NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

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

1.2 This guidance is not intended to affect the position of patients whose treatment with azacitidine was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Azacitidine (Vidaza, Celgene) has a marketing authorisation for 'the treatment of adult patients aged 65 years or older who are not eligible for haematopoietic stem cell transplant with acute myeloid leukaemia with more than 30% marrow blasts, according to the World Health Organisation (WHO) classification'. Azacitidine also has a marketing authorisation for 'the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with acute myeloid leukaemia with 20% to 30% blasts and multi-lineage dysplasia, according to WHO classification', which is outside the scope of this appraisal.

2.2 The summary of product characteristics notes that azacitidine is most commonly associated with haematological reactions (71.4%) including thrombocytopenia, neutropenia and leukopenia (usually grade 3 to 4) and gastrointestinal events (60.6%) including nausea, vomiting (usually grade 1 to 2) or injection site reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Azacitidine is available at a list price of £321.00 per 100-mg vial (excluding VAT, BNF, March 2016). It is administered subcutaneously at a recommended dose of 75 mg/m^2 body surface area 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 have a minimum of 6 cycles. The drug cost of a cycle of azacitidine treatment is £4,494.00 (excluding VAT) assuming the list price, 7 treatments in a cycle, vial wastage and a body surface area of 1.8 m^2.

The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of azacitidine with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee considered evidence submitted by Celgene and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical effectiveness

3.1 The company presented evidence from 1 randomised controlled trial, AZA-AML-001. This was an international, multicentre, controlled, phase 3 study with an open-label, parallel-group design. It included 488 adults of 65 years and older who had newly diagnosed acute myeloid leukaemia with more than 30% bone marrow blasts and an eastern cooperative oncology group (ECOG) performance status of 0 to 2 with adequate organ function. Before randomisation patients were screened and assigned to one of 3 conventional care regimens: intensive chemotherapy with anthracycline and cytarabine plus best supportive care; low-dose chemotherapy with cytarabine plus best supportive care; and best supportive care only. Patients were then randomised to have either azacitidine (n=241) or the preselected conventional care regimen (n=247).

3.2 The primary outcome was overall survival. AZA-AML-001 was powered to detect a difference in overall survival between azacitidine and the combined conventional care regimen, which comprised intensive chemotherapy with anthracycline and cytarabine plus best supportive care, low-dose chemotherapy with cytarabine plus best supportive care and best supportive care alone. The secondary outcomes included 1-year overall survival rate, overall remission rate, duration of remission, cytogenetic complete remission rate, partial remission, stable disease, safety and tolerability, patient-reported quality-of-life outcomes (assessed using the European Organization for Research and Treatment of Cancer [EORTC-QLQ-30] questionnaire), measures of healthcare resource use and transfusion status. Patients were not allowed to switch treatments during the study, but further treatments were allowed after the study drug was stopped. After stopping, 67 patients in the azacitidine arm and 75 patients in the conventional care arm had further treatments.

3.3 Azacitidine was associated with improvements in overall survival compared with the combined conventional care regimen. However, the intention-to-treat analysis showed that azacitidine was not statistically significantly superior to the combined conventional care regimen (see table 1).

Table 1 Clinical effectiveness outcomes in AZA-AML-001; summary of overall survival in the intention-to-treat population

Median overall survival (95% confidence interval [CI]), months	Azacitidine (n=241): • 10.4 (8.0 to 12.7) Conventional care regimen (CCR; n=247): • 6.5 (5.0 to 8.6)
Difference (95% CI), months	3.8 (1.0 to 6.5)
Hazard ratio (azacytidine to CCR [AZA:CCR]; 95% CI)	0.85 (0.69 to 1.03)
Stratified log-rank test: p value	0.1009
Hazard ratio (AZA:CCR; 95% CI)	0.84 (0.69 to 1.02)
Unstratified log-rank test: p value	0.0829

3.4 Secondary outcomes, including measures of haematological response, duration of remission and remission-free survival, were similar between azacitidine and the combined conventional care regimen, with no statistically significant differences between treatments. Azacitidine and the combined conventional care regimen were associated with general improvements in health-related quality of life in the 4 prespecified QLQ-C30 domains of fatigue, dyspnoea, global health status and physical functioning. Statistical analyses were not presented in the submission for health-related quality of life.

3.5 In response to the use of further treatments after stopping the study drug in the clinical trial, the company presented a series of sensitivity analyses that censored patients at the date of first subsequent therapy (see table 2). The company indicated that these results suggested that the subsequent therapies may be confounding the treatment effect of azacitidine.

