NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Venetoclax with azacitidine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Venetoclax with azacitidine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

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 AbbVie**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Leukaemia Care
   b. Royal College of Pathologists-British Society for Haematology
   c. Jazz Pharmaceuticals

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

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

Venetoclax with azacitidine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable

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	Company	AbbVie	AbbVie have presented a revised economic base case, supporting scenario analyses and further clinical validation to address the Committee's reservations regarding the cure assumption. As the Committee recognised, venetoclax is a promising new treatment which can offer a step change in the management in AML when intensive chemotherapy (IC) is unsuitable, and is now widely recommended as standard of care for these patients around the world, in line with international guidelines.1, 2 The revised base case includes a 3-year cure timepoint and a reduced dose intensity, in line with the preferences of the Committee and clinical experts. This revised base case is associated with an incremental cost-effectiveness ratio (ICER) well below the willingness-to-pay threshold of £50,000 for medicines which reach the end-of-life criteria and thus demonstrates venetoclax to be a cost-effective use of NHS resources; £28,736 for VenAZA versus AZA in the 20–30% blasts subgroup, £40,094 for VenAZA versus LDAC and £11,368 for VenLDAC versus LDAC in the >30% blasts subgroup. Scenarios were explored where the 'Cure' health state was removed and the proportion of patients remaining in remission in the long term informed by mixture cure modelling, providing validation for the base case approach. A cost-effective treatment that is considered to be standard of care in other geographies should also be routinely commissioned in the UK. AbbVie therefore urge the Committee to reconsider the evidence and work with AbbVie to make venetoclax available for this patient population under routine commissioning.	Thank you for your comment. Following the updated modelling, the committee recommended venetoclax plus azacitidine as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable.
2	Company	AbbVie	**Further validation demonstrates the cure assumption to be clinically plausible** During the ACM, both clinical experts strongly supported the notion of venetoclax delivering a cure for some patients. During further consultation following the ACM, clinicians have firmly reiterated that in their experience a proportion of patients receiving venetoclax are able to achieve a cure and will therefore require no further treatment. Given this, the company have completed an additional modelling exercise to validate the original cure assumption and reviewed further clinical evidence to support the basis for the cure assumption. The Committee suggested exploring mixture cure models (MCMs) to validate the proportion of patients remaining in the 'Remission' health state over time. The company therefore conducted analyses removing the 'Cure' health state from the model and exploring mixture cure models (MCMs) to extrapolate transitions from the 'Remission' state (time-to-relapse and time-to-death). These two transitions collectively determine the overall rate of transition out of the 'Remission' state, which in turn determines the proportion of patients who remain in the 'Remission' state in the long term. In line with the framework outlined by Lambert et al. (2007),3 survival of cured patients was considered to follow the general population mortality as per the England and Wales life tables (2017–19), and the survival of patients who were not cured was estimated using	Thank you for your comment. The committee agreed that it was plausible that some people could be considered cured, although the evidence for including a cure state in the model was uncertain. See FAD section 3.5.

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			standard parametric survival distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma). Full details of the MCMs explored are presented in Appendix 3, including consideration of statistical fit, visual fit and clinical validation. For VenAZA and VenLDAC in the >30% blasts subgroup, regardless of the MCM curves selected, the proportions of patients predicted by the model to remain in remission through years 2–5 were very similar to those predicted by the company base case submitted at technical engagement, and considerably higher than the revised company base case submitted as part of this response. This is despite the variation in cure fractions observed across models for some of the transitions, providing support for the inclusion of the cure state in the model. In line with feedback from clinical experts, these analyses indicate that the revised company base case (3-year cure point) is conservative, demonstrating the upper limit of uncertainty in terms of the timepoint of the cure assumption. For VenAZA in the 20–30% blasts subgroup, clinical experts did not consider the best fitting extrapolations of time-to-relapse in terms of statistical fit to be plausible (see Figure 2). Similarly, the proportions of the overall cohort predicted to be in the 'Remission' state for this subgroup reflect an ongoing high rate of relapse, and were therefore considered to be implausible, given that the vast majority of relapses are expected to occur before 2–3 years. The Gompertz model was considered to be the only potentially plausible extrapolation of time-to-relapse; when this model is selected, the proportions of the overall cohort predicted to be in the 'Remission' state are similar to the proportions predicted by the revised company base case (3-year cure point), providing support for the inclusion of the cure state in the model. It is also worth noting that clinical experts stated that they would not expect a significant difference in long term survivorship between blast groups for VenAZA (given the arbitrary threshold of 30% blasts), so the differences in proportions of the overall cohort predicted to be in the remission between the 20–30% and >30% blast groups, except when the Gompertz model is selected, are clinically implausible. In these MCMs, a proportion of 'cured' patients (the 'cure fraction') is predicted as an output of the statistical model, based on the inputted clinical data from the VIALE trial populations. However, it should be noted that the need to stratify the VIALE trial populations by blast cell count subgroups results in small numbers of patients and events informing these extrapolations; this is reflected in variation in the predicted cure fractions for several transitions. Reliance on MCMs to predict long-term survival ignores the surrogacy relationship between sustaining CR + CRi and long-term survivorship, relying on limited trial data alone to predict the proportion of 'cured' patients. This increases the uncertainty associated with long-term survival compared to the inclusion of the cure state, which underwent extensive clinical validation. Given that the relationship between sustained CR + CRi and long-term survivorship is clinically established, the inclusion of the cure state is the most appropriate approach to address the uncertainty, and the use of MCMs to extrapolate survival was not considered in the base case. The similarities between the long-term survival estimates predicted by the base case and the MCM scenarios provide strong support that a cure is plausible for patients treated with venetoclax combinations, and thus that it is appropriate to include a cure assumption in the model. The Committee's preference to remove the cure assumption would not reflect the benefit that VenAZA is bringing to patients and the NHS in this indication.	
3	Company	AbbVie	**Venetoclax combinations deliver similar clinical outcomes to IC, which has an accepted**	Thank you for your comment. The FAD

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			capacity for cure The evidence suggests that VenAZA represents a step-change from previous non-intensive treatments and has demonstrated extraordinary clinical outcomes which are aligned to agents with an accepted capacity for cure. Section 3.5 (page 8) of the ACD report states: "The company stated that the VIALE-A results showed that complete remission rates with venetoclax plus azacitidine were similar to those seen in patients over 60 receiving intensive chemotherapy, and that rates of sustained deep remission were higher with venetoclax plus azacitidine than with azacitidine alone. It argued that it was therefore plausible to assume that patients having venetoclax plus azacitidine could be considered cured." This explanation of the modelled cure assumption fails to recognise the well-characterised surrogacy relationship between achievement of complete remission (CR + CRi) and long-term survival, on which the cure assumption is built.4 Disease relapse represents the major cause of treatment failure in adults treated with IC.4 Furthermore, the majority of patients who relapse do so within the first two years of treatment, and the risk of relapsing is small in those who maintain CR in the long term.1,5-9 Thus, patients who achieve a deep remission that is sustained for 2–3 years after completion of IC are likely to achieve long-term disease-free survival, which can be considered akin to cure. Clinical experts consulted explained that patients treated with venetoclax combinations who achieve a sustained deep remission have the potential to achieve long-term survivorship and maintain quality of life, whereby their outcomes are in line with those of the general population. VenAZA provides deep and durable complete remission rates (CR + CRi with/without measurable residual disease [MRD]) that have historically only been associated with IC.10-13 This is supported by the recent review conducted by Short et al. (2021), which reports that VenAZA has a longer median survival, and improved two year survival, compared with IC treatments (7+3 regimen and CPX-351).14 This is despite the fact that patients receiving VenAZA were older and less fit than IC recipients.14 Considering the high proportions of patients treated with VenAZA who achieve durable CR + CRi, it is plausible that VenAZA can deliver a cure for some patients, similar to that seen in patients treated with IC, and thus it is appropriate to include a 'Cure' health state in the model for those patients who achieve and sustain CR + CRi.	has been amended to state that the company considered there was an established relationship between complete remission and long-term survival. The committee agreed that it was plausible that some people could be considered cured, although the evidence for including a cure state in the model was uncertain. See FAD section 3.5.
4	Company	AbbVie	**Venetoclax is currently being utilised for patients eligible for IC, who would normally be treated with curative intent** There are currently no consensus guidelines for objectively determining patient eligibility for IC. However, decisions are largely based on assessment of the risk of treatment-related mortality (TRM) by experienced haematologists, based on factors such as age and the presence of comorbidities. Given the established link between CR + CRi and long-term survivorship, a cure assumption should apply regardless of ability to tolerate IC due to risk factors for TRM, provided that equivalent CR + CRi outcomes are observed across treatments. Rather, as stated in the company submission, there are currently no curative treatment options available for patients who are not able to tolerate IC. The current NHS England interim treatment policy (NG161) has provided access to venetoclax combinations in those patients who would normally be eligible to receive IC, in order to prevent prolonged hospitalisation during the COVID-19 pandemic.15 This guidance states that treatment with venetoclax can allow these patients to achieve remission rates (CR + CRi) which parallel those achieved in older patients treated with IC. Therefore, venetoclax is currently being utilised in the NHS for patients who would normally be treated with	Thank you for your comment. The committee agreed that it was plausible that some people could be considered cured, although the evidence for including a cure state in the model was uncertain. See FAD section 3.5.

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			curative intent, and it is therefore appropriate to conclude that patients who are ineligible for IC could also achieve a cure with venetoclax provided they achieve equivalent CR + CRi outcomes (which have been clearly demonstrated in the VIALE-A trial).16	
5	Company	AbbVie	**Acceptance of a less conservative cure assumption in the gilteritinib appraisal (TA642) is relevant to this appraisal** The Company disagree with the Committee's assertion that the gilteritinib appraisal (TA642) is not relevant to this appraisal because it was conducted in a different population.17 Whilst these populations do differ, as patients in TA642 had relapsed or refractory AML and a proportion of patients received a stem cell transplant (SCT), SCT was not a condition of cure in the model, and it was assumed that all patients who were alive at 3 years were 'cured'. Furthermore, the population included in the gilteritinib appraisal (relapsed or refractory AML) represents a population who may have poorer prognosis than the population in this appraisal (untreated AML). Given the evidence presented in this response, it would be inconsistent to dismiss the possibility of a cure assumption in the population of relevance in this appraisal when a cure was previously accepted in a relapsed refractory AML population with a poorer prognosis. It is also important to note that, based on clinical feedback, the cure assumption modelled in this appraisal is more conservative than the cure assumption applied in TA642, with cure only possible for those patients who achieve and sustain CR + CRi.	Thank you for your comment. The FAD has been updated to state that the committee also noted that the cure assumption in the gilteritinib model applied to both the intervention and treatment arms, which it did not in the venetoclax plus azacitidine model. See FAD section 3.5.
6	Company	AbbVie	**The revised Company base case assumption regarding the timepoint of cure** The company acknowledge that there was some discussion amongst clinical experts regarding the timepoint of the cure assumption, specifically that clinical experts suggested the timepoint of the cure assumption may be closer to three years. However, it is important to note that clinical experts were all strongly supportive of potential for cure for patients with long term CR +CRi, and their uncertainty focused entirely on the timing of the cure assumption. As described in Section 3.3.5 of the company submission, two years was initially selected as the cure timepoint in the original company base case as the rate of relapse after two years is low (based on experience of patients treated with IC).1,5-9, 18, 19 Furthermore, this corroborates the plateau in the VIALE-A Kaplan–Meier curves which is observed at ~24 months of treatment for VenAZA (in 20–30% and >30% blast populations).16 However, the company acknowledge the discussion surrounding the timepoint of the cure assumption, and in line with feedback from clinical experts during the ACM, a 3-year cure timepoint has been included in the revised base case. This is considered to demonstrate the upper limit of uncertainty in terms of the timepoint of the cure assumption. Moving the cure timepoint to three years increases the ICER, however this remains comfortably below the cost-effectiveness threshold of £50,000 for end-of-life treatments; £28,736 for VenAZA versus AZA in the 20–30% blasts subgroup, £40,094 for VenAZA versus LDAC and £11,368 for VenLDAC versus LDAC in the >30% blasts subgroup. When the 3-year cure point is applied, the proportions of patients predicted to enter the cure state are [redacted]% for VenAZA in the 20–30% blasts subgroup, [redacted]% and [redacted]% for VenAZA and VenLDAC in the >30% blasts subgroup. These predictions are lower than those when the 2-year cure point is applied: [redacted]% for VenAZA in the 20–30% blasts subgroup, [redacted]% and [redacted]% for VenAZA and VenLDAC in the >30% blasts subgroup. Feedback from clinical experts suggested that predictions for the 3-year timepoint are lower than would be expected in clinical practice. However, the company has aligned with the feedback received during the ACM and adopted the 3-year cure timepoint as a	Thank you for your comment. Because all of the plausible ICERs were within the range that NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life, the committee recommended venetoclax plus azacitidine as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable. See FAD section 3.11.

