Single Technology Appraisal

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Contents:

The following documents are made available to stakeholders:

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

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Servier
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments
1	**Relative effect of IVO+AZA versus VEN+AZA** The AGILE study provides a comparison between IVO+AZA and AZA alone, though as discussed in the first appraisal committee (AC) meeting, the standard of care in the UK is now VEN+AZA, in line with the recommendation reached in NICE TA765. Consequently, the economic model relies on an indirect comparison (ITC), which is informed by the results of a Bayesian network meta-analysis (NMA). The NMA takes the relative effects reported by the VIALE-A study of VEN+AZA versus AZA and the AGILE study of IVO+AZA versus AZA, to indirectly estimate the relative effects of IVO+AZA versus VEN+AZA. The Bayesian NMAs for event-free survival (EFS) and overall survival (OS) allow for the estimation of point estimates of hazard ratios (HRs), as well as credible intervals (CrI's) to quantify the uncertainty in the point estimates. As highlighted by the AC, the CrI's for both endpoints (EFS and OS) include 1. However, this should not be interpreted as evidence that IVO+AZA and VEN+AZA are equivalent, and conclusions concerning statistical significance cannot be drawn from CrI's. Based on a posterior sample drawn from the outputs of the Bayesian NMA (previously provided in the submitted economic model file), there is a(n) [redacted]% and a(n) [redacted]% probability that the HR for OS and EFS is less than 1 (i.e., favouring IVO+AZA), respectively. As an alternative metric, the surface under the cumulative ranking curve (SUCRA) placed IVO+AZA as the best treatment option with a high probability ([redacted]% probability for OS and [redacted]% probability for EFS). These analyses show that while the point estimates are uncertain, the evidence available supports the expectation of added benefit for IVO+AZA versus VEN+AZA. The fact that the CrI's from the NMA include a value of 1 should be considered alongside the nature of the evidence informing the NMA. To facilitate a comparison of IVO+AZA with VEN+AZA, data from two studies (AGILE and VIALE-A) provide connections. These are the only two studies which provide a means of comparing these treatment regimens. VIALE-A was conducted in a larger sample of patients, as this study did not restrict inclusion by mutation status. If more studies were available to inform the network, and/or the included studies included a larger number of patients, we would expect the width of the CrI's outputted by the NMA to be narrower The Company considers it important to re-iterate the reasons why there is uncertainty present in the results of the NMA. Indirect comparisons in their very nature are less precise than direct evidence, given the variance of the indirect estimate captures the combined variance from direct estimates. IDH1 is a rare mutation, occurring in approximately 8% of patients with AML. Considering that the population considered in this appraisal is people with IDH1-mutated AML who are ineligible for intensive induction chemotherapy, it is in line with expectation that the sample size of the AGILE study is relatively small (compared to a trial where inclusion is not defined by a specific mutation). The original enrolment estimate was 392 patients[1], whereas recruitment in the AGILE study was discontinued when approximately half this number of participants were enrolled,

on the recommendation of the independent data monitoring committee (IDMC) for ethical reasons due to a difference in the number of deaths favouring IVO+AZA. The Company highlights that 330 patients would have been needed in the AGILE study to obtain a 95% CrI excluding 1 for OS in the NMA, whereas this study was stopped when half this number was included. This was determined based on hypothetical NMA scenario analyses conducted by the Company for the outcome of OS, assuming an unchanging point estimate for the original HR and varying only the standard error of the original HR (log-scale) in AGILE to evaluate the sample size required in AGILE to reach statistical significance in the NMA.

In the DG and the External Assessment Report (EAR), reference is made to *post-hoc* analyses of VIALE-A data providing efficacy estimates specifically for patients with an IDH1 mutation. One of these is from the forest plot of the VIALE-A study, and another refers to the Pollyea *et al.*, (2022)[2] study which includes data pooled from multiple studies. These analyses do not have strong statistical support, and are contradictory to clinical advice which suggests no anticipated difference in treatment effect for VEN+AZA for patients with and without an IDH1 mutation, based on the biological mechanism of action of venetoclax, when given in combination with azacitidine. Whilst data started to point to a treatment effect in IDH mutated AML patients - when the data was analysed separating IDH1 and IDH 2 mutated patients, it was the latter where a treatment effect for Ven Aza was seen compared to IDH1 mutated patients. Referring specifically to the Pollyea *et al.* values, these results are based on a *post-hoc* subgroup where imbalances in baseline characteristics were observed, in particular a higher percentage of patients with less favourable cytogenetic risk in the PBO + AZA arm, resulting in an unreliable estimate for the treatment effect. Overall, the Company does not consider any published estimates specifically in an IDH1 mutation positive population for VEN+AZA to be sufficiently robust to conclude a difference in efficacy, as opposed to an all-comers population treated with VEN+AZA.

