome	Azacitidine	CCR	Difference
Celgene base case	Costs	[redacted]	£40,608	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£20,648
A = Corrected base case[a]	Costs	[redacted]	£45,954	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£62,518
A + B = A **and** Calibrating number of treatment cycles[b]	Costs	[redacted]	£50,064	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£131,698
A + C = A **and** Using the same costs of Relapse/PD across treatments[c]	Costs	[redacted]	£68,688	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£159,352
A + D = A **and** Overall survival adjusted for treatment switching in both arms[d]	Costs	[redacted]	£52,225	[redacted]
	QALYs	[redacted]	0.728	[redacted]
	ICER (cost per QALY gained)			£47,482
A + E = A **and** Kaplan-Meier RFS curves for each trial arm[e]	Costs	[redacted]	£46,221	[redacted]
	QALYs	[redacted]	0.636	[redacted]
	ICER (cost per QALY gained)			£63,569
A + F = A **and** Kaplan-Meier PFS curves for each trial arm[e]	Costs	[redacted]	£45,753	[redacted]
	QALYs	[redacted]	0.635	[redacted]
	ICER (cost per QALY gained)			£75,471
A + G = A **and** Relative OS effects from adjusted parametric curves[f]	Costs	[redacted]	£44,818	[redacted]
	QALYs	[redacted]	0.622	[redacted]
	ICER (cost per QALY gained)			£65,188

Key: CCR, conventional care regimen; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PD, progressive disease; PFS, progression-free survival; QALY, quality-adjusted life year; RFS, relapse-free survival

Notes: a, See *Table 57*; b, See *Section 5.4.2.1*; c, See *Section 5.4.2.2*; d, See *Section 5.4.2.3*, also note that PFS and RFS are adjusted as a side effect; e, See *Section 5.4.2.4*; f, See *Section 5.4.2.5*

Table 59: Derivation of the ERG's preferred base case

Analysis[a]	Outcome	Azacitidine	CCR	Difference
Celgene base case	Costs	[redacted]	£40,608	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£20,648
A = Corrected base case	Costs	[redacted]	£45,954	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£62,518
A + B	Costs	[redacted]	£50,064	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£131,698
A + B + C	Costs	[redacted]	£72,798	[redacted]
	QALYs	[redacted]	0.637	[redacted]
	ICER (cost per QALY gained)			£238,674
A + B + C + D	Costs	[redacted]	£91,847	[redacted]
	QALYs	[redacted]	0.728	[redacted]
	ICER (cost per QALY gained)			£171,511
A + B + C + D + E	Costs	[redacted]	£92,676	[redacted]
	QALYs	[redacted]	0.727	[redacted]
	ICER (cost per QALY gained)			£174,205
A + B + C + D + E + F	Costs	[redacted]	£98,046	[redacted]
	QALYs	[redacted]	0.724	[redacted]
	ICER (cost per QALY gained)			£246,488
A + B + C + D + E + F + G = ERG preferred base case	Costs	[redacted]	£71,138	[redacted]
	QALYs	[redacted]	0.621	[redacted]
	ICER (cost per QALY gained)			£273,308

Key: CCR, conventional care regimens; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year
Note: a, See *Table 58*

6.1 Exploratory analyses

The ERG explored the extreme case that no healthcare costs are incurred in the Relapse/PD state, which resulted in an ICER of £73,953 per QALY.

In another scenario, in which no inpatient hospitalisations occur in the Relapse/PD state, the resulting ICER was £105,611 per QALY. This scenario may be relevant if 100% of inpatient days in the Relapse/PD phase are incurred due to terminal care; it seems plausible to ERG

that the cost estimate of terminal care of £5,705 in the Celgene model could already account for most hospital costs in PD, and therefore assuming zero inpatient costs may be a plausible scenario.

The base case analysis preferred by ERG included costs of monitoring tests and transfusions for the whole duration of the Remission and Non-remission phases of the model (as well as for the Relapse/PD phase). This was viewed as a correction of Celgene's analysis, which only measured these costs up to the time the patient stopped treatment. The ERG explored the effects of adopting Celgene's assumption: the ICER changed from £273,308 to £260,190 per QALY. Celgene's assumption is unlikely to be correct with respect to transfusions as acknowledged by Celgene's own definition of BSC (Source: Celgene submission, Section 4.3.5, p. 49, and Section 5.2.3, p. 108):

> *BSC: Including but is not limited to red cell or whole blood transfusions, fresh frozen plasma transfusions, platelet transfusions, antibiotic and/or antifungal therapy, and nutritional support). This is continued until death.*

Other scenarios included revising the costs of monitoring tests and transfusions during Relapse/PD to values estimated by a clinical expert consulted by ERG, whereby two units each of red blood cell transfusions and adult doses of platelet transfusions are given on average per 4 week cycle, whilst no bone marrow aspirates or biopsies nor extractions for cytogenetic testing, four blood tests, and two each of peripheral blood smears and serum blood chemistry are given during PD. The resulting ICER was £257,211 per QALY.

Exploratory subgroup analyses by preselected CCR treatment using the changes A–F described in *Table 58* by the ERG produce ICERs above £100,000 per QALY for all subgroups (*Table 60*). Exploratory subgroup analyses were also conducted by preselected CCR treatment using changes A, B and D–F (i.e., leaving in place Celgene's assumptions regarding costs in Relapse/PD), with the result that for patients preselected to intensive chemotherapy an ICER of £73,728 per QALY was obtained, while for other patients the ICER remained over £100,000 per QALY. An adjustment for baseline covariates, which is not reliable due to the small sample sizes available within each group, would be expected to increase the ICERs overall.

Table 60: Scenarios explored for subgroup analysis explored by ERG

Scenario			Pre-selected CCR therapy subgroup	Incremental		ICER (cost per QALY)[a]
Analysis	**PFS and RFS**	**OS**		**Costs**	**QALYs**	
Celgene, adjusted for subsequent therapies	Exponential and Weibull	IPCW applied to CCR arm for switching to azacitidine	IC	[redacted]	[redacted]	-£52,184
	Gompertz and Weibull		LDAC	[redacted]	[redacted]	£25,136
	Exponential and Weibull		BSC	[redacted]	[redacted]	-£169,672
Celgene, unadjusted for subsequent therapies	PH Gompertz and PH Weibull	Exponential	IC	[redacted]	[redacted]	-£85,266
		Gompertz	LDAC	[redacted]	[redacted]	£41,671
		Exponential	BSC	[redacted]	[redacted]	-£50,300
ERG[b]	Kaplan-Meier	Exponential, censored at switch for any active AML treatment	IC	[redacted]	[redacted]	£352,918
			LDAC	[redacted]	[redacted]	£282,589
			BSC	[redacted]	[redacted]	£152,093
ERG[b,c]	Kaplan-Meier	Exponential, censored at switch for any active AML treatment	IC	[redacted]	[redacted]	£73,728
			LDAC	[redacted]	[redacted]	£131,349
			BSC	[redacted]	[redacted]	£135,230
ERG[b]	Kaplan-Meier	ITT, Kaplan-Meier	IC	[redacted]	[redacted]	£414,304
			LDAC	[redacted]	[redacted]	£500,493
			BSC	[redacted]	[redacted]	£137,449

Key: AML, acute myeloid leukaemia; BSC, best supportive care; CCR, conventional care regimens; ERG, Evidence Review Group; IC, intensive chemotherapy; ICER, incremental cost-effectiveness ratio; IPCW, inverse probability of censoring weight; ITT, intention-to-treat; LDAC, low-dose cytarabine; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; QALY, quality-adjusted life year; RFS, relapse-free survival

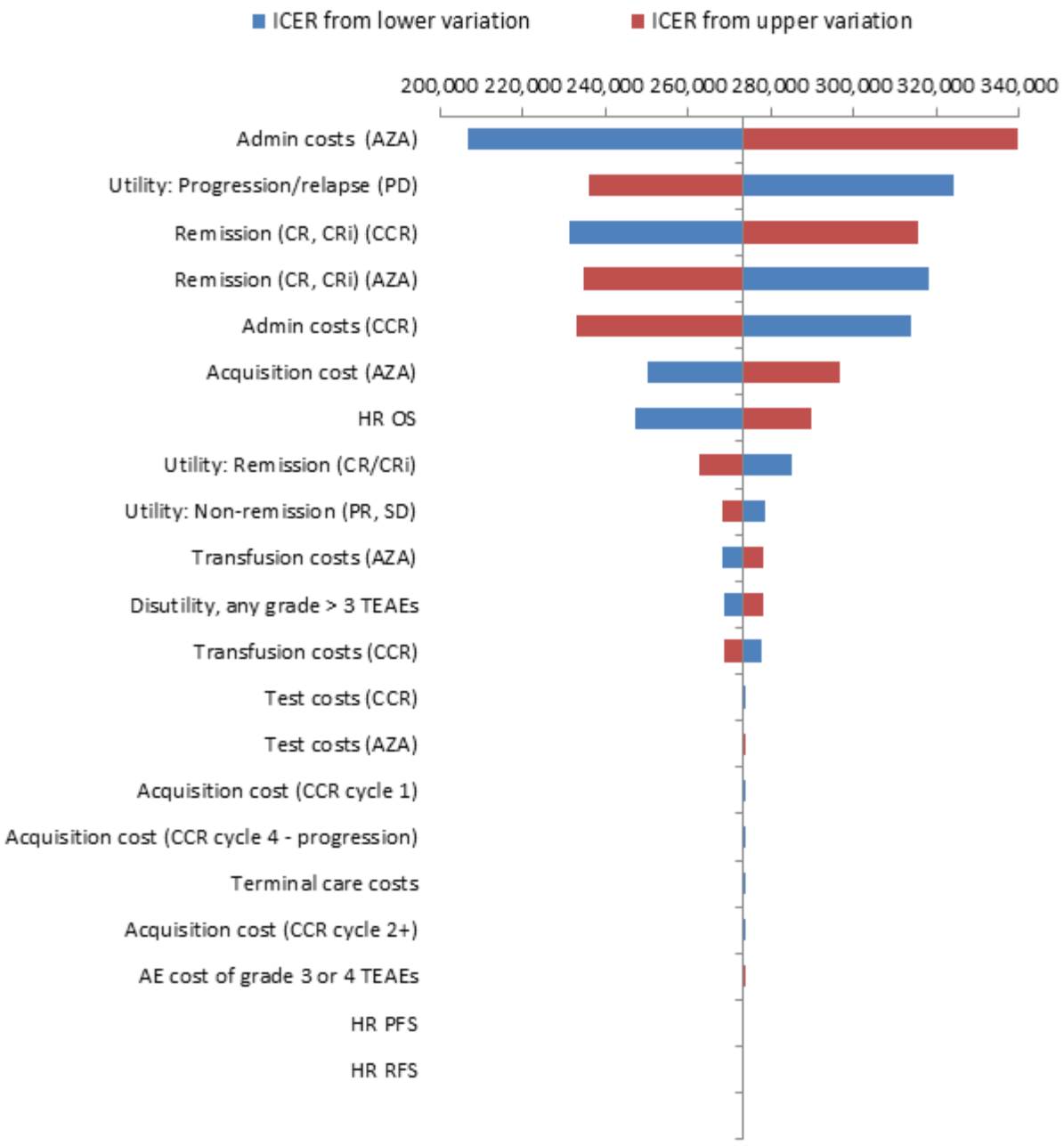
Notes: a, Negative ICERs indicate azacitidine is dominant; b, Includes corrections and changes as described in *Table 59* except for component 'G' (i.e., not including adjustment for baseline covariates); c, Not including component 'C' (i.e., retaining Celgene's estimates for costs in Relapse/PD)

To assess the validity of these analyses, the ERG derived an ICER for the whole population using a weighted average of the incremental costs and QALYs across the three CCR therapy preselected subgroups. The resulting ICER was £269,714 per QALY, compared to an ICER of £246,488 per QALY using changes A–F for the whole population (*Table 59*). This is a discrepancy of less than 10%.

