NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy [ID3892]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy [ID3892]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from Celgene UK, a BMS company**
   a. ACD response form
   b. Additional data

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Leukaemia Care

4. **Comments on the Appraisal Consultation Document from experts:**
   a. Professor Charles Craddock – clinical expert, nominated by Celgene

5. **Comments on the Appraisal Consultation Document received through the NICE website**

6. **Evidence Review Group critique of company comments on the ACD**
   a. ERG critique
   b. ERG analyses

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

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

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	Celgene, a BMS company	**1. SUMMARY** BMS would like to reiterate that the base case assumptions used in our submission confirm that Onureg® (oral azacitidine) is a clinically and cost-effective option in the maintenance setting for AML patients that have undergone induction therapy and are not candidates for haematopoietic stem cell transplantation. The QUAZAR trial provides mature data with long follow-up (90 months), resulting in greater certainty in clinical and economic outcomes for the Committee. This is evident from the stability of both the deterministic and probabilistic company base case ICERs, £32,718/QALY vs £32,480/QALY respectively, which is comparable to the ERG's probabilistic base case ICER of £33,925/QALY. Additional scenarios have been provided in this response, at the request of the Committee, that highlight the stability of the ICER to variation in other potentially clinically plausible assumptions. BMS' understanding is that treatment waning is considered by NICE when extrapolating treatment duration and the possibility of reduced efficacy over time. Considering the maturity and completeness of the QUAZAR trial data, the inclusion of assumptions such as treatment waning are not warranted. At the Committee's request, scenarios with treatment waning have been explored and confirm that the company's base case is fully justified due to the stability of the ICER when a clinically plausible waning effect is applied. We maintain that the indicated population for oral azacitidine meets both End-of-Life criteria: the majority of patients in the control arm of QUAZAR did not live beyond 24 months and this is anticipated to reflect clinical practice for those who do not receive a HSCT. Consequently, and following the precedent of previous NICE appraisal TA788, we ask that the Committee reconsider the short life expectancy End-of-Life criterion. As discussed in the Appraisal Committee meeting, there is clear inequality of access to stem cell transplantation between different ethnic groups and people living in different geographic areas. Further evidence on this has been provided in our response. Access to oral azacitidine will provide an alternative treatment option, with a demonstrated survival advantage, for patient unable to access transplantation, and thereby reduce these ethnic and geographic inequalities.	Comments noted. The committee considered the consultation response and new evidence from the company. Please see responses to individual issues below.
2	Consultee (company)	Celgene, a BMS company	**2. Impact of curve selection on cost-effectiveness of oral azacitidine**	Comments noted. The committee understood that the company's joint and individual modelling

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Joint survival curves selected in the company's base case, in line with NICE DSU criteria[1], are most appropriate The survival models selected for the company's base case analysis remain the best-fitting, and lead to clinically plausible extrapolations. **Justification for selection of joint survival curves** As discussed in the company response to technical engagement, the unstratified Cox PH model estimated oral azacitidine to result in a reduced rate of mortality compared to placebo (HR: [redacted]; 95% CI: [redacted], based on EU subgroup), as well as a reduced rate of relapse (HR: [redacted]; 95% CI: [redacted]). The log-cumulative hazard plots showed violation of the PH assumption (*Figure 1 and 2*), indicating that survival models which assume a proportional hazards relationship may not be appropriate for OS and RFS. However, the suitability of AFT models was explored in line with NICE DSU TSD 14[1] with quantile-quantile plots showing no violation of the AFT assumption (*Figure 3 and 4*). Therefore, joint curves were considered the most plausible option by the company. **Figure 1: Log-cumulative hazard plot from unstratified Cox PH model – OS (September 2020 data cut) EU subgroup** [redacted] **Figure 2: Log-cumulative hazard plot from unstratified Cox PH model – RFS (July 2019 data-cut) EU subgroup**	results were comparable and that the impact of choosing between these approaches was likely minor. It concluded that the company's joint modelling approach was appropriate for estimating overall survival and relapse-free survival in the EU-subgroup. Please see section 3.11 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 **Figure 3: Quantile-quantile (Q-Q) plot for OS (September 2020 data-cut) EU-Subgroup** 	

Figure 4: Quantile-quantile (Q-Q) plot for RFS (July 2019 data-cut) EU-Subgroup

Systematic assessment of model fit[1]

We assessed the fit of alternative survival models using the criteria specified in NICE DSU Technical Support Document 14[1]. A range of parametric models were reviewed and compared, to avoid an arbitrary choice of survival model.

For overall survival, the joint generalised gamma model was selected: this has the lowest AIC and BIC values among all distributions, indicating it has the best statistical fit to the observed data. Visual inspection of the joint generalised gamma survival function (*Figure 5*) supports this conclusion, in that the generalised gamma curves most closely fit the data, and lead to extrapolations which are clinically plausible based on expert opinion.

Figure 5: KM curves and parametric model fitted to the OS outcomes in the QUAZAR AML-001 trial EU subgroup - generalized gamma distribution, joint model

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 For relapse-free survival, the joint log-logistic model was selected. This model has the best statistical fit to the data (with the lowest AIC and BIC values among all joint models). This model has a very good visual fit (*Figure 6*) and is viewed by experts as clinically plausible. **Figure 6: KM curves and parametric model fitted to the RFS outcomes in the QUAZAR-001 trial EU subgroup – log-logistic distribution, joint model**	

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			 **Alternative individual survival curve scenarios have limited impact on the ICER** BMS acknowledges the Committee's concern about the extrapolation of overall survival from the QUAZAR trial, considering this may overestimate the expected treatment benefit of oral azacitidine. We note that the ERG explored individually fitting models as an alternative to the joint curves presented in the company's base case. In Section 3.11 of the ACD it states that the ERG selected the generalized gamma for both arms in OS and log-logistic for both arms in RFS with the Committee noting these results slightly reduced the base case ICER with the ERG's assumptions. At Committee's request we have explored more fully the impact of selecting alternative individual survival curves. A range of individual parametric models have been fit, without any treatment waning, for the overall population using the EU-subgroup data (with data for the FLT-3 subgroup presented separately in *Appendix 1*). **Systematic assessment of individual model fit[1]** We assessed the fit of alternative, individual survival models using the criteria specified in NICE DSU Technical Support Document 14[1]. A range of parametric models were reviewed and compared. For overall survival, the individual generalised gamma model was selected as the best-fitting individual model: this has the lowest AIC and BIC values among all individual survival models, indicating it has the best statistical fit to the observed data. Visual inspection shows the model provides the best fit to KM curves, and clinical plausibility has been verified by clinical experts. The next-best fitting model was the individual log-normal; other models had poor statistical fits and did not produce good visual fits.	

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For relapse-free survival, the individual log-logistic model was selected as the best-fitting individual model. This model has the best visual fit to the data, a clinically plausible fit, and the second-best statistical fit to the data (based on AIC and BIC values). The individual Gompertz model had a slightly better statistical fit (highest AIC and BIC values of all individual models) but visual inspection shows the model provides a clinically implausible fit.
Table 1 reports the assessment for the best-fitting individual model for each outcome, compared to the joint models used in the company's base case analysis.

Table 1: Summary of model fit assessments for parametric models (EU-subgroup)

CEA		Model Fit Assessment			
Model	**Visual Inspection - Parametric Model vs KM curve**	**AIC**	**BIC**	**Visual Inspection - Log-cumulative Hazard Plots**	**Conclusion**
Overall Survival					
Company Base Case: Joint Generalized Gamma	Curves most closely fit the data and are clinically plausible	[redacted]	[redacted]	Best fit to the KM curves	Lowest AIC and BIC among all distributions, indicating best statistical fit Visual inspection shows model provides the best fit to KM curves. AFT model not reliant on PH assumption
Best-fitting individual model: Individual Generalized Gamma	Curves closely fit the data and are clinically plausible	[redacted]	[redacted]	Best fit to the KM curves	Lowest AIC and BIC among individual models Visual inspection shows model provides the best fit to KM curves
Relapse-free Survival					
Company Base Case: Joint Log-logistic	Curves most closely fit the data and are clinically plausible	[redacted]	[redacted]	Best fit to the KM curves	Lowest AIC and BIC among all clinically plausible curves Visual inspection shows model provides the best fit to KM curves AFT model not reliant on PH assumption
Best-fitting individual model:		[redacted]	[redacted]	Best fit to the KM curves	Next best statistical fit among individual models

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Individual Log-logistic	Curves closely fit the data and are clinically plausible				Visual inspection shows model provides a clinically plausible fit

Minimal impact of survival curves on cost-effectiveness
There is little uncertainty associated with the selection of survival curves on the cost-effectiveness or oral azacitidine. The best-fitting individual models ICER using the company's base case assumptions was only £1k/QALY (+3.1%) higher from the joint curve base case ICER, demonstrating that the choice of individually fitting or joint models has minimal impact on the cost-effectiveness of oral azacitidine (*Table 2*).

The company modelling of individual models closely matches the ERG's preferred scenario (*corrected Scenario 5 in slide 32 from the 1st Appraisal Committee Meeting**). The same individual models for OS and RFS were selected by the company and the ERG, and the same marginal impact on the ICER (<2%) was observed.

* To avoid any confusion, we note that the ICER in the ERG's Scenario 5 ('Individual modelling of OS and RFS) has been re-calculated and now stands at £33,767, within 1% of the ERG's base case ICER.

<u>Conclusion</u>: The company's base case ICERs are insensitive to the choice of survival curves

Although the joint survival models do not overestimate the expected treatment benefit with oral azacitidine (*Figure 5 and Figure 6* – note the original Committee slides show the data for the ITT population rather than the EU subgroup, which has been presented here), the individual models show minimal change in the ICER, meaning that the Committee can be reassured of the benefit of oral azacitidine over standard of care.

