NICE National Institute for Health and Care Excellence

NICE guidance

Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy

Technology appraisal guidance
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1 Recommendations

1.1 Oral azacitidine is recommended, within its marketing authorisation, as an option for maintenance treatment for acute myeloid leukaemia (AML) in adults who:

- are in complete remission, or complete remission with incomplete blood count recovery, after induction therapy with or without consolidation treatment, and
- cannot have or do not want a haematopoietic stem cell transplant.

It is recommended only if the company provides oral azacitidine according to the commercial arrangement.

Why the committee made these recommendations

There are no standard maintenance treatment options for most people with AML who cannot have or do not want a haematopoietic stem cell transplant. Some people with FLT3-mutation-positive AML can have targeted maintenance treatment with midostaurin. Therefore, oral azacitidine would likely be of most benefit to people whose AML does not have an FLT3-mutation. The clinical trial evidence shows that if people take oral azacitidine it takes longer for their cancer to relapse, and they live longer than if they have placebo.

Oral azacitidine meets NICE's criteria to be considered a life-extending treatment at the end of life. The most likely cost-effectiveness estimates for oral azacitidine are within what NICE normally considers an acceptable use of NHS resources for end of life treatments. So, oral azacitidine is recommended.

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2 Information about oral azacitidine

Marketing authorisation indication

2.1 Oral azacitidine (Onureg, Celgene, a Bristol Myers Squibb company) is indicated 'as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT)'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for oral azacitidine.

Price

2.3 The list price for oral azacitidine is £5,867 for a 200-mg or 300-mg pack of 7 tablets (excluding VAT; price confirmed by the company). The company has a commercial arrangement. This makes oral azacitidine available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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3 Committee discussion

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

New treatment option

People with acute myeloid leukaemia would welcome a new treatment option

3.1 Acute myeloid leukaemia (AML) is a rapidly progressing cancer of the blood and bone marrow that is usually diagnosed in older people. Treatment options for AML include chemotherapy and a stem cell transplant (see section 3.2). The committee understood the substantial psychological, social and physical impact of living with AML for people with the condition and their carers and families. The patient expert described how being diagnosed with AML and the potential prospect of living for only a few months, had a significant emotional impact on them and their family. The clinical experts explained how intensive chemotherapy is associated with morbidity and that each treatment cycle often requires a prolonged hospital stay over several weeks. They explained that because a person's immune system is likely to weaken with chemotherapy, this increases their likelihood of contracting a life-threatening infection, which is an additional worry for people having treatment. The clinical experts explained that for people who are well enough to have intensive chemotherapy, a stem cell transplant remains the most effective treatment option. The committee understood that the decision to have a transplant depends on a person's fitness, choice, response to chemotherapy, and donor availability. The clinical experts highlighted that most people with AML are aged over 60 and are often unable to have a transplant because of co-morbidities and frailty. They also explained that there is a lack of donor availability for people from a minority ethnic family background. Therefore, some people cannot have, or do not want to have a stem cell transplant. The clinical experts

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explained that the risk of relapse in people who do not have a transplant is around 70% to 80%. They added that this would most likely occur within the first year after reaching complete remission. They highlighted that there are no effective treatment options after relapse in this population and that their prognosis and quality of life is poor. The committee noted that while stem cell transplants have the potential to be curative, they are associated with significant morbidity and mortality. The patient expert described how their treatment in preparation for a stem cell transplant was painful and invasive and made them feel too unwell to carry out their regular activities. The committee heard how the financial implications of having a transplant, such as regular travel to hospital and having to take time off work, can have a significant impact on quality of life for people with AML, their carers and families. It understood that oral azacitidine would benefit people who cannot have, or do not want to have a stem cell transplant because it can be taken at home. The committee concluded that people with AML would welcome a new treatment option that would improve their life expectancy and quality of life.