Table 2 Summary of sensitivity analyses on overall survival (intention-to-treat population)

Median overall survival (95% confidence interval [CI]), months	Azacitidine (n=241): • 12.1 (9.2 to 14.2) Conventional care regimen (n=247): • 6.9 (5.1 to 9.6)
Hazard ratio (azacytidine to CCR) [AZA:CCR]; 95% CI)	0.76 (0.60 to 0.96)
Stratified log-rank test: p value	0.0190
Hazard ratio (AZA:CCR; 95% CI)	0.75 (0.59 to 0.95)
Stratified log-rank test: p value	0.0147

3.6 The company stated that there was heterogeneity in the study population as well as possible confounding in the results because of subsequent therapies. It did post-hoc analyses using Cox proportional hazards, inverse probability of censoring weighted analysis and regression-based imputation to estimate the effect on overall survival when baseline covariates and subsequent treatment were adjusted for. One inverse probability of censoring weighted analysis adjusted for any subsequent treatments in both trial arms and another adjusted only for the use of azacitidine in the conventional care regimen arm. The latter analysis was presented as academic in confidence and cannot be included here. Using these methods, azacitidine was shown to statistically significantly improve overall survival compared with the conventional care regimen (see table 3).

Table 3 Post-hoc overall survival estimates adjusted for baseline characteristics and/or subsequent therapy

Cox proportional hazard – adjusted for subsequent therapy: hazard ratio (HR) for azacytidine (AZA) versus conventional care regimen (CCR)	0.75 (95% confidence interval [CI] 0.59 to 0.94, p=0.0130)
Cox proportional hazard – adjusted for baseline characteristics: HR for AZA versus CCR	0.80 (95% CI 0.66 to 0.99; p=0.0355)
Cox proportional hazard – adjusted for subsequent therapy and baseline characteristics: HR for AZA versus CCR	0.69 (95% CI 0.54 to 0.88; p=0.0027)

Inverse probability of censoring weighted Cox proportional hazards models – unadjusted for baseline characteristics: HR for AZA versus CCR	0.77 (95% CI 0.61 to 0.98, p=0.0310)
Inverse probability of censoring weighted Cox proportional hazards models – adjusted for baseline characteristics: HR for AZA versus CCR	0.71 (95% CI 0.56 to 0.90, p=0.0047)
Regression-based imputation analysis – adjusted for subsequent therapy: HR for AZA versus CCR	0.76 (95% CI 0.62 to 0.93, p=0.007)

The inverse probability of censoring weighted Cox proportional hazards models was adjusted for subsequent therapy in both treatment arms.

3.7 The company presented an exploratory analysis of azacitidine compared with the individual components of the conventional care regimen. AZA-AML-001 was not powered to detect differences between azacitidine and individual treatments.

- Median overall survival was 5.8 months in the azacitidine group (95% confidence interval [CI] 3.6 to 9.7, n=44) compared with 3.7 months in the best supportive care group (95% CI 2.8 to 5.7, n=45). There was a 40% reduction in the risk of death for patients having azacitidine (hazard ratio [HR] 0.60; 95% CI 0.38 to 0.95, unstratified log rank test p=0.0288).
- Median overall survival was 11.2 months in the azacitidine group (95% CI 8.8 to 13.4, n=154) compared with 6.4 months in the low-dose chemotherapy group (95% CI 4.8 to 9.1, n=158). There was a 10% reduction in the risk of death for patients having azacitidine (HR 0.90; 95% CI 0.70 to 1.16, unstratified log rank test p=0.4270).
- Median overall survival was 13.3 months in the azacitidine group (95% CI 7.2 to 19.9, n=43) compared with 12.2 months in the intensive chemotherapy group (95% CI 7.5 to 15.1, n=44). There was a 15% reduction in the risk of death for patients having azacitidine (HR 0.85; 95% CI 0.52 to 1.38, unstratified log rank test p=0.5032).

3.8 The company presented results for event-free survival and relapse-free survival for azacitidine compared with the individual components of the conventional care regimen.

- Event-free survival was 4.5 months in the azacitidine group (n=44) compared

with 3.1 months in the best supportive care group (n=45). There was a 33% reduction in the risk of an event for patients in the azacitidine group (HR 0.67; 95% CI 0.43 to 1.04, p=0.0756). Relapse-free survival results were not presented for this comparison.

- Event-free survival was 7.3 months in the azacitidine group (n=154) compared with 4.8 months in the low-dose chemotherapy group (n=158). There was an 11% reduction in the risk of an event for patients in the azacitidine group (HR 0.89; 95% CI 0.70 to 1.13, p=0.3563). Relapse-free survival was 8.6 months in the azacitidine group (n=154) compared with 9.9 months in the low-dose chemotherapy group (n=158). There was an 11% reduction in the risk of relapse for patients in the low-dose chemotherapy group (HR 1.11; 95% CI 0.68 to 1.81, p=0.6638).