Table 2: Summary of cost-effectiveness for parametric models (EU-subgroup)

CEA						
Model	**Treatment**	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER £/QALY**
Overall Survival						
Company's base case: Joint	***Oral AZA***	[redacted]	[redacted]	[redacted]	[redacted]	***32,718***

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Generalized Gamma							
	BSC	[redacted]	[redacted]	-	-	-
Best-fitting individual model Individual Generalized Gamma	***Oral AZA***	[redacted]	[redacted]	[redacted]	[redacted]	**33,136**
	BSC	[redacted]	[redacted]	-	-	-
Relapse-free Survival							
Company's base case: Joint Log-logistic	***Oral AZA***	[redacted]	[redacted]	[redacted]	[redacted]	***32,718***
	BSC	[redacted]	[redacted]	-	-	-
Best-fitting individual model: Individual Log-logistic	***Oral AZA***	[redacted]	[redacted]	[redacted]	[redacted]	**33,281**
	BSC	[redacted]	[redacted]	-	-	-
Individual curves scenario (best fitting individual models according to model fit statistics)							
OS: individual generalized gamma RFS: individual log-logistic	***Oral AZA***	[redacted]	[redacted]	[redacted]	[redacted]	**33,728**
	BSC	[redacted]	[redacted]	-	-	-

References:

1) NICE Decision Support Unit (DSU) Technical Support Document 14 – Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data (last updated March 2013). Available at https://nicedsu.sites.sheffield.ac.uk/tsds/survival-analysis-tsd. Accessed 12 July 2022

3	Consultee (company)	Celgene, a BMS company	**3. Impact on cost-effectiveness of clinically-plausible assumptions for waning of the treatment effect** **Modelling treatment waning is not warranted due to a complete dataset**	Comments noted. The committee took into consideration analyses presented by the company and the ERG relating to this issue. It

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
Data from the QUAZAR trial provide outcomes data for almost all patients. The trial followed up patients to 90 months, at which time no patients in the treatment arm remained on therapy. The waning of treatment effect during the trial has already been captured in the survival data from the trial; the impact of any potential waning of treatment effect post-trial follow-up will be minor.

Waning assumptions have minimal impact on the cost-effectiveness results
However, BMS acknowledges the Committee's preference to model declining relative treatment effect over time beyond the follow-up period of the QUAZAR trial to explore any uncertainty regarding treatment waning. We have therefore modelled the impact of clinically plausible treatment waning for each of the parametric models considered earlier.
We assumed a conservative waning of treatment, with equivalence of hazards between oral azacitidine and no active therapy assumed from Month 90 (the end of the QUAZAR trial follow-up).

Table 3 illustrates the impact of treatment waning (post-end of QUAZAR trial follow-up) on the best-fitting joint (company's base case) and individual survival curves.
This demonstrates that clinically plausible treatment waning has a minimal impact (<1%) on the cost-effectiveness of oral azacitidine, regardless of the selection of survival curve. The visual impact of this treatment waning assumption can be observed in the best-fitting joint and individual survival curves in Figures 7-8.

Table 3: Summary of cost-effectiveness for parametric models with and without treatment waning (EU-subgroup)
<table>
<tr><th colspan="3">CEA</th></tr>
<tr><th>Model</th><th>ICER £/QALY
(no treatment waning)</th><th>ICER £/QALY
(with treatment waning*)</th></tr>
<tr><td colspan="3">Overall Survival</td></tr>
<tr><td>Company Base Case: Joint Generalized Gamma</td><td>32,718</td><td>32,764
(+0.1%)</td></tr>
<tr><td>Best-fitting individual model: Individual Generalized Gamma</td><td>33,136</td><td>33,123
(<-0.1%)</td></tr>
<tr><td colspan="3">Relapse-free Survival</td></tr>
<tr><td>Company Base Case: Joint Log-logistic</td><td>32,718</td><td>32,764
(+0.1%)</td></tr>
<tr><td>Best-fitting individual model:
Individual Log-logistic</td><td>33,281</td><td>33,330
(+0.1%)</td></tr>
<tr><td colspan="3">Individual curves scenario (best fitting individual models according to model fit statistics)</td></tr>
</table>
</td><td>concluded that the company's approach to modelling treatment effect waning does not have a significant impact on the cost-effectiveness results. Please see section 3.12 of the FAD.</td></tr>
</table>

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OS: individual generalized gamma RFS: individual log-logistic	33,728	33,714 (<-0.1%)

** Treatment waning: equivalence of hazards between Oral AZA and no active therapy assumed from Month 90 (end of QUAZAR AML-001 trial OS follow-up in September 2020 data-cut) onward.*

Figure 7: Overall survival; joint curves, with treatment waning – GenGamma for OS, LogLogistic for RFS)

Figure 8: Overall survival; individual curves, with treatment waning – GenGamma for OS, LogLogistic for RFS

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>[redacted]</td><td></td></tr>
<tr><td>4</td><td>Consultee (company)</td><td>Celgene, a BMS company</td><td><u>4. Rationale for applying NICE's End-of-Life criteria in this appraisal</u>

The indicated population for oral azacitidine meets the <24 months End-of-Life criterion

In its assessment, the NICE Appraisal Committee did not consider oral azacitidine to meet the short life expectancy (<24 months) criterion. This decision was based on extrapolated mean OS estimates from the model exceeding 24 months (overall population based on EU subgroup = [redacted] months).

The company does not agree with the Committee's decision since the extrapolated means are not reflective of the life expectancy of most patients with AML in clinical practice. Specifically, the trial data clearly show that the majority of patients in the control arm do not live beyond two years. In the overall population represented by the EU subgroup of the QUAZAR study (September 2020 data-cut), median OS in the no active treatment arm was [redacted] months, with only [redacted] of patients alive at 24 months. When discussed at the first Appraisal Committee meeting, the clinical experts confirmed that the majority of patients (approx. 80%) that they treat who are not eligible for a stem cell transplant, relapse within the first 12 months. For those patients, the expected survival is <24 months.

Table 4 shows the breakdown of the number of patients at risk over time in the no active treatment arm of the QUAZAR trial, within the EU subgroup. Only [redacted] patients contribute to the survival data beyond 24 months, and by 60 months, this decreases further to just [redacted] patients, highlighting the long tail of the survival curve which is contributing to a higher mean OS.

Table 4. Number at Risk Over Time for Patients Surviving ≥24 Months (OS, EU subgroup – BSC arm)
<table><tr><th>Time (months)</th><th>Number at risk – BSC arm-, EU subgroup (% of patients at risk)</th><th><u>% Survival (KM method)</u></th></tr></table></td><td>Comments noted. The committee considered the totality of the evidence including the mean and median survival estimates, clinical opinion from the first committee meeting and consultation comments from all stakeholders. It also noted data from the QUAZAR trial was mature and this reduced the uncertainty in the results. The committee reconsidered its conclusions from the first meeting and accepted that the short life expectancy criterion was met. It concluded that oral azacitidine meets the criteria to be considered a life-extending treatment at the end of life. Please see sections 3.13 and 3.14 of the FAD.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

0	[redacted]	[redacted]
24	[redacted]	[redacted]
30	[redacted]	[redacted]
36	[redacted]	[redacted]
42	[redacted]	[redacted]
48	[redacted]	[redacted]
54	[redacted]	[redacted]
60	[redacted]	[redacted]
66	[redacted]	[redacted]
72	[redacted]	[redacted]
78	[redacted]	[redacted]
84	[redacted]	[redacted]

*Last observation in the placebo arm was at 81.3 months.
Abbreviations: BSC = best supportive care; EU = European; NA = not available; OS = overall survival.

NICE STA precedent (Appeal of TA788)[2]
NICE Technology Appraisal TA788 (2021) was appealed on similar grounds. The NICE Committee concluded that the short life expectancy criterion (<24 months) had not been met, noting that the best estimate of expected survival came from modelling mean life expectancy, not the median overall survival estimates from the trial.

The NICE Appeal Panel concluded it would be unreasonable to 'state that life expectancy was not "normally less than 24 months" even if the mean life expectancy was greater than 24 months, if 65% of patients, the significant majority, in the modelled cohort had died prior to 24 months'. In the QUAZAR study, a very similar proportion of patients, [redacted] in the EU subgroup, did not survive beyond 24 months, and so it is similarly unreasonable to claim that the short life expectancy criterion does not apply in this case.

As a consequence, we maintain that the indicated population for oral azacitidine meets both End-of-Life criteria. Consequently, we ask that the Committee give additional weight to the QALYs achieved through the use of oral azacitidine.

References:
2) NICE (2021). Advice on avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum-based chemotherapy [ID3735]: Decision of the panel. Available online at: https://www.nice.org.uk/guidance/ta788/documents/appeal-decision-2. Accessed: 13 July 2022.