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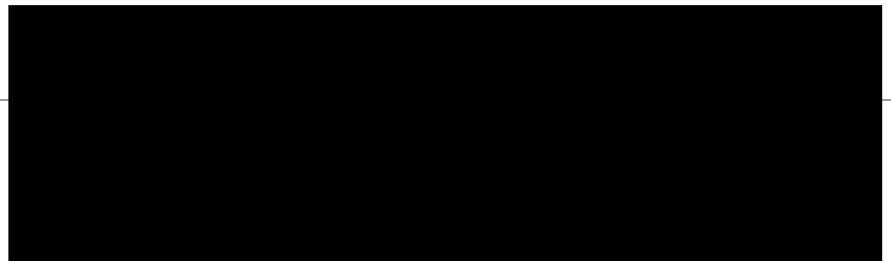
			conservative assumption in the revised base case. Venetoclax remains a cost-effective use of NHS resources with this conservative assumption adopted, which should mitigate the Committee's concerns surrounding the cure assumption.	
7	Company	AbbVie	**Venetoclax remains cost-effective when the assumptions around relapse are varied** Whist the Chyn Chua et al. (2021) study provides a supportive result for the continued efficacy of venetoclax post-discontinuation, the company believe that this study is inappropriate to inform reimbursement decision-making due to a number of substantial limitations.20 This retrospective study included a very small sample size (n=28), and thus considerable uncertainty remains regarding the generalisability of this study to wider real-world practice. It should also be noted that this study was not designed to investigate the impact of time in CR + CRi on relapse. Following the ACM, the company conducted discussions with the authors, who explained that this study was designed to provide clinicians with evidence to inform discussions with patients upon intent to discontinue treatment. As such, the timing of treatment discontinuation was based on patient request and not necessarily determined by the time in which the patient had been in complete remission, as would be the case in clinical practice. Therefore, this study should not be used to validate the cure assumption or be used to inform decision-making. Furthermore, it was explained that the late relapses observed in the Chyn Chua et al. (2021) study were often new and distinct forms of AML, rather than a relapse of the original disease. This new phenomenon is thought to be observed due to the increased survival length of AML patients treated with venetoclax, and this should not be considered to be a failure of the treatment. Moreover, in general the recording of outcomes as part of a retrospective study is less robust than that of randomised control trials (RCTs) such as the VIALE trials, and the preference for RCTs is stated by NICE.21 Therefore, the clear post 24-month plateau in survival observed in VIALE-A,16 the low rate of relapse observed after two years in IC patients,1,5-9 and clinical expert feedback stating that the vast majority of relapses occur before two years should supersede the findings of this study.16 The company believes that RCT evidence, clinical opinion, continuous model validation, and published literature submitted as part of this appraisal should act as the guide for robust reimbursement decision-making and inform any assumptions around the curative properties of venetoclax in older AML patients with comorbidities. Any real-world evidence (RWE) evidence endorsed as part of this appraisal should incorporate a substantially larger sample size, and have clear recruitment criteria and treatment aims that fully align with the gold standard pivotal venetoclax trials in AML (VIALE-A and VIALE-C). As correctly stated by the Committee, the company's base case model did not permit any relapse to occur after two years. This approach was deemed appropriate given the vast majority of relapses occur before this timepoint, as shown in Figure 1 (adapted from Yanada et al. [2007]), which reports on treatment failure following achievement of CR in 1,069 patients receiving a variety of therapies but who had not undergone SCT.22 **Figure 1: Proportion of AML patients relapsing after achieving first CR** 	Thank you for your comment. Because all of the plausible ICERs were within the range that NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life, the committee recommended venetoclax plus azacitidine as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable. See FAD section 3.11.

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			Footnotes: Figure adapted from Yanada et al. (2021),22 calculated as the number of relapses reported within each timeframe as a proportion of the total number of relapses. Abbreviations: CR: complete remission. However, as late-stage relapse may occur in a small minority of patients, further scenario analyses have been conducted in which only a proportion of patients in the 'Remission' health state transition to the 'Cure' state following the cure timepoint. Patients remaining in the 'Remission' health state continue to experience the risk of relapse and death as determined by the extrapolated time-to-relapse/death data, not general population mortality. Clinical expert opinion suggested that, of those patients who sustain CR + CRi for 2 years, approximately 20% may experience late relapses, with the vast majority of these relapses occurring between 2 and 3 years. This is supported by findings from Yanada et al. (2007), which show that 10.5% of recurrences occurred after 2 years in CR and just 3.3% of recurrences occurred after 3 years in CR. Out of a cohort of 1,069 patients with AML, this provides robust evidence that the risk of relapse after 3 years is negligible. Considering the evidence, a scenario was explored where 90% of patients in remission at three years transition into the 'Cure' state (Appendix 2), with the remaining patients continuing to transition to the 'Relapse/PD' and 'Death' states from the 'Remission' state according to the selected time-to-relapse and time-to-death curves. Scenarios were also explored in which 80% and 70% of patients in remission transition into the 'Cure' state at two years. All ICERs remain comfortably below the cost-effectiveness threshold of £50,000 for end-of-life treatments, ranging from £18,813–£28,736 for VenAZA versus AZA in the 20–30% blast subgroup, £35,469–£40,094 for VenAZA versus LDAC and £9,383–£11,368 for VenLDAC versus LDAC in the >30% blasts subgroup.	
8	Company	AbbVie	**Venetoclax remains cost-effective when utility in the 'Cure' state is informed by the VIALE trial data for patients in remission (CR + CRi)** On page 11 of the ACD document, clinical experts highlighted "that many people would return to the same quality of life after treatment as could be expected in the general population, but that some would not." Based on feedback from clinical experts, patients who reside within the 'Cure' state were assumed to receive the utility of the general population, given the substantial transfusion-	Thank you for your comment. The committee accepted that using the remission state utility value in the cure state did not affect the cost-effectiveness results. See FAD section 3.6.

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			independence benefit associated with CR + CRi, allowing patients to return to normal life. The company would also like to highlight that a scenario was requested by the ERG at the clarification question stage to assume patients in the 'Cure' health state have the same utility as patients in the 'Remission' health state (where utility was informed by data for patients in CR + CRi from the VIALE trials), given the uncertainty surrounding the assumption that patients in the cure state experience the same quality of life as the general population. As stated in the company response to the ERG clarification questions, there are only small numerical differences between the utility values describing the remission health state and the cure health state. Given patients have a mean age of [redacted] years at the original 2-year cure point, the age-adjusted general population utility of 0.7465 is always less than that of the remission health state utility of [redacted]. Therefore, when applying the 'Remission' health state utility to patients in the 'Cure' state capped by the utility of the general population, there were only minor changes in inputs. This minor deviation in the utility, in addition to rounding, has no impact on cost-effectiveness outcomes.	
9	Company	AbbVie	**The revised Company base case algins with the Committee's preferences regarding the dose intensity of venetoclax** On page 11 of the ACD document, the Committee state: "in clinical practice in England, almost all patients with acute myeloid leukaemia would have concomitant treatment with azoles such as posaconazole as antifungal prophylaxis. Azoles are strong CYP3A inhibitors, which affects the metabolism of venetoclax and increases its plasma level. Therefore, in line with the summary of product characteristics advice on managing potential venetoclax interactions with CYP3A inhibitors, the dose of venetoclax used in clinical practice would be much lower than in the trial, usually 100 mg a day rather than 400 mg". Clinical expert feedback during the ACM, and guidance from the NHS England interim treatment policy (NG161), recommends a dose intensity of 25% in cycle 1 (i.e. 100 mg a day rather than 400 mg) in combination with a strong CYP3A inhibitor, which can potentially drop to 12.5% from cycle 2 onwards (i.e. 100 mg on days 1–14).15 Therefore, in line with the Committee's preferences, and in order to accurately reflect the dose of venetoclax that may be used in clinical practice, a dose intensity of 25% in the first cycle, followed by 12.5% from cycle 2 onwards, has been modelled for the venetoclax component of VenAZA. Similarly, a dose intensity of 16.7% in the first cycle (i.e. 100 mg rather than the full 600 mg dose), followed by 8.3% (i.e. 100 mg on days 1–14) from cycle 2 onwards, has been modelled for the venetoclax component of VenLDAC. Whilst the company acknowledge that a dose intensity as low as 12.5% after the first cycle was received by some patients in clinical practice during the interim COVID-19 policy, additional clinical expert opinion sought after the ACM has reiterated that the required dose is ultimately dependent on the duration of treatment with concomitant strong/moderate CYP3A inhibitors, and dose interruptions required to manage cytopenia, and thus there might be some variation in clinical practice. For completeness, a conservative scenario was explored where dose intensity was aligned with the assumptions made in the original appraisal (Appendix 2); ICERs remain below the cost-effectiveness threshold of £50,000 for end-of-life treatments. It is important to note that patients receiving a 100 mg venetoclax daily dose in combination with azoles are not expected to experience any reduction in efficacy compared to patients receiving a 400 mg daily dose. This is because azoles are strong CYP3A inhibitors, and as such increase	Thank you for your comment. The committee concluded that the company's updated modelling of dose intensity was appropriate and reflected clinical practice. See FAD section 3.8.

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			venetoclax drug exposure when administered concomitantly. A pharmacokinetic study has demonstrated that a 100 mg venetoclax dose administered in combination with a strong CYP3A inhibitor produces a drug exposure between that of venetoclax (alone) at the therapeutic dose of 400 mg once daily, and the established safe maximal administered dose of 1,200 mg once daily (as measured by the area under a drug concentration-time curve over the 24 hour dosing period [AUC24]).23 Post-hoc analysis of data from VIALE-A has demonstrated that rates of CR + CRi as a best response were similar with concomitant use of moderate (61%) and strong (64%) CYP3A inhibitor with adjusted-dose venetoclax versus no use of CYP3A inhibitor (67%).24 Furthermore, cytopenia within the VIALE-A trial was successfully managed using dose modifications of venetoclax, including cycle delays and reduction in the number of dosing days within cycle.25, 26 Additional UK RWE for patients receiving VenAZA or VenLDAC (N=[redacted]) via the COVID interim treatment policy found that [redacted]of patients received a 100 mg dose of venetoclax with concomitant use of a strong CYP3A inhibitor, and amongst this cohort [redacted]% of patients achieved CR + CRi and median OS was [redacted]months (95% CI: 10.9, NR). Median follow-up was 8.2 months (95% CI: [redacted]).27 Taken together, these data provide strong evidence that reduced dose intensity in real world use should not substantially impact on the efficacy of venetoclax.	
10	Consultee	The Royal College of Pathologists (RCPath) British Society for Haemathology (BSH)	We are concerned that the committees decision puts UK patients at odds with what is standard of care for AML treatment for patients unsuitable for intensive chemotherapy around the world. Reviewing the ERGs cost-effectiveness assessment using the currently NICE approved dosing schedule (100mg daily with Posaconazole) the cure assumption time-point appears to be the critical factor in the uncertainty of the evidence presented that hinders a positive outcome. To this end a recent study published since the committee meeting provides additional support for the cure assumption. Cherry et al. Blood Advances Oct 2021 (10.1182/bloodadvances.2021005538) retrospectively assessed 143 patients receiving Ven/Aza with similar numbers receiving intensive chemotherapy. Kaplan-Meier survival curves (showing median OS) are presented for all patients and a propensity matched cohort of patients (the latter shown below). The red line shows patients receiving ven/aza the blue intensive chemotherapy. Not only is there a trend to better outcomes for patients in this propensity matched group receiving ven/aza but there is a clear levelling of the survival curve in the ven/aza group. While acknowledging the limitation of real world data we believe this is credible evidence to further support the cure assumption point. This is in keeping with evidence levels supportive of other TAs which have had favourable approvals for (gilteritinib and midostaurin).	Thank you for your comment. Because all of the plausible ICERs were within the range that NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life, the committee recommended venetoclax plus azacitidine as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable. See FAD section 3.11.

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			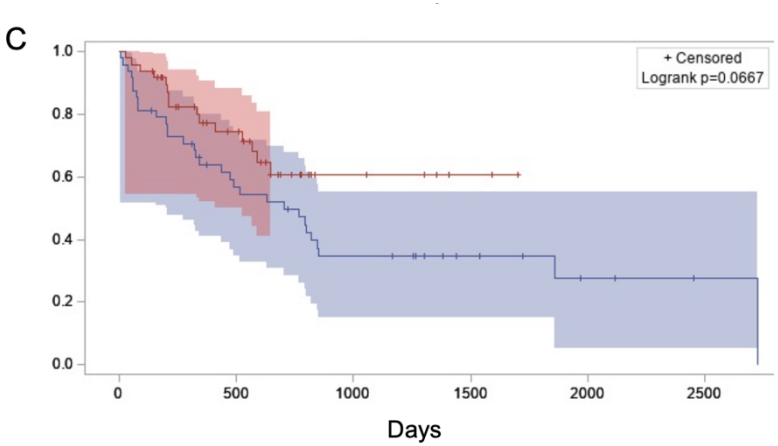	
11	Consultee	Leukaemia Care	We would prefer that this treatment be recommended for baseline commissioning. However, if significant uncertainties remain, we would welcome the CDF as an option for resolving these whilst giving patients access and hope that all parties would work towards achieving this.	Thank you for your comment. Because all of the plausible ICERs were within the range that NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life, the committee recommended venetoclax plus azacitidine as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable. See FAD section 3.11.

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
12	Commentator	Jazz Pharmaceuticals	Jazz agree there is an unmet need for a new treatment option for people with acute myeloid leukaemia for whom intensive chemotherapy is unsuitable. Availability of venetoclax in its licenced indication via the Cancer Drug Fund will be a positive step towards ensuring this treatment option is available for patients.	Thank you for your comment. Because all of the plausible ICERs were within the range that NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life, the committee recommended venetoclax plus azacitidine as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable. See FAD section 3.11.
13	Web comment	NHS Professional	Venetoclax+azacitidine has rapidly become the standard-of-care treatment for patients with AML around the world who are unable to receive intensive chemotherapy. It is an important advance for our older patients for whom our recently completed randomized "pick-a-winner" NCRI LI1 trial (the largest in history) failed to identify any beneficial treatments despite testing many over the best part of a decade. Detailed comments are annotated in the relevant sections but to summarise: 1. This is a biologically distinctive and novel therapeutic advance 2. It produces high rates of MRD negative remission, unlike traditional treatments and approaching levels seen with high dose chemotherapy 3. Emerging data are consistent with a cure in a small proportion of patients, something hitherto not seen with traditional non-intensive treatments 4. Although perhaps not part of NICE's brief, not having venetoclax+azacitidine available as a standard treatment for our older patients will render any future randomized trials in this population virtually impossible in the UK, much to its detriment. • Section 3.4 Comparing venetoclax+azacitidine with 'historical non-intensive treatments' with regard to long-term outcomes is not appropriate. There is biological plausibility that this combination is distinctive as shown in various publications eg Pollyea DA, et al. Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. Nat Med. 2018 Dec;24(12):1859-1866. doi: 10.1038/s41591-018-0233-1. Epub 2018 Nov 12. PMID: 30420752; PMCID: PMC7001730. and Jin S, et al. 5-Azacitidine Induces NOXA to Prime AML Cells for Venetoclax-Mediated Apoptosis. Clin Cancer Res. 2020 Jul 1;26(13):3371-3383. doi: 10.1158/1078-0432.CCR-19-1900. Epub 2020 Feb 13. PMID: 32054729.. Venetoclax+azacitidine has been repeatedly shown to result in high rates of MRD-negative remission (1. Vazquez R, et al. Venetoclax combination therapy induces deep AML remission with eradication of leukemic stem cells and remodeling of clonal haematopoiesis. Blood Cancer J. 2021 Mar 19;11(3):62. doi: 10.1038/s41408-021-00448-w. PMID: 33741892; PMCID:	Thank you for your comment. Because all of the plausible ICERs were within the range that NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life, the committee recommended venetoclax plus azacitidine as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable. See FAD section 3.11.