Comparators

Low dose cytarabine and subcutaneous azacitidine are not routinely used for maintenance treatment

3.2 Treatment for AML depends on whether a person is able to have intensive chemotherapy. If intensive chemotherapy is unsuitable, low dose chemotherapy may be given. If intensive chemotherapy is suitable, induction chemotherapy is initially given to achieve complete remission followed by consolidation chemotherapy. After induction or consolidation chemotherapy, some people may be able to have a stem cell transplant. People who have FLT3-mutation-positive AML may also have concomitant treatment with midostaurin during induction and consolidation chemotherapy and continue with midostaurin alone as maintenance treatment to prolong their remission (see NICE's technology appraisal guidance on midostaurin for untreated acute myeloid leukaemia). The committee discussed the company's positioning of oral azacitidine as a maintenance treatment for people who are in complete

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remission after induction chemotherapy, with or without consolidation chemotherapy, and who cannot have or do not want a stem cell transplant. The final scope for this appraisal included established clinical management without oral azacitidine (which may include a watch and wait strategy with best supportive care, low dose cytarabine or subcutaneous azacitidine) as a comparator. The committee noted that the company had not included low dose cytarabine and subcutaneous azacitidine as part of established clinical management. The company's clinical experts considered that these treatments are not used as maintenance treatment in the population who would be considered for treatment with oral azacitidine. The committee discussed the stakeholder comments that low dose cytarabine and subcutaneous azacitidine are not used routinely after induction and consolidation chemotherapy but are used when intensive chemotherapy is unsuitable. It noted the company's response to technical engagement which referenced data from the Haematological Malignancy Research Network (HMRN), which is an ongoing UK population-based cohort. The company presented subgroup data from the HMRN which was aligned to the eligibility criteria of the key clinical trial of oral azacitidine (see section 3.4). This indicated that very few people had maintenance treatment with low dose cytarabine and subcutaneous azacitidine (actual figures are confidential and cannot be reported here). Therefore, the committee concluded that these treatments would not likely be used routinely as maintenance treatment in people who are in complete remission.

Midostaurin is a relevant comparator for people with FLT3-mutation-positive AML

3.3 The committee noted that the company's clinical experts considered that around 25% of people with AML have FLT3-mutation-positive AML. Most of these people will have a stem cell transplant after reaching remission, leaving around 10% who would likely have maintenance therapy with midostaurin. The clinical experts explained that most people with FLT3-mutation positive AML would have targeted treatment with midostaurin during induction, consolidation and maintenance treatment and would be unlikely to switch to oral azacitidine. The committee heard how midostaurin is often not well tolerated, so having an alternative treatment option such as oral azacitidine would be important for this

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population. It recognised that the proportion of people with FLT3-mutation-positive AML who would have oral azacitidine in clinical practice would likely be small, but that it was still a relevant population. Therefore, the committee concluded that midostaurin was a relevant comparator for people with FLT3-mutation-positive AML.

Clinical evidence

Oral azacitidine improves overall survival and relapse-free survival compared with placebo

3.4 The clinical evidence came from QUAZAR AML-001 (from now, referred to as QUAZAR), a phase 3, double-blind, randomised controlled trial that compared oral azacitidine plus best supportive care (from now, referred to as oral azacitidine) with placebo plus best supportive care (from now, referred to as placebo). The company considered that the placebo arm represented the watch and wait comparator. The population included adults with AML in complete remission after intensive induction chemotherapy with or without consolidation chemotherapy, who were not able to have a stem cell transplant. The company reported data from the trial's first data cut (July 2019, median follow up 41.2 months) for all outcomes. It also reported data from a second data cut (September 2020, median follow up 51.7 months) for the primary outcome of overall survival. In the intention-to-treat (ITT) population, oral azacitidine increased median overall survival compared with placebo from 14.8 months to 24.7 months (hazard ratio 0.69; 95% confidence interval 0.56 to 0.86, p value 0.0008). In the ITT population, oral azacitidine increased median relapse-free survival compared with placebo from 4.8 months to 10.2 months (hazard ratio 0.65; 95% confidence interval 0.52 to 0.81, p value 0.0001). The committee welcomed the mature trial data from QUAZAR and concluded that oral azacitidine improves overall survival and relapse-free survival compared with placebo.