5	Consultee (company)	Celgene, a BMS company	**5. Equality issues raised during the appraisal**	Comments noted. The committee acknowledged that unequal

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Oral azacitidine should be available to all people who are not able to have a transplant, including those from ethnic minority groups who may not have access to a suitable donor As noted by clinical experts during the 1st Appraisal Committee meeting, many people with AML who are in complete remission are unable to have a transplant because of a lack of donor availability. This results in inequitable access to a potentially curative treatment option, and disproportionately affects substantial numbers of people, particularly from ethnic minority groups. Published evidence further corroborates this, as discussed below. **Background** According to the 2019 Census, Black, Asian, and Minority Ethnic (BAME) groups make up 15.2% of the total population of England and Wales. Specifically, people of Asian race make up 8.0%, Black race 3.5%, Mixed race 1.8%, and Other race 1.9%.[3] Despite accounting for only 15.2% of the population, in 2020 one-third of the people in the UK waiting for a transplant of any type were from a BAME group.[4] A large driver of this disparity is the lack of BAME-registered donors, as only 15% of registered donors are from a BAME group.[5] Black donors make up only 1.2% of potential donors on the British Bone Marrow Registry.[6] **Access to HSCT: disparity in donor availability** The 2016 Anthony Nolan Stem Cell Registry estimated that only 61% of BAME patients can find a suitably matched stem cell donor compared to 96% of White Northern European patients.[7] The disparity in access is widened by the low chances of finding optimally-matched (10/10 matched) unrelated donors.[8] According to the 2021 All-Party Parliamentary Group report, patients from a minority ethnic background are estimated to have only a 37% chance of finding an optimally-matched unrelated donor compared to 72% for British, Irish, or Northern European patients.[8] In addition, a 2018 review looking into BAME blood, stem cell and organ donation found that a BAME patient had only a 20% chance of finding a "best possible" donor match compared to a 69% chance for White Northern European patients.[6] **Access to HSCT: geographical barriers** There are 35 allograft centres across the UK, so whilst patients may have access to a regional centre, it is often not their local hospital. The All-Party group report gives examples of how "... *many patients have to travel significant distances to their nearest transplant centre. Concerns were raised in the Inquiry that longer distances, and increased travel, impact on both access to transplant and post-transplant care and follow up."*[7] There are multiple barriers to access to HSCT, a potentially curative treatment option for patients with AML that have been highlighted above. This is particularly significant for patients from ethnic minority groups, where availability of a matched donor is severely limited. **Summary: Value of oral azacitidine in reducing inequalities**	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 considered that issues around healthcare implementation cannot be addressed in a technology appraisal. Because the committee decided to recommend oral azacitidine for people with acute myeloid leukaemia, it considered that this may help to reduce some of the potential equality issues raised during the appraisal. Please see section 3.16 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Oral azacitidine will provide an alternative treatment option, that has demonstrated a survival advantage, for patients who are unable to access a HSCT. In doing so, it will alleviate the disparities we see in access to other life-extending treatments. **References:** 3) Population estimates by ethnic group and religion, England and Wales: 2019. (2021) Office for National Statistics. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/populationestimatesbyethnicgroupandreligionenglandandwales/2019 4) Organ Donation and Transplantation data for Black, Asian and Minority Ethnic (BAME) communities (2018-2019-2020) Available from https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16918/organ-donation-and-transplantation-bame-activity-report-2018-2019.pdf 5) NHSBT Organ and Tissue Donation and Transplantation Activity Report 2020/2021. Available from https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/23461/activity-report-2020-2021.pdf 6) Ending the silent crisis. A REVIEW INTO BLACK, ASIAN, MIXED RACE AND MINORITY ETHNIC (BAME) BLOOD, STEM CELL AND ORGAN DONATION. Available from: BAME-Donation-review-29.5.18.pdf (nbta-uk.org.uk) 7) Anthony Nolan and NHS Stem Cell Registry (2016) The Anthony Nolan and NHS Stem Cell Registry Annual Review of 2016: From Strength to Strength. Available from https://www.anthonynolan.org/sites/default/files/202101/1257CM_State_Of_The_Registry_2017_AW_lr2.pdf 8) No patient left behind: The barrier stem cell transplant patients face when accessing treatment and care (2021) All-Party Parliamentary Group on Stem Cell Transplantation. Available from https://www.anthonynolan.org/sites/default/files/2021-05/no_patient_left_behind_final.pdf	
6	Clinical expert	Professor Charles Craddock	I do not believe the importance of CC486 as a strategy to increase equity of access to effective treatment options for patients from particular ethnic backgrounds has been appropriately recognised. As highlighted in the recently published Report of the UK Stem Cell Strategic Oversight Committee (which I have uploaded-please see p22 and onwards) the current inability to identify a donor for many patients from non-Caucasian ethnic backgrounds results in these patients being denied access to stem cell transplantation which is currently the most effective form of therapy for many adults with AML. The demonstration in the QUAZAR trial that CC486 significantly improves outcomes in patients compared with chemotherapy alone is therefore a major breakthrough in terms of offering effective treatment options for patients unable to proceed to transplant because of lack of donor availability –one of the commonest causes of which is patient ethnicity. Failure to support the use of CC486 for such patients would therefore represent an unnecessary restriction of treatment options for many patients from ethnic minorities.	Comments noted. 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. Because the committee decided to recommend oral azacitidine for people with acute myeloid leukaemia, it considered that this may help to reduce some of the potential equality issues raised during the appraisal. Please see section 3.16 of the FAD.
7	Clinical expert	Professor Charles Craddock	Although I am not a health economist I am surprised that NICE has come to the decision that the putative treatment population do not fulfil criteria for “end of life” considerations since there is abundant evidence that the life expectancy for the great majority (c80%) of the patient population under	Comments noted. The committee considered the totality of the evidence including the mean and

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			consideration is under 24 months. In fact for the substantial majority of patients survival is less than 12 months and it is only a minority of patients who would survive more than 24 months. Thus the great majority of patients clearly fulfil “end of life” criteria and it would seem perverse that simply because a small number of patients survive long term the great majority of patients for whom there is a clear unmet need might be denied effective therapy.	median survival estimates, clinical opinion from the first committee meeting and consultation comments from all stakeholders. It also noted data from the QUAZAR trial was mature and this reduced the uncertainty in the results. The committee reconsidered its conclusions from the first meeting and accepted that the short life expectancy criterion was met. It concluded that oral azacitidine meets the criteria to be considered a life-extending treatment at the end of life. Please see sections 3.13 and 3.14 of the FAD.
8	Consultee	Leukaemia Care	We are concerned by NICE’s evaluation that the treatment does not meet the criteria to be considered life-extending at the end-of-life stage. The end-of-life criteria (6.2.10) require that “the treatment is indicated for patients with a short life expectancy, normally less than 24 months”. As set out in the ACD, the median life expectancy of the patient population under consideration is normally less than 24 months, whilst the mean life expectancy falls above 24 months. The NICE criteria make no explicit reference to the use of either a mean or a median average when calculating overall survival. Furthermore, there is a precedent for using the median life-expectancy for the short life expectancy criterion, for example in the appraisal of inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [TA541]. In this appraisal we have concerns that a small group of people who might have been cured for life from the treatment could skew the mean, meaning that the drug does not fit the end-of-life criteria, even if it is considered life-extending for majority of people who are otherwise facing a short life. We support the clinical experts on this point. On this basis, we submit that a decision to base the life expectancy on the mean average is unreasonable considering the uncertainties around calculating the mean and the clinical expert evidence submitted to NICE.	Comments noted. The committee considered the totality of the evidence including the mean and median survival estimates, clinical opinion from the first committee meeting and consultation comments from all stakeholders. It also noted data from the QUAZAR trial was mature and this reduced the uncertainty in the results. The committee reconsidered its conclusions from the first meeting and accepted that the short life expectancy criterion was met. It concluded that oral azacitidine meets the criteria to be considered a life-extending treatment at the end of life. Please see sections 3.13 and 3.14 of the FAD.
9	Consultee	Leukaemia Care	Another concern is the committee’s consideration of the role this treatment could play in addressing inequalities. As people from ethnic minority backgrounds are less likely to find a stem cell donor match, they are less likely to be offered this potentially life saving treatment. Oral azacitidine, when used as	Comments noted. The committee acknowledged that unequal access to transplants because of

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			maintenance therapy to prevent relapse after chemotherapy, gives people who might not be able to find a stem cell donor (through no fault of their own) an alternative. It is crucial to fully consider and address this inequality in the accessibility of cancer treatment to people from different ethnic backgrounds.	ethnicity was a relevant consideration and it was mindful of its obligations in relation to the Equality Act 2010. Because the committee decided to recommend oral azacitidine for people with acute myeloid leukaemia, it considered that this may help to reduce some of the potential equality issues raised during the appraisal. Please see section 3.16 of the FAD.
10	Public	Patient 1	I am an AML in remission patient on oral azacitidine since October 2015 as part of the Quazar trial, as extended. It has kept me alive for almost seven years but as the trial ends in three months I will no longer receive the drug. I believe that your assessment does not give sufficient weight to age related problems accessing other therapies (I am 74 now) and your recommendation 1.2 does not take account of people in my situation where the funding was external to the NHS although the drug given within the NHS.	Comments noted. The committee considered the views of people with acute myeloid leukaemia when formulating its recommendations. It considered that the most likely cost-effectiveness estimates are within the range that NICE considers to be an acceptable use of NHS resources. So, the committee decided to recommend oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy. Please see sections 1.1 and 3.15 of the FAD.

Bristol Myers Squibb™

Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy [ID3892] Appraisal Consultation Document – BMS response

14 July 2022

Dear [redacted]

Thank you for giving us the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. We are disappointed with the Committee's draft recommendation, as we have demonstrated that oral azacitidine is clinically and cost-effective in its licensed population. The uncertainty in the company's base case ICER has been fully explored with multiple scenario and sensitivity analyses, demonstrating the stability of the base case ICER to variations in all important input parameters.

We welcome the Committee's acceptance of oral azacitidine as a new treatment option which improves overall survival and relapse-free survival compared with placebo, the appropriateness of comparators selected for this appraisal, and the EU-subgroup of the QUAZAR trial as i) generalisable to clinical practice in England, and ii) appropriate for decision-making.

In this response, BMS has addressed the issues raised in the ACD; in particular:

1. The impact of curve selection on cost-effectiveness of oral azacitidine;
2. The impact on cost-effectiveness of clinically plausible assumptions for treatment effect waning;
3. The rationale for applying NICE's End-of-Life criteria in this appraisal; and
4. Equality issues (e.g., access to HSCT) raised by stakeholders in this appraisal.

A positive recommendation for oral azacitidine will ensure that equitable access to this effective and well-tolerated maintenance treatment, with a clear survival advantage, is available for all AML patients who are in remission and cannot have, or do not want, a haematopoeitic stem cell transplant (HSCT).

Yours sincerely

[redacted]

On behalf of Bristol Myers Squibb.