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
			PMC7979724. 2. Pratz et al. Measurable residual disease response in acute myeloid leukemia treated with venetoclax and azacitidine. https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.7018) This level of MRD negativity is not seen with non-intensive regimens and approaches that seen in the over 60s with intensive chemotherapy protocols. Prolonged remissions have also been shown by several groups in addition to the VIALE-A data, albeit with small numbers, with a plateau in survival at around 3 years, again similar to results with intensive chemo (Cherry E, et al. Venetoclax and Azacitidine Compared to Induction Chemotherapy for Newly Diagnosed Patients with Acute Myeloid Leukemia. Blood Adv. 2021 Oct 5:bloodadvances.2021005538. doi: 10.1182/bloodadvances.2021005538. Epub ahead of print. PMID: 34610123. Vazquez R, et al. Venetoclax combination therapy induces deep AML remission with eradication of leukemic stem cells and remodeling of clonal haematopoiesis. Blood Cancer J. 2021 Mar 19;11(3):62. doi: 10.1038/s41408-021-00448-w. PMID: 33741892; PMCID: PMC7979724. Maiti A, et al. Prognostic value of measurable residual disease after venetoclax and decitabine in acute myeloid leukemia. Blood Adv. 2021 Apr 13;5(7):1876-1883. doi: 10.1182/bloodadvances.2020003717. PMID: 33792630; PMCID: PMC8045494.) A proportion of patients who have stopped treatment are also maintaining long term remissions (Chyn Chua et al, TREATMENT FREE REMISSION (TFR) AFTER CEASING VENETOCLAX-BASED THERAPY IN PATIENTS WITH ACUTE MYELOID LEUKEMIA, EHA2021, abstract EP249) The data are consistent with operational cure in a small proportion of patients and this should be taken into account in the model.	
14	Web comment		• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No. • Section 3.5 - The evidence is too uncertain to include a cure health state in the model "At technical engagement, a professional organisation highlighted a small study by Chyn Chua et al. comparing stopping venetoclax treatment in remission with continuing it until relapse. The results suggested that venetoclax could be stopped after 2 years in remission without a negative impact on outcomes. However, the committee noted that in this study, a number of relapses occurred after 2 years." Re: Potential for treatment-free remission in AML after venetoclax-based therapy As co-authors, we would like to comment on an abstract we recently presented at the European	Thank you for your comment. The FAD has been updated to state that in this study, most of the late relapses were associated with new molecular or cytogenetic abnormalities, suggesting they were not relapses of the original disease. See FAD section 3.5.

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
			Hematology Association meeting in June 2021. Our unit at the Alfred Hospital in Melbourne, Australia, has been treating patients with AML using venetoclax-based therapy since 2014. We therefore have some of the longest follow-up in the world with this group of patients. Based on our extensive experience with this regimen we presented some observations we have made in the EHA meeting abstract. This was based on our experience that some patients were surviving for >5 years, despite ceasing AML treatment several years prior- a highly unusual scenario for elderly AML. Our practice was to cease therapy in patients in remission after receiving at least 12 cycles of therapy, whereas our colleagues at MD Anderson had a practice of continuing therapy until disease progression. We therefore decided to present our clinical experience of 28 patients. Our hypothesis was that for some patients, Ven-based therapy is so effective, that it is possible that some patients may be functionally cured (defined as not relapsing within 5 years of diagnosis). The only way to prove this was cease therapy in some patients and our clinical sense was that this could be possible after 12 months of treatment. Among 14 patients with treatment electively ceased after 12 months, about half have relapsed. The treatment-free remission duration in this group was 45.8 months (95% confidence interval 9.6 months to not reached). 75% of patients were still alive at 36 months, and 29% were alive at 60 months (with an additional 29% alive but not yet reach 60 months) after commencing initial venetoclax-based therapy. As alluded to in the NICE appraisal, patients who ceased therapy did not perform worse than those who continued treatment in our retrospective study, using a landmark analysis starting from 19.0 months after diagnosis, which corresponded to the median time treatment was ceased in the STOP group. This suggests that a proportion of patients may be cured from their initial AML. Of note, a small number of patients in our study did have late relapse and of these, approximately 70% had acquired new cytogenetic and/or molecular abnormalities at time of relapse, suggesting that the relapse leukaemic clone was different to the original AML detected at initial diagnosis. Therefore, we could interpret that such patients actually had a new or therapy-related AML, rather than relapse of their original disease. This may reflect an inherent predisposition to leukaemic re-transformation, as approximately 70% of these patients had a preleukaemic molecular mutation such as DNMT3A, TET2 or ASXL1 persisting during remission. We believe that patients in true CR and with MRD negativity could be candidates for treatment cessation after 12 months, especially if NPM1 or IDH2 mutant, and we are planning a prospective study to address this question. We hope that these comments are useful in NICE's consideration of venetoclax for AML in the U.K.	

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
			Regards Dr Chyn Chua (COI includes travel funding by AbbVie to ASH 2019 conference) Prof Andrew Wei (COI includes honoraria, advisory board participation, consultancy, research funding and royalties in relation to the development of venetoclax from the Walter and Eliza Hall Institute of Medical Research)	
15	Web comment	NHS professional	• Has all of the relevant evidence been taken into account? No, the UK has a large real-world data set for venetoclax based treatments collected during the COVID19 pandemic (n>300), we would be happy to make this available to NICE if that would be helpful. • Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? No, the assumptions regarding cure state are problematic, as discussed below. • Are the recommendations sound and a suitable basis for guidance to the NHS? No, the assumptions regarding cure state are problematic, as discussed below. • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No • Section 3.4 - The evidence is too uncertain to include a cure health state in the model The issues around cure state clearly require further work as both the company position (considering all patients in remission at two years as being cured) and the ERG position (exclusion of the cure state from the model altogether) are overly simplistic and do not reflect the clinical realities of this disease. I was one of the first AML physicians to treat patients with venetoclax in the UK and consequently see a number of patients that have now been in remission for 3-4 years, have been consistently MRD negative and have stopped treatment. These patients are very likely (though not certain) to have been cured. In AML we can never say with 100% certainty that a patient will never relapse, indeed relapses have very rarely been observed 10-20 years out from treatment. Rather what we know is that	Thank you for your comment. Because all of the plausible ICERs were within the range that NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life, the committee recommended venetoclax plus azacitidine as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable. See FAD section 3.11.

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
			the risk of relapse declines very dramatically during the first 2-3 years after treatment for patients in ongoing remission, i.e. the chance of being cured increases very markedly over that period, and then continues to increase further with each further year of follow up. A much more appropriate model would be to consider patients in remission at two years to have a particular chance of being cured (say, 80%) with that figure increasing over time (say, 90% at 3 years, and so on). This would reflect reality much more accurately than either the original base case model or the ERG position. It appears to be the case that patients in particular molecular subgroups (e.g. NPM1, IDH1, IDH2) are more likely to experience cure, however this remains insufficiently defined for inclusion in modelling. Finally in my opinion, most patients will decide to stop treatment after 2 or 3 years especially with emerging evidence showing that this does not particularly effect the risk of relapse, which at that point remains very low.	

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NICE National Institute for Health and Care Excellence

Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

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	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):	**AbbVie**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

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Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

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Name of commentator person completing form:	[redacted]

Comment number	Comments
1	AbbVie have presented a revised economic base case, supporting scenario analyses and further clinical validation to address the Committee's reservations regarding the cure assumption. As the Committee recognised, venetoclax is a promising new treatment which can offer a step change in the management in AML when intensive chemotherapy (IC) is unsuitable, and is now widely recommended as standard of care for these patients around the world, in line with international guidelines.[1, 2] The revised base case includes a 3-year cure timepoint and a reduced dose intensity, in line with the preferences of the Committee and clinical experts. This revised base case is associated with an incremental cost-effectiveness ratio (ICER) well below the willingness-to-pay threshold of £50,000 for medicines which reach the end-of-life criteria and thus demonstrates venetoclax to be a cost-effective use of NHS resources; £26,760 for VenAZA versus AZA in the 20–30% blasts subgroup, £38,900 for VenAZA versus LDAC and £10,948 for VenLDAC versus LDAC in the >30% blasts subgroup. Scenarios were explored where the 'Cure' health state was removed and the proportion of patients remaining in remission in the long term informed by mixture cure modelling, providing validation for the base case approach. A cost-effective treatment that is considered to be standard of care in other geographies should also be routinely commissioned in the UK. AbbVie therefore urge the Committee to reconsider the evidence and work with AbbVie to make venetoclax available for this patient population under routine commissioning.
2	**Further validation demonstrates the cure assumption to be clinically plausible** During the ACM, both clinical experts strongly supported the notion of venetoclax delivering a cure for some patients. During further consultation following the ACM, clinicians have firmly reiterated that in their experience a proportion of patients receiving venetoclax are able to achieve a cure and will therefore require no further treatment. Given this, the company have completed an additional modelling exercise to validate the original cure assumption and reviewed further clinical evidence to support the basis for the cure assumption. The Committee suggested exploring mixture cure models (MCMs) to validate the proportion of patients remaining in the 'Remission' health state over time. The company therefore conducted analyses removing the 'Cure' health state from the model and exploring mixture cure models (MCMs) to extrapolate transitions from the 'Remission' state (time-to-relapse and time-to-death). These two transitions collectively determine the overall rate of transition out of the 'Remission' state, which in turn determines the proportion of patients who remain in the 'Remission' state in the long term. In line with the framework outlined by Lambert *et al.*

	(2007),[3] survival of cured patients was considered to follow the general population mortality as per the England and Wales life tables (2017–19), and the survival of patients who were not cured was estimated using standard parametric survival distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma). Full details of the MCMs explored are presented in Appendix 3, including consideration of statistical fit, visual fit and clinical validation. For VenAZA and VenLDAC in the >30% blasts subgroup, regardless of the MCM curves selected, the proportions of patients predicted by the model to remain in remission through years 2–5 were very similar to those predicted by the company base case submitted at technical engagement, and considerably higher than the revised company base case submitted as part of this response. This is despite the variation in cure fractions observed across models for some of the transitions, providing support for the inclusion of the cure state in the model. In line with feedback from clinical experts, these analyses indicate that the revised company base case (3-year cure point) is conservative, demonstrating the upper limit of uncertainty in terms of the timepoint of the cure assumption. For VenAZA in the 20–30% blasts subgroup, clinical experts did not consider the best fitting extrapolations of time-to-relapse in terms of statistical fit to be plausible (see Figure 2). Similarly, the proportions of the overall cohort predicted to be in the 'Remission' state for this subgroup reflect an ongoing high rate of relapse, and were therefore considered to be implausible, given that the vast majority of relapses are expected to occur before 2–3 years. The Gompertz model was considered to be the only potentially plausible extrapolation of time-to-relapse; when this model is selected, the proportions of the overall cohort predicted to be in the 'Remission' state are similar to the proportions predicted by the revised company base case (3-year cure point), providing support for the inclusion of the cure state in the model. It is also worth noting that clinical experts stated that they would not expect a significant difference in long term survivorship between blast groups for VenAZA (given the arbitrary threshold of 30% blasts), so the differences in proportions of the overall cohort predicted to be in the remission between the 20–30% and >30% blast groups, except when the Gompertz model is selected, are clinically implausible. In these MCMs, a proportion of 'cured' patients (the 'cure fraction') is predicted as an output of the statistical model, based on the inputted clinical data from the VIALE trial populations. However, it should be noted that the need to stratify the VIALE trial populations by blast cell count subgroups results in small numbers of patients and events informing these extrapolations; this is reflected in variation in the predicted cure fractions for several transitions. Reliance on MCMs to predict long-term survival ignores the surrogacy relationship between sustaining CR + CRi and long-term survivorship, relying on limited trial data alone to predict the proportion of 'cured' patients. This increases the uncertainty associated with long-term survival compared to the inclusion of the cure state, which underwent extensive clinical validation. Given that the relationship between sustained CR + CRi and long-term survivorship is clinically established, the inclusion of the cure state is the most appropriate approach to address the uncertainty, and the use of MCMs to extrapolate survival was not considered in the base case. The similarities between the long-term survival estimates predicted by the base case and the MCM scenarios provide strong support that a cure is

Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

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	plausible for patients treated with venetoclax combinations, and thus that it is appropriate to include a cure assumption in the model. The Committee's preference to remove the cure assumption would not reflect the benefit that VenAZA is bringing to patients and the NHS in this indication.
3	**Venetoclax combinations deliver similar clinical outcomes to IC, which has an accepted capacity for cure** The evidence suggests that VenAZA represents a step-change from previous non-intensive treatments and has demonstrated extraordinary clinical outcomes which are aligned to agents with an accepted capacity for cure. Section 3.5 (page 8) of the ACD report states: *"The company stated that the VIALE-A results showed that complete remission rates with venetoclax plus azacitidine were similar to those seen in patients over 60 receiving intensive chemotherapy, and that rates of sustained deep remission were higher with venetoclax plus azacitidine than with azacitidine alone. It argued that it was therefore plausible to assume that patients having venetoclax plus azacitidine could be considered cured."* This explanation of the modelled cure assumption fails to recognise the well-characterised surrogacy relationship between achievement of complete remission (CR + CRi) and long-term survival, on which the cure assumption is built.[4] Disease relapse represents the major cause of treatment failure in adults treated with IC.[4] Furthermore, the majority of patients who relapse do so within the first two years of treatment, and the risk of relapsing is small in those who maintain CR in the long term.[1,5-9] Thus, patients who achieve a deep remission that is sustained for 2–3 years after completion of IC are likely to achieve long-term disease-free survival, which can be considered akin to cure. Clinical experts consulted explained that patients treated with venetoclax combinations who achieve a sustained deep remission have the potential to achieve long-term survivorship and maintain quality of life, whereby their outcomes are in line with those of the general population. VenAZA provides deep and durable complete remission rates (CR + CRi with/without measurable residual disease [MRD]) that have historically only been associated with IC.[10-13] This is supported by the recent review conducted by Short *et al.* (2021), which reports that VenAZA has a longer median survival, and improved two year survival, compared with IC treatments (7+3 regimen and CPX-351).[14] This is despite the fact that patients receiving VenAZA were older and less fit than IC recipients.[14] Considering the high proportions of patients treated with VenAZA who achieve durable CR + CRi, it is plausible that VenAZA can deliver a cure for some patients, similar to that seen in patients treated with IC, and thus it is appropriate to include a 'Cure' health state in the model for those patients who achieve and sustain CR + CRi.
4	**Venetoclax is currently being utilised for patients eligible for IC, who would normally be treated with curative intent**

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	There are currently no consensus guidelines for objectively determining patient eligibility for IC. However, decisions are largely based on assessment of the risk of treatment-related mortality (TRM) by experienced haematologists, based on factors such as age and the presence of comorbidities. Given the established link between CR + CRi and long-term survivorship, a cure assumption should apply regardless of ability to tolerate IC due to risk factors for TRM, provided that equivalent CR + CRi outcomes are observed across treatments. Rather, as stated in the company submission, there are currently no curative treatment options available for patients who are not able to tolerate IC. The current NHS England interim treatment policy (NG161) has provided access to venetoclax combinations in those patients who would normally be eligible to receive IC, in order to prevent prolonged hospitalisation during the COVID-19 pandemic.[15] This guidance states that treatment with venetoclax can allow these patients to achieve remission rates (CR + CRi) which parallel those achieved in older patients treated with IC. Therefore, venetoclax is currently being utilised in the NHS for patients who would normally be treated with curative intent, and it is therefore appropriate to conclude that patients who are ineligible for IC could also achieve a cure with venetoclax provided they achieve equivalent CR + CRi outcomes (which have been clearly demonstrated in the VIALE-A trial).[16]
5	**Acceptance of a less conservative cure assumption in the gilteritinib appraisal (TA642) is relevant to this appraisal** The Company disagree with the Committee's assertion that the gilteritinib appraisal (TA642) is not relevant to this appraisal because it was conducted in a different population.[17] Whilst these populations do differ, as patients in TA642 had relapsed or refractory AML and a proportion of patients received a stem cell transplant (SCT), SCT was not a condition of cure in the model, and it was assumed that all patients who were alive at 3 years were 'cured'. Furthermore, the population included in the gilteritinib appraisal (relapsed or refractory AML) represents a population who may have poorer prognosis than the population in this appraisal (untreated AML). Given the evidence presented in this response, it would be inconsistent to dismiss the possibility of a cure assumption in the population of relevance in this appraisal when a cure was previously accepted in a relapsed refractory AML population with a poorer prognosis. It is also important to note that, based on clinical feedback, the cure assumption modelled in this appraisal is more conservative than the cure assumption applied in TA642, with cure only possible for those patients who achieve and sustain CR + CRi.
6	**The revised Company base case assumption regarding the timepoint of cure** The company acknowledge that there was some discussion amongst clinical experts regarding the timepoint of the cure assumption, specifically that clinical experts suggested the timepoint of the cure assumption may be closer to three years. However, it is important to note that clinical experts were all strongly supportive of potential for cure for patients with long term CR +CRi, and their uncertainty focused entirely on the timing of the cure assumption. As described in Section 3.3.5 of the company submission, two years was initially selected as the cure timepoint in the original company base case as the rate of relapse after two years is

	low (based on experience of patients treated with IC).[1,5-9, 18, 19] Furthermore, this corroborates the plateau in the VIALE-A Kaplan–Meier curves which is observed at ~24 months of treatment for VenAZA (in 20–30% and >30% blast populations).[16] However, the company acknowledge the discussion surrounding the timepoint of the cure assumption, and in line with feedback from clinical experts during the ACM, a 3-year cure timepoint has been included in the revised base case. This is considered to demonstrate the upper limit of uncertainty in terms of the timepoint of the cure assumption. Moving the cure timepoint to three years increases the ICER, however this remains comfortably below the cost-effectiveness threshold of £50,000 for end-of-life treatments; £28,736 for VenAZA versus AZA in the 20–30% blasts subgroup, £40,094 for VenAZA versus LDAC and £11,368 for VenLDAC versus LDAC in the >30% blasts subgroup. When the 3-year cure point is applied, the proportions of patients predicted to enter the cure state are [redacted]% for VenAZA in the 20–30% blasts subgroup, [redacted]% and [redacted]% for VenAZA and VenLDAC in the >30% blasts subgroup. These predictions are lower than those when the 2-year cure point is applied: [redacted]% for VenAZA in the 20–30% blasts subgroup, [redacted]% and [redacted]% for VenAZA and VenLDAC in the >30% blasts subgroup. Feedback from clinical experts suggested that predictions for the 3-year timepoint are lower than would be expected in clinical practice. However, the company has aligned with the feedback received during the ACM and adopted the 3-year cure timepoint as a conservative assumption in the revised base case. Venetoclax remains a cost-effective use of NHS resources with this conservative assumption adopted, which should mitigate the Committee's concerns surrounding the cure assumption.
7	**Venetoclax remains cost-effective when the assumptions around relapse are varied** Whist the Chyn Chua *et al.* (2021) study provides a supportive result for the continued efficacy of venetoclax post-discontinuation, the company believe that this study is inappropriate to inform reimbursement decision-making due to a number of substantial limitations.[20] This retrospective study included a very small sample size (n=28), and thus considerable uncertainty remains regarding the generalisability of this study to wider real-world practice. It should also be noted that this study was not designed to investigate the impact of time in CR + CRi on relapse. Following the ACM, the company conducted discussions with the authors, who explained that this study was designed to provide clinicians with evidence to inform discussions with patients upon intent to discontinue treatment. As such, the timing of treatment discontinuation was based on patient request and not necessarily determined by the time in which the patient had been in complete remission, as would be the case in clinical practice. Therefore, this study should not be used to validate the cure assumption or be used to inform decision-making. Furthermore, it was explained that the late relapses observed in the Chyn Chua *et al.* (2021) study were often new and distinct forms of AML, rather than a relapse of the original disease. This new phenomenon is thought to be observed due to the increased survival length of AML patients treated with venetoclax, and this should not be considered to be a failure of the treatment. Moreover, in general the recording of outcomes as

part of a retrospective study is less robust than that of randomised control trials (RCTs) such as the VIALE trials, and the preference for RCTs is stated by NICE.[21] Therefore, the clear post 24-month plateau in survival observed in VIALE-A,[16] the low rate of relapse observed after two years in IC patients,[1,5-9] and clinical expert feedback stating that the vast majority of relapses occur before two years should supersede the findings of this study.[16]

The company believes that RCT evidence, clinical opinion, continuous model validation, and published literature submitted as part of this appraisal should act as the guide for robust reimbursement decision-making and inform any assumptions around the curative properties of venetoclax in older AML patients with comorbidities. Any real-world evidence (RWE) evidence endorsed as part of this appraisal should incorporate a substantially larger sample size, and have clear recruitment criteria and treatment aims that fully align with the gold standard pivotal venetoclax trials in AML (VIALE-A and VIALE-C).

As correctly stated by the Committee, the company's base case model did not permit any relapse to occur after two years. This approach was deemed appropriate given the vast majority of relapses occur before this timepoint, as shown in Figure 1 (adapted from Yanada *et al.* [2007]), which reports on treatment failure following achievement of CR in 1,069 patients receiving a variety of therapies but who had not undergone SCT.[22]

Figure 1: Proportion of AML patients relapsing after achieving first CR

Footnotes: Figure adapted from Yanada *et al.* (2021),[22] calculated as the number of relapses reported within each timeframe as a proportion of the total number of relapses.
Abbreviations: CR: complete remission.

However, as late-stage relapse may occur in a small minority of patients, further scenario analyses have been conducted in which only a proportion of patients in the 'Remission' health state transition to the 'Cure' state following the cure timepoint. Patients remaining in the 'Remission' health state continue to experience the risk of relapse and death as determined by the extrapolated time-to-relapse/death data, not general population mortality. Clinical expert opinion suggested that, of those patients who sustain CR + CRi for 2 years, approximately 20% may experience late relapses, with the vast majority of these relapses occurring between 2 and 3 years. This is supported by findings from Yanada *et al.* (2007),

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	which show that 10.5% of recurrences occurred after 2 years in CR and just 3.3% of recurrences occurred after 3 years in CR. Out of a cohort of 1,069 patients with AML, this provides robust evidence that the risk of relapse after 3 years is negligible. Considering the evidence, a scenario was explored where 90% of patients in remission at three years transition into the 'Cure' state (Appendix 2), with the remaining patients continuing to transition to the 'Relapse/PD' and 'Death' states from the 'Remission' state according to the selected time-to-relapse and time-to-death curves. Scenarios were also explored in which 80% and 70% of patients in remission transition into the 'Cure' state at two years. All ICERs remain comfortably below the cost-effectiveness threshold of £50,000 for end-of-life treatments, ranging from £18,813–£28,736 for VenAZA versus AZA in the 20–30% blast subgroup, £35,469–£40,094 for VenAZA versus LDAC and £9,383–£11,368 for VenLDAC versus LDAC in the >30% blasts subgroup.
8	**Venetoclax remains cost-effective when utility in the 'Cure' state is informed by the VIALE trial data for patients in remission (CR + CRi)** On page 11 of the ACD document, clinical experts highlighted *"that many people would return to the same quality of life after treatment as could be expected in the general population, but that some would not."* Based on feedback from clinical experts, patients who reside within the 'Cure' state were assumed to receive the utility of the general population, given the substantial transfusion-independence benefit associated with CR + CRi, allowing patients to return to normal life. The company would also like to highlight that a scenario was requested by the ERG at the clarification question stage to assume patients in the 'Cure' health state have the same utility as patients in the 'Remission' health state (where utility was informed by data for patients in CR + CRi from the VIALE trials), given the uncertainty surrounding the assumption that patients in the cure state experience the same quality of life as the general population. As stated in the company response to the ERG clarification questions, there are only small numerical differences between the utility values describing the remission health state and the cure health state. Given patients have a mean age of [redacted] years at the original 2-year cure point, the age-adjusted general population utility of 0.7465 is always less than that of the remission health state utility of [redacted]. Therefore, when applying the 'Remission' health state utility to patients in the 'Cure' state capped by the utility of the general population, there were only minor changes in inputs. This minor deviation in the utility, in addition to rounding, has no impact on cost-effectiveness outcomes.
9	**The revised Company base case algins with the Committee's preferences regarding the dose intensity of venetoclax** On page 11 of the ACD document, the Committee state: "*in clinical practice in England, almost all patients with acute myeloid leukaemia would have concomitant treatment with azoles such as posaconazole as antifungal prophylaxis. Azoles are strong CYP3A inhibitors,*

	which affects the metabolism of venetoclax and increases its plasma level. Therefore, in line with the summary of product characteristics advice on managing potential venetoclax interactions with CYP3A inhibitors, the dose of venetoclax used in clinical practice would be much lower than in the trial, usually 100 mg a day rather than 400 mg". Clinical expert feedback during the ACM, and guidance from the NHS England interim treatment policy (NG161), recommends a dose intensity of 25% in cycle 1 (i.e. 100 mg a day rather than 400 mg) in combination with a strong CYP3A inhibitor, which can potentially drop to 12.5% from cycle 2 onwards (i.e. 100 mg on days 1–14).[15] Therefore, in line with the Committee's preferences, and in order to accurately reflect the dose of venetoclax that may be used in clinical practice, a dose intensity of 25% in the first cycle, followed by 12.5% from cycle 2 onwards, has been modelled for the venetoclax component of VenAZA. Similarly, a dose intensity of 16.7% in the first cycle (i.e. 100 mg rather than the full 600 mg dose), followed by 8.3% (i.e. 100 mg on days 1–14) from cycle 2 onwards, has been modelled for the venetoclax component of VenLDAC. Whilst the company acknowledge that a dose intensity as low as 12.5% after the first cycle was received by some patients in clinical practice during the interim COVID-19 policy, additional clinical expert opinion sought after the ACM has reiterated that the required dose is ultimately dependent on the duration of treatment with concomitant strong/moderate CYP3A inhibitors, and dose interruptions required to manage cytopenia, and thus there might be some variation in clinical practice. For completeness, a conservative scenario was explored where dose intensity was aligned with the assumptions made in the original appraisal (Appendix 2); ICERs remain below the cost-effectiveness threshold of £50,000 for end-of-life treatments. It is important to note that patients receiving a 100 mg venetoclax daily dose in combination with azoles are not expected to experience any reduction in efficacy compared to patients receiving a 400 mg daily dose. This is because azoles are strong CYP3A inhibitors, and as such increase venetoclax drug exposure when administered concomitantly. A pharmacokinetic study has demonstrated that a 100 mg venetoclax dose administered in combination with a strong CYP3A inhibitor produces a drug exposure between that of venetoclax (alone) at the therapeutic dose of 400 mg once daily, and the established safe maximal administered dose of 1,200 mg once daily (as measured by the area under a drug concentration-time curve over the 24 hour dosing period [AUC_{24}]).[23] Post-hoc analysis of data from VIALE-A has demonstrated that rates of CR + CRi as a best response were similar with concomitant use of moderate (61%) and strong (64%) CYP3A inhibitor with adjusted-dose venetoclax versus no use of CYP3A inhibitor (67%).[24] Furthermore, cytopenia within the VIALE-A trial was successfully managed using dose modifications of venetoclax, including cycle delays and reduction in the number of dosing days within cycle.[25, 26] Additional UK RWE for patients receiving VenAZA or VenLDAC (N=301) via the COVID interim treatment policy found that 81% of patients received a 100 mg dose of venetoclax with concomitant use of a strong CYP3A inhibitor, and amongst this cohort 70% of patients achieved CR + CRi and median OS was 12.8 months (95% CI: 10.9, NR). Median follow-up was 8.2 months (95% CI: 7.8, 9.0).[27] Taken together, these data provide strong evidence that

	reduced dose intensity in real world use should not substantially impact on the efficacy of venetoclax.