The results from the QUAZAR EU-subgroup are generalisable to clinical practice in England and should be used for decision-

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making

3.5 The QUAZAR trial included 148 sites and included a large number of people from Europe (known as the EU-subgroup) and a small number of people from the UK (the actual numbers are considered confidential by the company and cannot be reported here). The EU-subgroup was part of the company's pre-specified subgroup analyses. The company considered that the baseline characteristics of people in QUAZAR aligned to the AML population in the UK who cannot have a transplant, with some exceptions:

- age (the trial was limited to people aged 55 and over)

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- cytogenetic risk (the trial included people with intermediate and poor risk cytogenetics, but people with favourable risk cytogenetics are less likely to have a transplant in first complete remission).

  The clinical experts explained that the treatment pathway for younger people would be the same as for those aged over 55 years. They explained that because of the toxicity associated with intensive chemotherapy, many younger people are also unable to have a transplant because they are not well enough or do not have a suitable donor. The ERG highlighted differences between the UK subgroup and other populations analysed in the trial (specifically the EU-subgroup and the ITT population). This included the proportion of people who were unable to have a stem cell transplant because of not having an appropriate donor. The ERG also noted inconsistencies between the number of pre-trial consolidation cycles observed in the UK subgroup and the company's clinical expert estimates of consolidation therapy use in people with AML who cannot have a transplant. Because of these differences, and because only a small number of people from the UK were included in the trial, the ERG considered that the EU-subgroup may be more relevant to UK clinical practice. In response to technical engagement, the company revised its base case to use data for the EU-subgroup (rather than the original ITT population) which reduced the incremental cost-effectiveness ratio (ICER). The company highlighted that the baseline characteristics of the subgroup from the HMRN report (aligned to the QUAZAR trial eligibility criteria) were in line with the EU-subgroup. The committee noted that stakeholders had commented that the QUAZAR trial was generally representative of UK clinical practice. The clinical experts considered that there was no strong evidence to suggest that the UK subgroup in the trial was not representative of the UK population, but they noted that the numbers in this subgroup were small. They explained that the QUAZAR study included European people, and that the baseline characteristics for this subgroup reflected the population who would have oral azacitidine in the NHS. The committee concluded that the trial results from the EU-subgroup were generalisable to clinical practice in England and should be used for decision-making.

The number of cycles of pre-trial consolidation therapy in QUAZAR likely reflects NHS clinical practice

3.6 The ERG noted that in QUAZAR, most people had 1 or no cycles of pre-

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trial consolidation therapy. The committee understood that 20% of people in the trial did not have any pre-trial consolidation therapy (based on the ITT population). The ERG considered that previous NICE technology appraisals for untreated AML imply that consolidation therapy is standard practice, but the number of cycles of consolidation is unclear. In response to technical engagement, the company's clinical experts suggested that there is variability in the number of consolidation cycles and that up to 60% of people in the UK are likely to have only 1 or no cycles in routine practice. The company presented data from the HMRN report which highlighted that in the NHS, a proportion of people whose cancer responded to intensive induction therapy did not have any cycles of consolidation chemotherapy (actual numbers are confidential and cannot be reported here). The ERG considered that there is some disparity between the HMRN report findings and the NHS website which suggests that all people with AML have consolidation therapy. It noted that the European Society for Medical Oncology's (ESMO) clinical practice guideline on acute myeloid leukaemia in adult patients (2020) recommends that people should have consolidation therapy after reaching complete remission after induction treatment. The ERG considered that consolidation therapy is expected so it initially preferred to use a subpopulation of the EU-subgroup who had had at least 1 cycle of consolidation therapy for its base case. This subpopulation was known as the EU-consolidation subgroup. The committee noted that the EU-consolidation subgroup slightly increased the ICER. The clinical experts explained that in clinical practice, many people can only have a single course of consolidation chemotherapy, because of delayed blood count recovery, toxicity or patient choice. They described how optimum best practice includes 3 to 4 cycles of consolidation chemotherapy; however, this is difficult to achieve particularly in an older population. The clinical expert described that around 20% of people will have the optimum number of consolidation cycles. They explained that the QUAZAR trial reflects the use of consolidation chemotherapy in clinical practice. The committee noted that data from the trial suggested that overall survival was improved irrespective of whether a person had consolidation treatment. The committee concluded that although most people would likely have at least 1 cycle of consolidation therapy, there may be people who would not have any consolidation treatment after induction chemotherapy. It concluded that the number of cycles of pre-trial

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consolidation therapy in QUAZAR likely reflects NHS clinical practice.