6.2 Univariate sensitivity analyses

The univariate sensitivity analysis with the base case preferred by ERG is presented in the tornado analysis of *Figure 23*; plausible variation of parameter values results in ICERs above £200,000 per QALY.

Figure 23: Tornado diagram of ERG's preferred base case deterministic analysis



Key: AZA, azacitidine; CCR, conventional care regimens; CR, complete remission; CRi, complete remission with incomplete blood count recovery; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RFS, relapse-free survival; SD, stable disease; TEAE, treatment emergent adverse event

6.3 Probabilistic sensitivity analysis

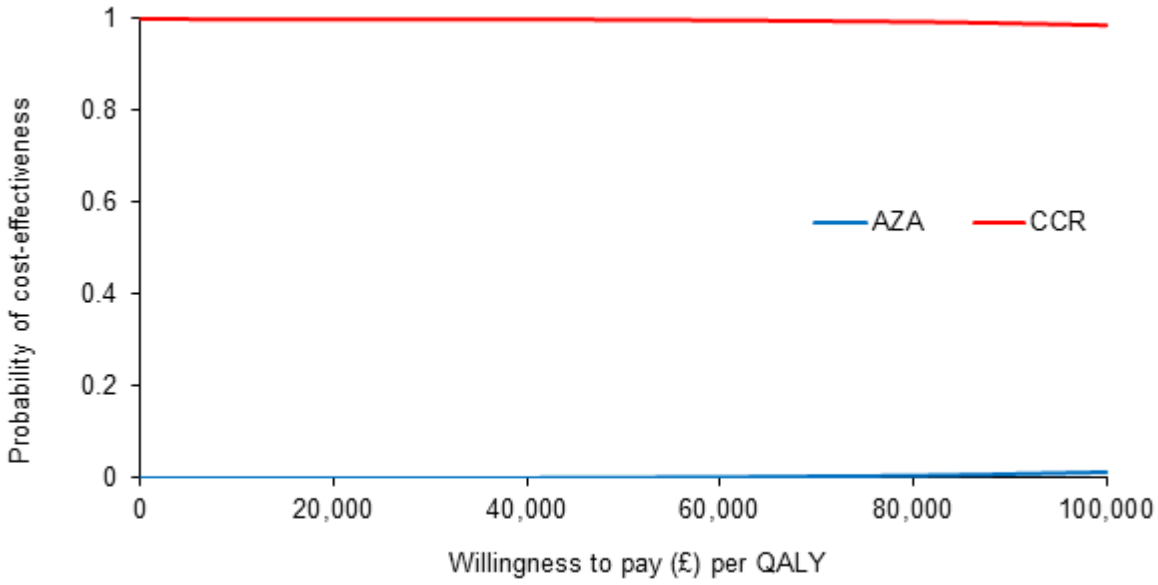
A probabilistic sensitivity analysis was conducted for the ERG's preferred base case (*Table 61*). An ICER of £277,123 per QALY was obtained, which is similar to the deterministic ICER of £273,308 per QALY. *Figure 24* presents the cost-effectiveness acceptability curves from the probabilistic sensitivity analysis in the ERG's preferred base case. At a willingness to pay threshold of £100,000 the probability of azacitidine being cost-effective is less than 5%.

Table 61: Cost-effectiveness results for ERG's preferred base case probabilistic sensitivity analysis

Arm	Total			Incremental			ICER (cost per QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
CCR	£73,152	0.8863	0.6218	—	—	—	—
Azacitidine	[redacted]	1.3302	[redacted]	[redacted]	0.4439	[redacted]	£277,123

Key: CCR; conventional care regimens; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 24: Cost-effectiveness acceptability curves from ERG's preferred base case probabilistic sensitivity analysis



Key: AZA, azacitidine; CCR, conventional care regimens; ERG, Evidence Review Group; QALY, quality-adjusted life year

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts

Errata

Location in report	Original text	Corrected text
Section 1.7, p.17	The ERG preferred base case ICER is £169,606 compared to the company's base case ICER of £20,648 per QALY.	The ERG preferred base case ICER is £273,308 compared to the company's base case ICER of £20,648 per QALY.
Section 1.7, p. 17	Adjusting overall survival for baseline covariates (reduces ICER from £246,488 to £169,606 per QALY).	Adjusting overall survival for baseline covariates (reduces ICER from £246,488 to £273,308 per QALY).
Section 5.3.1, p. 99	EQ-5D survey mapped from disease specific single trial data using a published mapping algorithm.	EQ-5D survey mapped from disease specific single trial data using a published mapping algorithm; a second published algorithm was used for sensitivity analysis.
Section 5.3.1, p. 102	Cycle length is 4 months.	Cycle length is 4 weeks.
Section 5.3.1, p. 103	An error was found in the way parameter values for the number of treatment cycles was inputted in the model, which resulted in a large underestimation in costs of drug acquisition, monitoring tests, transfusions and the company's drug ICER	An error was found in the way parameter values for the number of treatment cycles was inputted in the model, which resulted in a large underestimation in costs of drug acquisition and administration, monitoring tests, transfusions and the company's drug ICER.
Section 5.3.4, p. 106	However, the way parameter values for the number of treatment cycles were implemented in the model was incorrect, resulting in a mean number of treatment cycles in the azacitidine group of 5.6 instead of the intended 8.8, in the CCR group IC of 1.86 instead of 2 (initiation and consolidation) and 4.4 when estimating drug acquisition costs and 5.3 when calculating the costs of drug administration, tests and transfusion instead of 6.10 in the CCR group LDAC.	However, the way parameter values for the number of treatment cycles were implemented in the model was incorrect, resulting in a mean number of treatment cycles in the azacitidine group of 5.6 instead of the intended 8.8, in the CCR group IC of 2.61 instead of 2 (initiation and consolidation), 4.4 when estimating drug acquisition costs and 5.3 when calculating the costs of drug administration, tests and transfusion instead of 6.10 in the CCR group LDAC.

Section 5.3.6.2, p114	The ERG undertook diagnostic tests of the proportional hazards assumption on the adjusted Cox PH OS curves by comparing the cumulative log-log plot of the azacitidine and CCR arms directly as well as testing for time and treatment effect interactions and Schoenfeld residuals (see details in *Appendix 2*). The results of these tests suggest the constant proportional hazards assumption is not supported by the data.	The ERG undertook diagnostic tests of the proportional hazards assumption on the adjusted Cox PH OS curves by comparing the cumulative log-log plot of the azacitidine and CCR arms directly by Schoenfeld residual test; the proportional hazard assumption is not rejected at the 5% level, p=0.068, but graphical inspection suggest the test may not be robust and cast doubt on the appropriateness of the assumption in these data (see details in *Appendix 2*).
Section 5.3.6.2, p.117, Table 53	Bathtub Adjusted for baseline covariates, Azacitidine, AIC 640, BIC	Bathtub Adjusted for baseline covariates, Azacitidine, AIC 648, BIC 718
Section 5.3.6.2, p.117, Table 53	Bathtub Adjusted for baseline covariates, CCR, AIC 645, BIC	Bathtub Adjusted for baseline covariates, CCR, AIC 646, BIC 716
Section 5.3.6.2, p.117, Table 53	Bathtub Notes	Bathtub[c] Notes: c, Bathtub survival function $\exp(-(\exp[(\lambda t)^{\rho}]-1))$. Further details available from ERG upon request.
Section 5.3.6.2, p.117	The adjusted exponential model fitted to both arms results in a HR of 0.64 and has a predicted difference in OS of 3.64 months, in favour of azacitidine; details are presented in the *Appendix 2*.	The adjusted exponential model fitted to both arms results in a HR of 0.65 and has a predicted difference in OS of 3.64 months, in favour of azacitidine; details are presented in the *Appendix 2*.
Section 5.3.6.2, p. 117	*Figure 22* presents the ITT Kaplan-Meier data and the fitted adjusted exponential OS model to data censored at switch to subsequent AML therapy in both trial arms.	*Figure 22* presents the Kaplan-Meier data (censored at switch) and the fitted adjusted exponential OS model to data censored at switch to subsequent AML therapy in both trial arms.
Figure 22, p. 118 (Caption)	Figure 22: Overall survival in AZA-AML-001 – ITT Kaplan-Meier data and adjusted exponential model fitted to censor-at-switch (any AML therapy) data	Figure 22: Overall survival in AZA-AML-001 – Kaplan-Meier data (censored at switch) and adjusted exponential model fitted to censor-at-switch (any AML therapy) data
Figure 22, p. 118	[Figure]	[See Figure 22 below]
Section 5.3.6.2, p.119	As a conservative approach, the ERG's preferred base case analysis adopted the exponential OS HR estimates adjusted for baseline covariates used by the IPCW method, including sex, age, ECOG status, preselected CCR treatment, time since initial AML diagnosis, comorbidity score, in data censored at switch to any subsequent AML treatment from both trial arms in the dataset provided by Celgene to ERG. The resulting HR estimate, 0.64, is more favourable to azacitidine than the respective estimates from applying IPCW to subsequent azacitidine use in CCR	As a conservative approach, the ERG's preferred base case analysis adopted the exponential OS HR estimates adjusted for baseline covariates used by the IPCW method, including sex, age, ECOG status, preselected CCR treatment, time since initial AML diagnosis, comorbidity score, in data censored at switch to any subsequent AML treatment from both trial arms in the dataset provided by Celgene to ERG. The resulting HR estimate, 0.65, is more favourable to azacitidine than the respective estimates from applying IPCW to subsequent azacitidine use in CCR