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Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

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Appendix 1: Updates to company base case

The following updates were made in the revised company base case post ACD, in line with feedback from the Committee and clinical experts during the ACM:

- Inclusion of the 'Cure' state with a 3-year cure point, given the vast majority of relapses occur prior to 3 years, in line with the extensive rationale provided in this response and advice received during the ACM

- Based on feedback receiving during the ACM, a dose intensity of 25% in the first cycle, followed by 12.5% from cycle 2 onwards, has been modelled for the venetoclax component of VenAZA. Accordingly, a dose intensity of 16.7% in the in the first cycle (i.e. 100 mg, as opposed to the full 600 mg dose), followed by 8.3% (i.e. 100 mg on day 1–14) from cycle 2 onwards, has been modelled for the venetoclax component of VenLDAC

The following updates were made in the revised company base case (and all scenarios presented in Appendix 2) in line with the ERG's feedback on the company Technical Engagement Response:

- Subsequent treatment cost of AZA/LDAC treatment arms corrected to £563.06 from £536.06 as per the ERG's preference

- Alternate adverse event costs applied to company base case and subsequent ERG scenarios account for long-stay admissions for atrial fibrillation, dyspnoea, febrile neutropenia, pyrexia and sepsis in response to clarification queries

The updated company base case following the ACD response, incorporating the above changes, is presented in Table 1 and Table 2 for 20–30% blasts and >30% blasts respectively. The ICERs demonstrate that venetoclax is a cost-effective use of NHS resources at a £50,000 willingness-to-pay threshold.

Table 1: Revised company base case results for VenAZA versus AZA 20–30% blasts at Ven PAS price (deterministic)

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Company base case post Technical Engagement	[redacted]	[redacted]	£25,074
Revised company base case post ACD	[redacted]	[redacted]	£26,760

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; Ven: venetoclax.

Table 2: Revised company base case results for >30% blasts at Ven PAS price (deterministic)

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
VenAZA versus LDAC			
Company base case post Technical Engagement	[redacted]	[redacted]	£41,557
Revised company base case post ACD	[redacted]	[redacted]	£38,900
VenLDAC versus LDAC			

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Company base case post Technical Engagement	[redacted]	[redacted]	£36,652
Revised company base case post ACD	[redacted]	[redacted]	£10,948

[a] Includes the additional corrections suggested by the ERG (See Appendix 1).
Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; LDAC: low dose cytarabine QALY: quality-adjusted life year; Ven: venetoclax.

Table 3: Revised company base case results for 20–30% blasts subgroup: Proportion cured

Intervention	Proportion of overall cohort receiving VenAZA	Year in model			
		2	3	4	5
Company base case post TE (2-year cure point)	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case post ACD (3-year cure point)	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Table 4: Revised company base case results for >30% blasts subgroup: Proportion cured

Intervention	Proportion of overall cohort receiving VenAZA/VenLDAC	Year in model			
		2	3	4	5
VenAZA					
Company base case post TE (2-year cure point)	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case post ACD (3-year cure point)	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]
VenLDAC					
Company base case post TE (2-year cure point)	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case post ACD (3-year cure point)	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; Ven: venetoclax.

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Appendix 2: Additional scenario analysis results

Cure proportion analysis

Based on feedback from the Committee surrounding the possibility of relapse after 2 years in remission, scenario analyses have been explored varying the proportion of patients in CR + CRi who transition to the cure state at a two-year and three-year cure point. The results of the scenario analyses are presented in Table 5 to Table 12. Venetoclax combinations remain cost-effective in all scenarios.

2-year cure timepoint

The results of the scenario analyses varying the proportion cured at 2 years in remission are presented in Table 5 to Table 8. The results of the scenario analyses show that when 80% or 70% of patients in remission at 2 years are assumed to be cured, venetoclax is comfortably below the £50,000 willingness-to-pay threshold in all blast count subgroups.

Table 5: Cost-effectiveness results from scenario analyses – impact of alternative cure proportion at 2 years in remission for VenAZA versus AZA 20–30% blasts at Ven PAS price

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cure proportion: 80%	[redacted]	[redacted]	£18,813
Cure proportion: 70%	[redacted]	[redacted]	£21,437

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; Ven: venetoclax.

Table 6: Results from scenario analyses – impact of alternative cure proportion at 2 years in remission for 20–30% blasts at Ven PAS price: Proportion cured

Intervention	Proportion of overall cohort receiving VenAZA	Year of the model			
		2 (cure point)	3	4	5
Cure proportion: 80%	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]
Cure proportion: 70%	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Table 7: Cost-effectiveness results from scenario analyses – impact of impact of alternative cure proportion at 2 years in remission for >30% blasts at Ven PAS price

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
VenAZA versus LDAC			
Cure proportion: 80%	[redacted]	[redacted]	£35,469
Cure proportion: 70%	[redacted]	[redacted]	£36,908

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VenLDAC versus LDAC			
Cure proportion: 80%	[redacted]	[redacted]	£9,383
Cure proportion: 70%	[redacted]	[redacted]	£10,146

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; LDAC: low dose cytarabine; QALY: quality-adjusted life year; Ven: venetoclax.

Table 8: Results from scenario analyses – impact of alternative cure proportion at 2 years in remission for >30% blasts at Ven PAS price: Proportion cured

Intervention	Proportion of overall cohort receiving VenAZA/VenLDAC	Year of the model			
		2 (cure point)	3	4	5
VenAZA					
Cure proportion: 80%	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]
Cure proportion: 70%	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]
VenLDAC					
Cure proportion: 80%	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]
Cure proportion: 70%	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; LDAC: low dose cytarabine; Ven: venetoclax.

3-year cure timepoint

The results of the scenario analyses varying the proportion cured at 3 years in remission are presented in Table 9 to Table 12. The results of the scenario analyses show that when 90% of patients in remission at 3 years are assumed to be cured (note this proportion is higher than those explored at 2 years, given relapses after 3 years in remission are extremely rare), venetoclax is still cost-effective at a £50,000 willingness-to-pay threshold.

Table 9: Cost-effectiveness results from scenario analyses – impact of alternative cure proportion at 3 years in remission for VenAZA versus AZA 20–30% blasts at Ven PAS price

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Cure proportion: 90%	[redacted]	[redacted]	£28,736

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; Ven: venetoclax.

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Table 10: Results from scenario analyses – impact of alternative cure proportion at 3 years in remission for 20–30% blasts at Ven PAS price: Proportion cured

Intervention	Proportion of overall cohort receiving VenAZA	Year of the model			
		2	3 (cure point)	4	5
Cure proportion: 90%	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Table 11: Cost-effectiveness results from scenario analyses – impact of alternative cure proportion at 3 years in remission for >30% blasts at Ven PAS price

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
VenAZA versus LDAC			
Cure proportion: 90%	[redacted]	[redacted]	£40,094
VenLDAC versus LDAC			
Cure proportion: 90%	[redacted]	[redacted]	£11,368

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; LDAC: low dose cytarabine QALY: quality-adjusted life year; Ven: venetoclax.

Table 12: Results from scenario analyses – impact of alternative cure proportion at 3 years in remission for >30% blasts at Ven PAS price: Proportion cured

Intervention	Proportion of overall cohort receiving VenAZA/VenLDAC	Year of the model			
		2	3	4	5
VenAZA versus LDAC					
Cure proportion: 90%	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]
VenLDAC versus LDAC					
Cure proportion: 90%	In the 'cure' state	[redacted]	[redacted]	[redacted]	[redacted]
	Remaining in the 'remission' state	[redacted]	[redacted]	[redacted]	[redacted]
	In CR + CRi (across cure/remission states)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Dose intensity

For completeness, a conservative scenario has been explored where the original dose intensity assumptions are applied (50% in all cycles for the venetoclax component of VenAZA, and [redacted]% in all cycles for the venetoclax component of VenLDAC).

Table 13: Cost-effectiveness results from scenario analyses – dose intensity assumptions

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)

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VenAZA versus AZA (20–30% blasts)	[redacted]	[redacted]	£40,433
VenAZA versus LDAC (>30% blasts)	[redacted]	[redacted]	£49,044
VenLDAC versus LDAC (>30% blasts)	[redacted]	[redacted]	£47,835

Abbreviations: AZA: azacitidine; ICER: incremental cost-effectiveness ratio; LDAC: low-dose cytarabine; QALY: quality-adjusted life year; Ven: venetoclax.

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Appendix 3: Mixture cure models

Time-to-event data informing health state transitions

As described in Section B.3.3.3 of the company submission, the proportions of patients remaining in the 'Remission' or 'Non-remission' heath states, or transitioning to the 'PD/relapse' or 'Death' state at each monthly model cycle were based on time-dependent hazards derived from time-to-event data from the VIALE-A and VIALE-C trials.[16, 28] The hazard at any one time point is calculated using the following formula:

$$h_{(t)} = \frac{S_{(t-1)} - S_{(t)}}{S_{(t-1)}}$$

The EFS outcome collected in the trials does not distinguish between events of progression, relapse or death. In order to isolate the risk of PD/relapse and death independently, events were defined separately for the transitions to the 'PD/relapse' and 'Death' health states to capture the specific hazard reflected in each transition. Definitions of events were complementary, such that events included in one transition were censored in the other and vice versa, in order to avoid double counting. Time-to-relapse and time-to-PD were used to define transitions from 'Remission' and 'Non-remission' to 'PD/relapse', respectively. Relapse and PD were captured as events for time-to-relapse and time-to-PD, respectively, and patients who experienced death events or who were lost to follow-up were censored. Time-to-death data were used to inform transitions from 'Remission' and 'Non-remission' to 'PD/relapse' health states to 'Death'. For time-to-death, death was captured as an event, and patients who experienced PD, relapse or who were lost to follow-up were censored. The time-to-event data used to inform health state transitions in the model are presented in Table 14.

Table 14: Summary of time-to-event data informing health state transitions

Transition	Eligible patient population	Index time	Event	Censor[a]
Non-remission to PD	Patients who did not achieve CR + CRi	Randomisation	Confirmed MR/PD or treatment failure	Death or last follow-up
Non-remission to Death			Death	Confirmed MR/PD, treatment failure or last follow-up
Remission to relapse	Patients who achieved CR + CRi	First date of CR + CRi	Confirmed MR/PD or treatment failure	Death or last follow-up
Remission to Death			Death	Confirmed MR/PD, treatment failure or last follow-up
PD/relapse to Death	Patients who had confirmed morphologic relapse (MR)[b], progressed disease (PR), or treatment failure	Time of confirmed MR/PD or treatment failure	Death	Last follow-up

Footnotes: [a] Censoring occurs when patients who experience an event not captured by the transition are censored, this allows the model to capture the risk of PD and death independently of each other without double counting. [b] Morphologic relapse is defined by the IWG as reappearance of ≥5 blasts after CR + CRi in the peripheral blood or bone marrow or development of extramedullary disease.

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Abbreviations: CR: complete remission; CRi: complete remission with incomplete recovery; MR: morphologic relapse; PD: progressed disease.

Mixture cure models

As reported in Section B.3.3.4 of the company submission, a range of standard parametric distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma) were explored for extrapolation.[29] More advanced statistical techniques (e.g. spline) outlined in the NICE DSU 21 were deemed inappropriate due to the large degree of uncertainty associated with small sample sizes in the blast count subgroups.[30] The choice of parametric survival curves was deemed sufficient to capture the long-term survival of patients beyond the follow up of the trials, when combined with the cure assumption, whereby patients receiving VenAZA or VenLDAC who are in the 'Remission' health state after 2 years (27 model cycles) were cured and thus transitioned to the 'Cure' health state.

Mixture cure models (MCMs) represent an alternative approach to survival analysis that can potentially account for more complex hazard functions in a manner that also reflects an underlying clinical process. Such models can be used where there is evidence to support that a proportion of the population treated with the intervention can be considered to be 'cured' (the 'cure fraction'). The cure fraction can be interpreted as a proportion of the population who would only be subject to background mortality (i.e. natural mortality of general population). This is reflected in the parameterisation of the mixture cure model, which models the population as a mixture of two subpopulations: one representing cured patients (the cure fraction), who are at the same risk of death as the general population, and one representing non-cured patients, who are at a risk of death as defined by a parametric survival model.