The results of the company's indirect treatment comparison in people with FLT3-mutation-positive AML are highly uncertain

3.7 The company did not identify any direct evidence comparing the efficacy of oral azacitidine to midostaurin as maintenance treatment in people with FLT3-mutation-positive AML. Therefore, it did an anchored indirect treatment comparison using data from QUAZAR and a phase 3, randomised, placebo-controlled study of midostaurin plus standard chemotherapy in adults with newly diagnosed FLT3-mutation-positive AML (known as RATIFY). Because individual patient data was available from QUAZAR, the company matched the population in QUAZAR to the eligibility criteria in RATIFY, so that only people with FLT3-mutation-positive AML in complete remission were included in the analysis. The company considers the results of the indirect treatment comparison to be confidential and so they cannot be reported here. However, the company noted significant differences between QUAZAR and RATIFY including differences in:

- Trial design: RATIFY was not prospectively designed to assess the efficacy of midostaurin as maintenance therapy but as an addition to induction and consolidation therapy. The QUAZAR trial was designed to specifically assess oral azacitidine in the maintenance setting.
- Time to randomisation: RATIFY included a maintenance therapy phase but people in the trial were not re-randomised before the start of maintenance therapy. In QUAZAR, people were randomised to have maintenance treatment.
- Age and AML status: RATIFY mainly included younger people (aged 18 to 59) and only included people with FLT3-mutation-positive AML unlike QUAZAR.
- Cytogenetic risk: people with favourable cytogenetic risk were included in RATIFY but not in QUAZAR.
- Stem cell transplant eligibility: this was not a formal exclusion criterion in the RATIFY trial but was in QUAZAR

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- History of consolidation therapy and definitions of time-to-event outcomes.

The company considered that many of these variables are known prognostic factors and potential effect modifiers and so the indirect estimates of oral azacitidine and midostaurin are likely limited in their validity and generalisability. The ERG also considered that survival analyses for this population are likely to be biased because of limitations associated with the indirect treatment comparison. The committee concluded that the results of the indirect treatment comparison comparing oral azacitidine with midostaurin were highly uncertain and considered this in its decision making.

Cost effectiveness

There is uncertainty about whether the company's model captures the long-term benefit after a stem cell transplant

3.8 The company presented a partitioned survival model with 3 health states: relapse-free survival, relapse and death. In the relapse-free health state, people could either be on or off treatment with oral azacitidine (the same utility value was applied). All people in the watch and wait plus best supportive care arm (from now, referred to as best supportive care), were assumed to be off treatment. The model included a cycle length of 28 days with a half-cycle correction over a lifetime time horizon. In the model, stem cell transplant was not included as a separate health state but was implicitly included in the modelling through the survival analysis of the QUAZAR ITT population. The company considered that because oral azacitidine has a marketing authorisation for people who cannot have a transplant, it would be unlikely in clinical practice that people will go on to have a transplant after oral azacitidine unless they had relapsed. In the trial, 6.3% of people in the oral azacitidine arm and 13.7% in the placebo arm had a transplant after stopping treatment. Costs and a temporary disutility associated with stem cell transplant were included in the model. The committee noted that the ERG's preference was to include stem cell transplant as a health state in the model. In response to technical engagement, the company stated that the QUAZAR trial did not collect sufficient data to allow modelling of stem cell transplant as a separate health state and this data