	only, [redacted] and [redacted] (Celgene's base case), IPCW to any AML in both arms arms, 0.77 and 0.71, and the ITT value of 0.85.[45]	only, [redacted] and [redacted] (Celgene's base case), IPCW to any AML in both arms arms, 0.77 and 0.71, and the ITT value of 0.85.[45]
Section 5.3.6.2, p.120	The subgroup analyses were thus based on the original censor-at switch exponential OS curves estimates used by the company in their model.	The subgroup analyses were thus based on the original censor-at switch exponential OS curves estimates used by the company in their model (alongside Kaplan-Meier curves for censor at switch PFS and RFS data available in the Celgene excel model).
Section 5.3.7, p.120	The QALY impact of AEs was modelled as the probability of at least one TEAE of Grade > 3 per 100 person-years multiplied by the utility of grade > 3 TEAEs. In the model, the effect of AEs on QALYs in azacitidine have been modelled for a maximum of 8.8 treatment cycles, which is effectively less than the mean 8.8 in the trial, while for CCR as a whole they were counted for a maximum number of cycles of 5.1 which is more than the mean number of 2 cycles with IC. These calculations are likely to overestimate the additional costs of CCR relative to azacitidine but this bias had a small effect on the results given other issues identified by the ERG in the model.	The QALY impact of AEs was modelled as the probability of at least one TEAE of Grade ≥ 3 per 100 person-years multiplied by the utility of grade ≥ 3 TEAEs. In the model, the effect of AEs on QALYs in azacitidine have been modelled for a maximum of 8.8 treatment cycles, which is effectively a mean of 6.43 in the model rather than the mean 8.8 cycles in the trial, while for CCR as a whole they were counted for a maximum number of cycles of 5.1, which resulted in a mean of 4.23 treatment cycles instead of the mean number of 2 cycles with IC in the trial. These calculations are likely to overestimate the additional QALY losses due to disutility of CCR relative to azacitidine treatment but this bias had a small effect on the results given other issues identified by the ERG in the model.
Section 5.3.8.1, p. 122	Likewise the correct maximum number of cycles for LDAC in CCR is 10 cycles (the 1.6 cycles used for IC in CCR modelled by Celgene is practically correct). In correcting the probabilistic sensitivity analysis ERG chose SE 3 for azacitidine, 1 LDAC and (0.06 for IC as used by Celgene's base case is correct), to calibrate the respective model outputs to the reported figures for mean minus one standard error in the number of cycles reported by Dombret et al. 2015.[45] As documented below, correcting this error of implementation to calibrate the model outputs with the summary statistic reported by the trial increases the ICER from a level around £20,000 to £84,000 per QALY gained.	Likewise the correct maximum number of cycles for LDAC in CCR is 10 cycles and 2 cycles for IC in CCR. In correcting the probabilistic sensitivity analysis ERG chose SE 3 for azacitidine, and 1 for LDAC (0.06 for IC as used by Celgene's base case is correct), to calibrate the respective model outputs to the reported figures for mean minus one standard error in the number of cycles reported by Dombret et al. 2015.[45] As documented below, correcting this error of implementation to calibrate the model outputs with the summary statistic reported by the trial increases the ICER from a level around £60,000 (Celgene's corrected base case) to around £130,000 per QALY gained.
Section 5.3.8.2, p.123	Another limitation was that the costs of managing AEs in patients from azacitidine and CCR groups were estimated as the product of the probability of at least one TEAE of	Another limitation was that the costs of managing AEs in patients from azacitidine and CCR groups were estimated as the product of the probability of at least one TEAE of

	Grade > 3 per 100 person-years and the average cost of managing grade 3 or 4 TEAEs observed in the AZA-AML-001 trial.	Grade ≥ 3 per 100 person-years and the average cost of managing grade 3 or 4 TEAEs observed in the AZA-AML-001 trial.
Section 5.3.10, p. 126	Our corrected results presented in *Section 6* (*page 130*) are subject to this caveat.	However, the ERG corrected base case results presented in *Section 6* (*page130*) were found to be replicable by the weighted average method within a 5-10% margin of error.
Section 5.4.2.3, p.128	The ERG set the OS curves to the Censor At Switch analysis mode in Celgene's model, keeping the exponential functional form adopted in Celgene's base-case. This choice was associated with a hazard ratio of 0.72, which corresponded to the analysis that was unadjusted for baseline covariates. Given the high ICERs that were obtained after the preceding revisions in *Sections 5.4.2.1* and *5.4.2.2*, the effect of adopting the smaller hazard that resulted from censored at switch analysis that adjusted for baseline covariates was investigated in exploratory analyses.	The ERG set the OS curves to the Censor At Switch analysis mode in Celgene's model, keeping the exponential functional form adopted in Celgene's base-case. This choice was associated with a hazard ratio of 0.72, which corresponded to the analysis that was unadjusted for baseline covariates. In addition, the Censor At Switch analysis in the Celgene model alters the estimates of relative effects of azacitidine on PFS and RFS, from the Celgene base case HR values of 0.84 and 0.85 to 0.83 and 0.76, respectively. Given the high ICERs that were obtained after the preceding revisions in *Sections 5.4.2.1* and *5.4.2.2*, the effect of adopting the smaller hazard that resulted from censored at switch analysis that adjusted for baseline covariates was investigated in separate exploratory analyses.
Secton 5.4.2.5, p. 128	The effect of using the OS hazard ratio estimate of 0.64 from the exponential model adjusted for baseline covariates, which found support in statistical tests conducted by the ERG, was investigated.	The effect of using the OS hazard ratio estimate of 0.65 from the exponential model adjusted for baseline covariates, which found support in statistical tests conducted by the ERG, was investigated.
Section 5.4.3, p. 128	The ERG sought to perform some exploratory assessment of the subgroup analysis by preselected CCR treatment, while acknowledging that for PFS and RFS outcomes, the sample sizes make subgroup-specific time to event data highly unreliable. Thus in these analyses subgroup specific differences in OS outcomes were allowed using censor-at-switch data, while keeping common PFS and RFS curves across the three subgroups.	Since resource use data in the Celgene model was obtained from a survey of clinical experts' estimates, and because the ERG's preferred cost estimates for Relapse/PD were those estimated by Celgene's experts for the BSC (i.e. the most costly) subgroup during Relapse/PD, the effect of uncertainty from these values on the ICER was explored in extreme scenarios where costs of Relapse/PD were zero and, separately, where no inpatient costs were incurred (apart from what is already included in the model 'Terminal care' costs). In its preferred base case analysis, Celgene measured costs of monitoring tests and transfusions only while patients were on azacitidine, LDAC or

		IC. The ERG instead included costs for these items for the duration of the patients in Remission and Non-Remission states as well as during Relapse/ Progressive Disease. The ERG explored the effects of adopting Celgene's assumption that no such costs would occur after treatment active treatment stopped. Other scenarios included revising the costs of monitoring tests and transfusions during Relapse/PD to values estimated by a clinical expert consulted by the ERG, whereby two units each of red blood cell transfusions and adult doses of platelet transfusions are given on average per 4 week cycle, whilst no bone marrow aspirates or biopsies nor extractions for cytogenetic testing, four blood tests, and two each of peripheral blood smears and serum blood chemistry are given during PD. In addition, the ERG sought to perform some exploratory assessment of the subgroup analysis by preselected CCR treatment, while acknowledging that for PFS and RFS outcomes, the sample sizes make subgroup-specific time to event data highly unreliable. In these analyses subgroup specific differences in OS, PFS, and RFS outcomes were allowed using censor-at-switch data, using the exponential (OS) and Kaplan-Meier (PFS and RFS) curves provided by Celgene in the Excel model for each arm in the three subgroups.
Section 6, pp. 130–136	[Section 6 and all included tables (58 to 61) and figures (23 and 24) superseded by the ERG Addendum following correction of an error in the final stage of the derivation of the ERG preferred base case]	
Section 8, p. 138	Of the key changes made to the economic model by the ERG in arriving at their preferred base case (ICER £169,606 per QALY), the following might be considered to be differences of opinion between the company and the ERG:	Of the key changes made to the economic model by the ERG in arriving at their preferred base case (ICER £273,308 per QALY), the following might be considered to be differences of opinion between the company and the ERG:
Section 8, p. 138	The base case analysis preferred by the ERG has the limitation that the sum of the cohort proportions in PFS and RFS exceeds the proportion alive by the third cycle in the model. Celgene included an adjustment in the model to eliminate such anomalies, but nevertheless this remains a deficiency of the model structure. The ERG has not attempted to correct this, due to the	[This is no longer the case after correcting the error in estimating the ERG's adjusted exponential OS baseline hazard; Appendix has been corrected below]

	difficulties of fitting plausible parametric models to the PFS and RFS data (as discussed in this critique) and adjusting for baseline covariates, given the small samples available for analysis.	
Appendix 2, Figure A1 (caption)	Figure A1: Log-log plots of OS probability adjusted for subsequent azacitidine use in the CCR arm using the IPCW method – unadjusted for baseline covariates	Figure A1: Log-log plots of OS probability adjusted for subsequent azacitidine use in the CCR arm using the IPCW method – adjusted for baseline covariates
Appendix 2, Figure A1, footnotes	Note: Not adjusted for differences in baseline covariates	[Note deleted]
Appendix 2, Figure A1	[Figure]	[See Figure A1 below]
Appendix 2, Section A2.1		Append following subsection: A2.1.2 Schoenfeld residual plots Figure A2: Schoenfeld residual plots and local polynomial regression, adjusted for subsequent azacitidine use in the CCR arm – adjusted for baseline covariates [Figure A2] Key: CCR, conventional care regimens Source: ERG analysis using individual patient data provided by Celgene
Appendices 2–4	[Figure numbering]	[Renumber figures]
Appendix 2, Section A2.4	Model estimated using effects coding to obtain average baseline. Mean time to death Azacitidine = 0.0973354^{-1} = 10.27 months; CCR =$(1.549388 \times 0.0973354)^{-1}$ = 6.63 months (HR azacitidine vs. CCR = 1.549388^{-1} = 0.6454162)	Model estimated using effects coding to obtain average baseline. Mean time to death Azacitidine = 0.058019^{-1} = 17.24 months; CCR =$(1.549388 \times 0.058019)^{-1}$ = 11.12 months (HR azacitidine vs. CCR = 1.549388^{-1} = 0.6454162)
Appendix 2, Section A2.4	This model adjusted for baseline covariates sex, age, ECOG, cytogenetic risk, CCR preselected treatment, comorbidity group, AML days, platelet transfusion status, geographical region, used in Celgene's IPCW analysis (fixed covariates), using effects-coding, in order to estimate the average baseline (intercept) coefficient in the sample. Blast group was not effects-coded but included in order to adjust for blast group <25 (blastgrp2 indicates 5-24% blasts; blastgrp4 indicates blastgrp<5%), so that estimated baseline coefficient of 0.0973354 is average in sample with blasts≥25% group.	This model adjusted for baseline covariates sex, age, ECOG, cytogenetic risk, CCR preselected treatment, comorbidity group, AML days, platelet transfusion status, geographical region, used in Celgene's IPCW analysis (fixed covariates). The predicted baseline hazard rate was obtained by evaluating the estimated equation and mean valued of the covariates for the whole. Blast group was not evaluated at 0 in order to adjust for blast group <25 (blastgrp2 indicates 5-24% blasts; blastgrp4 indicates blastgrp<5%), so that estimated baseline coefficient of 0.058019 is average in sample with blasts≥25% group.