- Event-free survival was 8.1 months in the azacitidine group (n=43) compared with 9.7 months in the intensive chemotherapy group (n=44). There was a 2% reduction in the risk of an event for patients in the intensive chemotherapy group (HR 1.02; 95% CI 0.64 to 1.63, p=0.9196). Relapse-free survival was 10.8 months in the azacitidine group (n=43) compared with 12.1 months in the intensive chemotherapy group (n=44). There was a 21% decrease in the risk of relapse for patients in the intensive chemotherapy group (HR 1.21; 95% CI 0.58 to 2.51, p=0.6135).

3.9 Subgroup analyses for patients with a poor cytogenetic risk and patients with myelodysplastic syndrome-related changes were included in the submission. Median overall survival for patients with myelodysplastic syndrome-related changes was 12.7 months in the azacitidine group compared with 6.3 months in the conventional care regimen group (HR 0.69; 95% CI 0.48 to 0.98, p=0.357). The median overall survival 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 conventional care regimen group (HR 0.68; 95% CI 0.68 to 0.94, p=0.0185).

3.10 The company reported that azacitidine was generally well tolerated in AZA-AML-001, with more than 50% of patients in the azacitidine treatment group having 6 or more treatment cycles and one-third having 12 or more cycles. The most common haematological treatment-related adverse events with azacitidine were febrile neutropenia, neutropenia and thrombocytopenia. All frequent haematological adverse events were generally lower with azacitidine than with

other conventional care regimen treatments. The most common non-haematological treatment-related adverse events were constipation, nausea and diarrhoea. In general, non-haematological adverse events occurred more frequently in the azacitidine group compared with the conventional care regimen treatments. The most common serious adverse events reported in the azacitidine group included febrile neutropenia, pneumonia and pyrexia.

Cost effectiveness

3.11 The company presented a semi-Markov model based on 4 states: remission, non-remission, relapsed or progressive disease, and death. The model used a cycle length of 4 weeks with a lifetime time horizon of 10 years. In the base case, the company compared azacitidine with the combined conventional care regimen. In the combined conventional care regimen, 18% of patients had intensive chemotherapy, 64% had low-dose chemotherapy and 18% had best supportive care. A comparison with the individual conventional care regimen 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.

3.12 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 included subgroup analysis for patients with cytogenetic risk factors and myelodysplasia-related changes. 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 distributions respectively.

3.13 Health-related quality of life was incorporated into the model by applying utility scores to each health state. Utilities were mapped from trial-based disease-specific EORTC-QLQ-C30 data using published algorithms. Two mapping algorithms were incorporated in the model, one from Proskorovsky et al. (2014) which was used for the base case and the other from McKenzie and Van der Pol (2009), used for a scenario analysis. The model also included the effect on

quality of life of adverse effects, by applying utility decreases (decrements) for each effect of severity grade 3 or above.

3.14 The model incorporated costs in each health state, including costs associated with acute myeloid leukaemia treatment, management of adverse events (events of severity grade 3 or above), transfusion costs, best supportive care monitoring costs, tests to monitor disease and care at the end of life. Treatment costs included drug acquisition, administration and dispensing for azacitidine and the conventional care regimens.

3.15 In the company's base case, the incremental cost-effectiveness ratio (ICER) for azacitidine compared with the combined conventional care regimen was £20,648 per quality-adjusted life year (QALY) gained. In the probabilistic sensitivity analysis the ICER was £17,423 per QALY gained. The incremental costs and QALYs were marked commercial in confidence and cannot be included here.

3.16 The company's deterministic sensitivity analysis showed that the model results were most sensitive to the administration costs associated with the conventional care regimen, the hazard ratio for overall survival and the conventional care regimen remission rates.

3.17 The company presented scenario analyses to explore the effect of assumptions about survival modelling, treatment sequences and the proportions of patients having each of the conventional treatments. These scenario analyses demonstrated that the ICERs were most sensitive to changes in the proportions of patients assumed to have each of the conventional treatments, the use of the individual treatment regimens rather than the combined conventional care regimen, and the use of the censor at switch data to calculate overall survival.

ERG's comments

3.18 The ERG stated that there were limitations to the company's systematic review searches and inclusion criteria. However, it concluded that the company did not appear to have missed any evidence. The ERG noted that AZA-AML-001 was well designed and well conducted. It also stated that although unavoidable, the open-label design of the trial increased the risk of bias. It noted some limitations in this

trial – in particular, the primary end point was a comparison of overall survival for patients randomised to azacitidine and patients randomised to the combined conventional care regimen. The trial was underpowered to compare azacitidine with each of the individual conventional care regimens. The ERG also commented that the use of subsequent therapies after stopping study treatments resulted in confounded estimates for the primary efficacy end point and other end points. Additionally, statistical analyses of time-to-event outcomes relied on the proportional hazards assumption, which the ERG considered not to be justified.