In line with the comments from the Committee, the company considered removing the 'Cure' health state from the model and exploring MCMs to extrapolate transitions in the long term, in order to further validate the cure assumption. As per the assumption in the original appraisal, it was assumed that cure was only possible for those who achieved remission, and thus MCMs were only explored to extrapolate transitions from the 'Remission' state (time-to-relapse and time-to-death, as per Table 14). As per the original submission, current non-intensive treatments are not used with curative intent in clinical practice, and therefore it is not clinically plausible to explore MCMs for patients receiving AZA and LDAC.[31, 32]

In line with the framework outlined by Lambert *et al.* (2007), MCMs took the following form:[3]

$$S(t) = \pi + (1 - \pi) S_u t$$

Where π is the proportion cured and $S_u(t)$ is the survival function for the uncured individuals. The R *flexsurvcure* package was used for parameterisation. Survival of cured patients was considered to follow the general population mortality as per the England and Wales life tables (2017–19). The survival of patients who were not cured was estimated using standard parametric survival distributions (exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma).

When considering the clinical plausibility of the survival curves and cure fractions, it is important to bear in mind that patients can transition out of the 'Remission' state due to relapse *or* due to death events, but these events are captured by independent transitions (as described in Table 14) that are not reflected in the survival curves of the individual events. Collectively, these two transitions determine the overall rate of transition out of

the 'Remission' state, which in turn determines the health state distribution over time, but the presented survival curves correspond to the individual events in isolation.

VenAZA in 20–30% blasts

The time-to-event data informing transitions from the 'Remission' state for VenAZA in the 20–30% blasts group are presented in Table 15.

Table 15: Time to event data informing transitions from the 'Remission' state for VenAZA in 20–30% blasts

Transition	Event type	N	Events	Censors
Remission to relapse	Relapse	[redacted]	[redacted]	[redacted]
Remission to death	Death	[redacted]	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Remission to relapse transition (time-to-relapse)

The results of the mixture cure models for the remission to relapse transition are presented below, including the extrapolations of six mixture cure models, cure fractions and the AIC/BIC values showing statistical fit. The Weibull and generalized gamma models provided a poor visual fit to the observed data, failing to capture the tail observed in the Kaplan–Meier curve. The exponential model also failed to capture the general shape of the observed data. There is also substantial variation in the predicted cure fractions ([redacted]% to [redacted]%), with the majority of models predicting a cure fraction under [redacted]%. Clinical experts consulted as part of this response did not consider these low cure fractions to be clinically plausible for VenAZA in this 20–30% blasts group, particularly given the high cure fractions observed for the time-to-death transition in this subgroup and the consistent cure fractions observed in the >30% blasts subgroup. The high variation in cure fraction is likely driven by the very small number of patients and events informing these transitions (see Table 15) given the need to explore blast-restricted subgroups, suggesting there are not sufficient data for MCMs to produce reliable long-term extrapolations in this subgroup.

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Figure 2: Overlay of KM versus 6 mixture cure models for time-to-relapse from the 'Remission' state: VenAZA in 20–30% blasts (mixture cure models)

Abbreviations: AZA: azacitidine; KM: Kaplan-Meier; Ven: venetoclax.

Table 16: Summary of goodness-of-fit data for extrapolations of time-to-relapse from the 'Remission' state for VenAZA in 20–30% blast (mixture cure models)

Distribution	Cure rate	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; UK: United Kingdom; Ven: venetoclax.

Remission to death transition (time-to-death)

The results of the mixture cure models for the remission to death transition are presented below, including the extrapolations of six mixture cure models, cure fractions and the AIC/BIC values showing statistical fit. With the exception of the generalized gamma model which did not converge, all models produced very similar long-term predictions and provided reasonable visual fit to the observed data, with high and consistent cure fractions.

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Figure 3: Overlay of KM versus 6 mixture cure models for time-to-death from the 'Remission' state: VenAZA in 20–30% blasts (mixture cure models)

Abbreviations: AZA: azacitidine; KM: Kaplan-Meier; Ven: venetoclax.

Table 17: Summary of goodness-of-fit data for the extrapolations of time-to-death from the 'Remission' state for VenAZA in 20–30% blast (mixture cure models)

Distribution	Cure rate	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit. [b] Generalised Gamma model couldn't converge and was not included in the table.

VenAZA in >30% blasts

The time-to-event data informing transitions from the 'Remission' state for VenAZA in the >30% blasts group are presented in Table 18.

Table 18: Time to event data informing transitions from the 'Remission' state for VenAZA in >30% blasts

Transition	Event type	N	Events	Censors

Remission to relapse	Relapse	[redacted]	[redacted]	[redacted]
Remission to death	Death	[redacted]	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Remission to relapse transition (time-to-relapse)

The results of the mixture cure models for the remission to relapse transition are presented below, including the extrapolations of six mixture cure models, cure fractions and the AIC/BIC values showing statistical fit. With the exception of the exponential model, all models provided reasonable visual fit to the observed data. There was some variation in cure fraction, but the three best fitting models according to AIC and BIC produced similar long-term extrapolations, and consistent cure fractions.

Figure 4: Overlay of KM versus 6 mixture cure models for time-to-relapse from the 'Remission' state: VenAZA in >30% blasts (mixture cure models)

Abbreviations: AZA: azacitidine; LDAC: low dose cytarabine; KM: Kaplan-Meier; Ven: venetoclax.

Table 19: Summary of goodness-of-fit data for extrapolations of time-to-relapse from the 'Remission' state for VenAZA in >30% blasts (mixture cure models)

Distribution	Cure rate	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; UK: United Kingdom; Ven: venetoclax.

Remission to death transition (time-to-death)

The results of the mixture cure models for the remission to death transition are presented below, including the extrapolations of six mixture cure models, cure fractions and the AIC/BIC values showing statistical fit. All models provided reasonable visual fit to the observed data, with the exponential and Gompertz model most closely following the observed plateau. There was substantial variation in the predicted cure fraction.

Figure 5: Overlay of KM versus 6 mixture cure models for time-to-death from the 'Remission' state: VenAZA in >30% blasts (Mixture cure models)

Abbreviations: AZA: azacitidine; LDAC: low dose cytarabine; KM: Kaplan-Meier; Ven: venetoclax.

Table 20: Summary of goodness-of-fit data for the extrapolations of time-to-death from the 'Remission' state for VenAZA in >30% blasts (mixture cure models)

Distribution	Cure rate	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; UK: United Kingdom; Ven: venetoclax.

VenLDAC in >30% blasts

The time-to-event data informing transitions from the 'Remission' state for VenLDAC in the >30% blasts group are presented in Table 21.

Table 21: Time to event data informing transitions from the 'Remission' state for VenLDAC in >30% blasts

Transition	Event type	N	Events	Censors
Remission to relapse	Relapse	[redacted]	[redacted]	[redacted]
Remission to death	Death	[redacted]	[redacted]	[redacted]

Abbreviations: AZA: azacitidine; Ven: venetoclax.

Remission to relapse transition (time-to-relapse)

The results of the mixture cure models for the remission to relapse transition are presented below, including the extrapolations of six mixture cure models, cure fractions and the AIC/BIC values showing statistical fit. All models provided reasonable visual fit to the observed data. There was some variation in cure fraction, but the three best fitting models according to AIC and BIC produced similar long-term extrapolations and consistent cure fractions.

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Figure 6: Overlay of KM versus 6 mixture cure models for time-to-relapse from the 'Remission' state: VenLDAC in >30% blasts (mixture cure models)

Abbreviations: AZA: azacitidine; LDAC: low dose cytarabine; KM: Kaplan-Meier; Ven: venetoclax.

Table 22: Summary of goodness-of-fit data for the extrapolations of time-to-relapse from the 'Remission state' for VenLDAC in >30% blasts (mixture cure models)

Distribution	Cure rate	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; UK: United Kingdom; Ven: venetoclax.

Remission to death transition (time-to-death)

The results of the mixture cure models for the remission to death transition are presented below, including the extrapolations of six mixture cure models, cure fractions and the AIC/BIC values showing statistical fit. With the exception of the exponential model, all models provided reasonable visual fit to the observed data. There was some variation in cure fraction, but the three best fitting models according to AIC and BIC produced similar long-term extrapolations and consistent cure fractions.

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Figure 7: Overlay of KM versus 6 mixture cure models for time-to-death from the 'Remission' state: VenLDAC in >30% blasts (Mixture cure models)

Abbreviations: AZA: azacitidine; LDAC: low dose cytarabine; KM: Kaplan-Meier; Ven: venetoclax.

Table 23: Summary of goodness-of-fit data for extrapolations of time-to-death from the 'Remission' state for VenLDAC in >30% blasts (Mixture cure models)

Distribution	Cure rate	AIC[a]	AIC rank	BIC[a]	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] A small AIC or BIC value represents a better goodness of fit.
Abbreviations: AIC: Akaike information criterion; AZA: azacitidine; BIC: Bayesian information criterion; UK: United Kingdom; Ven: venetoclax.

Results

As described above, patients can transition out of the 'Remission' state due to relapse *or* due to death events, but these events are captured by independent transitions that are not reflected in the survival curves of the individual events presented above. Collectively, these two transitions determine the overall rate of transition out of the 'Remission' state, which in turn determines the health state distribution over time. In order to validate the long-term outcomes, scenario analyses were therefore explored where transitions from the

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'Remission' state and the resulting health state distribution in the cost-effectiveness model were informed by combinations of the three best statistically fitting extrapolations of time-to-relapse and time-to-death based on AIC/BIC. The Gompertz model was also explored for time-to-relapse in the 20–30% blasts subgroup, given all other models were considered to be implausible by clinical experts. The proportions of the overall cohort predicted to be in the 'Remission' state between two and five years based on these extrapolations are presented in Table 24, alongside the proportion of patients predicted to be in remission in the company base case post technical engagement and the revised company base case submitted as part of this ACD response.

For VenAZA in the 20–30% blasts subgroup, clinical experts did not consider the best fitting extrapolations of time-to-relapse in terms of statistical fit to be plausible. Similarly, the proportions of the overall cohort predicted to be in the 'Remission' state for this subgroup (Table 24) reflect an ongoing high rate of relapse, and were therefore considered to be implausible, given that the vast majority of relapses are expected to occur before 2–3 years. The Gompertz model was considered to be the only potentially plausible extrapolation of time-to-relapse; when this model is selected, the proportions of the overall cohort predicted to be in the 'Remission' state are similar to the proportions predicted by the revised company base case (3-year cure point), providing support for the inclusion of the cure state in the model.

For VenAZA and VenLDAC in the >30% blasts subgroup, all MCMs explored produced very similar proportions of patients remaining in the 'Remission' state between two and five years compared with the company base case post technical engagement, and considerably higher predictions than the revised company base case submitted as part of this response. This is despite the variation in cure fractions observed across models for some of the transitions, providing support for the inclusion of the cure state in the model. In line with feedback from clinical experts, these analyses indicate that the revised company base case (3-year cure point) is conservative, demonstrating the upper limit of uncertainty in terms of the timepoint of the cure assumption.

Whilst these analyses provide support for the original cure assumption, the use of MCMs to extrapolate survival was not considered in the base case, given the variation in cure fractions observed for some transitions and the small patient and event numbers informing these transitions. This would increase the uncertainty associated with long-term survival compared to the inclusion of the cure state, which underwent extensive clinical validation. Given that the relationship between sustained CR + CRi and long-term survivorship is clinically established, the inclusion of the cure state is the most appropriate to address the uncertainty.

Table 24: Proportion of overall cohort in remission between 2–5 years (mixture cure models)

Blast count subgroup	Remission to relapse extrapolation	Remission to death extrapolation	Proportion of overall cohort in remission (%)			
			2 years	3 years	4 years	5 years
VenAZA 20–30%	BC post TE: 2-year cure plus an SMR of 1.2		[redacted]	[redacted]	[redacted]	[redacted]
	Revised BC post ACD: 3-year cure plus an SMR of 1.2		[redacted]	[redacted]	[redacted]	[redacted]
	Weibull[a]	Log Normal	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
		Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]
	Log Normal[a]	Log Normal	[redacted]	[redacted]	[redacted]	[redacted]

Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Consultation on the appraisal consultation document – deadline for comments 5pm on 25 October 2021 **Return via:** NICE DOCS

		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
		Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]
	Log Logistic[a]	Log Normal	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
		Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	Log Normal	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
		Log Logistic	[redacted]	[redacted]	[redacted]	[redacted]
VenAZA >30%	BC post TE: 2-year cure plus an SMR of 1.2		[redacted]	[redacted]	[redacted]	[redacted]
	Revised BC post ACD: 3-year cure plus an SMR of 1.2		[redacted]	[redacted]	[redacted]	[redacted]
	Log Normal	Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Log Logistic	Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised Gamma	Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
VenLDAC >30%	BC post TE: 2-year cure plus an SMR of 1.2		[redacted]	[redacted]	[redacted]	[redacted]
	Revised BC post ACD: 3-year cure plus an SMR of 1.2		[redacted]	[redacted]	[redacted]	[redacted]
	Log Normal	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
	Generalised Gamma	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
	Log Logistic	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
		Weibull	[redacted]	[redacted]	[redacted]	[redacted]
		Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]

[a] Not considered to be plausible by clinical experts.
Abbreviations: AZA: azacitidine; BS: base case; LDAC: low dose cytarabine; TE: technical engagement; Ven: venetoclax.

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Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Consultation on the appraisal consultation document – deadline for comments 5pm on 25 October 2021 **Return via:** NICE DOCS

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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.	n/a
Name of commentator person completing form:	[redacted]

Comment number	Comments

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Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Consultation on the appraisal consultation document – deadline for comments 5pm on 25 October 2021 **Return 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 would prefer that this treatment be recommended for baseline commissioning. However, if significant uncertainties remain, we would welcome the CDF as an option for resolving these whilst giving patients access and hope that all parties would work towards achieving this.
2	
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.
- 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.