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CONTENTS ..... Page

1. SUMMARY

BMS would like to reiterate that the base case assumptions used in our submission confirm that Onureg® (oral azacitidine) is a clinically and cost-effective option in the maintenance setting for AML patients that have undergone induction therapy and are not candidates for haematopoietic stem cell transplantation.

The QUAZAR trial provides mature data with long follow-up (90 months), resulting in greater certainty in clinical and economic outcomes for the Committee. This is evident from the stability of both the deterministic and probabilistic company base case ICERs, £32,718/QALY vs £32,480/QALY respectively, which is comparable to the ERG's probabilistic base case ICER of £33,925/QALY. Additional scenarios have been provided in this response, at the request of the Committee, that highlight the stability of the ICER to variation in other potentially clinically plausible assumptions.

BMS' understanding is that treatment waning is considered by NICE when extrapolating treatment duration and the possibility of reduced efficacy over time. Considering the maturity and completeness of the QUAZAR trial data, the inclusion of assumptions such as treatment waning are not warranted. At the Committee's request, scenarios with treatment waning have been explored and confirm that the company's base case is fully justified due to the stability of the ICER when a clinically plausible waning effect is applied.

We maintain that the indicated population for oral azacitidine meets both End-of-Life criteria: the majority of patients in the control arm of QUAZAR did not live beyond 24 months and this is anticipated to reflect clinical practice for those who do not receive a HSCT. Consequently, and following the precedent of previous NICE appraisal TA788, we ask that the Committee reconsider the short life expectancy End-of-Life criterion.

As discussed in the Appraisal Committee meeting, there is clear inequality of access to stem cell transplantation between different ethnic groups and people living in different geographic areas. Further evidence on this has been provided in our response. Access to oral azacitidine will provide an alternative treatment option, with a demonstrated survival advantage, for patient unable to access transplantation, and thereby reduce these ethnic and geographic inequalities.

2. Impact of curve selection on cost-effectiveness of oral azacitidine

Joint survival curves selected in the company's base case, in line with NICE DSU criteria[1], are most appropriate

The survival models selected for the company's base case analysis remain the best-fitting, and lead to clinically plausible extrapolations.

Justification for selection of joint survival curves

As discussed in the company response to technical engagement, the unstratified Cox PH model estimated oral azacitidine to result in a reduced rate of mortality compared to placebo (HR: [redacted]; 95% CI: [redacted], based on EU subgroup), as well as a reduced rate of relapse (HR: [redacted]; 95% CI: [redacted]). The log-cumulative hazard plots showed violation of the PH assumption (*Figure 1 and 2*), indicating that survival models which assume a proportional hazards relationship may not be appropriate for OS and RFS. However, the suitability of AFT models was explored in line with NICE DSU TSD 14[1] with quantile-quantile plots showing no violation of the AFT assumption (*Figure 3 and 4*). Therefore, joint curves were considered the most plausible option by the company.

Figure 1: Log-cumulative hazard plot from unstratified Cox PH model – OS (September 2020 data cut) EU subgroup

[redacted]

Figure 2: Log-cumulative hazard plot from unstratified Cox PH model – RFS (July 2019 data-cut) EU subgroup

Figure 3: Quantile-quantile (Q-Q) plot for OS (September 2020 data-cut) EU-Subgroup

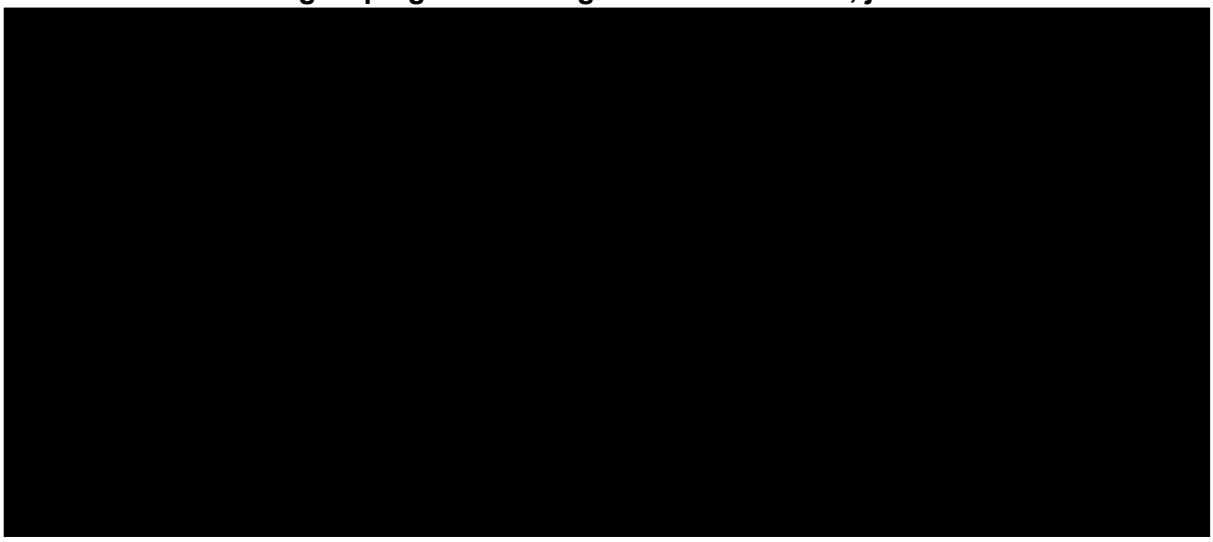
Figure 4: Quantile-quantile (Q-Q) plot for RFS (July 2019 data-cut) EU-Subgroup

Systematic assessment of model fit[1]

We assessed the fit of alternative survival models using the criteria specified in NICE DSU Technical Support Document 14[1]. A range of parametric models were reviewed and compared, to avoid an arbitrary choice of survival model.

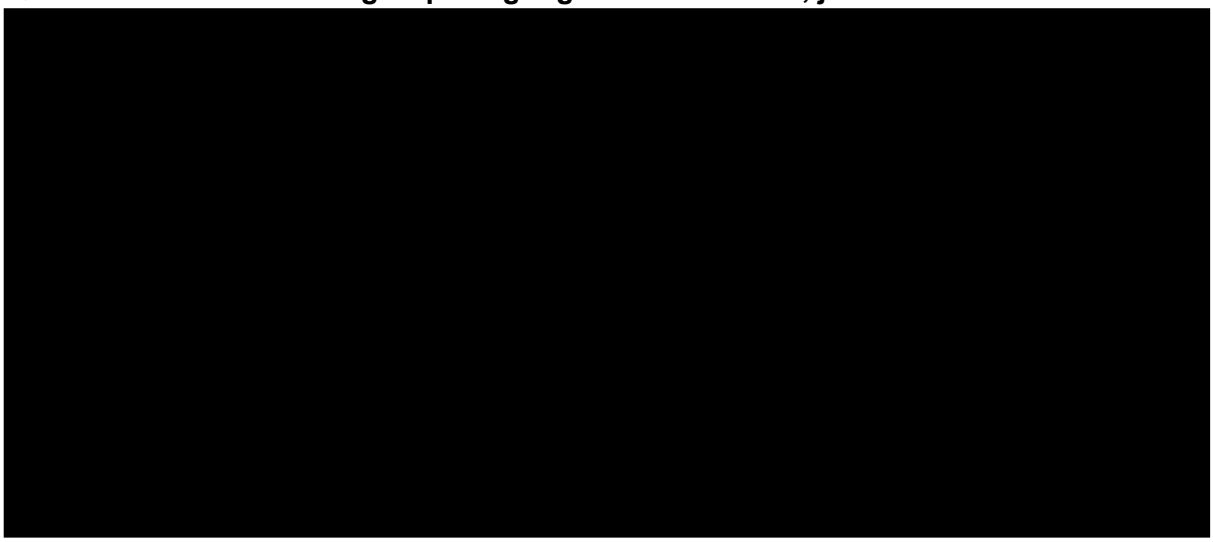
For overall survival, the joint generalised gamma model was selected: this has the lowest AIC and BIC values among all distributions, indicating it has the best statistical fit to the observed data. Visual inspection of the joint generalised gamma survival function (*Figure 5*) supports this conclusion, in that the generalised gamma curves most closely fit the data, and lead to extrapolations which are clinically plausible based on expert opinion.

Figure 5: KM curves and parametric model fitted to the OS outcomes in the QUAZAR AML-001 trial EU subgroup - generalized gamma distribution, joint model



For relapse-free survival, the joint log-logistic model was selected. This model has the best statistical fit to the data (with the lowest AIC and BIC values among all joint models). This model has a very good visual fit (*Figure 6*) and is viewed by experts as clinically plausible.

Figure 6: KM curves and parametric model fitted to the RFS outcomes in the QUAZAR-001 trial EU subgroup – log-logistic distribution, joint model



Alternative individual survival curve scenarios have limited impact on the ICER

BMS acknowledges the Committee's concern about the extrapolation of overall survival from the QUAZAR trial, considering this may overestimate the expected treatment benefit of oral azacitidine. We note that the ERG explored individually fitting models as an alternative to the joint curves presented in the company's base case. In Section 3.11 of the ACD it states that the ERG selected the generalized gamma for both arms in OS and log-logistic for both arms in RFS with the Committee noting these results slightly reduced the base case ICER with the ERG's assumptions.

At Committee's request we have explored more fully the impact of selecting alternative individual survival curves. A range of individual parametric models have been fit, without any treatment waning, for the overall population using the EU-subgroup data (with data for the FLT-3 subgroup presented separately in *Appendix 1*).

Systematic assessment of individual model fit[1]

We assessed the fit of alternative, individual survival models using the criteria specified in NICE DSU Technical Support Document 14[1]. A range of parametric models were reviewed and compared.