3.19 The ERG commented on the company's analyses that adjusted overall survival as a result of subsequent therapy. The ERG noted that the submission lacked clarity about which treatments the analyses had adjusted for. The ERG noted that the company presented inverse probability of censoring weighted (IPCW) analysis, in which 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 in which only subsequent azacitidine use in the conventional care regimen arm was adjusted for. The ERG stated that the analysis in which both arms were adjusted was more appropriate when the mix of subsequent treatments did not reflect that used in clinical practice. The ERG also stated that the company misinterpreted the NICE decision support unit technical support document 16, which outlines the appropriate methods of adjustment when treatments are switched. The ERG noted that the IPCW analysis relied on assumptions that it could not assess fully from the available clinical trial data. The ERG commented on the 3 Cox proportional hazards models of survival. It stated that the results of the models were all susceptible to bias. The treatment effect in the model that did not adjust for subsequent treatment was likely to be biased because of subsequent treatment use. However, the adjustments made in the models for subsequent treatments assumed that prognoses are the same for both people who switch and people who do not. The adjustments conversely suggest that prognoses for these groups of people are different but evenly distributed across arms, and that subsequent treatments have the same average effect across arms. The ERG stated that in general the more sophisticated post-hoc adjustment methods appeared to make little difference compared with the sensitivity analyses that used simpler censoring at switch methods.

3.20 The ERG reviewed the company's economic model, and commented that it was transparent and simple. It 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 azacitidine or the combined conventional care regimen. It noted that this is inconsistent with AZA-AML-001, in which 29% of patients had active second-line treatment. Advice from clinical experts suggests that active second-line treatment is considered for some patients in the NHS.

3.21 The ERG identified 4 key areas of concern in the company's economic modelling, extrapolation of key outcomes and health resource use, including incorrect costs and treatment cycles:

- 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 the results from AZA-AML-001.
- Overall survival in the azacitidine arm was not adjusted for subsequent active treatment, resulting in an inconsistency between the modelled health outcomes and costs, because only the costs of best supportive care were modelled following azacitidine.
- There were significant differences in the costs associated with the relapsed and progressive disease state between the azacitidine and conventional care regimen arms, even though patients in both arms were expected to be receiving best supportive care at this point. The ERG noted that the biggest difference was in the number of inpatient days in the relapsed and progressive disease state, which were 1.73 for azacitidine and 2.61 for the conventional care regimen. The effect of this was that cost differences accumulated at a rate of £628 per month despite all patients having best supportive care.
- The mean number of treatment cycles in the model did not reflect the mean number of treatment cycles in AZA-AML-001. In the azacitidine arm the mean number of treatment cycles was 5.6 instead of 8.8. In the conventional care regimen arm, intensive chemotherapy was calculated as 2.61 instead of 2.00 cycles (initiation and consolidation), and low-dose chemotherapy 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.

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.

ERG's exploratory analysis

3.22 The ERG identified 12 implementation errors in the company model of which 9 affected the base-case analysis. They mainly related to the formula used to calculate health care resource use, but also to the extrapolation of outcomes. The amendments that increased the ICER the most were:

- In the conventional care regimen arm, patients receiving best supportive care incurred drug administration costs in the remission and non-remission states. However, for other active treatments the costs of administering best supportive care were not included after stopping treatment until relapse or progression.
- In the azacitidine and conventional care regimen arms, costs of tests and transfusions were not modelled for patients in the relapsed or progressive disease state.
- In the azacitidine and conventional care regimen arms, drug administration, monitoring tests and transfusion costs were double-counted during the first model cycle.

  Conversely one of the errors overestimated the base-case ICER. In the azacitidine and conventional care regimen arms, the formula used to calculate the costs of drug administration, monitoring tests and transfusions for patients in the non-remission (stable disease) state was incorrect. Amending the 9 implementation errors increased the ICER in the base-case analysis from £20,648 to £62,518 per QALY gained.

3.23 The ERG then made a series of changes to the parameter values to reflect current UK practice and to make the model logical. The effect of each of the

individual changes to the corrected base-case ICER of £62,518 per QALY gained is shown below.

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 increased the ICER to £131,698 per QALY gained.

Costs of relapsed and progressive disease

The costs of best supportive care for relapsed and progressive disease were set to be the same in the azacitidine and conventional care regimen arms. This increased the ICER to £159,352 per QALY gained.