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Consultation on the appraisal consultation document – deadline for comments 5pm on 25 October 2021 **Return via:** NICE DOCS

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[The Royal College of Pathologists (RCPath) British Society for Haemathology (BSH)]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**]
Name of commentator person completing form:	[redacted]

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Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

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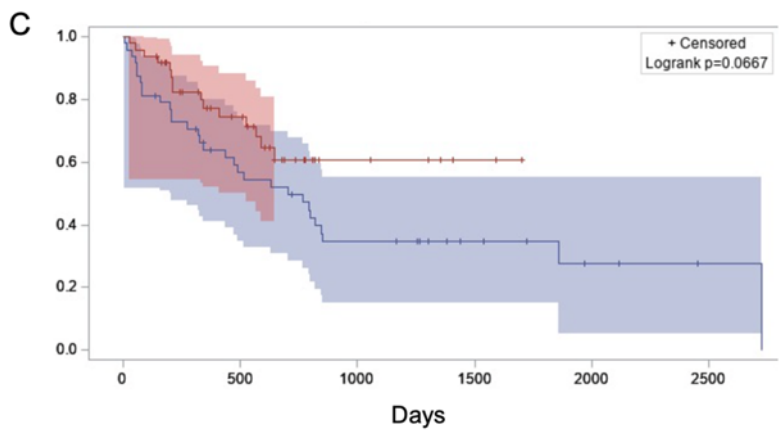
Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the committees decision puts UK patients at odds with what is standard of care for AML treatment for patients unsuitable for intensive chemotherapy around the world. Reviewing the ERGs cost-effectiveness assessment using the currently NICE approved dosing schedule (100mg daily with Posaconazole) the cure assumption time-point appears to be the critical factor in the uncertainty of the evidence presented that hinders a positive outcome. To this end a recent study published since the committee meeting provides additional support for the cure assumption. Cherry *et al.* Blood Advances Oct 2021 (10.1182/bloodadvances.2021005538) retrospectively assessed 143 patients receiving Ven/Aza with similar numbers receiving intensive chemotherapy. Kaplan-Meier survival curves (showing median OS) are presented for all patients and a propensity matched cohort of patients (the latter shown below). The red line shows patients receiving ven/aza the blue intensive chemotherapy. Not only is there a trend to better outcomes for patients in this propensity matched group receiving ven/aza but there is a clear levelling of the survival curve in the ven/aza group. While acknowledging the limitation of real world data we believe this is credible evidence to further support the cure assumption point. This is in keeping with evidence levels supportive of other TAs which have had favourable approvals for (gilteritinib and midostaurin). 
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Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Consultation on the appraisal consultation document – deadline for comments 5pm on 25 October 2021 **Return via:** NICE DOCS

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- 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 reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Jazz Pharmaceuticals
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

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Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

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Comment number	Comments 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.
1	Jazz agree there is an unmet need for a new treatment option for people with acute myeloid leukaemia for whom intensive chemotherapy is unsuitable. Availability of venetoclax in its licenced indication via the Cancer Drug Fund will be a positive step towards ensuring this treatment option is available for patients.

Checklist for submitting comments

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- 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.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
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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	University College London Hospitals NHS Foundation Trust
Location	Not specified
Conflict	No
Notes	
Comments on the ACD:	

Venetoclax+azacitidine has rapidly become the standard-of-care treatment for patients with AML around the world who are unable to receive intensive chemotherapy. It is an important advance for our older patients for whom our recently completed randomized "pick-a-winner" NCRI LI1 trial (the largest in history) failed to identify any beneficial treatments despite testing many over the best part of a decade.
Detailed comments are annotated in the relevant sections but to summarise:
1. This is a biologically distinctive and novel therapeutic advance
2. It produces high rates of MRD negative remission, unlike traditional treatments and approaching levels seen with high dose chemotherapy
3. Emerging data are consistent with a cure in a small proportion of patients, something hitherto not seen with traditional non-intensive treatments
4. Although perhaps not part of NICE's brief, not having venetoclax+azacitidine available as a standard treatment for our older patients will render any future randomized trials in this population virtually impossible in the UK, much to its detriment.

- Section 3.4

Comparing venetoclax+azacitidine with 'historical non-intensive treatments' with regard to long-term outcomes is not appropriate. There is biological plausibility that this combination is distinctive as shown in various publications eg Pollyea DA, et al. Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. Nat Med. 2018 Dec;24(12):1859-1866. doi: 10.1038/s41591-018-0233-1. Epub 2018 Nov 12. PMID: 30420752; PMCID: PMC7001730.

and

Jin S, et al. 5-Azacitidine Induces NOXA to Prime AML Cells for Venetoclax-Mediated Apoptosis. Clin Cancer Res. 2020 Jul 1;26(13):3371-3383. doi: 10.1158/1078-0432.CCR-19-1900. Epub 2020 Feb 13. PMID: 32054729..

Venetoclax+azacitidine has been repeatedly shown to result in high rates of MRD-negative remission (1. Vazquez R, et al. Venetoclax combination therapy induces deep AML remission with eradication of leukemic stem cells and remodeling of clonal haematopoiesis. Blood Cancer J. 2021 Mar 19;11(3):62. doi: 10.1038/s41408-021-00448-w. PMID: 33741892; PMCID: PMC7979724.
2. Pratz et al. Measurable residual disease response in acute myeloid leukemia treated with venetoclax and azacitidine. https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.7018)

This level of MRD negativity is not seen with non-intensive regimens and approaches that seen in the over 60s with intensive chemotherapy protocols.

Prolonged remissions have also been shown by several groups in addition to the VIALE-A data, albeit with small numbers, with a plateau in survival at around 3 years, again similar to results with intensive chemo (Cherry E, et al. Venetoclax and Azacitidine Compared to Induction Chemotherapy for Newly Diagnosed Patients with Acute Myeloid Leukemia. Blood Adv. 2021 Oct 5:bloodadvances.2021005538. doi: 10.1182/bloodadvances.2021005538. Epub ahead of print. PMID: 34610123.

Vazquez R, et al. Venetoclax combination therapy induces deep AML remission with eradication of leukemic stem cells and remodeling of clonal haematopoiesis. Blood Cancer J. 2021 Mar 19;11(3):62. doi: 10.1038/s41408-021-00448-w. PMID: 33741892; PMCID: PMC7979724.
Maiti A, et al. Prognostic value of measurable residual disease after venetoclax and decitabine in acute myeloid leukemia. Blood Adv. 2021 Apr 13;5(7):1876-1883. doi: 10.1182/bloodadvances.2020003717. PMID: 33792630; PMCID: PMC8045494.)

A proportion of patients who have stopped treatment are also maintaining long term remissions (Chyn Chua et al,
TREATMENT FREE REMISSION (TFR) AFTER CEASING VENETOCLAX-BASED THERAPY IN PATIENTS WITH ACUTE MYELOID LEUKEMIA, EHA2021, abstract EP249)

The data are consistent with operational cure in a small proportion of patients and this should be taken into account in the model.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	[redacted]
Notes	

Comments on the ACD:

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No.

- Section 3.5 - The evidence is too uncertain to include a cure health state in the model “At technical engagement, a professional organisation highlighted a small study by Chyn Chua et al. comparing stopping venetoclax treatment in remission with continuing it until relapse. The results suggested that venetoclax could be stopped after 2 years in remission without a negative impact on outcomes. However, the committee noted that in this study, a number of relapses occurred after 2 years.”

Re: Potential for treatment-free remission in AML after venetoclax-based therapy

As [redacted], we would like to comment on an abstract we recently presented at the [redacted] meeting in June 2021.

Our unit at the [redacted] in Melbourne, Australia, has been treating patients with AML using venetoclax-based therapy since 2014. We therefore have some of the longest follow-up in the world with this group of patients.

Based on our extensive experience with this regimen we presented some observations we have made in the EHA meeting abstract. This was based on our experience that some patients were surviving for >5 years, despite ceasing AML treatment several years prior- a highly unusual scenario for elderly AML. Our practice was to cease therapy in patients in remission after receiving at least 12 cycles of therapy, whereas our colleagues at MD Anderson had a practice of continuing therapy until disease progression. We therefore decided to present our clinical experience of 28 patients.

Our hypothesis was that for some patients, Ven-based therapy is so effective, that it is possible that some patients may be functionally cured (defined as not relapsing within 5 years of diagnosis). The only way to prove this was cease therapy in some patients and our clinical sense was that this could be possible after 12 months of treatment. Among 14 patients with treatment electively ceased after 12 months, about half have relapsed. The treatment-free remission duration in this group was 45.8 months (95% confidence interval 9.6 months to not reached).

75% of patients were still alive at 36 months, and 29% were alive at 60 months

(with an additional 29% alive but not yet reach 60 months) after commencing initial venetoclax-based therapy. As alluded to in the NICE appraisal, patients who ceased therapy did not perform worse than those who continued treatment in our retrospective study, using a landmark analysis starting from 19.0 months after diagnosis, which corresponded to the median time treatment was ceased in the STOP group.

This suggests that a proportion of patients may be cured from their initial AML. Of note, a small number of patients in our study did have late relapse and of these, approximately 70% had acquired new cytogenetic and/or molecular abnormalities at time of relapse, suggesting that the relapse leukaemic clone was different to the original AML detected at initial diagnosis. Therefore, we could interpret that such patients actually had a new or therapy-related AML, rather than relapse of their original disease. This may reflect an inherent predisposition to leukaemic re-transformation, as approximately 70% of these patients had a preleukaemic molecular mutation such as DNMT3A, TET2 or ASXL1 persisting during remission.

We believe that patients in true CR and with MRD negativity could be candidates for treatment cessation after 12 months, especially if NPM1 or IDH2 mutant, and we are planning a prospective study to address this question.

We hope that these comments are useful in NICE's consideration of venetoclax for AML in the U.K.

Regards

[redacted]

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

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

No, the UK has a large real-world data set for venetoclax based treatments collected during the COVID19 pandemic (n>300), we would be happy to make this available to NICE if that would be helpful.

- Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

No, the assumptions regarding cure state are problematic, as discussed below.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No, the assumptions regarding cure state are problematic, as discussed below.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

- Section 3.4 - The evidence is too uncertain to include a cure health state in the model

The issues around cure state clearly require further work as both the company position (considering all patients in remission at two years as being cured) and the ERG position (exclusion of the cure state from the model altogether) are overly simplistic and do not reflect the clinical realities of this disease.

I was one of the first AML physicians to treat patients with venetoclax in the UK and consequently see a number of patients that have now been in remission for 3-4 years, have been consistently MRD negative and have stopped treatment. These patients are very likely (though not certain) to have been cured.

In AML we can never say with 100% certainty that a patient will never relapse, indeed relapses have very rarely been observed 10-20 years out from treatment. Rather what we know is that the risk of relapse declines very dramatically during the first 2-3 years after treatment for patients in ongoing remission, i.e. the chance of being cured increases very markedly over that period, and then continues to increase further with each further year of follow up.

A much more appropriate model would be to consider patients in remission at two years to have a particular chance of being cured (say, 80%) with that figure increasing over time (say, 90% at 3 years, and so on).

This would reflect reality much more accurately than either the original base case model or the ERG position.

It appears to be the case that patients in particular molecular subgroups (e.g. NPM1, IDH1, IDH2) are more likely to experience cure, however this remains insufficiently defined for inclusion in modelling.

Finally in my opinion, most patients will decide to stop treatment after 2 or 3 years especially with emerging evidence showing that this does not particularly effect the risk of relapse, which at that point remains very low.

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia unsuitable for intensive chemotherapy [ID1564]

ERG critique of the company response to the Appraisal Consultation Document (ACD)

Produced by: Aberdeen HTA Group

Authors: Charlotte Kennedy[1]
Graham Scotland[1]

[1] Health Economics Research Unit, University of Aberdeen, UK

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University of Aberdeen, Health Economics Research Unit
Foresterhill, Aberdeen, AB25 2ZD
Email: g.scotland@abdn.ac.uk

Date completed: **2 November 2021**

Contains: [redacted]

Following the first appraisal committee meeting for this appraisal, the committee released an appraisal consultation document (ACD) indicating that they were minded not to recommend venetoclax plus azacitidine for routine commissioning, but that they considered it may be suitable for use in the cancer drugs fund. The company was invited to submit a proposal for including venetoclax plus azacitidine in the Cancer Drugs Fund for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable.

In their response to the ACD, the company provided a revised economic base case and outlined further arguments to support their approach in relation to several assumptions which the committee expressed reservations about.

1. The cure assumptions
2. The health state utility of the cure state
3. The dose intensity of venetoclax

They urge the committee to reconsider the evidence and to make venetoclax available for this indication under routine commissioning.

In this document, the ERG provides a brief commentary/critique of the company's response and their revised economic modelling. It should be read in conjunction with the company's response to the ACD. The focus is on the updates made to the economic model and their rationale. The ERG will provide a further cPAS appendix that reproduces the company's revised analysis and the ERG's additional scenario analyses (table 1) using the confidential PAS prices available for azacitidine and gilteritinib (subsequent therapy).

1. Support for a cure assumption

The company's arguments to support the application of a cure assumption for venetoclax focus on:

a) Further validation based on clinical expert onion and mixture cure models (MCMs)
b) The ability of venetoclax to achieve similar outcomes to intensive chemotherapy (IC), which has an accepted capacity for cure
c) Its current use as a substitute treatment for patients who would normally be eligible for IC and treated with curative intent.
d) The acceptance of a less conservative cure assumption in the NICE gilteritinib appraisal (TA642).
e) The robustness of the cost-effectiveness findings to varying the proportion of patients in remission who are assumed cured at selected timepoints.
f) Of those who relapse, the majority do before 3 years.

a) Validation using mixture cure models

The company note the views of clinical experts present at the first committee meeting, and subsequently reiterated following the ACD, that a proportion of patients receiving venetoclax are able to achieve a cure and therefore require no further treatment.