Appendix 2, Section A2.4	[Stata output from streg command]	[Stata output as shown below]

Figure 22: Overall survival in AZA-AML-001 – Kaplan-Meier data (censored at switch) and adjusted exponential model fitted to censor-at-switch (any AML therapy) data

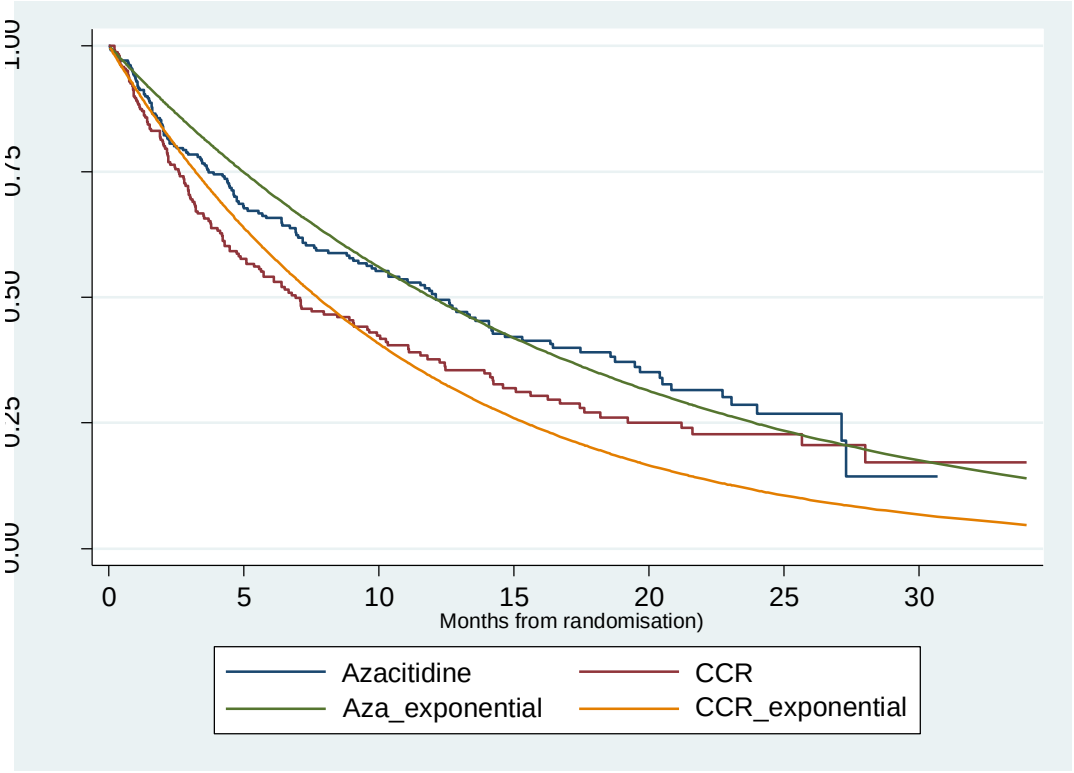


Figure A1: Log-log plots of OS probability adjusted for subsequent azacitidine use in the CCR arm using the IPCW method – adjusted for baseline covariates

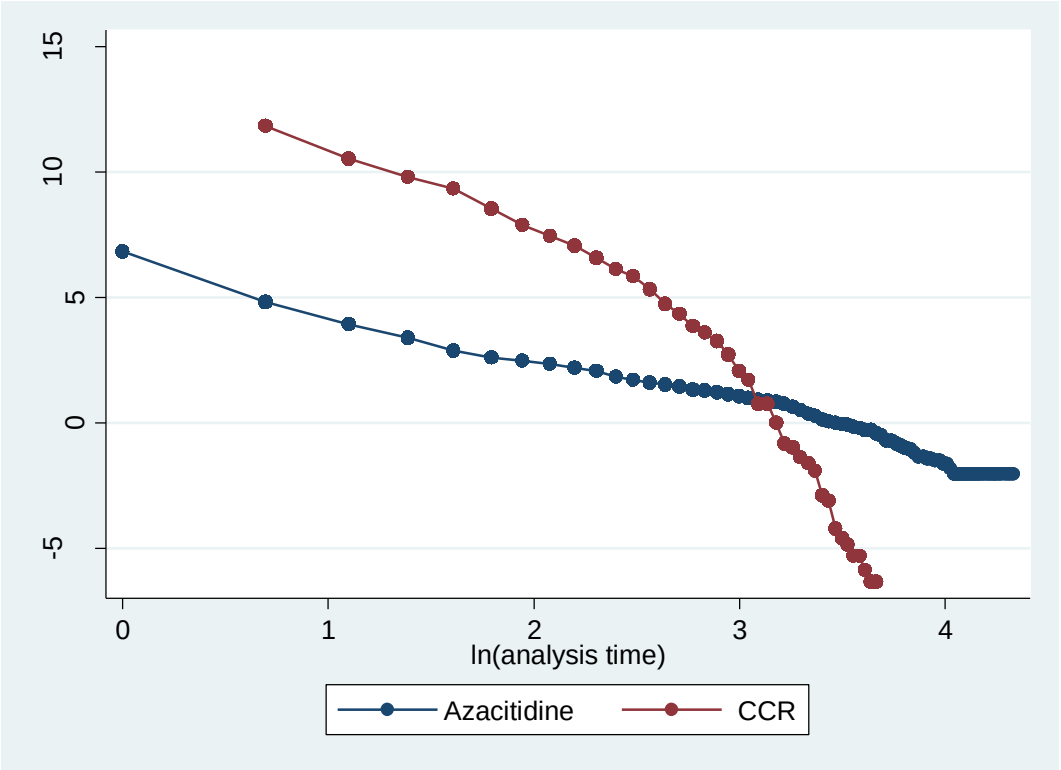
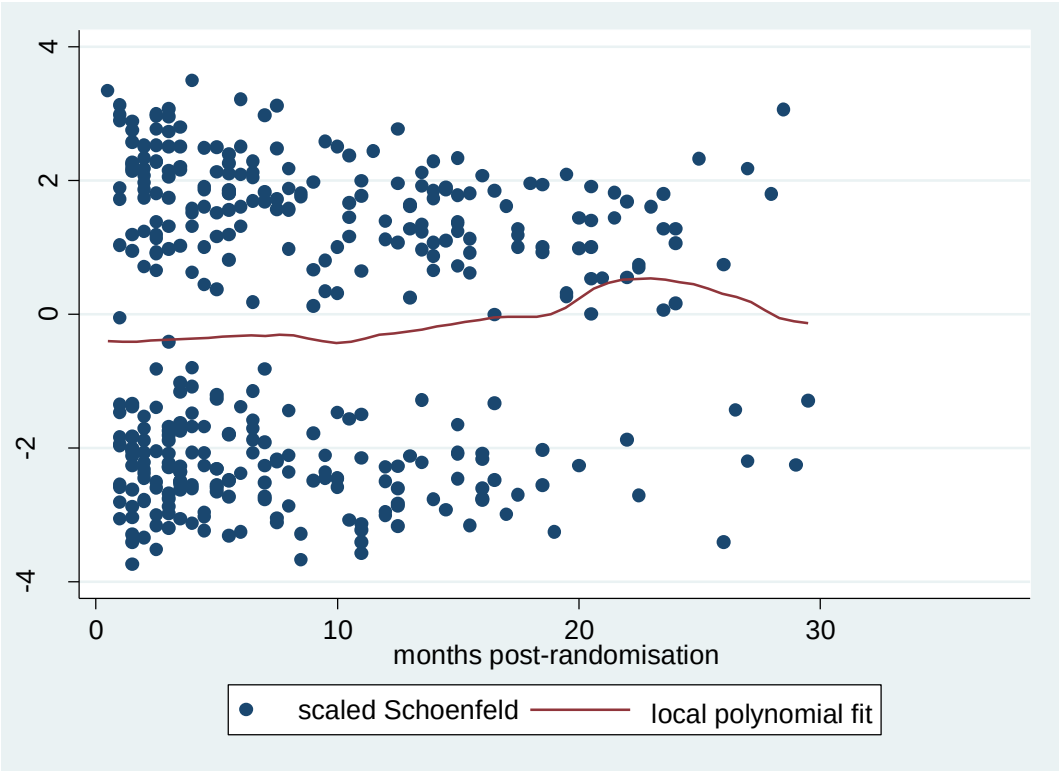


Figure A2: Schoenfeld residuals and local polynomial regression, adjusted for subsequent azacitidine use in the CCR arm – adjusted for baseline covariates



Revised Stata output for streg command (Section A2.4)

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
ccr	1.549388	.1874601	3.62	0.000	1.222288	1.964024
sex2	1.028439	.126573	0.23	0.820	.8080132	1.308996
agegrp2	1.633048	.2117287	3.78	0.000	1.266597	2.10552
ECOG2	1.490963	.2070571	2.88	0.004	1.135681	1.957389
CYTO2	2.117182	.2584642	6.14	0.000	1.666649	2.689505
blastgrp2	.379288	.149469	-2.46	0.014	.1751981	.8211239
blastgrp4	.1908186	.1924331	-1.64	0.100	.0264373	1.377286
randpr2	.3804746	.0875254	-4.20	0.000	.242389	.5972257
randpr3	.4458237	.0697034	-5.17	0.000	.3281557	.6056844
comorbis3	1.386397	.220576	2.05	0.040	1.014989	1.893712
aml1	1.033729	.3199961	0.11	0.915	.5635249	1.896272
aml2	1.181031	.358463	0.55	0.584	.6514894	2.140994
aml3	.933583	.2925007	-0.22	0.826	.5051998	1.725213
pltstat2	.6219478	.0802252	-3.68	0.000	.4830113	.8008489
georeg1	1.159714	.2316993	0.74	0.458	.7839519	1.715586
georeg2	2.366019	.4000999	5.09	0.000	1.698549	3.295783
georeg3	1.194632	.2019344	1.05	0.293	.8577316	1.66386
_cons	.0591534	.0223448	-7.49	0.000	.0282126	.1240269

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts [ID829]

You are asked to check the ERG report from Peninsula Technology Assessment Group (PenTAG) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Friday 19 February 2016 (changed to Wednesday 24th February 2016)** 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.