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. Because of the model coding, modelling of relapse-free and progression-free survival also switched to being censored for treatment switching in both arms. The effect of this analysis was to reduce the ICER to £47,482 per QALY gained.

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 by Kaplan–Meier curves. This increased the ICER to £75,471 per QALY gained.
- The relapse-free survival curves were replaced by Kaplan–Meier curves. This had little impact on the ICER (£63,569 per QALY gained).

Adjusting overall survival for baseline covariates

Overall survival was adjusted for treatment switching (censoring at switch in both arms) and baseline covariates. This increased the ICER to £65,188 per QALY gained. 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.

The cumulative effect of all these changes was to increase the ICER to £273,308 per QALY gained.

3.24 The ERG did some exploratory analyses using the individual conventional care regimen treatments. It stated that for progression-free survival and relapse-free survival outcomes, the sample sizes make subgroup-specific time-to-event data highly unreliable. In the exploratory analyses subgroup-specific differences in overall survival outcomes were allowed using censor-at-switch data, while keeping common progression-free survival and relapse-free survival curves across the 3 subgroups. These exploratory analyses with the ERG changes (but without controlling for baseline covariates) produced ICERs above £100,000 per QALY gained for each of the individual conventional care regimens.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of azacitidine, having considered evidence on the nature of acute myeloid leukaemia and the value placed on the benefits of azacitidine by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee noted that no clinical or patient experts were available to attend the committee meeting but statements were received as part of the evidence submission stage of the NICE technology appraisal process. The committee heard from the company about acute myeloid leukaemia. The committee understood that azacitidine has a marketing authorisation which has been extended to include treatment of acute myeloid leukaemia with more than 30% bone marrow blasts in adults of 65 years or older who are not eligible for haematopoietic stem cell transplant. The company stated that this is a difficult-to-treat group with few treatment options currently available. The committee understood that patients with acute myeloid leukaemia with more than 30% bone marrow blasts tend to be older, are often diagnosed late and their prognosis is poor. The committee asked for clarification about why the marketing authorisation specified people over 65. The committee heard from the company that this was the group enrolled in the clinical trial. Furthermore, the incidence of acute myeloid leukaemia increases in people over 65 and that this group, with more than 30% marrow blasts, represents people with the most severe disease. The committee understood the severity of the disease and its effect on patients and their families. The committee concluded that there is an important unmet need for people with acute myeloid leukaemia.

4.2 The committee discussed the relevant comparators for azacitidine. The committee was aware that the NICE scope specified 3 separate comparators: intensive chemotherapy with an anthracycline and cytarabine, low-dose chemotherapy with cytarabine, and best supportive care alone. The company noted that current clinical practice is based on a number of patient and disease-related prognostic factors. The committee was aware from the clinical and patient expert statements received that people with a good performance status are likely to be offered intensive chemotherapy with an anthracycline and

cytarabine or low-dose chemotherapy with cytarabine. People unlikely to tolerate chemotherapy because of poor performance status receive best supportive care. The company emphasised that there is no defined treatment algorithm for deciding who receives which treatment and that azacitidine would be expected to replace all 3 treatments. Therefore, in its submission the company combined the comparators as in their clinical trial into a single combined conventional care regimen. The committee discussed the use of the single combined conventional care regimen. It noted that in work done for previous NICE appraisals, the NICE decision support unit advised against the use of such 'blended' comparators. The committee concluded that the relevant comparators for the appraisal were those specified in the NICE scope, that is, intensive chemotherapy with an anthracycline and cytarabine, low-dose chemotherapy with cytarabine and best supportive care. The committee expressed concerns about the company's decision problem in which the individual regimens were combined into a single conventional care regimen.

Clinical effectiveness

4.3 The committee noted that the key clinical effectiveness evidence was from the AZA-AML-001 trial, in which azacitidine was compared with a combined conventional care regimen. The committee discussed the use of a combined conventional care regimen in the clinical trial rather than a single comparator. The committee understood that there was some uncertainty about which patients would be most likely to receive each of the comparators and that clear criteria did not exist. Nevertheless, the committee considered that treatment allocation was associated with performance status. The committee considered that although there was no clear distinction between groups in the individual conventional care regimens these could be regarded as separate patient groups seen in clinical practice. The committee concluded that using the combined conventional care regimen in the clinical trial was not optimal for decision-making. However, in this instance its use was partly justified by the uncertainties in treatment allocation and the relatively small numbers in 2 of the 3 treatment groups in the clinical trial (see sections 4.4 and 4.6). The committee concluded that it was appropriate to not only consider the outcomes of the combined conventional care arm, but also the outcomes for the individual treatment subgroups.