For overall survival, the individual generalised gamma model was selected as the best-fitting individual model: this has the lowest AIC and BIC values among all individual survival models, indicating it has the best statistical fit to the observed data. Visual inspection shows the model provides the best fit to KM curves, and clinical plausibility has been verified by clinical experts. The next-best fitting model was the individual log-normal; other models had poor statistical fits and did not produce good visual fits.

For relapse-free survival, the individual log-logistic model was selected as the best-fitting individual model. This model has the best visual fit to the data, a clinically plausible fit, and the second-best statistical fit to the data (based on AIC and BIC values). The individual Gompertz model had a slightly better statistical fit (highest AIC and BIC values of all individual models) but visual inspection shows the model provides a clinically implausible fit.

Table 1 reports the assessment for the best-fitting individual model for each outcome, compared to the joint models used in the company's base case analysis.

Table 1: Summary of model fit assessments for parametric models (EU-subgroup)

CEA		Model Fit Assessment			
Model	**Visual Inspection - Parametric Model vs KM curve**	**AIC**	**BIC**	**Visual Inspection - Log-cumulative Hazard Plots**	**Conclusion**
Overall Survival					
Company Base Case: Joint Generalized Gamma	Curves most closely fit the data and are clinically plausible	[redacted]	[redacted]	Best fit to the KM curves	Lowest AIC and BIC among all distributions, indicating best statistical fit Visual inspection shows model provides the best fit to KM curves. AFT model not reliant on PH assumption
Best-fitting individual model: Individual Generalized Gamma	Curves closely fit the data and are clinically plausible	[redacted]	[redacted]	Best fit to the KM curves	Lowest AIC and BIC among individual models Visual inspection shows model provides the best fit to KM curves
Relapse-free Survival					
Company Base Case: Joint Log-logistic	Curves most closely fit the data and are clinically plausible	[redacted]	[redacted]	Best fit to the KM curves	Lowest AIC and BIC among all clinically plausible curves Visual inspection shows model provides the best fit to KM curves AFT model not reliant on PH assumption
Best-fitting individual model: Individual Log-logistic	Curves closely fit the data and are clinically plausible	[redacted]	[redacted]	Best fit to the KM curves	Next best statistical fit among individual models Visual inspection shows model provides a clinically plausible fit

Minimal impact of survival curves on cost-effectiveness

There is little uncertainty associated with the selection of survival curves on the cost-effectiveness or oral azacitidine. The best-fitting individual models ICER using the company's base case assumptions was only £1k/QALY (+3.1%) higher from the joint curve base case ICER, demonstrating that the choice of individually fitting or joint models has minimal impact on the cost-effectiveness of oral azacitidine (*Table 2*).

The company modelling of individual models closely matches the ERG's preferred scenario (*corrected Scenario 5 in slide 32 from the 1st Appraisal Committee Meeting**). The same individual models for OS and RFS were selected by the company and the ERG, and the same marginal impact on the ICER (<2%) was observed.

**To avoid any confusion, we note that the ICER in the ERG's Scenario 5 ('Individual modelling of OS and RFS) has been re-calculated and now stands at £33,767, within 1% of the ERG's base case ICER.*

<u>Conclusion</u>: The company's base case ICERs are insensitive to the choice of survival curves

Although the joint survival models do not overestimate the expected treatment benefit with oral azacitidine (*Figure 5 and*

– note the original Committee slides show the data for the ITT population rather than the EU subgroup, which has been presented here), the individual models show minimal change in the ICER, meaning that the Committee can be reassured of the benefit of oral azacitidine over standard of care.

Table 2: Summary of cost-effectiveness for parametric models (EU-subgroup)

CEA						
Model	**Treatment**	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER £/QALY**
Overall Survival						
Company's base case: Joint Generalized Gamma	***Oral AZA***	[redacted]	[redacted]	[redacted]	[redacted]	***32,718***
	BSC	[redacted]	[redacted]	-	-	-
Best-fitting individual model Individual Generalized Gamma	***Oral AZA***	[redacted]	[redacted]	[redacted]	[redacted]	**33,136**
	BSC	[redacted]	[redacted]	-	-	-
Relapse-free Survival						
Company's base case: Joint Log-logistic	***Oral AZA***	[redacted]	[redacted]	[redacted]	[redacted]	***32,718***
	BSC	[redacted]	[redacted]	-	-	-
Best-fitting individual model: Individual Log-logistic	***Oral AZA***	[redacted]	[redacted]	[redacted]	[redacted]	**33,281**
	BSC	[redacted]	[redacted]	-	-	-
Individual curves scenario (best fitting individual models according to model fit statistics)						
OS: individual generalized gamma RFS: individual log-logistic	***Oral AZA***	[redacted]	[redacted]	[redacted]	[redacted]	**33,728**
	BSC	[redacted]	[redacted]	-	-	-

3. Impact on cost-effectiveness of clinically-plausible assumptions for waning of the treatment effect

Modelling treatment waning is not warranted due to a complete dataset

Data from the QUAZAR trial provide outcomes data for almost all patients. The trial followed up patients to 90 months, at which time no patients in the treatment arm remained on therapy. The waning of treatment effect during the trial has already been captured in the survival data from the trial; the impact of any potential waning of treatment effect post-trial follow-up will be minor.

Waning assumptions have minimal impact on the cost-effectiveness results

However, BMS acknowledges the Committee's preference to model declining relative treatment effect over time beyond the follow-up period of the QUAZAR trial to explore any uncertainty regarding treatment waning. We have therefore modelled the impact of clinically plausible treatment waning for each of the parametric models considered earlier.

We assumed a conservative waning of treatment, with equivalence of hazards between oral azacitidine and no active therapy assumed from Month 90 (the end of the QUAZAR trial follow-up).

Table 3 illustrates the impact of treatment waning (post-end of QUAZAR trial follow-up) on the best-fitting joint (company's base case) and individual survival curves.

This demonstrates that clinically plausible treatment waning has a minimal impact (<1%) on the cost-effectiveness of oral azacitidine, regardless of the selection of survival curve. The visual impact of this treatment waning assumption can be observed in the best-fitting joint and individual survival curves in *Figures 7-8.*

Table 3: Summary of cost-effectiveness for parametric models with and without treatment waning (EU-subgroup)

CEA		
Model	**ICER £/QALY (no treatment waning)**	**ICER £/QALY (with treatment waning*)**
Overall Survival		
Company Base Case: Joint Generalized Gamma	***32,718***	***32,764 (+0.1%)***
Best-fitting individual model: Individual Generalized Gamma	33,136	33,123 (<-0.1%)
Relapse-free Survival		
Company Base Case: Joint Log-logistic	***32,718***	***32,764 (+0.1%)***
Best-fitting individual model: Individual Log-logistic	33,281	33,330 (+0.1%)
Individual curves scenario (best fitting individual models according to model fit statistics)		
OS: individual generalized gamma RFS: individual log-logistic	33,728	33,714 (<-0.1%)

** Treatment waning: equivalence of hazards between Oral AZA and no active therapy assumed from Month 90 (end of QUAZAR AML-001 trial OS follow-up in September 2020 data-cut) onward.*

Figure 7: Overall survival; joint curves, with treatment waning – GenGamma for OS, LogLogistic for RFS)

Figure 8: Overall survival; individual curves, with treatment waning – GenGamma for OS, LogLogistic for RFS

4. Rationale for applying NICE's End-of-Life criteria in this appraisal

The indicated population for oral azacitidine meets the <24 months End-of-Life criterion

In its assessment, the NICE Appraisal Committee did not consider oral azacitidine to meet the short life expectancy (<24 months) criterion. This decision was based on extrapolated mean OS estimates from the model exceeding 24 months (overall population based on EU subgroup = [redacted] months).

The company does not agree with the Committee's decision since the extrapolated means are not reflective of the life expectancy of most patients with AML in clinical practice. Specifically, the trial data clearly show that the majority of patients in the control arm do not live beyond two years. In the overall population represented by the EU subgroup of the QUAZAR study (September 2020 data-cut), median OS in the no active treatment arm was [redacted] months, with only [redacted] of patients alive at 24 months. When discussed at the first Appraisal Committee meeting, the clinical experts confirmed that the majority of patients (approx. 80%) that they treat who are not eligible for a stem cell transplant, relapse within the first 12 months. For those patients, the expected survival is <24 months.

Table 4 shows the breakdown of the number of patients at risk over time in the no active treatment arm of the QUAZAR trial, within the EU subgroup. Only [redacted] patients contribute to the survival data beyond 24 months, and by 60 months, this decreases further to just [redacted] patients, highlighting the long tail of the survival curve which is contributing to a higher mean OS.

Table 4. Number at Risk Over Time for Patients Surviving ≥24 Months (OS, EU subgroup – BSC arm)

Time (months)	Number at risk – BSC arm-, EU subgroup (% of patients at risk)	% Survival (KM method)
0	[redacted]	[redacted]
24	[redacted]	[redacted]
30	[redacted]	[redacted]
36	[redacted]	[redacted]
42	[redacted]	[redacted]
48	[redacted]	[redacted]
54	[redacted]	[redacted]
60	[redacted]	[redacted]
66	[redacted]	[redacted]
72	[redacted]	[redacted]
78	[redacted]	[redacted]
84	[redacted]	[redacted]

*Last observation in the placebo arm was at 81.3 months.
Abbreviations: BSC = best supportive care; EU = European; NA = not available; OS = overall survival.

NICE STA precedent (Appeal of TA788)[2]

NICE Technology Appraisal TA788 (2021) was appealed on similar grounds. The NICE Committee concluded that the short life expectancy criterion (<24 months) had not been met, noting that the best estimate of expected survival came from modelling mean life expectancy, not the median overall survival estimates from the trial.

The NICE Appeal Panel concluded it would be unreasonable to 'state that life expectancy was not "normally less than 24 months" even if the mean life expectancy was greater than 24 months, if 65% of patients, the significant majority, in the modelled cohort had died prior to 24 months'. In the QUAZAR study, a very similar proportion of patients, [redacted] in the EU subgroup, did not survive beyond

24 months, and so it is similarly unreasonable to claim that the short life expectancy criterion does not apply in this case.