Issue 1 Use of CCR as a comparator; not investigating individual treatments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the report (example Table 1, pg. 24), the ERG have	It should be stated that:	Stating that the company have not assessed whether azacitidine	The company have not *adequately* assessed whether azacitidine

stated that CCR was used as a comparator rather than IC LDAC and BSC, and as a result the company have not assessed whether azacitidine demonstrates clinical and cost effectiveness compared with each treatment within CCR	The company have used CCR in their base case analysis; however they have provided sensitivity analyses comparing patients receiving each of the treatments making up CCR	demonstrates clinical and cost effectiveness compared with each treatment within CCR is factually inaccurate, and leads the reader to conclude that the company have not investigated individual treatments.	demonstrates clinical and cost-effectiveness compared with each treatment within CCR for the following reasons: 1. The pivotal RCT was not powered for such comparisons. 2. There are significant inconsistencies between the results of the company's base case and subgroup analyses (ERG report, p. 125). In the stated example the ERG considers it is clear that the focus of the critique is the base case. The ERG report does include the subgroup analyses and therefore a full reading of the ERG report would not lead the reader to conclude that the company have not investigated individual treatments. **No action taken.**

Issue 2 Suggestion that the literature review for clinical effectiveness studies was poor

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pg. 28, the ERG state "The ERG believes the literature searching for clinical effectiveness studies was poorly conducted and reported". They also state that their own	Suggested text: The methodology used in the literature, although less thorough than expected, did not miss any	It is factually inaccurate to suggest that the methodology was poor if it identified all relevant studies.	The ERG rejects this proposed amendment. The ERG critique remains an accurate reflection on the quality of the company's submission

searches did not identify any additional studies.	studies found by the ERG's own literature search.		as it relates to study identification. **No action taken.**

Issue 3 The dropout rates due to an AE look imbalanced for azacitidine (36.9%) compared to the CCR group (26.7%)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 3 pg.36 the ERG state "The drop-outs provided by Celgene represent the figures reported in the RCT. However, neither Celgene nor the RCT report the drop outs for the three CCR treatments separately, therefore it is unknown whether the actual treatments that make up the CCR are comparatively different to azacitidine. The dropout rates due to an AE look imbalanced for azacitidine (36.9%) compared to the CCR group (26.7%)". This is a misleading statement.	Text should state: Within the single technology appraisal (STA) company evidence submission document, dated 25 November 2015, Figure 7, the CONSORT diagram for AZA-AML-001 depicts the disposition of subjects in the intent-to-treat (ITT) population for the Treatment Phase, with each of the three CCR treatment arms presented individually. Also, as seen in the STA submission document, the duration of therapy is considerably longer in the azacitidine group compared with the individual CCR groups and this must be considered when interpreting these data. In Study AZA-AML-001, the median duration of treatment for the azacitidine group (164.5 days) was longer than that observed for the BSC-only (65.0 days), low-dose cytarabine (98.0 days), or intensive chemotherapy (55.5 days) groups.	The original statement in the ERG report is misleading without providing text to explain this difference.	The company is correct to indicate that Figure 7 provides the detail which the ERG originally said was not reported. **The ERG agrees to change the statement in Table 3 to:** The ERG has no further comments.

	The total treatment exposure expressed in person-years was higher in the azacitidine group (174.9) than in the other groups (82.9, 14.1, and 9.6 for low-dose cytarabine, intensive chemotherapy, and BSC-only groups, respectively).		

Issue 4 Statement that none of the published registry data provided information on the population with >30% blasts

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 66 of the ERG report, it is stated that "None of the published registry data (Austrian azacitidine registry (NCT01595295); Spanish AMLA registry and French compassionate patient named programme) provided information on the population with >30% bone marrow blasts, a population requirements for the Scope for this report."	This statement should be removed.	The registry data discussed do include information on patients with >30% bone marrow blasts; therefore the ERG's statement is factually inaccurate.	The ERG's intended meaning was that results pertaining only to the subpopulation with >30% blasts was not presented (not that patients with >30% blasts were not represented at all). However, the ERG acknowledges that results were presented for a relevant subpopulation from the Austrian Azacitidine Registry. **The ERG agrees to replace the paragraph with the following:** Both the Spanish AMLA registry and French compassionate patient named programme failed to provide outcomes for the specific population with >30% bone marrow blasts. Instead only the proportion of patients with >30% bone marrow

			blasts was reported. Outcomes were reported combined irrespective of bone marrow blast status. The Austrian azacitidine registry (AAR, NCT01595295) report outcomes for the total patient population irrespective of bone marrow blasts status. In addition, they also report outcomes for those with >30% bone marrow blasts and a WBC <15g/L receiving azacitidine and compare baseline and treatment characteristics for these patients to the azacitidine arm of the AZA-AML-001 trial. Baseline and treatment characteristics were similar between the two groups of patients receiving azacitidine except for the following differences: Baseline characteristics for AML classification: AML-NOS was higher (63.5 %) in the AZA-AML-001 trial than the AAR (24.2%) and for AML-MRF, the AAR reported higher proportions (66.3%) than the AZA-AML-001 trial (31.1%). Outcomes appear to be similar for the registry and the AZA-AML-001 trial. For AE, treatment-emergent thrombocytopenia and anaemia both had significantly higher (47.4% and 31.6% respectively) incidences in the

			Austrian azacitidine registry than from the AZA-AML-001 trial (15.7% and 26.3% respectively).

Issue 5 Statement that the ERG's preferred base case equalises the costs in the relapse/progressive disease health state across the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Throughout the report, the ERG make reference to their preferred base case of setting relapse/PD health state costs to be equal across the model. For example on pg.15 they say "The ERG also identified that there were significant differences in the cost associated with the Relapse/progressive disease state between the AZA and CCR arm, even though all patients (in both arms) are expected to be receiving BSC at this point." This is further detailed in section 5.3.8.2 on pages 122-123. In Appendix 3 of the ERG report, the ERG state that they have applied the data for the BSC cohort to all cohorts within the relapse/PD state. The ERG also state that it is questionable that the sequence of treatments studied in the model i.e., AZA followed by BSC and CCR	A statement should be added by the ERG in relation to their preferred base case, that setting setting relapse/PD health state costs to be equal across the model is not reflective of the AZA-AML-001 trial, the conclusions drawn by the clinical questionnaire designed to elicit resource use (from 7 UK clinicians), or the clinical opinion given to the ERG. In addition, it should be noted that applying the BSC cohort data to all cohorts in the relapse/PD state is inappropriate and not representative of clinical practice.	There is inconsistent messaging from the ERG; one message of setting relapse/PD health state costs to be equal across the model, and the other than patients would receive active treatment after 1st line. The combination of the AZA-AML-001 trial, the conclusions drawn by the clinical questionnaire designed to elicit resource use (from 7 UK clinicians), as well as clinical opinion given to the ERG, suggests that patient resource use is likely to vary after 1st line treatment. Applying the BSC cohort data to all cohorts in the relapse/PD state is inappropriate and not representative of clinical practice.	The proposed statements are not appropriate. The ERG had to work within the limitations of the structure of the Celgene model. The ERG's limited aim was to correct the OS effectiveness parameter values in Celgene's model to make them consistent with the model's assumption that no subsequent active therapy would be used in AZA or CCR after 1st line treatment; see Celgene submission, Section 5.6.2., Table 54, p. 141 "Assumption: There is no treatment switching. Justification Clinical expert opinion. Only a very small percentage of patients at this stage of disease would be fit for a second treatment after failing their first." ERG's corrections do not imply endorsement of Celgene's assumptions. The model should have

followed by BSC) is realistic, suggesting subsequent therapy may be given in clinical practice (as was seen in the AZA-AML-001 trial). In addition, the ERG states (pg. 129) "Advice from clinical experts suggests that active second-line treatment is considered for some patients in the NHS".			allowed for the cost and effects of subsequent treatments used in the trial which would also be used in routine NHS practice, by modelling second line treatment. However, Celgene's model assumed that no such treatment was available after relapse/PD. As stated in ERG's report, Section 5.3.6.2, p. 116. "To remedy the contradiction between the model structure, on the one hand, and the methodology underlying the OS treatment effect estimates, on the other, two options were available to the ERG. One was to correct the model to include the costs of subsequent treatments used in the AZA-AML-001 and left unadjusted for in the statistical analysis that produced the base case OS treatment effect estimates. This option was not feasible because the required data on the dates of start and end of subsequent treatments as well as treatment dosages and frequencies of administration were not available to ERG." Note that setting relapse/PD costs to be equal across the model was simply done for consistency with the model assumptions; i.e. Celgene assume that patients in this state are all managed by BSC and it was not clear why there should be differences in costs by initial treatment (i.e. AZA

			vs CCR). Different costs may apply to the relapse/PD phase (and ERG presented results of varying these), but claiming that costs should be different between cohorts is questionable given the lack of data and difficulties of defining these CCR preselected subgroups a priori. Further, Celgene did not provide any evidence in its submission that the resource use survey addressed the role of the specific subsequent treatments used in AZA-AML-001. **No action taken.**

Issue 6 Statement that combined PFS and RFS curves cross OS curve at cycle 69

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 110, the ERG state "The inadequacy of the statistical analysis may be illustrated by comparing the estimated time to event curves used by Celgene in their base case analysis, combining PFS with RFS and contrasting it with OS. **Error! Reference source not found.** below illustrates the problem for the CCR arm. By cycle 69, that is, just after the start of the sixth year after first receiving treatment the estimated curves imply that there are more	This statement should be removed.	This is factually inaccurate. Having checked the model, the curves do not cross. A possible reason for the ERG's interpretation may be that they have compared the wrong settings: RFS and PFS in columns H and I of the Model worksheets can exceed OS in column J because they are comprised from different denominators: in fact, OS from column J must be compared with	The ERG stands by its comment. The ERG confirms it has considered the appropriate columns. The reason these curves, as implemented in the Excel model, do not cross is that in the Excel model Celgene applied an adjustment so that when crossing would have occurred the survival probabilities distributed the OS time proportionately to PFS and RFS; e.g. in Celgene Model AZA sheet cell L23 the formula is:

patients in the treated cohort who are either in Remission or non-remission (stable disease) than there are patients alive.”		RFS and PFS from columns K and L, respectively.	= IF((RFS*'PSA inputs'!$D$22+PFS*'PSA inputs'!$D$24)>OS,OS*'PSA inputs'!$D$22/('PSA inputs'!$D$22+'PSA inputs'!$D$24),RFS*'PSA inputs'!$D$22). This correction avoids having PFS + RFS larger than OS, but does not address concerns about the validity of Celgene’s chosen parametric survival curves for assigning time to Remission and Non-remission versus relapse/PD states in the model. **No action taken.**