4.4 The committee asked the company to clarify the proportions of patients randomised to the individual components of the conventional care regimen. The committee heard that the anticipated patient distribution between intensive chemotherapy, low-dose chemotherapy and best supportive care was 50:30:20 respectively (see section 3.17). The committee was told that the actual patient distribution for the individual components of the conventional care regimen was 18:64:18. The committee heard from the company that it considered the 18% of people randomised to intensive chemotherapy treatment to reflect current clinical practice in the NHS. However, the proportions of patients randomised to low-dose chemotherapy and best supportive care in the trial appeared different to current practice in the NHS. The company noted that it is difficult to identify the exact proportions of patients receiving each type of treatment because there is no widely accepted risk algorithm that clinicians use in England to decide which patients will receive treatment. The committee concluded that there were some differences in treatment allocation in the clinical trial and in NHS clinical practice which could affect the generalisability of the results to NHS clinical practice.

4.5 The committee discussed the results from AZA-AML-001. The committee noted that while this trial demonstrated gains favouring azacitidine in its primary efficacy end point of overall survival, it failed to reach statistical significance when comparing azacitidine with the combined conventional care regimen. Also there were no statistically significant differences for the secondary outcomes. The company noted that in this difficult-to-treat and heterogeneous patient group, clinical trials often fail to reach statistical significance for overall survival. Furthermore, the company considered that the use of subsequent treatments in the trial had confounded the results. The committee expressed concern about the absence of statistically significant results for the end points when using intention-to-treat analysis, but concluded that the use of subsequent treatments would have affected the results and agreed it was appropriate to consider analyses that controlled for treatment switching.

4.6 The committee then considered the results of AZA-AML-001 that compared azacitidine with the individual components of the conventional care regimen. The committee understood that the trial was not powered for these comparisons, which were based on small patient numbers. The committee noted that for overall survival azacitidine was more effective than intensive chemotherapy, low-dose

chemotherapy and best supportive care. However, only the comparison with best supportive care reached statistical significance. The committee noted that these results were not always intuitive, for example for the comparison with low-dose chemotherapy the hazard ratio was closest to 1.00, but the difference in median overall survival was the biggest. The committee heard from the evidence review group (ERG) that this was because the trial arms converged at about 2 years, which indicated that proportional hazards models were not appropriate. The committee also noted that for event-free survival and relapse-free survival the individual chemotherapy conventional care regimens appeared to do better than azacitidine. The committee concluded that the degree to which azacitidine was more effective than any of the individual conventional care regimens was very uncertain.

4.7 The committee discussed the company analyses that adjusted for treatment switching and baseline covariates. The committee understood that during the trial no crossover between any treatment groups was allowed and once randomised to a conventional care regimen patients could not change to a different conventional care regimen. However, patients who stopped the study treatment could receive subsequent therapy during study follow-up. The committee was told that 67 patients in the azacitidine arm and 75 patients in the conventional care arm received further treatments after stopping treatment. The company therefore adjusted overall survival outcomes for treatment switching using a range of different methodological approaches. The committee considered that the approaches used by the company were all susceptible to bias because they relied on the proportional hazards assumption, which the committee did not consider was appropriate. The committee noted that the ERG had concluded that the more complex methods of adjusting for treatment switching had not added anything to the simpler censoring methods. However, the committee noted that the assumptions behind the simpler methods preferred by the ERG were also not supported by the data or by NICE technical support documents. The committee considered that a more robust method such as the Branson and Whitehead adjustment method would have been more appropriate. The company and ERG both noted that they had not considered this method. The committee concluded that there were limitations in the approaches used by both the company and the ERG and that an approach that adjusted for treatment switching in both arms, but which did not rely on an assumption of proportional hazards, would have been more appropriate.

Cost effectiveness

4.8 The committee considered the cost-effectiveness evidence presented by the company and the exploratory analyses presented by the ERG. It heard that the ERG considered the model to be simple and transparent. The committee considered the company's model in detail, and discussed 4 key areas of concern about the company's approach: the extrapolation of overall survival and adjustment for treatment switching, implementation errors in the model, health resource use estimates and costs of the relapsed and progressive disease state.

4.9 The committee discussed the implementation errors in the company model identified by the ERG. These mainly related to the formula used to calculate healthcare resource use, but also to the extrapolation of outcomes. The committee understood that 3 of the errors identified related only to sensitivity analyses, and that of the others, 8 increased the estimate of the incremental cost-effectiveness ratio (ICER) and 1 reduced it. The committee noted that the cumulative effect of the corrections was to increase the company base-case ICER from £21,000 to £63,000 per quality-adjusted life year (QALY) gained. The company told the committee that they accepted these model errors and the implementation changes needed to correct them. The committee accepted these changes made by the ERG and concluded that the base-case ICER in the company model was £63,000 per QALY gained.