Nevertheless, further analysis was carried out by the Company in an attempt to reduce the uncertainty in the ITC comparing IVO+AZA and VEN+AZA. A feasibility analysis and subsequent ITC using matching-adjusted indirect comparison (MAIC) methodology was conducted. In total, three MAICs were conducted:

1. An *anchored* MAIC of *OS* for IVO+AZA versus VEN+AZA using the VIALE-A ITT population.
2. An *anchored* MAIC of *EFS* for IVO+AZA versus VEN+AZA using the VIALE-A ITT population.
3. An *unanchored* MAIC of *OS* for IVO+AZA versus VEN+AZA using the VIALE-A IDH1m subgroup.

Further details of the MAIC, in terms of both methodology and results, are provided separately in an addendum to this response. The MAICs yielded similar results to the NMA suggesting limited impact of study differences on the ITC results. In addition, several of the confidence intervals (CI's) for the MAIC analysis do not include 1 in this additional analysis. Following this additional analysis, both types of indirect comparison produce consistent results and therefore underpin the expected benefit of IVO+AZA compared to VEN+AZA (in terms of both OS and EFS). The Company retains its preference for the NMA, as this maintains the randomisation within each study, but has provided these alternative approaches for an ITC as an additional, alternative, and supportive analyses.

The latest OS data from both the AGILE and VIALE-A[3] studies indicate a survival benefit IVO+AZA versus VEN+AZA, with a median OS of 29.3 months (95% CI: 13.2, NE) for IVO+AZA in AGILE, versus 14.7 months (95% CI: 11.9, 18.7) for VEN+AZA in VIALE-A (using the ITT population of VIALE-A). The Company considers it unlikely that such a notable numerical difference in median OS could solely relate to the differences in baseline characteristics across the studies. The similar outcomes of the AZA control arms in both trials may also be considered reassuring in this regard (7.9 months for AGILE and 9.6 months in VIALE-A), noting that median OS is lower in AGILE than VIALE-A. In other words, median OS is more than double for IVO+AZA versus VEN+AZA, despite the VIALE-A population exhibiting slightly better median OS on the control arm.

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Supportive data to show real world efficacy of IVO+AZA versus VEN+AZA have also become available following the original submission. A real-world evidence study of 283 patients for IVO + hypomethylating agent (HMA), compared with VEN+HMA in IDH1m patients ineligible for intensive chemotherapy was recently published.[4] Complete response (CR) plus CR with incomplete count or incomplete platelet recovery (CRi/p) rates were 63.2% vs 49.5% for IVO+HMA vs VEN+HMA (p=0.025), with the difference based on the higher CR rate for IVO+HMA (42.9% vs 26.7%; p=0.007). A competing risks regression showed that 6-month EFS (CR within 24 weeks, and no relapse or death) favoured IVO+HMA vs VEN+HMA (56.0% vs 39.6%, HR of 0.773; p=0.044).

There are previous examples of appraisals where the CrI for a given endpoint included 1, and the AC concluded that there was sufficient evidence to support a clinical benefit. For example:

- In TA741[5] (apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer), the final guidance states: *"The results suggested that people having apalutamide plus ADT survive longer than people having placebo plus ADT and people having docetaxel plus ADT. The committee noted that although the hazard ratio was below 1, which indicates a benefit, the confidence interval included the possibility of no benefit. … The committee concluded that the company's indirect treatment comparison suggests that apalutamide plus ADT has an advantage over docetaxel plus ADT for efficacy and is well tolerated."*
- In TA666[6] (atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma), the final guidance states: *"Atezolizumab plus bevacizumab is likely to be more clinically effective than Lenvatinib. 3.5 The company's base-case NMA produced the following results for atezolizumab plus bevacizumab: • increased progression-free survival compared with lenvatinib (HR 0.91, 95% credible interval [CrI] 0.23 to 3.65) • increased overall survival compared with lenvatinib (HR 0.63, 95% CrI 0.32 to 1.25)."* … *"The* [AC] *agreed that the NMA results suggested atezolizumab plus bevacizumab was more effective than lenvatinib."*
- In TA587[7] (lenalidomide plus dexamethasone for previously untreated multiple myeloma), the final guidance states: *"Lenalidomide plus dexamethasone is more clinically effective than VMP. 3.8 Based on the results of the indirect comparison, lenalidomide plus dexamethasone improved overall survival compared with VMP (hazard ratio [HR] 0.70, 95% credible interval [CrI] 0.50 to 0.98). For progression-free survival, the hazard ratio for lenalidomide plus dexamethasone compared with VMP was 0.74 (95% CrI 0.52 to 1.05)."* … *"Based on the evidence presented, and acknowledging potential confounding, the* [AC] *concluded that lenalidomide plus dexamethasone was more clinically effective than VMP, although by how much was uncertain."*

Taking into consideration all of the points above, it is the Company's view that there is clear evidence to support an expectation of improved EFS and OS for IVO+AZA versus VEN+AZA for patients with IDH1 mutated AML who are ineligible for intensive chemotherapy. As such, it would be inappropriate to consider analyses where these estimates of relative effect are removed from the model. Furthermore, the NMA provides the most robust point estimates to inform decision-making, and so these point estimates are retained in all analyses provided by the Company as part of this response.

Summary of company's key points:

- The available evidence concerning the relative efficacy of IVO+AZA versus VEN+AZA supports the expectation of added benefit of IVO+AZA, though this is subject to uncertainty primarily related to data availability.
- To address the uncertainty in the NMA, the Company has run an alternative analysis with a range of robust statistical methodologies (using MAIC) and has provided real-world evidence for IVO+AZA versus VEN+AZA.
- Taking into consideration the above, the totality of evidence supports that IVO + AZA (combination) confers a clinical relevant survival advantage compared to VEN + AZA. Therefore, the Company does not consider a scenario where all relative treatment effects

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

	are removed from the model to be appropriate for decision making, and so this scenario has not been provided – the NMA is preferred
2	**Evidence for IDH1 mutation as a treatment effect modifier for VEN+AZA** Consistent with the Company's view expressed at the first AC meeting, there is no conclusive evidence which supports the expectation that IDH1 mutation is a treatment effect modifier for venetoclax + azacitidine, or that IDH1 is a prognostic factor, and therefore it is the Company's view that the HRs obtained from the ITT analysis of VIALE-A represent an appropriate estimate of the treatment effect for VEN+AZA versus AZA alone to inform the NMA. The Company highlights for completeness that there is an important distinction to make between IDH1 mutations and IDH2 mutations. IVO is only indicated for the treatment of people with an IDH1 mutation, in combination with AZA. Recent data from the VIALE-A study, published in February 2024 (Pratz *et al.*, [2024][3]), further demonstrate that IDH1 is *not* a treatment effect modifier for venetoclax. More specifically: • Median OS for pooled IDH mutated patients including IDH1 and IDH2 mutated patients in VIALE-A was 19.9 months, compared with 14.7 months for the full ITT population. • When separated by IDH1 and IDH2, the respective median OS estimates were 10.2 versus 27.5 months, respectively. • This demonstrates that any observed differences in OS between patients with IDH1 or IDH2 versus the full ITT population are driven mostly by IDH2, *not* IDH1. The mOS from the mIDH1 subgroup was aligned with the mOS observed in the full IIT Viale A population. • In total, there were only n=23 patients receiving VEN+AZA that were IDH1 in VIALE-A, compared to n=40 that were IDH2, and n=286 in the ITT population. The corresponding numbers for the AZA arm were n=11 (IDH1), n=18 (IDH2), and n=145 (ITT). In addition to the VIALE-A study additional follow-up, several other studies provide further information concerning IDH1 and VEN+AZA: • DiNardo *et al.*, (2020)[8] showed that in IDH-mutated AML, survival was particularly favourable for IDH2m. High response rates and durable remissions were seen with *IDH2* mutations only. The association between IDH1m and prognosis was less clear. The median OS for patients with IDH1m was not significantly different from patients with IDH1 wild-type (18.3 vs 12.7 months; P = 0.79).The mOS seen here in mIDH1 patients is again reflective of the mOS seen in the ITT population for Viale A , inferring no additional treatment effect is seen with mIDH1 • Lachowiez *et al.*, (2023)[9] presented findings from a retrospective analysis of 331 patients treated with venetoclax with a median age of 75. IDH2 (n=43) was associated with a better outcome compared to IDH1 (n=19). The authors put forward a conjecture of biological rationale to explain differences in sensitization to venetoclax between IDH1m and IDH2m AML cells. The rationale stated that IDH1/2m destabilize the mitochondria and increase the AML cells' vulnerability to venetoclax. This process may (but has not proven to be) more outspoken in IDH2m AML than IDH1m AML because IDH2m is mitochondrial, and the produced D-2-HG is thus closer to the site of action (= COX) in IDH2m AML than in IDH1m AML. Or the D-2-HG concentration produced by IDH2m may more ideal than the D-2-HG accumulation that results from IDH1m. • Martinez-Cuadron *et al.*, (2023)[10] retrospectively assessed the characteristics, therapeutic approaches, and outcomes of unfit patients with AML according to IDH mutational status, and found no significant differences in response to treatment or OS when comparing mIDH1 and WT IDH AML patients. This included an analysis of those treated with venetoclax where a median OS of 11.1 months was observed in those patients with mIDH1 status. • A manuscript currently in peer review reports on an international real-world study that includes the use of a database from the USA (Cancer Outcomes Tracking and Analysis [COTA]) that captures information on the m*IDH1/2* populations aims to present real-world, US data on OS in AML patients with m*IDH1*, m*IDH2*, and wildtype *IDH1/2*.[11] There was shown to be no survival advantage in the m*IDH1* population versus wildtype *IDH1/2*