As a consequence, we maintain that the indicated population for oral azacitidine meets both End-of-Life criteria. Consequently, we ask that the Committee give additional weight to the QALYs achieved through the use of oral azacitidine.

5. Equality issues raised during the appraisal

Oral azacitidine should be available to all people who are not able to have a transplant, including those from ethnic minority groups who may not have access to a suitable donor

As noted by clinical experts during the 1st Appraisal Committee meeting, many people with AML who are in complete remission are unable to have a transplant because of a lack of donor availability. This results in inequitable access to a potentially curative treatment option, and disproportionately affects substantial numbers of people, particularly from ethnic minority groups. Published evidence further corroborates this, as discussed below.

Background

According to the 2019 Census, Black, Asian, and Minority Ethnic (BAME) groups make up 15.2% of the total population of England and Wales. Specifically, people of Asian race make up 8.0%, Black race 3.5%, Mixed race 1.8%, and Other race 1.9%.[3] Despite accounting for only 15.2% of the population, in 2020 one-third of the people in the UK waiting for a transplant of any type were from a BAME group.[4] A large driver of this disparity is the lack of BAME-registered donors, as only 15% of registered donors are from a BAME group.[5] Black donors make up only 1.2% of potential donors on the British Bone Marrow Registry.[6]

Access to HSCT: disparity in donor availability

The 2016 Anthony Nolan Stem Cell Registry estimated that only 61% of BAME patients can find a suitably matched stem cell donor compared to 96% of White Northern European patients.[7] The disparity in access is widened by the low chances of finding optimally-matched (10/10 matched) unrelated donors.[8] According to the 2021 All-Party Parliamentary Group report, patients from a minority ethnic background are estimated to have only a 37% chance of finding an optimally-matched unrelated donor compared to 72% for British, Irish, or Northern European patients.[8] In addition, a 2018 review looking into BAME blood, stem cell and organ donation found that a BAME patient had only a 20% chance of finding a "best possible" donor match compared to a 69% chance for White Northern European patients.[6]

Access to HSCT: geographical barriers

There are 35 allograft centres across the UK, so whilst patients may have access to a regional centre, it is often not their local hospital. The All-Party group report gives examples of how "... *many patients have to travel significant distances to their nearest transplant centre. Concerns were raised in the Inquiry that longer distances, and increased travel, impact on both access to transplant and post-transplant care and follow up."*[7]

There are multiple barriers to access to HSCT, a potentially curative treatment option for patients with AML that have been highlighted above. This is particularly significant for patients from ethnic minority groups, where availability of a matched donor is severely limited.

Summary: Value of oral azacitidine in reducing inequalities

Oral azacitidine will provide an alternative treatment option, that has demonstrated a survival advantage, for patients who are unable to access a HSCT. In doing so, it will alleviate the disparities we see in access to other life-extending treatments.

6. References

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5) NHSBT Organ and Tissue Donation and Transplantation Activity Report 2020/2021. Available from https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/23461/activity-report-2020-2021.pdf
6) Ending the silent crisis. A REVIEW INTO BLACK, ASIAN, MIXED RACE AND MINORITY ETHNIC (BAME) BLOOD, STEM CELL AND ORGAN DONATION. Available from: BAME-Donation-review-29.5.18.pdf (nbta-uk.org.uk)
7) Anthony Nolan and NHS Stem Cell Registry (2016) The Anthony Nolan and NHS Stem Cell Registry Annual Review of 2016: From Strength to Strength. Available from https://www.anthonynolan.org/sites/default/files/202101/1257CM_State_Of_The_Registry_2017_AW_lr2.pdf
8) No patient left behind: The barrier stem cell transplant patients face when accessing treatment and care (2021) All-Party Parliamentary Group on Stem Cell Transplantation. Available from https://www.anthonynolan.org/sites/default/files/2021-05/no_patient_left_behind_final.pdf

7. Appendix 1 – Clinical and cost-effectiveness analyses for the FLT-3 population

As was demonstrated for the overall EU subgroup, in the FLT-3 subgroup there is only a small impact of selecting alternative survival curves or modelling treatment waning

BMS acknowledges Committee's concern over the uncertainty in the clinical comparison in this subgroup, which represents a small proportion of the overall AML population, and that Committee is not seeking an optimised recommendation for oral azacitidine in this population. However, the analyses requested have been presented to help address Committee's request in the Appraisal Consultation Document for additional scenario analyses of the FLT-3 subgroup.

Survival analyses – FLT-3 subgroup

The cost-effectiveness and model fit assessments based on NICE's DSU TSD 14[1] (and described in detail above) for the EU-subgroup have been replicated for the FLT-3 subgroup, and the results are presented below.

Table 5 illustrates the stability of model results between the base case (joint generalized gamma for OS and 1 knot, odds linear predictor for RFS) and the second best-fitting curves, with and without treatment waning in the FLT-3 subgroup.

The treatment waning effect applied (as above for the total EU subgroup) assumes equivalence of the hazards between oral azacitidine and no active therapy from Month 90 (end of QUAZAR AML-001 trial OS follow-up in September 2020 data cut) onward.

Alternative survival curves have limited impact on the ICER

As was found for the overall EU-subgroup, the impact of selecting best-fitting alternative models for is modest, increasing the resulting ICER by £3,691 to £22,754 (OS model) and decreasing the ICER by 30% to £13,374 (RFS model). For the scenario where we use both best-fitting OS and RFS models, the ICER decreases to £12,386/QALY.

Waning assumptions have minimal effect on cost-effectiveness

As was shown for the overall EU-subgroup, modelling the impact of treatment waning after the end of the QUAZAR trial has a marginal impact on cost-effectiveness in the FLT-3 subgroup, with the ICER either decreasing, or increasing by under 1%.

Table 5: Summary of cost-effectiveness and model fit assessments for parametric models (FLT-3 subgroup)

CEA			Model Fit Assessment				
Model	**ICER vs No Active Tx £/QALY (no treatment waning)**	**ICER vs No active Tx £/QALY (with treatment waning*)**	**Visual Inspection - Parametric Model vs KM curve**	**AIC**	**BIC**	**Visual Inspection - Log-cumulative Hazard Plots**	**Conclusion**
Overall Survival							
***Company Base Case**: Generalized Gamma*	19,063	19,188	Curves most closely fit the data and are clinically plausible Only model that does not underestimate the tail in the placebo arm Does not overestimate treatment arm survival	[redacted]	[redacted]	Best fit to the KM curves	Lowest AIC and BIC among all parametric distributions Visual inspection shows model provides the best fit to KM curves and log-cumulative hazard data AFT model not reliant on PH assumption
Second best-fitting: 1 knot, odds	22,754 (+19%)	22,160	Curves closely fit the data Curves are clinically plausible	[redacted]	[redacted]	NA	Visual inspection shows model provides a clinically plausible fit
Relapse-free Survival							
***Company Base Case**: 1 knot, odds*	19,063	19,188	Curves most closely fit the data and are clinically plausible	[redacted]	[redacted]	NA	Lowest AIC and BIC among all clinically plausible curves Visual inspection shows model provides the best fit to KM curves and log-cumulative hazard data Spline model provides better fit than parametric models
Second-best fitting: Log-normal	13,374 (-30%)	13,361	Poor fit - overestimates beginning of KM curve, underestimates tail	[redacted]	[redacted]	Poor fit to the KM curves	Visual inspection shows model does not estimate KM curves well

* Treatment waning: equivalence of hazards between Oral AZA and no active therapy assumed from month 90 (end of QUAZAR AML-001 trial OS follow-up in 2020 datacut) onward.

Comparison of risks (hazards) using individual models for overall survival and relapse-free survival – EU-subgroup

Overall Survival

The smoothed hazard plot was generated from the individual generalized gamma model (solid lines) for overall survival (OS) in the EU-subgroup of the QUAZAR study and showed similar mortality risks between oral azacitidine and no active therapy after approximately [redacted]-months (**Figure 1**). The dotted lines are the smoothed hazards derived from the Kaplan-Meier (KM) curves. As demonstrated in Figure 1, the generalized gamma model captures the underlying hazards in the trial data, namely the increase in initial hazard and stabilizing low hazard after 7 and 14 months in the no active therapy and oral azacitidine arms, respectively. Of note, the observed crossing of KM hazards at the [redacted]-month timepoint is expected to be an artifact of statistical noise given the clinical expectation of hazards crossing being considered implausible, its brief nature, and its occurrence as numbers at risk are decreasing. The smoothed hazards derived from individual generalized gamma model for OS are presented in

Time (Months)	Hazard – Oral AZA	Hazard – No Active Therapy
0.0100	[redacted]	[redacted]
0.6861	[redacted]	[redacted]
1.3623	[redacted]	[redacted]
2.0384	[redacted]	[redacted]
2.7146	[redacted]	[redacted]
3.3907	[redacted]	[redacted]
4.0668	[redacted]	[redacted]
4.7430	[redacted]	[redacted]
5.4191	[redacted]	[redacted]
6.0953	[redacted]	[redacted]
6.7714	[redacted]	[redacted]
7.4475	[redacted]	[redacted]
8.1237	[redacted]	[redacted]
8.7998	[redacted]	[redacted]
9.4760	[redacted]	[redacted]
10.1521	[redacted]	[redacted]
10.8282	[redacted]	[redacted]
11.5044	[redacted]	[redacted]
12.1805	[redacted]	[redacted]
12.8567	[redacted]	[redacted]
13.5328	[redacted]	[redacted]
14.2089	[redacted]	[redacted]
14.8851	[redacted]	[redacted]
15.5612	[redacted]	[redacted]
16.2374	[redacted]	[redacted]
16.9135	[redacted]	[redacted]
17.5896	[redacted]	[redacted]
18.2658	[redacted]	[redacted]
18.9419	[redacted]	[redacted]
19.6180	[redacted]	[redacted]
20.2942	[redacted]	[redacted]

20.9703						
21.6465						
22.3226						
22.9987						
23.6749						
24.3510						
25.0272						
25.7033						
26.3794						
27.0556						
27.7317						
28.4079						
29.0840						
29.7601						
30.4363						
31.1124						
31.7886						
32.4647						
33.1408						
33.8170						
34.4931						
35.1693						
35.8454						
36.5215						
37.1977						
37.8738						
38.5500						
39.2261						
39.9022						
40.5784						
41.2545						
41.9307						
42.6068						
43.2829						
43.9591						
44.6352						
45.3114						
45.9875						
46.6636						
47.3398						
48.0159						
48.6921						
49.3682						
50.0443						
50.7205						
51.3966						
52.0728						
52.7489						
53.4250						

54.1012		[redacted]			[redacted]	
54.7773						
55.4534						
56.1296						
56.8057						
57.4819						
58.1580						
58.8341						
59.5103						
60.1864						
60.8626						
61.5387						
62.2148						
62.8910						
63.5671						
64.2433						
64.9194						
65.5955						
66.2717						
66.9478						
67.6240						

.