Issue 7 The use of censor at switch analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 116 to 120, the ERG describe using censor at switch methodology to model the OS. They acknowledge that they did this because they were not able to perform the IPCW analysis to adjust for subsequent therapy for both treatment groups. The ERG also acknowledge that (pg. 129) “Advice from clinical experts	It should be noted along with the ERG’s preferred base case ICER that the methodology used for modelling OS is not optimal, and does not fit with the AZA-AML-001 trial, the conclusions drawn by the clinical questionnaire designed to elicit resource use (from 7 UK clinicians), as well as clinical opinion given to the ERG, all of which suggest patients could receive	The ERG’s base case ICER is misleading without acknowledging the limitations of the OS modelling whenever the base case is mentioned.	The ERG’s preferred base case is the best possible use of the available data given Celgene’s model logic. It does not represent ERG’s view of what UK routine practice is or an endorsement of Celgene’s structural assumptions, whose correction was beyond the scope of ERG’s STA review as defined by NICE. We acknowledge this in ERG report Section 5.3.6.2, p. 117: “Whether the

suggests that active second-line treatment is considered for some patients in the NHS"	subsequent therapy.		assumption that no subsequent active treatment would be available to UK patients in routine practice is plausible may of course be questioned, but the point here is that applying IPCW adjustment for subsequent treatment to the outcome data of the CCR but not the azacitidine arm in the AZA-AML-001 trial is inconsistent with the economic model which the overall survival IPCW analysis was designed to inform." Please also see our response to Issue 6. **<u>No action taken.</u>**

Issue 8 OS modelling methods and results are unrealistic and misleading

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG describes their preferred base case for OS modelling (pg. 116-120), as well as the use of KM data for PFS and RFS (pg. 128). The ERG state the uncertainty around the PH assumption for OS (pg.114). The ERG's methodology uses a censor-at-switch analysis and does	It should be noted in the report that the ERG's preferred base case is unrealistic as it: - Extends OS but uses KM data for PFS and RFS leading to clinical implausibility. In addition, it can be seen that, even in isolation, the KM data for PFS and RFS is not	Given the ERG's stated uncertainty around the PH assumption with OS, the clinical implausibility of the ERG's modelling of OS in relation to PFS and RFS, removing subsequent therapy and the way the changes in the ERG's base case interact with each other, the ERG's methodology is misleading. Stating the ERG preferred base case	The ERG disagrees with Celgene's view. In response to each point in proposed amendments: ERG chose KM curves for PFS and RFS because they are a) as observed in the trial and b) non-parametric, i.e. free from risk of bias in fitting a parametric curve, which Celgene's own analysis identified as an issue. The resulting PFS and RFS

not allow for any subsequent therapy; this does not represent the view of the clinical expert consulted by the ERG, the data from the AZA-AML-001 trial or the clinician questionnaire used to calculate HRU by the Company. Pg. 118 of ERG report: text states that their OS modelling is "conservative" i.e. it is unrealistically increases the ICER, because it is biased in favour of AZA for OS. PFS and RFS are not increased (ERG uses KM data in their base case). The ERG's modelling of OS interacts with two other influential ERG changes 1. Scenario "E", the use of KM data only for RFS and PFS (which we have shown is inappropriate), and 2. Scenario "B", the calibration of relapse/PD HRU and costs. The unrealistic combination of these changes is misleading.	appropriate - Pushes patients into the PD disease state for longer which combines with other ERG changes such as equalised costs and HRU across all PD for both arms thus biasing against azacitidine - Suggests no subsequent therapy is received after 1st line therapy despite consistent evidence that this is unrealistic	without acknowledging its limitations and implausibility clearly is misleading to the reader.	data may have been affected by the use of subsequent therapies although it appears that at least for CCR arm subsequent azacitidine use occurred in few instances and their effect was negligible (this was confirmed by Celgene's response to ERG's questions for clarification). Acknowledging that the ERG's preferred base-case analysis results in a longer incremental period in relapse/PD under azacitidine than those of Celgene's base case, ERG have undertaken considerable sensitivity analyses. All of these show that the ICER is >£70,000 per QALY even when relapse/PD costs are zero. Please see our response to Issues 5 & 7. **No action taken.**

Issue 9 The use of KM curves from the trial for RFS and PFS within the model

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th></tr>
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<td>
ERG preferred base case uses KM data for RFS and PFS. Section 5.4.2.4, page 128.

RFS and PFS KM curves, for all regimens, are not completely observed. The table below provides the final survival data from the observed KM curves; in the case of RFS in particular we would argue that some modelling is required.

Identifying the optimal fitting functional form is uncertain, however retaining KM data only underestimates benefit in all regimens.

The ERG's preferred modelling for OS increases OS compared with the Company's base case.

Survival rates in the KM curves are below:
<table>
<tr><th></th><th colspan="2">AZA</th><th colspan="2">CCR</th></tr>
<tr><th></th><th>Minimum PFS</th><th>Minimum RFS</th><th>Minimum PFS</th><th>Minimum RFS</th></tr>
<tr><td>All patients</td><td>0.0149</td><td>0.1390</td><td>0.0161</td><td>0.1014</td></tr>
<tr><td>IC</td><td>0.0938</td><td>0.1455</td><td>0.0588</td><td>0.1604</td></tr>
<tr><td>LDC</td><td>0.0362</td><td>0.1128</td><td>0.0242</td><td>0.0515</td></tr>
<tr><td>BSC</td><td>0.0909</td><td>0.2857</td><td>0.0588</td><td>N/a</td></tr>
<tr><td>Intermediate risk</td><td>0.0266</td><td>0.1581</td><td>0.0353</td><td>0.1039</td></tr>
<tr><td>Poor risk</td><td>0.0266</td><td>0.1581</td><td>0.0353</td><td>0.1039</td></tr>
<tr><td>With myelodysplasia-related changes</td><td>0.0845</td><td>0.2591</td><td>0.0484</td><td>0.0879</td></tr>
<tr><td>Without myelodysplasia-related changes</td><td>0.0155</td><td>0.0917</td><td>0.0245</td><td>0.1261</td></tr>
</table>
</td>
<td>
It should be noted in the report that KM data for RFS and PFS are not completely observed, and that some modelling is required.

It should be noted that the ERG's preferred base case increases OS, but does not increase PFS or RFS, and that there is no clinical reason for this.
</td>
<td>
It is factually inaccurate to suggest the KM data is complete for PFS and RFS.

It is misleading and clinically implausible to extend OS whilst not extending PFS and RFS.
</td>
</tr>
</table>

ERG response
The ERG accepts that its use of KM curves result in underestimation ('censoring') of time in the Remission state. However, this affects a minority of patients, i.e. those with a CR/CRi response, 28% in AZA and 25% in CCR, and given that the difference in censoring in AZA vs. CCR is 3.76 percentage points (0.1390 minus 0.1014) the bias against azacitidine is small and unlikely to be of significance to the results. **No action taken.**

Issue 10 The suggestion that EOL criteria are met based on restricted mean value

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
When assessing whether EOL criteria are met, on page 136, table 62 the ERG state "ERG analyses based on restricted mean survival at 30 months suggest an extension to life of 1.8–2.5 months" The ERG also state that "Extension to life should be assessed considering differences in mean overall survival in addition to median OS" The ERG also conclude (pg. 117) that the mean predicted difference in OS from their base case model is 3.64 months in favour of azacitidine.	It should be explicitly stated that using the restricted mean to determine the mean OS gain for the target population is inappropriate. The restricted mean underestimates the mean OS and is therefore not representative of the target population. It should also be stated that the median OS gain from the trial, as well as the mean OS gain from the cost effectiveness model indicate that EOL criteria are met.	It is factually inaccurate to state that the extension to OS is not met; the restricted mean is not suitable for basing the conclusion about the extension to life. The median OS gain from the AZA-AML-001 is 3.8 months and the modelled mean OS for corrections individually implemented by the ERG each produce a mean OS gain of >3 months. Additionally, the ERG conclude (pg. 117) that the mean predicted difference in OS from their base case model is 3.64 months in favour of azacitidine.	Overall survival curves have converged by 30 months in the ITT analysis (Celgene submission, Figure 8), and arguably also in the censor-at-switch analysis (Celgene submission, Figure 9). For this reason the difference in restricted mean survival (observed) is considered to be an unbiased estimate of the difference in unrestricted mean survival (unobserved); i.e., the restricted mean *is* a suitable basis for the conclusion about the extension to life. The ERG do not consider it necessary to state that restricted mean survival is an underestimate of unrestricted mean survival since this is widely understood and the ERG

			did not suggest anything to contradict this. The ERG note that even if median OS gain is preferred over mean OS gain (as estimated using restricted mean OS gain), the estimate is not robustly over 3 months, with a 95% CI of 1.0 to 6.5 months. **No action taken.**

Issue 11 Unexplained model results due to ERG changes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The combination of ERG changes do not explain changes in model results. Switching off all of the ERG changes results in an ICER of £36,931, not £20,648, the original base case. The ERG note on the worksheet "ERG changes" of the model that additional changes relate to Table 32 of the report; this table contains unit costs. It is not clear how the ERG have implemented their changes and why the ICER with ERG changes switched off is different to the Company's base case ICER.	More explanation of modifications made by the ERG	The ERG amendments cannot be checked for accuracy and the explanation does not seem to fit with the actual change in ICER. The ERG changes may interact with the changes that are listed. This can be seen by comparing Table 58 (piecewise changes) and Table 59 (cumulative changes). This interaction may be significant because of the impact in particular of the ERG's "A" and "B" amendments to the model.	Due to the high number of corrections made by the ERG to the model submitted by Celgene and due to the time constraints, option buttons were created only for major corrections. The list of corrections to the implementation of Celgene's model is shown in Table 57 of the ERG's report. An additional model correction, made by the ERG and discussed in section 5.3.11.2 of the report (p. 126), was implemented in the model as "MAX operator" option buttons.

			The duration of monitoring tests and transfusions implemented in the ERG's base case is described in section 6.1 (p. 134) of our report: "The base case analysis preferred by ERG included costs of monitoring tests and transfusions for the whole duration of the Remission and Non-remission phases of the model (as well as for the Relapse/PD phase)." In the executable model, all corrected cells are highlighted in yellow. **Action: ERG have produced a full listing of corrections to Celgene's model (below)**

Full listing of corrections made to Celgene's model

The ERG present below a full listing of corrections made to Celgene's model. Each correction is presented as an individual correction to Celgene's original model, i.e., there is no accumulation of corrections shown. Correct implementation of all of these corrections leads to analysis A (corrected base case). ICERs are shown for AZA versus CCR in the deterministic base case. These corrections are listed in order of decreasing ICER.