The company conducted further analyses to fit MCMs to time-to-relapse and time-to-death from remission (CR/CRi). The company reports that in the >30% blast group the MCMs (for time-to-relapse) predict a cure fraction that is consistent with the proportion assumed cured at two years in the company's post technical engagement base case (see Figure of the company ACD response). In the 20-30% blasts group, they find the MCMs of time-to-relapse predict implausible cure fractions and extrapolations (see Figure 2 of the company ACD response), since they expect the vast majority of relapses to occur before 2–3 years. The company point to the Gompertz as offering the only potentially plausible extrapolation, and note that it suggests a cure fraction in line with its revised base case which assumes a cure for everyone still in remission at 3 years (based on standard parametric curves). The predicted cure fractions for the time-to-death transition are generally substantially higher in both the 20-30% and >30% blast count groups.

The company do not use the MCM extrapolations in their revised economic case and note the limited number of patients/events in the observed KM curves as undermining their robustness

and driving variability in the estimated cure fractions. They further believe that the MCMs ignore the surrogacy relationship between sustained CR/CRi and long-term survival.

The ERG agrees that the lack of data to inform the MCM models results in uncertainty with respect to their output. As advised in the Lambert et al. paper,(1) caution should be exercised in the application of these models where the cure fraction is determined by extrapolations beyond the range of observed follow up. Furthermore, all of the KM curves exhibit small numbers at risk in the tails which could lead to unreliable estimates of the fraction cured for some transitions. Therefore, the ERG finds that this analysis provides limited evidence to validate the cure fraction.

b) The ability of venetoclax to achieve similar outcomes to intensive chemotherapy (IC), which has an accepted capacity for cure

The company note the ability of VenAZA to achieve deep and durable complete remission rates (CR/CRi with/without MRD) comparable to those achieved in patients over 60 receiving IC. They further highlight the established relationship between complete remission (CR + CRi) and long-term survival (2). They also refer to several sources to support their assertion that the majority of relapses occur before two years in patients who achieve complete remission with IC, and that the risk of relapse is small in those who maintain CR in the long term (see company response for details). They further refer to a recent review which reports longer OS for older adults treated with venetoclax compared to adults treated with IC (3). This linked evidence base, they suggest, supports the application of a cure assumption for VenAZA.

Of relevance here is another recent paper cited in the ACD response of the Royal College of Pathologists, by Cherry et al. (4). This retrospective analysis examined response rates, overall survival, and progression free survival in 143 patients with AML receiving VenAZA and 149 patients receiving IC in a single US centre. It provides longer follow-up (median = 808 days) than the VIALE trials. The analysis showed similar rates of response (CR/CRi) in the two cohorts, and after propensity score matching, OS tended to favour VenAZA (sample size reduced to 48 per matched group). Of note, the Kaplan-Meier plots for OS and PFS in the 143 treated with VenAZA indicate notable flattening of the curves from about two to three years.

The ERG acknowledges that VenAZA induces complete remission rates comparable to those of IC, and that relapse events in those achieving complete remission with IC occur predominately in the first two years. However, the ERG has the following observations in relation to company's arguments:

- *Some of the studies referenced to support the diminishing rate of relapse in patients treated with IC focussed on patients who received allogeneic stem cell transplants (5-7), and allogeneic stem cell transplant is independently predictive of a reduced relapse risk in multivariate analyses that include response and MRD as explanatory variables (8). It is questionable to what extent the pattern of relapse in such patients can help inform relapse rates of those treated with VenAZA who achieve CR/CRi with/without MRD.*
- *Whilst studies support a greatly diminished rate of relapse beyond 2-3 years in cohorts that achieve CR/CRi with IC (without stem cell transplant) (8-11), they do not support a zero risk (10-11).*
- *Venetoclax is an ongoing oral therapy, and patients on-treatment with VenAZA and still in remission at 2 years may not be directly comparable with cohorts still in remission at two years after being induced with IC. That said, the data reported by Chua et al. (12) suggests that patients who stop VenAZA between 1-2 years do no worse than those who remain on treatment, so it may not be unreasonable to assume similar patterns of relapse rates following two years of remission on VenAZA and IC.*
- *The company disregard the data reported by Chua et al.(12) as being unsuitable for informing decision making, noting the small sample size and that the study was not designed to investigate the impact of time in CR + CRi on relapse. Whilst the ERG agrees the numbers are too small to accurately inform long-term relapse rates, the data still indicate that the risk of relapse following two years in remission is not zero.*

Reflecting on the additional evidence presented, the ERG believes that it is reasonable to expect a substantial proportion of VenAZA treated patients who remain in remission at two-three years to achieve long-term survival in line with the general population, akin to a cure. However, the exact timing and the proportion of those in complete remission at 2-3 years to which this applies remains uncertain. The assumption of zero risk of relapse beyond two or three years is a simplification that is not fully supported by the data. In this respect, the ERG

finds the company's scenarios which assume the cure applies to a fixed proportion of patients who remain in remission at two or three years to be useful.

c) Its current use as a substitute treatment for patients who would normally be eligible for IC and treated with curative intent.

The company refer to the fact that VenAZA is currently being used to treat patients considered eligible for IC, in which IC would be used with curative intent. They argue that this supports the plausibility of their cure assumption for VenAZA

The ERG acknowledges the ability of VenAZA to achieve complete remission rates comparable to those achieved in older patients eligible for IC, and also acknowledges the potential for venetoclax to achieve longer-term relapse rates and OS comparable to that of IC. However, this line of argument does not in itself directly address the validity of the cure assumptions as applied in the company's model; i.e. the exact timepoint or proportion to which it should apply.

d) The acceptance of a less conservative cure assumption in the gilteritinib appraisal (TA642).

The company refer to the fact that a less conservative cure assumption was accepted in the NICE appraisal of gilteritinib for relapsed or refractory FLT3-mutation-positive acute myeloid leukaemia in adults (TA642) (13). The company refer to the committee's view, as expressed in the ACD, that this is not relevant to the current appraisal because it focussed on a different population. The company note that the population in TA642 had relapsed or refractory AML and that a proportion had a SCT. However, they correctly point out that SCT was not a condition for application of the cure assumption in the model for TA642, and it was accepted that all patients alive at 3 years were considered 'cured'. They further note that patients with relapsed or refractor AML (as per TA642) may have a poorer prognosis compared to those with untreated AML (as per the current appraisal).

The ERG acknowledges that the cure assumption applied for venetoclax is more conservative in the sense it is only applied to those modelled to remain in remission at two or three years. In the gilteritinib appraisal (TA642), the cure assumption was applied to all those surviving at three years regardless of whether or not a stem cell transplant was performed. It was applied in both the intervention and the comparator arms (salvage chemotherapy, with or

without stem cell transplant), which could be considered conservative compared to only applying a cure assumption to the intervention arm. In the current appraisal (including the revised post-ACD scenarios), the company have only applied the cure assumption to the venetoclax arms. However, they argued that this is appropriate because the non-intensive treatments, AZA and LDAC, are not considered curative in the population not suitable for intensive chemotherapy. The ERGs clinical expert agreed with this point as stated in the original ERG report (section 4.2.6). The ERGs uncertainty related more to the evidence to support a cure assumption for venetoclax in this population. However, it is noted in point 3.5 of the ACD that the committee believed that any cure state in the model should have applied to both arms. Whilst the ERG urge caution on this assumption based on its clinical advice, it has added further scenarios to address the committees concern and to illustrate the impact this would have on the ICER (table 1).

e) The robustness of the cost-effectiveness findings to varying the proportion of patients in remission who are assumed cured at selected timepoints.

The company presents several scenarios in appendix 2 where differing proportions of patients still in remission at two years (70% and 80%) and three years (90%) are assumed cured in the model. These scenarios have a limited impact on the results where all scenarios exhibit ICERs of less than £50,000 per QALY gained. The company also presents a breakdown of the proportion of the cohort within the remission and cure states at incremental annual time points in the model.

The ERG believes that these scenarios may more accurately reflect the pattern of relapse observed in IC patients who achieve CR/CRi, where there is a low ongoing risk of relapse beyond 2 years. It is reassuring that the cost-effectiveness results are not sensitive to the explored variation in the proportion of remission patients who are assumed cured at 2 or 3 years. The ERG has added a few more conservative scenarios that reduce the proportion considered cured at three years further (Table 1).

f) Of those who relapse, the majority do before 3 years

The company has sought clinical advice throughout the appraisal process in order to gain more insight into the possibility of a cure for this population. In particular, the risk of relapse in patients who have achieved CR+CRi for more than two years. Clinical opinion finds that some patients would be considered cured in this population provided that they have also

achieved long term CR+CRi. The determination of what timepoint would constitute long term CR+CRi with respect to a cure has not been established through these discussions. However, clinical advice to the company suggests that the proportion of patients predicted to enter the cure state at 3 years in the model is lower than what would be expected in clinical practice ([redacted] for VenAZA (20-30%), VenAZA (>30%) and VenLDAC (>30%) respectively).

The ERG finds that this argument is relevant to consider as follow-up data of the VIALE trials may not be long enough to fully capture diminishing hazards with respect to relapse beyond two years. In this respect, the post-technical engagement ERG scenarios that removed the cure assumption and applied standard parametric extrapolations of time to relapse from the VIALE trials may be overly pessimistic. However, as stated in response to b), the ERG finds the assumption that 0 relapses occur after 2 or 3 years an oversimplification. The evidence explored by the company suggests that further relapses are to be expected albeit at a lower and diminishing rate. Based on the evidence provided, the ERG does find it reasonable to assume that a substantial proportion of patients who remain in remission at two-three years could be considered cured.

2. The health state utility of the cure state

The company has provided further clarification of the utility assumptions of the cure health state where patients are modelled to accrue utility in line with that of the age-matched general population. The decision to apply these utilities is founded on clinical advice to the company where patients who achieve CR+CRi would realise transfusion independence which allows them to return to normal life. The ACD document cites clinical expert opinion also, where patients would return to the same quality of life after treatment although concedes that some may not. The company points out that from the two-year time point in the model, the age-adjusted general population utility of the cure state is always lower than the health state utility of the remission state.

The ERG finds that the health state utilities favour the remission state from two-years in the model. Therefore, in scenarios where the cure assumption was removed, patients who would have been considered cured realised greater health state utility values within the remission state. However, it should be acknowledged that in this scenario patients continued to be at risk of progressive disease and a higher risk of mortality.

3. The dose intensity of venetoclax

During technical engagement, it was identified that the dose of venetoclax utilised in the VIALE trials is not in line with that used in clinical practice in England. This is due the use of concomitant treatment with azoles (CYP3A inhibitors). The company cites the NHS England interim treatment policy (NG161), which recommends 100mg per day for the first 28 days, then 100mg per day at a 50% dose intensity for all subsequent cycles (14). Clinical advice to the company finds that the dose of venetoclax is dependent on several factors including the duration of treatment with concomitant strong/moderate CYP3A inhibitors and dose interruptions for the management of cytopenia. The company provides several sources of evidence which show that:

1. Drug exposure to venetoclax remains between 400mg-1200mg in treatment with 100mg plus a CYP3A inhibitor (15).
2. Rates of CR+CRi of patients in the VIALE-A trial were similar between dose-adjusted venetoclax plus CY3PA inhibitor patients and patients who received venetoclax with no CYP3A inhibitor or dose adjustments (16).
3. Data from the UK during the COVID interim treatment policy which found that of the 81% of patients who received the 100mg dose of venetoclax with a strong CY3PA inhibitor, 70% of these patients achieved CR+CRi (see company response to the ACD).

Therefore, it is reasonable to assume that a reduced dose intensity would not have a substantive impact upon the efficacy of venetoclax.

The ERG agrees that a 100mg dose per day at a 50% dose intensity should be considered in the cost-effectiveness analysis. The evidence provides reassurance that the efficacy of venetoclax should not be affected by dose adjustments due to concomitant treatment with azoles.

The ERG provides a few additional scenarios around the cure assumption in Table 1 below. The ERG has provided a further confidential appendix replicating the company's further analyses, and the ERG scenarios below, using the confidential prices available for comparators and subsequent treatments.

Additional scenario analysis carried out by the ERG

Table 1. Cost-effectiveness results for additional scenarios explored by the ERG

Intervention	Incremental costs	Incremental QALYs	ICER (cost/QALY)
VenAZA versus AZA (20-30% blasts)			
Cure proportion: 80% at 3 years [A]	[redacted]	[redacted]	£30,683
Cure proportion: 70% at 3 years [A]	[redacted]	[redacted]	£32,718
Cure assumption applied to both arms at 2-years[B]	[redacted]	[redacted]	£18,584
Cure assumption applied to both arms at 3-years[B]	[redacted]	[redacted]	£27,650
VenAZA versus LDAC (>30% blasts)			
Cure proportion: 80% at 3 years [A]	[redacted]	[redacted]	£41,191
Cure proportion: 70% at 3 years [A]	[redacted]	[redacted]	£42,329
Cure assumption applied to both arms at 2-years[B]	[redacted]	[redacted]	£33,794
Cure assumption applied to both arms at 3-years[B]	[redacted]	[redacted]	£39,271
VenLDAC versus LDAC (>30% blasts)			
Cure proportion: 80% at 3 years [A]	[redacted]	[redacted]	£11,868
Cure proportion: 70% at 3 years [A]	[redacted]	[redacted]	£12,411
Cure assumption applied to both arms at 2-years[B]	[redacted]	[redacted]	£9,328
Cure assumption applied to both arms at 3-years[B]	[redacted]	[redacted]	£11,337

[A] *alternate cure proportions applied to those still in remission at 3 years in the venetoclax arms.* [B] *SMR of 1.2 applied to the cure state of the comparator arms as for the venetoclax arms in the company base case.*

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