Figure 1. Smoothed hazard plot of OS (2020 DBL) – individual generalized gamma model, EU Subgroup from QUAZAR AML-001

Note: the maximum time that the hazards are estimated is defined as the time at which ten patients remain at risk. Kernel smoothing methods were used to estimate smoothed hazards using the 'muhaz' R package.

Table 1: Smoothed hazards from individual generalized gamma model for OS (September 2020 DBL)

Time (Months)	Hazard – Oral AZA	Hazard – No Active Therapy
0.0100		
0.6861		
1.3623		
2.0384		
2.7146		
3.3907		
4.0668		
4.7430		
5.4191		
6.0953		
6.7714		
7.4475		
8.1237		
8.7998		
9.4760		

10.1521						
10.8282						
11.5044						
12.1805						
12.8567						
13.5328						
14.2089						
14.8851						
15.5612						
16.2374						
16.9135						
17.5896						
18.2658						
18.9419						
19.6180						
20.2942						
20.9703						
21.6465						
22.3226						
22.9987						
23.6749						
24.3510						
25.0272						
25.7033						
26.3794						
27.0556						
27.7317						
28.4079						
29.0840						
29.7601						
30.4363						
31.1124						
31.7886						
32.4647						
33.1408						
33.8170						
34.4931						
35.1693						
35.8454						
36.5215						
37.1977						
37.8738						
38.5500						
39.2261						
39.9022						
40.5784						
41.2545						
41.9307						
42.6068						

43.2829		[redacted]			[redacted]	
43.9591						
44.6352						
45.3114						
45.9875						
46.6636						
47.3398						
48.0159						
48.6921						
49.3682						
50.0443						
50.7205						
51.3966						
52.0728						
52.7489						
53.4250						
54.1012						
54.7773						
55.4534						
56.1296						
56.8057						
57.4819						
58.1580						
58.8341						
59.5103						
60.1864						
60.8626						
61.5387						
62.2148						
62.8910						
63.5671						
64.2433						
64.9194						
65.5955						
66.2717						
66.9478						
67.6240						

Relapse-free Survival

The smoothed hazard plot was generated from the individual log-logistic model (solid lines) for relapse-free survival (RFS) in the EU-subgroup of the QUAZAR study and showed similar risk of relapse between oral azacitidine and no active therapy after approximately [redacted]-months (**Figure 2**). The dotted lines are the smoothed hazards derived from the KM curves. A visual review of the smoothed hazard plots suggests that RFS for no active therapy has an underlying hazard with an early, pronounced single inflection point and a stabilising low hazard. In addition, a steeper decline in hazard is observed in the no active therapy arm between [redacted] and [redacted] months. The log-logistic models in both arms capture the underlying hazards, including the sharp decrease in hazards observed in the no active therapy arm. The observed crossing of KM hazards at the [redacted] -month timepoint is expected to be an artifact of statistical noise given the

clinical expectation of hazards crossing being considered implausible and its occurrence as numbers at risk are decreasing. The smoothed hazards derived from individual log-logistic model for RFS are presented in **Table 2**.

Figure 2. Smoothed hazard plot of RFS (2019 DBL) – individual log-logistic model, EU Subgroup from QUAZAR AML-001

Note: the maximum time that the hazards are estimated is defined as the time at which ten patients remain at risk. Kernel smoothing methods were used to estimate smoothed hazards using the ‘muhaz’ R package.

Table 2. Smoothed hazards from individual log-logistic model for RFS (2019 DBL)

Time (Months)	Hazard – Oral AZA			Hazard – No Active Therapy		
0.0100		[redacted]			[redacted]	
0.3461						
0.6822						
1.0183						
1.3544						
1.6905						
2.0266						
2.3627						
2.6988						
3.0349						
3.3710						
3.7071						
4.0432						
4.3793						
4.7154						
5.0515						
5.3876						
5.7237						
6.0598						
6.3959						
6.7320						
7.0681						
7.4042						
7.7403						
8.0764						
8.4125						
8.7486						
9.0847						
9.4208						
9.7569						
10.0930						
10.4291						
10.7652						
11.1013						
11.4374						
11.7734						
12.1095						
12.4456						
12.7817						
13.1178						
13.4539						
13.7900						
14.1261						
14.4622						
14.7983						

15.1344						
15.4705						
15.8066						
16.1427						
16.4788						
16.8149						
17.1510						
17.4871						
17.8232						
18.1593						
18.4954						
18.8315						
19.1676						
19.5037						
19.8398						
20.1759						
20.5120						
20.8481						
21.1842						
21.5203						
21.8564						
22.1925						
22.5286						
22.8647						
23.2008						
23.5369						
23.8730						
24.2091						
24.5452						
24.8813						
25.2174						
25.5535						
25.8896						
26.2257						
26.5618						
26.8979						
27.2340						
27.5701						
27.9062						
28.2423						
28.5784						
28.9145						
29.2506						
29.5867						
29.9228						
30.2589						
30.5950						
30.9311						
31.2672						

31.6033		[redacted]			[redacted]	
31.9394						
32.2755						
32.6116						
32.9477						
33.2838						
33.6199						

NICE National Institute for Health and Care Excellence

Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy [ID3892]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 14 July 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Leukaemia Care**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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NICE National Institute for Health and Care Excellence

Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy [ID3892]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 14 July 2022. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned by NICE's evaluation that the treatment does not meet the criteria to be considered life-extending at the end-of-life stage. The end-of-life criteria (6.2.10) require that "the treatment is indicated for patients with a short life expectancy, normally less than 24 months". As set out in the ACD, the median life expectancy of the patient population under consideration is normally less than 24 months, whilst the mean life expectancy falls above 24 months. The NICE criteria make no explicit reference to the use of either a mean or a median average when calculating overall survival. Furthermore, there is a precedent for using the median life-expectancy for the short life expectancy criterion, for example in the appraisal of inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [TA541]. In this appraisal we have concerns that a small group of people who might have been cured for life from the treatment could skew the mean, meaning that the drug does not fit the end-of-life criteria, even if it is considered life-extending for majority of people who are otherwise facing a short life. We support the clinical experts on this point. On this basis, we submit that a decision to base the life expectancy on the mean average is unreasonable considering the uncertainties around calculating the mean and the clinical expert evidence submitted to NICE.
2	Another concern is the committee's consideration of the role this treatment could play in addressing inequalities. As people from ethnic minority backgrounds are less likely to find a stem cell donor match, they are less likely to be offered this potentially life saving treatment. Oral azacitidine, when used as maintenance therapy to prevent relapse after chemotherapy, gives people who might not be able to find a stem cell donor (through no fault of their own) an alternative. It is crucial to fully consider and address this inequality in the accessibility of cancer treatment to people from different ethnic backgrounds.
3	
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5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.

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Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy [ID3892]

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- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Professor Charles Craddock, Professor of Haemato-oncology University of Birmingham
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Professor Charles Craddock

Comment number	Comments

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Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 14 July 2022. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I do not believe the importance of CC486 as a strategy to increase equity of access to effective treatment options for patients from particular ethnic backgrounds has been appropriately recognised. As highlighted in the recently published Report of the UK Stem Cell Strategic Oversight Committee (which I have uploaded-please see p22 and onwards) the current inability to identify a donor for many patients from non-Caucasian ethnic backgrounds results in these patients being denied access to stem cell transplantation which is currently the most effective form of therapy for many adults with AML. The demonstration in the QUAZAR trial that CC486 significantly improves outcomes in patients compared with chemotherapy alone is therefore a major breakthrough in terms of offering effective treatment options for patients unable to proceed to transplant because of lack of donor availability – one of the commonest causes of which is patient ethnicity. Failure to support the use of CC486 for such patients would therefore represent an unnecessary restriction of treatment options for many patients from ethnic minorities.
2	Although I am not a health economist I am surprised that NICE has come to the decision that the putative treatment population do not fulfil criteria for "end of life" considerations since there is abundant evidence that the life expectancy for the great majority (c80%) of the patient population under consideration is under 24 months. In fact for the substantial majority of patients survival is less than 12 months and it is only a minority of patients who would survive more than 24 months. Thus the great majority of patients clearly fulfil "end of life" criteria and it would seem perverse that simply because a small number of patients survive long term the great majority of patients for whom there is a clear unmet need might be denied effective therapy.
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without

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Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy [ID3892]

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reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the ACD:

- Recommendations – section 1

I am an AML in remission patient on oral azacitidine since October 2015 as part of the Quazar trial, as extended. It has kept me alive for almost seven years but as the trial ends in three months I will no longer receive the drug. I believe that your assessment does not give sufficient weight to age related problems accessing other therapies (I am 74 now) and your recommendation 1.2 does not take account of people in my situation where the funding was external to the NHS although the drug given within the NHS.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy [ID3892]