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is not available in the literature. Instead, it provided a scenario analysis which calculated a weighted average utility value for each treatment arm in the relapse health state. This was to account for the potential long-term health-related quality-of-life benefits of a transplant. The committee noted that the company's scenario analysis suggested only a small impact on the ICER. The ERG considered that it was unclear whether the model captured the long-term benefits of a stem cell transplant on a person's health-related quality of life (including after the company's scenario analysis). The committee agreed with the ERG's preference to remove the temporary disutility associated with a transplant, given that no benefit in health-related quality of life after having a transplant had been included in the model. It noted that the removal of this disutility had a small impact on the ICER. The committee considered the ERG's scenario analysis which included a utility increment for people who went on to have a stem cell transplant and noted that this slightly increased the ICER. The committee considered that it would have preferred the company to have included stem cell transplant as a health state in the model in line with NICE's technology appraisal guidance on midostaurin for untreated acute myeloid leukaemia. It noted that the company did not provide an updated model or any new evidence to support its approach to modelling a stem cell transplant in response to consultation. Therefore, the committee concluded that there is still uncertainty about whether the company's model captures the long-term benefits after a stem cell transplant.

Health-related quality of life after relapse should be calculated using data from the Tremblay (2018) study

3.9 The company considered that the QUAZAR trial did not capture health-related quality of life after relapse, except in some people who may have had an extended dose of oral azacitidine. This included people with a bone marrow blast count of 6% to 15% but not those with advanced disease (blast count greater than 15%). The company considered that using a utility value derived from this small cohort of people would be inappropriate and may overestimate the quality of life for people who relapse. Therefore, the company calculated the relapse utility based on a study by Joshi (2019) which used the composite time trade-off method to elicit utility values for AML from the UK general population. In the

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model, relapse utility was calculated as the difference between the relapse-free survival and relapse utilities in Joshi (2019) which was then applied to the relapse-free utility from QUAZAR. The ERG noted that the sample size in Joshi (2019) was small which resulted in a large standard error. The committee understood that the company considered alternative sources for relapse utilities including studies by Stein (2019) and Tremblay (2018). The ERG considered that both sources were not ideal because utility values were derived from US populations. In response to technical engagement, the company explained why the study by Joshi (2019) had been selected. It considered the utility elicitation methodology to be preferred by NICE, utility values were from individuals in the UK, and the utility value was clinically plausible. The ERG was unclear why the company preferred the composite time trade-off methodology, given that it was not part of the reference case in NICE's guide to the methods of technology appraisal 2013. In line with NICE's technology appraisal guidance on midostaurin for untreated acute myeloid leukaemia, the ERG used Tremblay (2018) to calculate health-related quality of life after relapse in its base case. This was because it considered that the method used to elicit utility values was more appropriate than Joshi (2019). The committee noted the company's scenario analyses using relapse utility values from Tremblay (2018) and Stein (2019) had a small impact on the ICER in the EU-subgroup. The company did not provide any new evidence to support its preferred approach to calculating utility after relapse in response to the appraisal consultation document. The committee agreed with the ERG's approach and concluded that health-related quality of life after relapse should be calculated using data from Tremblay (2018).

Utility for the relapse-free survival health state should be capped at age- and sex-matched general population values

3.10 The committee understood that the company had adjusted health state utility values for age in the model. It discussed the ERG's critique that the relapse-free survival utility was higher than the age-adjusted population norm in the UK. The committee considered that this did not make sense because it would mean that people with AML had a better quality of life than people without the disease. It noted that the ERG had asked the company to provide a scenario analysis capping the utility at general

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population levels which slightly increased the ICER (based on the ITT population). The company did not provide any new evidence on utility for the relapse-free survival health state in response to consultation. The committee noted the ERG's analysis which capped the utility value for the relapse-free survival health state at general population levels in the EU-subgroup. The results of the analysis suggested only a small impact on the ICER. The committee concluded that the utility value for the relapse-free survival health state in the model should be capped at age- and sex-matched general population levels.