Correction 1

Issue	In the CCR arm, the patients receiving BSC only are assumed to incur drug administration costs in the Remission and Non-remission states, although the costs of administering BSC are not included after discontinuation of other active treatments until relapse/progression.	
Cells affected	'Model CCR'!AB23:AB153	
Original formula		**Revised formula**
Formula in 'Model CCR'!AB23: ='PSA inputs'!$D$71+K23*IF(C23<7,'PSA inputs'!$D$72,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$72))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$73,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$73))		replaced with: =('PSA inputs'!$D$71+K23*IF(C23<7,'PSA inputs'!$D$72,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$72))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$73,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$73))) * ('PSA inputs'!$D$16+'PSA inputs'!$D$17)
Formula in 'Model CCR'!AB24: =K24*IF(C24<7,'PSA inputs'!$D$72,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$72))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$73,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$73))		replaced with: =(K24*IF(C24<7,'PSA inputs'!$D$72,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$72))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$73,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$73))) * ('PSA inputs'!$D$16+'PSA inputs'!$D$17) (Correct the formulas in the cells below)
ICER (cost per QALY)	£43,676	

Correction 2

Issue	In the AZA and CCR arms, costs of tests and transfusions are not modelled for patients in the Relapse/progressive disease state.
Cells affected	'Model AZA'!AC23:AD153, 'Model CCR'!AC23:AD153
Original formula	**Revised formula**
Formula in 'Model AZA'!AC23: ='PSA inputs'!$D$57+K23*IF(C23<7,'PSA inputs'!$D$58,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$58))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$59,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$59))	replaced with: ='PSA inputs'!$D$57+K23*IF(C23<7,'PSA inputs'!$D$58,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$58))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$59,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$59)) +M23*'PSA inputs'!$D$60
Formula in 'Model AZA'!AC24: =K24*IF(C24<7,'PSA inputs'!$D$58,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$58))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$59,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$59))	replaced with: =K24*IF(C24<7,'PSA inputs'!$D$58,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$58))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$59,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$59)) +M24*'PSA inputs'!$D$60 (Correct the formulas in the cells below)
Formula in 'Model CCR'!AC23: ='PSA inputs'!$D$76+K23*IF(C23<7,'PSA inputs'!$D$77,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$77))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$78,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$78))	replaced with: ='PSA inputs'!$D$76+K23*IF(C23<7,'PSA inputs'!$D$77,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$77))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$78,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$78)) +M23*'PSA inputs'!$D$79
Formula in 'Model CCR'!AC24: =K24*IF(C24<7,'PSA inputs'!$D$77,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$77))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$78,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$78))	replaced with: =K24*IF(C24<7,'PSA inputs'!$D$77,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$77))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$78,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$78)) +M24*'PSA inputs'!$D$79 (Correct the formulas in the cells below)
Formula in 'Model AZA'!AD23: ='PSA inputs'!$D$62+K23*IF(C23<7,'PSA inputs'!$D$63,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$63))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$64,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64))	replaced with: ='PSA inputs'!$D$62+K23*IF(C23<7,'PSA inputs'!$D$63,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$63))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$64,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64)) +M23*'PSA inputs'!$D$65

Formula in 'Model AZA'!AD24: =K24*IF(C24<7,'PSA inputs'!$D$64,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$64,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64))	replaced with: =K24*IF(C24<7,'PSA inputs'!$D$64,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$64,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64)) +M24*'PSA inputs'!$D$65 (Correct the formulas in the cells below)
Formula in 'Model CCR'!AD23: ='PSA inputs'!$D$62+K23*IF(C23<7,'PSA inputs'!$D$82,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$82))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$83,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$83))	replaced with: ='PSA inputs'!$D$62+K23*IF(C23<7,'PSA inputs'!$D$82,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$82))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$83,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$83)) +M23*'PSA inputs'!$D$84
Formula in 'Model CCR'!AD24: =K24*IF(C24<7,'PSA inputs'!$D$83,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$83))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$83,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$83))	replaced with: =K24*IF(C24<7,'PSA inputs'!$D$83,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$83))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$83,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$83)) +M24*'PSA inputs'!$D$84 (Correct the formulas in the cells below)
ICER (cost per QALY)	£37,381

Correction 3

Issue	In the AZA and CCR arms, drug administration, monitoring tests and transfusion costs are double-counted during the 1st model cycle.
Cells affected	‘Model AZA ‘!AB23, AC23 and AD23; ‘Model CCR’! AB23, AC23 and AD23
Original formula	**Revised formula**
Formula in ‘Model AZA’!AB23: ='PSA inputs'!$D$52+K23*IF(C23<7,'PSA inputs'!$D$53,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$53))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$54,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$54))	replaced with: ='PSA inputs'!$D$52
Formula in ‘Model AZA’!AC23: ='PSA inputs'!$D$57+K23*IF(C23<7,'PSA inputs'!$D$58,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$58))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$59,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$59))	replaced with: ='PSA inputs'!$D$57
Formula in ‘Model AZA’!AD23: ='PSA inputs'!$D$62+K23*IF(C23<7,'PSA inputs'!$D$63,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$63))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$64,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64))	replaced with: ='PSA inputs'!$D$62
Formula in ‘Model CCR’!AB23: ='PSA inputs'!$D$71+K23*IF(C23<7,'PSA inputs'!$D$72,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$72))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$73,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$73))	replaced with: ='PSA inputs'!$D$71
Formula in ‘Model CCR’!AC23: ='PSA inputs'!$D$76+K23*IF(C23<7,'PSA inputs'!$D$77,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$77))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$78,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$78))	replaced with: ='PSA inputs'!$D$76
Formula in ‘Model CCR’!AD23: ='PSA inputs'!$D$62+K23*IF(C23<7,'PSA inputs'!$D$82,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$82))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$83,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$83))	replaced with: ='PSA inputs'!$D$62
ICER (cost per QALY)	£35,532

Correction 4

Issue	In the CCR arm, transfusion costs in the Remission state from the 2nd cycle onwards are modelled using the transfusion costs for patients with stable disease.	
Cells affected	'Model CCR'!AD24:153	
Original formula		**Revised formula**
Formula: =K24*IF(C24<7,'PSA inputs'!$D$83,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$83))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$83,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$83))		replaced with: =K24*IF(C24<7,'PSA inputs'!$D$82,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$82))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$83,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$83))
ICER (cost per QALY)	£28,147	

Correction 5

Issue	In the AZA and CCR arms, monitoring tests and transfusions were modelled only while the patient remained on their initial treatment.
Cells affected	'Model AZA'!AC24:AD153; 'Model CCR'!AC24:AD153
Original formula	**Revised formula**
Formula in 'Model AZA'!AC24: =K24*IF(C24<7,'PSA inputs'!$D$58,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$58))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$59,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$59))	replaced with: =K24*'PSA inputs'!$D$58+MAX(L24-K24,0)*'PSA inputs'!$D$59 (Correct the formulas in the cells below)
Formula in 'Model AZA'!AD24: =K24*IF(C24<7,'PSA inputs'!$D$64,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$64,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64))	replaced with: =K24*'PSA inputs'!$D$64+MAX(L24-K24,0)*'PSA inputs'!$D$64 (Correct the formulas in the cells below)
Formula in 'Model CCR'!AC24: =K24*IF(C24<7,'PSA inputs'!$D$77,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$77))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$78,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$78))	replaced with: =K24*'PSA inputs'!$D$77+MAX(L24-K24,0)*'PSA inputs'!$D$78 (Correct the formulas in the cells below)
Formula in 'Model CCR'!AD24: =K24*IF(C24<7,'PSA inputs'!$D$83,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$83))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$83,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$83))	replaced with: =K24*'PSA inputs'!$D$83+MAX(L24-K24,0)*'PSA inputs'!$D$83 The wrong cell reference in this formula is discussed above. (Correct the formulas in the cells below)
ICER (cost per QALY)	£26,696

Correction 6

Issue	In the CCR arm, the patients receiving LDAC have costs of drug administration, tests and transfusions estimated based on the treatment duration of azacitidine, rather than the treatment duration of LDAC.	
Cells affected	'Model CCR'!AB23:AD153	
Original formula		**Revised formula**
Cell reference: 'PSA inputs'!$D$121		replaced with: 'PSA inputs'!$D$158
ICER (cost per QALY)	£26,537	

Correction 7

Issue	In the CCR arm, the patients receiving IC are assumed to incur drug administration costs after their treatment is discontinued (i.e., after cycle 2).	
Cells affected	'Model CCR'!AB25:AB153	
Original formula		**Revised formula**
Formula in 'Model CCR'!AB25: =K25*IF(C25<7,'PSA inputs'!$D$72,IF(C25>'PSA inputs'!$D$121,0,'PSA inputs'!$D$72))+MAX(L25-K25,0)*IF(C25<7,'PSA inputs'!$D$73,IF(C25>'PSA inputs'!$D$121,0,'PSA inputs'!$D$73))		replaced with: =(K25*IF(C25<7,'PSA inputs'!$D$72,IF(C25>'PSA inputs'!$D$121,0,'PSA inputs'!$D$72))+MAX(L25-K25,0)*IF(C25<7,'PSA inputs'!$D$73,IF(C25>'PSA inputs'!$D$121,0,'PSA inputs'!$D$73)))* ('PSA inputs'!$D$17+'PSA inputs'!$D$18) (Correct the formulas in the cells below)
ICER (cost per QALY)	£26,333	

Correction 8

Issue	In the CCR arm, transfusion costs in the pre-response period were modelled using transfusion costs for patients receiving azacitidine.	
Cells affected	'Model CCR'!AD23	
Original formula		**Revised formula**
Cell reference: 'PSA inputs'!$D$62		replaced with: 'PSA inputs'!$D$81
ICER (cost per QALY)	£21,742	

Correction 9

Issue	In the CCR arm, the daily dose of cytarabine for patients receiving LDAC is estimated assuming calculations using units of mg/m²/day, whereas the parameter used in AZA-AML-001 has units of mg/day.	
Cells affected	'HRU costs'!C115:117	
Original formula		**Revised formula**
Formula: ='PSA inputs'!D15*'PSA inputs'!D156		replaced with: 'PSA inputs'!D156
ICER (cost per QALY)	£20,648 (only affects scenario analyses)	