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

	population (1.00 [95% CI: 0.80-1.26]). There was a trend observed for longer survival in the m*IDH2* population versus wildtype *IDH1/2* population (HR 0.83 [95% CI: 0.69-1.02]). In patients receiving non-IC treatment, median OS was 14.6 months, 30.1 months and 14.9 months in patients with m*IDH1,* m*IDH2* and wildtype *IDH1/2*, respectively. This real-world study revealed that in patients receiving non-IC regimens, there was no significant prognostic impact of m*IDH1*, whereas m*IDH2* appeared to have more favorable clinical outcomes than m*IDH1* and wildtype *IDH1/2*. In conclusion, the company believes the current evidence, although while pointing to a treatment effect for IDH2 AML patients, does not support that a treatment effect for Venetoclax is seen with mIDH1 AML patients. The company reiterate that the prognostic impact of IDH1m on patients with AML has been assessed in several studies, with no clear evidence for an important difference in prognosis. As highlighted in the Company's submission, there are no consistent findings of IDH1 to be a molecular prognostic factor. This is also reflected in the ELN guidelines[12], which (as explained by the clinical expert during the first AC meeting), state that current evidence does not yet warrant the assignment of IDH1 mutation status to a distinct prognostic group. **Summary of company's key points:** • Overall, there is no conclusive evidence that IDH1 mutation is a treatment effect modifier for VEN+AZA. • However, there is evidence which suggests that AML patients with IDH2 mutations may have a enhanced response to Venetoclax and have a better prognosis vs non IDH2 patients, though this is not the population relevant to this appraisal. • European LeukemiaNet (ELN) guidelines do not establish IDH1 mutation status as a distinct prognostic group.
3	**Scenarios exploring the cure assumption in the submitted model** Following publication of the detailed advice document (DAD) by the SMC (on 11 March 2024, SMC2615); the SMC's base-case analysis is described, which includes a 2-year cure point, and concluded that IVO+AZA is accepted for use within NHSScotland.[13] As part of the SMC's assessment, several more pessimistic scenario analyses were provided, including assuming a cure point at 3 years and an SMR of 1.2, which the Company considered appropriate scenarios to explore given uncertainty in the specification of a cure assumption. Using functionality implemented within the submitted model, the Company has explored the following combinations of scenarios varying the time of the cure point and specification of a standardised mortality ratio (SMR), at the request of the AC: • Cure point at 2, 3, or 5 years • SMRs of 1.0, 1,1, 1.2, or 2.0 applied In total, this comprises 12 scenarios. The Company's revised base-case uses a cure point of 3 years and an SMR of 1.2. There is no clear evidence to support a specific SMR, but committee papers from TA765 suggest an SMR of 1.2 was preferred in this past appraisal, alongside a cure point of 3 years, and so for consistency the same SMR and cure point have been applied in this model. The Company highlights however that since an SMR of 1.2 is arbitrary, scenarios that do not apply an SMR may still be relevant for decision making. Relatedly, alternative cure points may provide further insight into the model results, but both a 2-year and 5-year cure point would be inconsistent with TA765. In addition to these scenarios, functionality has been included in the model to align the proportion of patients entering the cure state with the estimated proportion of patients in remission at the time of the cure point. For IVO+AZA, this was estimated to be 96.9%. Depending on the approach used to derive the estimate for VEN+AZA, this is estimated to be [redacted]% (Company's original base-case analysis) or [redacted]% (EAG's preferred analysis). The Company's revised base-case analysis uses