Joint survival models are appropriate for estimating overall survival and relapse-free survival in the EU-subgroup

3.11 The company used joint models (joint models apply a single distribution to both treatment arms) to estimate overall survival and relapse-free survival based on QUAZAR trial data. It used the generalised gamma accelerated failure time model for overall survival and the log-logistic accelerated failure time model for relapse-free survival in the ITT population. The company considered that the survival analyses in the EU-subgroup were aligned with the assessment for the ITT population. The committee considered that the joint modelled curves showed that the survival function was being underestimated in the model for the comparator arm (best supportive care) when compared with the Kaplan–Meier curves from the trial (based on the ITT population). It considered that this may be because accelerated failure time models assume that the treatment effect is constant over the entire lifetime of the model. In response to consultation, the company stated that the joint models selected in its base case did not overestimate the expected treatment benefit with oral azacitidine for the EU-subgroup. It presented a scenario analysis exploring the impact of using the best-fitting individual models for the EU-subgroup (generalised gamma models for overall survival and log-logistic models for relapse-free survival). The committee noted that the company's scenario analysis suggested only a small impact on the ICER. It discussed the ERG's scenario analysis which explored the impact of using the same individual parametric models and the committee's preferred assumptions from the first meeting, which also had a small impact on the ICER. The committee noted the ERG's critique that the company's joint and individual modelling results were

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comparable and that the impact of choosing between these approaches was likely minor. It was reassured that both approaches reflected the trial data and resulted in similar extrapolations. Therefore, the committee concluded that the company's joint modelling approach was appropriate for estimating overall survival and relapse-free survival in the EU-subgroup.

The company's approach to modelling treatment effect waning does not have a significant impact on the cost-effectiveness results

3.12 The company's base-case analysis assumed no treatment effect waning for oral azacitidine. The committee initially considered that it was highly optimistic to assume a constant treatment benefit with oral azacitidine based on the observed trial data. The committee understood that the company had presented a scenario analysis which tried to explore the impact of treatment effect waning. It did this using individual log-normal models for overall survival and log-logistic models for relapse-free survival (based on the ITT population). The results of the scenario analysis increased the ICER by 11%. The committee considered that this was not explored fully and it would be preferable to include an assumption that the relative treatment effectiveness would decline over time. Therefore, the committee considered that it would be helpful to see a range of scenarios for both the overall population (based on the EU-subgroup) and for people with FLT3-mutation-positive AML including:

- using individually fitted parametric models without any additional treatment effect waning (and comparing the risks of overall survival and relapse-free survival in each cycle between the treatment groups).

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- adding treatment effect waning in the above scenario to assume that the treatment benefit with oral azacitidine is lost at a range of clinically plausible time points (for example, after stopping treatment).

  In response to consultation, the company considered that the impact of treatment effect waning during the trial was already captured in the survival estimates. This was because the end of the trial follow up was 90 months (7.5 years) at which point no people remained on treatment with oral azacitidine. The company and ERG presented analyses exploring the relative treatment effect over time by comparing the risks of overall survival and relapse-free survival between treatment groups. This was based on using the best-fitting individual models for the EU-subgroup (see section 3.11). The results from both analyses showed a similar risk of death and relapse between treatment arms over time (actual numbers are considered confidential by the company and cannot be reported here). The committee noted that this suggested that treatment effect waning may be implicitly included when using an individual modelling approach. It discussed the ERG's scenario analyses which included the committee's preferred assumptions and explored the impact of using individual models with treatment effect waning at various timepoints (3 years, 5 years and 7.5 years) after randomisation. The results of the scenario analyses suggested only a small impact on the ICER. The committee recalled that the company's joint and individual modelling results were comparable (see section 3.11). Therefore, it considered that the impact of treatment effect waning using a joint modelling approach would also likely have a similar effect on the ICER based on its preferred assumptions. The committee concluded that the company's approach to modelling treatment effect waning did not have a significant impact on the cost-effectiveness results.

End of life

Oral azacitidine extends life by at least 3 months

3.13 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal 2013. The committee agreed that based on the trial evidence and the views of clinical experts, the overall survival gain with oral azacitidine would likely be more than 3 months. The company's

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model suggested that there was an increase in mean overall survival of 12.8 months (median 9.9 months in QUAZAR) for the ITT population. For the EU-subgroup, the company's model suggested that there was an increase in mean overall survival of 16.2 months (median overall survival gain was greater than 3 months in QUAZAR but the exact figure is confidential so cannot be reported here). The committee agreed that oral azacitidine meets the criterion for a life-extending treatment because it increases overall survival by more than 3 months.