4.10 The committee discussed the modelling of the number of treatment cycles. It heard from the ERG that, instead of using a mean of 8.8 cycles of treatment with azacitidine, the company had used a maximum number of 8 treatment cycles, which meant that the mean number of treatment cycles in the model was incorrectly calculated to be 5.6 cycles. The committee agreed with the ERG that the number of cycles in the model should reflect AZA-AML-001, in which a mean 8.8 cycles were received. The committee heard from the ERG that similar errors were made in the calculation of treatment cycles for the comparator treatments. The committee concluded that it was appropriate for the number of cycles of treatment in the model to reflect the number of cycles of treatment in the clinical trial. The committee noted that this change increased the ICER from £63,000 to £132,000 per QALY gained. The company accepted the ERG's changes and accepted the resulting increase in the ICER.

4.11 The committee discussed the ERG's further analysis relating to costs in the relapsed and progressive disease state. The committee heard that costs for the disease states were calculated using a healthcare resource-use questionnaire. The questionnaire was sent to 2 separate groups of 7 clinicians for azacitidine and the conventional care regimen. The methodology used by the company meant that in the relapsed and progressive disease health state in the model, different resource estimates were applied to the azacitidine group and the conventional care group despite both groups being treated with best supportive care. The committee noted that the main difference in estimates was for inpatient days; the company estimated that people in the azacitidine arm would have 1.73 inpatient days and 2.61 days in the conventional care regimen arm. The committee noted that this was one of the most expensive categories of healthcare resource use in the company model, so using an assumption of differing resource use led to an accumulation of differential costs in the groups. The committee considered that because all patients in this disease state would be receiving best supportive care, the resource use in the 2 groups would be the same. The committee heard from the ERG that the ICER was very sensitive to both the absolute resource use assumed and the difference in resource use between the azacitidine and conventional care groups. To test the sensitivity to the changes in costs, the ERG had set healthcare resource use in the progressive disease state to £0 and the ICER increased from £63,000 to approximately £74,000 per QALY gained. The committee concluded that equalising costs in both the azacitidine arm and the conventional care regimen arm for the progressive disease state was justified and noted that this change increased the ICER for £63,000 to £160,000 per QALY gained. However, the committee noted that the ERG had equalised the cost to the higher estimate of resource use, and that it might have been more reasonable to take an average of the resource use estimates for the 2 groups. The committee noted that the combined effect of correcting the model implementation errors, the number of treatment cycles and equalising the costs in the relapsed and progressive disease health state increased the ICER from £63,000 to £240,000 per QALY gained. However, it agreed that because of the use of the higher estimate of resource use, the ICER for azacitidine was likely to be somewhat overestimated.

4.12 The committee discussed the changes made by the ERG for treatment switching, adjusting for baseline covariates and the assumption of proportional hazards. The committee recalled the approaches used by the company and the ERG to adjust

for treatment switching and the limitations associated with these (see section 3.6). The committee did not consider that an assumption of proportional hazards was appropriate and accepted the changes made by the ERG to use Kaplan–Meier curves from each trial arm rather than fitting curves that assumed proportional hazards. The committee noted that individually these changes did not affect the ICER, but that when considered with the changes to cost estimates they had a larger effect. The committee was not convinced that the ERG's changes to adjust for treatment switching using censor at switch was any better than the methods used by the company. The committee understood that the company and therefore the ERG had presented an analysis that adjusted for baseline covariates. However, it understood that there were some limitations associated with adjusting because of small sample sizes in some groups. The committee concluded that an assumption of proportional hazards was not appropriate; it would have liked to have seen an estimate of the ICER that adjusted for treatment switching in both groups and did not use an assumption of proportional hazards. Nevertheless, considering the data presented, the committee concluded that issues associated with the extrapolation and survival modelling were of less importance than the issues associated with cost estimates, and these limitations did not prevent it from making a decision about the cost effectiveness of azacitidine.

4.13 The committee discussed the cost-effectiveness results presented by the company and the ERG's exploratory analyses. The committee considered the most plausible ICER for azacitidine compared with the conventional care regimen. It noted that the company's base-case ICER was £21,000 per QALY gained. With corrections to the implementation errors in the model, this increased to £63,000 per QALY gained. The committee accepted the changes to the number of treatment cycles in the company model and the equalising of costs in the relapse and progressive disease state (see sections 3.22 and 3.23). It noted that with these changes, the ICER increased further to £240,000 per QALY gained, but recognised that this ICER is likely to be somewhat overestimated because of the higher estimate of resource use used by the ERG. The committee also accepted the use of the Kaplan–Meier curves, which would lead to further increases in the ICER and reflected that there was considerable uncertainty due to the confounded overall survival data (section 4.7). However, the committee concluded that a reasonable estimate of the most plausible ICER was approximately £240,000 per QALY gained.