Correction 10

Issue	In the AZA and CCR arms, the formulae for calculating wastage with 30% tolerance (used in a scenario analysis) are incorrect.
Cells affected	'HRU costs'!E103, E109, E113, E117, E123, E127, E133, E137
Original formula	**Revised formula**
Formula in 'HRU costs'!E103: =IF(E102*(1-'Drug costs'!$L$14)<E101,E101,(E102*(1-'Drug costs'!$L$14)))	replaced with: = 'Drug costs'!$L$14*E101+(1-'Drug costs'!$L$14)*E102
Formula in 'HRU costs'!E109: =IF(E108*(1-'Drug costs'!$L$14)<E107,E107,(E108*(1-'Drug costs'!$L$14)))	replaced with: ='Drug costs'!$L$14*E107+(1-'Drug costs'!$L$14)*E108
Formula in 'HRU costs'!E113: =IF(E112*(1-'Drug costs'!$L$14)<E111,E111,(E112*(1-'Drug costs'!$L$14)))	replaced with: ='Drug costs'!$L$14*E111+(1-'Drug costs'!$L$14)*E112
Formula in 'HRU costs'!E117: =IF(E116*(1-'Drug costs'!$L$14)<E115,E115,(E116*(1-'Drug costs'!$L$14)))	replaced with: ='Drug costs'!$L$14*E115+(1-'Drug costs'!$L$14)*E116
Formula in 'HRU costs'!E123: =IF(E122*(1-'Drug costs'!$L$14)<E121,E121,(E122*(1-'Drug costs'!$L$14)))	replaced with: = 'Drug costs'!$L$14*E121+(1-'Drug costs'!$L$14)*E122
Formula in 'HRU costs'!E127: =IF(E126*(1-'Drug costs'!$L$14)<E125,E125,(E126*(1-'Drug costs'!$L$14)))	replaced with: ='Drug costs'!$L$14*E125+(1-'Drug costs'!$L$14)*E126
Formula in 'HRU costs'!E133: =IF(E132*(1-'Drug costs'!$L$14)<E131,E131,(E132*(1-'Drug costs'!$L$14)))	replaced with: ='Drug costs'!$L$14*'HRU costs'!E131+(1-'Drug costs'!$L$14)*'HRU costs'!E132
Formula in 'HRU costs'!E137: =IF('ERG changes'!V10 = 2,('Drug costs'!$L$14*E135+(1-'Drug costs'!$L$14)*E136),IF(E136*(1-'Drug costs'!$L$14)<E135,E135,(E136*(1-'Drug costs'!$L$14))))	replaced with: 'Drug costs'!$L$14*E135+(1-'Drug costs'!$L$14)*E136
ICER (cost per QALY)	£20,648 (only affects scenario analyses)

Correction 11

Issue	In the AZA and CCR arms, the Kaplan-Meier curves for OS, PFS and RFS (for use in scenario analyses) are incorrectly referenced to the curves for patients with IC as their pre-specified CCR.
Cells affected	'KM data'!DD6:DI49
Original formula	**Revised formula**
Formula in 'KM data'!DD6: =IF((CHOOSE(PatientGroup,BF6,BL6,BR6,BX6,CD6,CJ6,CP6))=0, NA, CHOOSE(PatientGroup,BF6,BL6,BR6,BX6,CD6,CJ6,CP6))	replaced with: =IF((CHOOSE(PatientGroup, AZ6,BF6,BL6,BR6,BX6,CD6,CJ6,CP6))=0, NA, CHOOSE(PatientGroup, AZ6,BF6,BL6,BR6,BX6,CD6,CJ6,CP6)) (Correct the formulas in the cells below)
Formula in 'KM data'!DE6: =IF((CHOOSE(PatientGroup,BG6,BM6,BS6,BY6,CE6,CK6,CQ6))=0, NA, CHOOSE(PatientGroup,BG6,BM6,BS6,BY6,CE6,CK6,CQ6))	replaced with: =IF((CHOOSE(PatientGroup, BA6,BG6,BM6,BS6,BY6,CE6,CK6,CQ6))=0, NA, CHOOSE(PatientGroup, BA6,BG6,BM6,BS6,BY6,CE6,CK6,CQ6)) (Correct the formulas in the cells below)
Formula in 'KM data'!DF6: =IF((CHOOSE(PatientGroup,BH6,BN6,BT6,BZ6,CF6,CL6,CR6))=0, NA, CHOOSE(PatientGroup,BH6,BN6,BT6,BZ6,CF6,CL6,CR6))	replaced with: =IF((CHOOSE(PatientGroup,BB6,BH6,BN6,BT6,BZ6,CF6,CL6,CR6))=0, NA, CHOOSE(PatientGroup,BB6,BH6,BN6,BT6,BZ6,CF6,CL6,CR6)) (Correct the formulas in the cells below)
Formula in 'KM data'!DG6: =IF((CHOOSE(PatientGroup,BI6,BO6,BU6,CA6,CG6,CM6,CS6))=0, NA, CHOOSE(PatientGroup,BI6,BO6,BU6,CA6,CG6,CM6,CS6))	replaced with: =IF((CHOOSE(PatientGroup, BC6,BI6,BO6,BU6,CA6,CG6,CM6,CS6))=0, NA, CHOOSE(PatientGroup, BC6,BI6,BO6,BU6,CA6,CG6,CM6,CS6)) (Correct the formulas in the cells below)
Formula in 'KM data'!DH6: =IF((CHOOSE(PatientGroup,BJ6,BP6,BV6,CB6,CH6,CN6,CT6))=0, NA, CHOOSE(PatientGroup,BJ6,BP6,BV6,CB6,CH6,CN6,CT6))	replaced with: =IF((CHOOSE(PatientGroup, BD6,BJ6,BP6,BV6,CB6,CH6,CN6,CT6))=0, NA, CHOOSE(PatientGroup, BD6,BJ6,BP6,BV6,CB6,CH6,CN6,CT6)) (Correct the formulas in the cells below)

Formula in 'KM data'!DI6: =IF((CHOOSE(PatientGroup,BK6,BQ6,BW6,CC6,CI6,CO6,CU6))=0, NA, CHOOSE(PatientGroup,BK6,BQ6,BW6,CC6,CI6,CO6,CU6))		replaced with: =IF((CHOOSE(PatientGroup, BE6,BK6,BQ6,BW6,CC6,CI6,CO6,CU6))=0, NA, CHOOSE(PatientGroup, BE6,BK6,BQ6,BW6,CC6,CI6,CO6,CU6)) (Correct the formulas in the cells below)
ICER (cost per QALY)	£20,648 (only affects scenario analyses)	

Correction 12

Issue	In the AZA and CCR arms, the costs of drug administration, monitoring tests and transfusions for patients in the Non-remission (stable disease) state were calculated assuming the proportion of such patients in the cohort is estimated by $PFS \times p_{SD} - RFS \times p_{Response}$ (or zero if this is negative) where $PFS \times p_{SD}$ is the correct formula, $p_{Response}$ is the proportion of patients with CR/CRi response and $pSD = 1 - p_{Response}$.
Cells affected	"Model AZA"! AB23:AD153; "Model CCR"! AB23:AD153

Original formula	**Revised formula**
Formula in 'Model AZA'!AB23: ='PSA inputs'!$D$52+K23*IF(C23<7,'PSA inputs'!$D$53,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$53))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$54,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$54))	replaced with: ='PSA inputs'!$D$52+K23*IF(C23<7,'PSA inputs'!$D$53,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$53))+L23*IF(C23<7,'PSA inputs'!$D$54,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$54))
Formula in 'Model AZA'!AB24: =K24*IF(C24<7,'PSA inputs'!$D$53,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$53))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$54,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$54))	replaced with: =K24*IF(C24<7,'PSA inputs'!$D$53,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$53))+L24*IF(C24<7,'PSA inputs'!$D$54,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$54)) (Correct the formulas in the cells below)
Formula in 'Model CCR'!AB23: ='PSA inputs'!$D$71+K23*IF(C23<7,'PSA inputs'!$D$72,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$72))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$73,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$73))	replaced with: ='PSA inputs'!$D$71+K23*IF(C23<7,'PSA inputs'!$D$72,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$72))+L23*IF(C23<7,'PSA inputs'!$D$73,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$73))
Formula in 'Model CCR'!AB24: =K24*IF(C24<7,'PSA inputs'!$D$72,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$72))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$73,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$73))	replaced with: =K24*IF(C24<7,'PSA inputs'!$D$72,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$72))+L24*IF(C24<7,'PSA inputs'!$D$73,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$73)) (Correct the formulas in the cells below)
Formula in 'Model AZA'!AC23: ='PSA inputs'!$D$57+K23*IF(C23<7,'PSA inputs'!$D$58,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$58))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$59,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$59))	replaced with: ='PSA inputs'!$D$57+K23*IF(C23<7,'PSA inputs'!$D$58,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$58))+L23*IF(C23<7,'PSA inputs'!$D$59,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$59))

Formula in ‘Model AZA’!AC24: =K24*IF(C24<7,'PSA inputs'!$D$58,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$58))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$59,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$59))	replaced with: =K24*IF(C24<7,'PSA inputs'!$D$58,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$58))+L24*IF(C24<7,'PSA inputs'!$D$59,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$59)) (Correct the formulas in the cells below)
Formula in ‘Model CCR’!AC23: ='PSA inputs'!$D$76+K23*IF(C23<7,'PSA inputs'!$D$77,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$77))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$78,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$78))	replaced with: ='PSA inputs'!$D$76+K23*IF(C23<7,'PSA inputs'!$D$77,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$77))+L23*IF(C23<7,'PSA inputs'!$D$78,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$78))
Formula in ‘Model CCR’!AC24: =K24*IF(C24<7,'PSA inputs'!$D$77,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$77))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$78,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$78))	replaced with: =K24*IF(C24<7,'PSA inputs'!$D$77,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$77))+L24*IF(C24<7,'PSA inputs'!$D$78,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$78)) (Correct the formulas in the cells below)
Formula in ‘Model AZA’!AD23: ='PSA inputs'!$D$62+K23*IF(C23<7,'PSA inputs'!$D$63,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$63))+MAX(L23-K23,0)*IF(C23<7,'PSA inputs'!$D$64,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64))	replaced with: ='PSA inputs'!$D$62+K23*IF(C23<7,'PSA inputs'!$D$63,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$63))+L23*IF(C23<7,'PSA inputs'!$D$64,IF(C23>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64))
Formula in ‘Model AZA’!AD24: =K24*IF(C24<7,'PSA inputs'!$D$64,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64))+MAX(L24-K24,0)*IF(C24<7,'PSA inputs'!$D$64,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64))	replaced with: =K24*IF(C24<7,'PSA inputs'!$D$64,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64))+L24*IF(C24<7,'PSA inputs'!$D$64,IF(C24>'PSA inputs'!$D$121,0,'PSA inputs'!$D$64)) (Correct the formulas in the cells below)
ICER (cost per QALY)	−£25,485 (AZA dominant)