ACD RESPONSE ADDENDUM

Produced by	Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre (UMC)
Authors	Robert Wolff, Managing Director, KSR Ltd, United Kingdom (UK) Willem Witlox, Health Economist, Maastricht UMC, The Netherlands Charlotte Ahmadu, Health Economist, KSR Ltd, UK Sabine Grimm, Health Economist, Maastricht UMC, The Netherlands Nigel Armstrong, Health Economics Manager, KSR Ltd, UK Kevin McDermott, Systematic Reviewer, KSR Ltd, UK Thomas Otten, Health Economist, Maastricht UMC, The Netherlands Caro Noake, Information Specialist, KSR Ltd, UK Manuela Joore, Health Economist, Maastricht UMC Jos Kleijnen, Founder and Owner, KSR Ltd, UK
Correspondence to	Robert Wolff, Kleijnen Systematic Reviews Ltd Unit 6, Escrick Business Park Riccall Road, Escrick York, YO19 6FD United Kingdom
Date completed	22/07/2022

The EAG aligns its base-case with the committee preferences as stated in the ACD, including:

- Using the EU-subgroup
- Relapse utility based on Tremblay (2018)
- Removing the temporary HSCT disutility
- Capping the RFS utility to the age-adjusted population norm in the UK

The EAG comments on the company's ACD response can be found below.

The impact of curve selection on cost-effectiveness of oral azacitidine

In response to the ACD, the company states that the survival models selected for the company's base case analysis (joint generalised gamma for OS, joint log-logistic for RFS) remain the best-fitting, and lead to clinically plausible extrapolations. These choices are based on statistical and visual fit, as well as expert opinion regarding the clinical plausibility of the extrapolations. In addition, the impact of selecting individual survival curves was explored. Based on the criteria specified in NICE DSU TSD 14 and in line with the scenario analysis provided by the EAG, the company selected the individual generalised gamma for OS and the individual log-logistic for RFS. The company's joint and individual modelling results are comparable, and the EAG agrees that the impact of choosing between these two approaches is likely minor.

The impact on cost-effectiveness of clinically plausible assumptions for treatment effect waning

To explore the impact of treatment waning, the company stated: "We assumed a conservative waning of treatment, with equivalence of hazards between oral azacitidine and no active therapy assumed from Month 90 (the end of the QUAZAR trial follow-up)". The company assessed the impact of treatment waning from 90 months onwards on the best-fitting joint (company's base case) and individual survival curves, which indicate that the treatment waning assumption has a minimal impact. The EAG would be interested to see scenario analyses exploring the impact of treatment waning kicking in earlier, for example from 36 and 60 months onwards.

The relative treatment effect on OS and RFS over time between oral azacitidine and no active treatment

In relation to the individual modelling scenarios and treatment waning, the committee requested that they would like to understand what is happening to the relative treatment effect over time by comparing OS and RFS between both treatment arms. The EAG therefore presents the modelled yearly reduction of OS and RFS (%) for oral azacitidine and no active treatment when selecting the individual generalised gamma (OS) and log-logistic (RFS) for both arms in Tables 1 and 2 below, i.e. each of the listed percentages was calculated as follows: (the proportion of patients alive in year x – the proportion of patients alive in year x-1), divided by the proportion of patients alive in year x-1. The tables show that the relative yearly OS and RFS reductions are similar for oral azacitidine and no active treatment from approximately 5 years onwards, which is an indication for the EAG that treatment waning may be implicitly incorporated in the survival curves when using an individual modelling approach.

The rationale for applying NICE's End-of-Life criteria in this appraisal

The EAG notes that the company challenged the committee decision that azacitidine meets the short life expectancy criterion of <24 months ("*This decision was based on extrapolated mean OS estimates from the model exceeding 24 months (overall population based on EU subgroup =* [redacted] *months)"*). The company presented a Table to demonstrate *"the long tail of the survival curve which is contributing to a higher mean OS"*. Furthermore, the company referred to an appeal of TA788 which, in its view, could be seen as a precedent. The EAG also notes that these comments appear to be shared by other stakeholders.

That being said, the EAG refers back to the comments made in Section 7 of the EAG report regarding end-of-life criteria, especially in regards to criterion 1.

Equality issues (e.g. access to HSCT) raised by stakeholders in this appraisal

In response to the ACD, the company as well as some other stakeholder noted potential equality issues, namely related to the disparity in donor availability (White Northern Europeans vs. BAME) and

geographical barriers (location of 35 allograft centres across the UK). The company stated that *"oral azacitidine will provide an alternative treatment option, that has demonstrated a survival advantage, for patients who are unable to access a HSCT. In doing so, it will alleviate the disparities we see in access to other life-extending treatments"*.

The EAG acknowledges these statements but would appreciate these comments to be assessed by the committee as well as experts representing NHS England.

Table 1: Modelled yearly reduction of OS (%) (risk of dying) for oral azacitidine and no active treatment when selecting the individual generalised gamma for both arms

Year	% reduction OS oral azacitidine	% reduction OS no active treatment
0-1		
1-2		
2-3		
3-4		
4-5		
5-6		
6-7		
7-8		
8-9		
9-10		
10-11		
11-12		
12-13		
13-14		
14-15		
15-16		

Table 2: Modelled yearly reduction of RFS (%) (risk of relapse or death) for oral azacitidine and no active treatment when selecting the individual log-logistic for both arms.

Year	% reduction RFS oral azacitidine	% reduction RFS no active treatment
0-1		
1-2		
2-3		
3-4		
4-5		
5-6		
6-7		
7-8		
8-9		
9-10		
10-11		
11-12		
12-13		
13-14		
14-15		
15-16		

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy [ID3892]

POST-ACD ERG ANALYSES

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre (UMC)

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Table 1: Updated ERG base-case and scenario analyses

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Deterministic company base-case (EU subgroup)					
Oral azacitidine	[redacted]	[redacted]			
w&w+BSC	[redacted]	[redacted]	[redacted]	[redacted]	32,718
Matter of judgement (Relapse utility using Tremblay)					
Oral azacitidine	[redacted]	[redacted]			
w&w+BSC	[redacted]	[redacted]	[redacted]	[redacted]	31,857
Matter of judgement (Remove HSCT disutility)					
Oral azacitidine	[redacted]	[redacted]			
w&w+BSC	[redacted]	[redacted]	[redacted]	[redacted]	32,749
Matter of judgement (RFS utility cap)					
Oral azacitidine	[redacted]	[redacted]			
w&w+BSC	[redacted]	[redacted]	[redacted]	[redacted]	33,958
Deterministic ERG base-case					
Oral azacitidine	[redacted]	[redacted]			
w&w+BSC	[redacted]	[redacted]	[redacted]	[redacted]	33,991
Probabilistic ERG base-case					
Oral azacitidine	[redacted]	[redacted]			
w&w+BSC	[redacted]	[redacted]	[redacted]	[redacted]	33,830
Scenario probabilistic ERG base-case + post HSCT utility increment					
Oral azacitidine	[redacted]	[redacted]			
w&w+BSC	[redacted]	[redacted]	[redacted]	[redacted]	36,887
Scenario probabilistic ERG base-case + individual OS and RFS models					
Oral azacitidine	[redacted]	[redacted]			
w&w+BSC	[redacted]	[redacted]	[redacted]	[redacted]	35,073
Scenario probabilistic ERG base-case + individual OS and RFS models + treatment waning at 3 years					
Oral azacitidine	[redacted]	[redacted]			
w&w+BSC	[redacted]	[redacted]	[redacted]	[redacted]	35,571
Scenario probabilistic ERG base-case + individual OS and RFS models + treatment waning at 5 years					
Oral azacitidine	[redacted]	[redacted]			
w&w+BSC	[redacted]	[redacted]	[redacted]	[redacted]	35,205
Scenario probabilistic ERG base-case + individual OS and RFS models + treatment waning at 7.5 years					
Oral azacitidine	[redacted]	[redacted]			
w&w+BSC	[redacted]	[redacted]	[redacted]	[redacted]	35,107

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS = Company Submission; ERG = Evidence Review Group; HSCT = hematopoietic stem cell transplantation; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years; w&w+BSC = watch & wait plus best supportive care					

Table 2: FLT3 subgroup updated ERG base-case

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY))	Pairwise ICER versus oral azacitidine
CS deterministic base-case						
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	£269,191	Oral azacitidine is dominant
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	£19,063	
w&w+BSC	[redacted]	[redacted]				£19,063
Matter of judgement Relapse utility using Tremblay)						
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	£237,034	Oral azacitidine is dominant
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	£19,048	
w&w+BSC	[redacted]	[redacted]				£19,048
Matter of judgement (Remove HSCT disutility)						
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	£269,861	Oral azacitidine is dominant
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	£19,076	
w&w+BSC	[redacted]	[redacted]				£19,076
Matter of judgement (RFS utility cap)						
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	£256,724	Oral azacitidine is dominant
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	£20,212	
w&w+BSC	[redacted]	[redacted]				£20,212
Deterministic ERG base-case						

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY))	Pairwise ICER versus oral azacitidine
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	£257,333	Oral azacitidine is dominant
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	£20,229	
w&w+BSC	[redacted]	[redacted]				£20,229
Probabilistic ERG base-case						
Midostaurin	[redacted]	[redacted]	[redacted]	[redacted]	£247,172	Oral azacitidine is dominant
Oral azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	£21,340	
w&w+BSC	[redacted]	[redacted]				£21,340

CS = company submission; ERG = Evidence Review Group; HSCT = hematopoietic stem cell transplantation; ICER = incremental cost effectiveness ratio; QALYs = quality-adjusted life years; w&w+BSC = watch & wait plus best supportive care