4.14 The committee considered the innovative nature of azacitidine. The committee heard from the company that it considers azacitidine to be an innovative treatment option both in its clinical effectiveness and because it provides another treatment option in an area of high unmet need for a difficult-to-treat population. The committee discussed the innovative nature of azacitidine. It concluded that azacitidine should not be considered a step change in the treatment of acute myeloid leukaemia and that there was a high degree of uncertainty about its clinical effectiveness relative to current conventional chemotherapy treatments.

4.15 The committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

  In addition, when taking these criteria into account, the committee must be persuaded that the estimates of the extension to life are sufficiently robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.16 The committee noted the evidence presented by the company that showed that people with acute myeloid leukaemia have a life expectancy of less than 24 months. The company presented evidence to show that azacitidine offers an extension to life, of at least an additional 3 months, compared with current NHS treatment. The company presented a median overall survival benefit of 3.8 months. The committee heard from the ERG that the estimates of extension to life were neither plausible nor robust because the azacitidine and conventional care regimen curves converged over time. The ERG suggested that using a restricted mean estimate was more appropriate than using a median estimate. The committee accepted the ERG's restricted mean overall survival estimate of 2.5 months. The committee concluded that azacitidine did not meet the criteria to be considered a life-extending, end-of-life treatment.

4.17 Taking into account that the most plausible ICER for azacitidine (approximately £240,000 per QALY gained, see section 4.11), that azacitidine should not be considered a step change (see section 4.14), and that azacitidine did not meet the criteria to be considered a life-extending, end-of-life treatment (see section 4.16), the committee concluded that it could not recommend azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts in people of 65 years or older who are not eligible for haematopoietic stem cell transplant as a cost-effective use of NHS resources.

4.18 The committee was aware of the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England. Under the new arrangements, drugs may be given a conditional recommendation by NICE and made available to NHS patients through the Cancer Drugs Fund. Such a drug will remain available within the Cancer Drugs Fund, normally for up to 2 years, while the company gathers more evidence. The committee considered that the most plausible ICER for azacitidine was substantially higher than the range normally considered a cost-effective use of NHS resources, and so azacitidine did not have the potential to satisfy the criteria for routine use (see section 4.13). The committee also considered that, given the uncertainties in the evidence it had seen, collecting outcomes data from people in the NHS would not be enough to inform an update of the guidance or cause the committee to reconsider its recommendations. The committee also heard from the company that it did not intend to submit a case for azacitidine's inclusion in the Cancer Drugs Fund. For these reasons, the committee therefore concluded that it could not recommend azacitidine for inclusion in the Cancer Drugs Fund.

4.19 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

4.20 The committee considered whether its recommendations were associated with

any potential issues related to the equality legislation and the requirement for fairness. It considered a consultee comment received during consultation which highlighted that around 75% of people with acute myeloid leukaemia are over the age of 60 years, and that these people may be less able to tolerate the toxicity and side effects associated with current treatments. The committee was aware that age is a protected characteristic as defined by the Equalities Act. The committee was also aware that azacitidine has a marketing authorisation for people of 65 years or older, and that it was this subgroup who were enrolled in the AZA-AML-001 trial that both underpinned the marketing authorisation for azacitidine (see section 4.1) and was the main focus of the company's submission. However, the committee was aware that it could only make recommendations in accordance with the marketing authorisation for azacitidine. However, the committee agreed that its recommendations were not made because of the age of the patients, but rather because azacitidine within its marketing authorisation was not cost effective, and that it had not identified any special factors which would require or justify making a positive recommendation despite the very high ICERs.

4.21 NICE's technology appraisal guidance on azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia recommends azacitidine as an option for acute myeloid leukaemia with 20% to 30% bone marrow blasts. The committee considered a consultee comment received during consultation, which highlighted that an inequitable situation would be created by not recommending azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts. The committee was aware that severity of disease is not a protected characteristic as defined by the Equalities Act, and that it did not fall within NICE's obligations to avoid discrimination while carrying out its functions. The committee noted that azacitidine had been considered by NICE separately for acute myeloid leukaemia with 20% to 30% and more than 30% bone marrow blasts because of the timing of the regulatory marketing authorisation approval process. However, the committee agreed that it would have been preferable to have developed a single piece of guidance for azacitidine in this indication.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Stuart Wood
Technical lead

Nicola Hay
Technical adviser

Stephanie Yates
Project manager

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