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

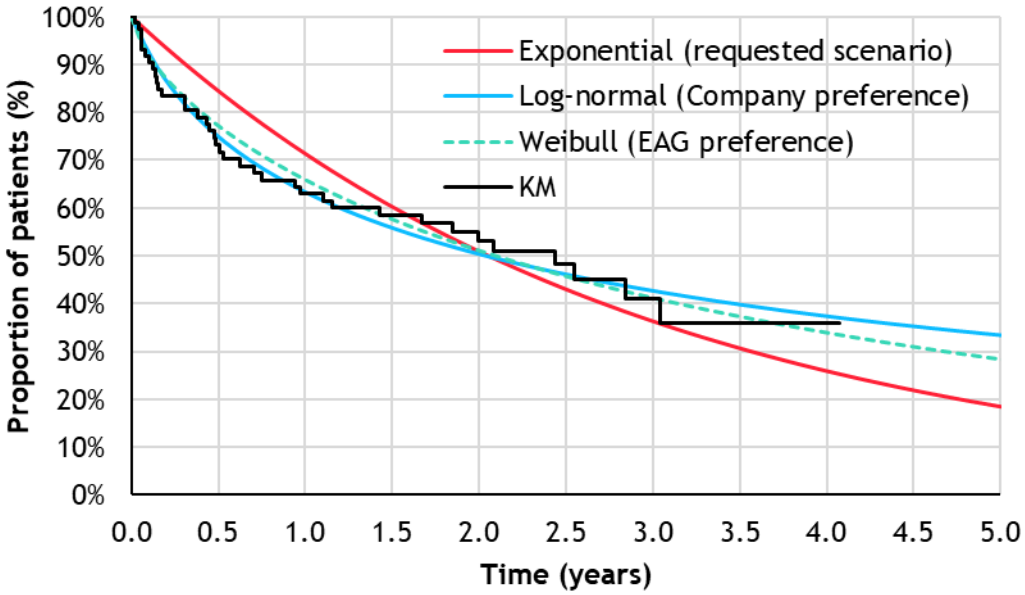
Draft guidance comments form

	[redacted]% for VEN+AZA, per the EAG's preferred analysis. **Summary of company's key points:** • Scenarios have been explored using alternative cure points and SMRs for 'cured' patients. • While the choice of SMR is arbitrary, an SMR of 1.2 has been applied in the revised base-case analysis for consistency with TA765. • The AC's preference of aligning estimated proportion in remission at cure point entering cure state has been included, with proportions estimated for each arm (using the EAG's preferred analysis for estimating this for VEN+AZA).
4	**Choice of extrapolation models for overall survival (OS) and event-free survival (EFS)** The estimation of overall survival (OS) and event-free survival (EFS) within the cost-effectiveness model relies upon selection of suitable parametric survival models. In the company's original base-case analysis, log-normal models were selected for both endpoints. In brief, these models were selected based on visual and statistical goodness-of-fit within the observed period of follow-up. In its report, the EAG explored alternative model fits, and expressed its preference for Weibull models for both OS and EFS. The EAG noted for the outcome of OS specifically that clinical advisers to both the company and the EAG considered Weibull as a suitable choice. The Draft Guidance highlights that the AC considered that the exponential curve may produce more clinically plausible estimates (of OS and EFS), and therefore it requested a scenario using the exponential curve to extrapolate both of these outcomes. Taking into consideration these differing viewpoints on the choice of extrapolation models, the Company agrees that Weibull provides a reasonable fit to the observed data, and (when combined with the cure assumption) produces plausible long-term survival estimates. However, an exponential model provides a poor fit to the data (as well as exhibiting the poorest statistical goodness-of-fit), and does not represent the expected pattern of survival for this patient population (that is, an initial drop in the survival curve, followed by a levelling out, and then [in the long-term] an increase in mortality risk in line with age). A simple comparison of the OS models preferred by the Company (log-normal) and the EAG (Weibull), as well as the scenario requested by the AC (exponential) is provided in the figure below. The fit of the exponential model is notably poorer than the other two models. However, despite the poor fit of the exponential model, as a scenario was explicitly requested by the AC, ICERs using exponential models have been produced and are provided at the end of this response. In terms of results (see addendum), the choice of OS model has a relatively small impact owing to the specification of the cure assumption.