The short life expectancy criterion is also met so oral azacitidine is considered to be a life-extending treatment at the end of life

3.14 The company confirmed that mean estimates were not available from QUAZAR, but the median overall survival for people who had placebo was 14.8 months (ITT population). The company's original base case for the ITT population predicted a mean overall survival of 33.6 months for people having best supportive care. The company's revised base case using the EU-subgroup predicted a mean overall survival of 31.5 months for people having best supportive care (median overall survival from QUAZAR for the EU-subgroup was also less than 24 months but the exact figure is confidential and so cannot be reported here). The committee acknowledged that using extrapolation models to estimate mean values involves assumptions and uncertainty. However, the committee noted that the mean estimates were higher than 24 months and that the cost-effectiveness analyses are based on mean survival estimates. The clinical experts explained that a significant number of people with AML are unable to have a stem cell transplant and that they have a high risk of relapse in the first year. After relapse, they would have palliative treatment within 12 months and a life expectancy of around 3 months at this point. The clinical experts explained that around 20% of people may be cured after intensive chemotherapy, and reach long-term survival. The ERG considered that because some people will live for much longer, this will skew the survival distribution where the mean is often higher than the median. The committee recalled that while the short-term prognosis for most people would be poor, a proportion of people (around 20%) would be cured and would therefore be expected to live beyond 2 years. It initially considered that the short life expectancy criterion had not been met. The committee considered comments

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received in response to consultation from the company, a clinical expert and a patient group which strongly reiterated that life expectancy for most people in this population is less than 24 months. The company highlighted the appeal decision in NICE's technology appraisal guidance on avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy (TA788). The appeal panel for TA788 concluded that it would be unreasonable to state that life expectancy was not normally less than 24 months given that the modelled mean life expectancy indicated that most people (65%) did not survive after 24 months. In this appraisal, the company highlighted that a similar proportion in the EU-subgroup did not survive beyond 24 months (the exact figure is considered confidential by the company and so cannot be reported here). The committee believed that the best estimate of life expectancy came from the mean survival for the relevant patient population, based on the decision model submitted by the company. However, it accepted a consultation comment that the NICE methods guide does not specifically state how this criterion should be assessed. It noted the appeal panel's conclusion for TA788 that the totality of evidence should be considered when assessing whether a technology meets the short life expectancy criterion. The committee took into consideration the mean and median survival estimates, clinical opinion from the first committee meeting and consultation comments from all stakeholders. It also recalled that the data from the QUAZAR trial was mature and this reduced the uncertainty in the results. The committee discussed that although there are different ways to estimate life expectancy, it is likely that the population who would be considered for treatment with oral azacitidine would live on average less than 24 months. Therefore, it accepted that the short life expectancy criterion was met and concluded that oral azacitidine meets the criteria to be considered a life-extending treatment at the end of life.

Cost-effectiveness estimates

The cost-effectiveness estimates are within the range that NICE considers to be an acceptable use of NHS resources

3.15 NICE's guide to the methods of technology appraisal 2013 notes that

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above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. At the first meeting, the committee considered that there was uncertainty around some of the assumptions used in the model which made the cost-effectiveness results uncertain. It considered that analyses which explored the use of individual models for extrapolating overall survival and treatment effect waning would reduce the uncertainty that the expected treatment benefit with oral azacitidine had been overestimated in the model (see section 3.11 and section 3.12). At the second committee meeting, the company and ERG presented these analyses which suggested that the cost-effectiveness results are robust to changes in survival modelling assumptions (see section 3.11 and section 3.12). The committee was therefore reassured that this uncertainty had now been adequately addressed. The ERG updated its base-case assumptions to align with the committee's preferences which remained unchanged from the first committee meeting. This included the following assumptions:

- using the EU-subgroup of the QUAZAR trial for the total population (see section 3.5)
- removing the temporary disutility associated with a stem cell transplant (see section 3.8)
- calculating health-related quality of life after relapse using data from Tremblay (2018; see section 3.9)

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- capping the utility value for the relapse-free survival health state at matched general population levels (see section 3.10).

The ERG's updated analyses included the committee's preferred deterministic and probabilistic ICERs for oral azacitidine compared with best supportive care, which were slightly above £30,000 per QALY gained. Exact ICERs are confidential and cannot be reported here, because they include the confidential patient access scheme for oral azacitidine and confidential comparator discounts. The committee considered that the most plausible ICERs were within the range that NICE considers to be an acceptable use of NHS resources for end of life treatments. It also noted the ICERs for all the scenarios presented for oral azacitidine compared with best supportive care and for oral azacitidine compared with midostaurin for the FLT3 subgroup. All the ICERs were within the range that NICE considers to be an acceptable use of NHS resources (including the confidential patient access scheme for oral azacitidine and confidential comparator discounts). It noted that the cost-effectiveness estimates for oral azacitidine compared with midostaurin were uncertain because of the limitations in the clinical evidence informing this treatment comparison (see section 3.7). However, the committee recalled that the proportion of people with FLT3-mutation-positive AML who would have oral azacitidine in clinical practice would be small. The committee also acknowledged that oral azacitidine could potentially address some of the equality issues raised by stakeholders (see section 3.16). Therefore, it recommended oral azacitidine as an option for people with AML.

Other factors

The recommendation for oral azacitidine may reduce some of the equality issues for people with AML

3.16 The committee discussed the potential equality issues raised during the appraisal. It noted a stakeholder comment that some people may struggle financially to have current treatment (such as a transplant) because of the cost of regular travel to hospital and reduced income from having to take time off work. Having a transplant may be especially difficult for people with caring responsibilities because of the significant time commitment needed. The stakeholder considered that these people

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should not be denied treatment and oral azacitidine would be a viable alternative to a transplant. The committee recognised that because oral azacitidine can be taken at home it may be more convenient and reduce the amount of time spent in hospital compared with having a transplant. It noted comments from stakeholders that many people with AML who are in complete remission are unable to have a transplant because of a lack of donor availability. Therefore, this results in an inequity of access to curative treatment and disproportionately affects people with a minority ethnic family background. The clinical experts explained that after a transplant there is a 70% reduction in the risk of relapse. They explained that in people of white family background, the likelihood of finding a suitably matched donor is around 80%, which reduces to around 30% to 40% in people with a minority ethnic family background. Stakeholders and clinical experts highlighted that oral azacitidine should therefore be available to all people who are not able to have a transplant, including those with a minority ethnic family background who do not have a suitable donor. The committee noted that this issue had been reiterated in comments received in response to the appraisal consultation document. The committee acknowledged that unequal access to transplants because of ethnicity was a relevant consideration and it was mindful of its obligations in relation to the Equality Act 2010. It noted that the company had also highlighted that there may be geographical barriers to accessing a stem cell transplant based on how far away a person lives from an allograft transplant centre. The committee considered that issues around healthcare implementation cannot be addressed in a technology appraisal. It concluded that because it had recommended oral azacitidine for people with AML that this may help to reduce some of the potential equality issues raised during the appraisal.

The benefits of oral azacitidine are captured in the cost-effectiveness analysis

3.17 The company and stakeholders considered oral azacitidine to be innovative because it improves survival, is well tolerated and because of its oral formulation. The committee recalled how treatment with oral azacitidine would offer benefits because people would be able to have treatment at home (see section 3.1). It heard how this would reduce time

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spent in hospital and allow people to spend more time with their family and friends. The committee agreed that these are important benefits and noted that oral azacitidine is the first maintenance treatment licensed for all people with AML. However, it concluded that it had not been presented with evidence of any additional benefits that could not be captured in the QALY calculations.

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4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has acute myeloid leukaemia and the doctor responsible for their care thinks that oral azacitidine is the right treatment, it should be available for use, in line with NICE's recommendations.

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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.

Anita Sangha and Anna Willis
Technical leads

Christian Griffiths
Technical adviser

Louise Jafferally
Project manager

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Accreditation

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