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Comparison of Company and EAG preferences, plus AC requested scenario, for OS



Key: AC, appraisal committee; EAG, External Assessment Group; KM, Kaplan-Meier; OS, overall survival.

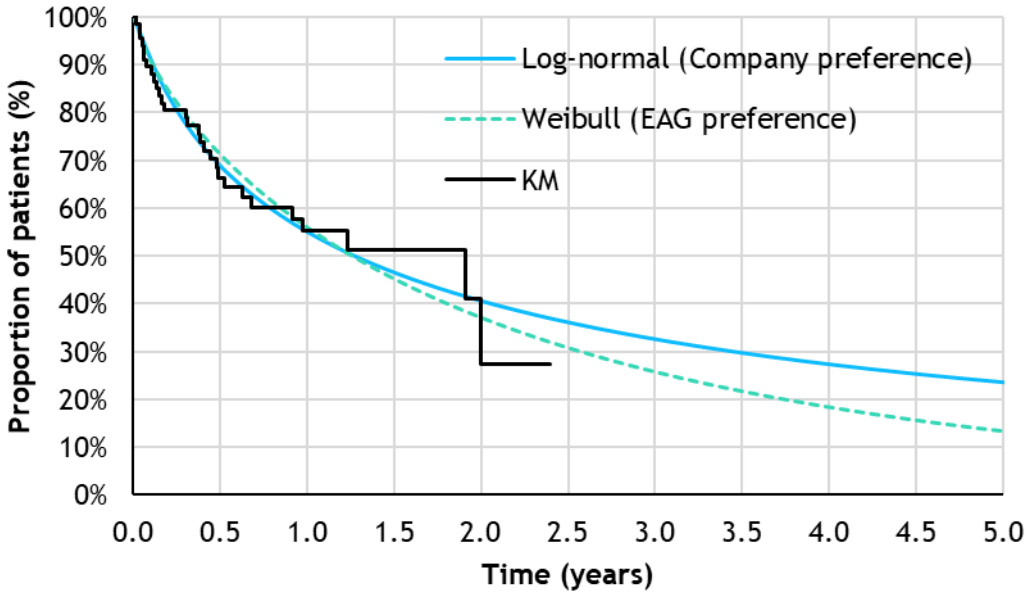
Determining a plausible extrapolation for EFS is challenging, since this represents a composite endpoint (i.e., it combines pre-relapse/pre-progression deaths with relapse/progressions). Despite challenges in determining a plausible extrapolation, it is the Company's view that the specification of a Weibull model for EFS does not adequately capture the expected pattern of hazards for an EFS event. Patients that remain event-free for a sustained period of time are most likely in remission – the economic model estimates that at 3 years, [redacted]% of event-free patients in the IVO+AZA arm are also in remission. This means that from t = 0 years to t = 3 years, the probability of an EFS event is expected to *decrease* as the proportion of patients that are both event-free *and* in remission *increases*.

Accordingly, and in line with clinical expectation, the initial hazard of an EFS event is expected to be relatively high, which will then reduce over time, plateauing at a rate similar to the risk of death in the age- and sex-adjusted general population. Both the exponential and Weibull model do not fully reflect this expected pattern. The hazard rate projected by the Weibull model leads to an over-estimation of EFS in the short-term, and an under-estimation of EFS in the long-term – this can be seen by comparing the two models fits in the diagram below.

Comparison of Company and EAG preferences for EFS

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form



Key: EAG, External Assessment Group; EFS, event-free survival; KM, Kaplan-Meier.

For completeness, the Company also highlights an inconsistency which is obtained when combining the choice of an exponential model for EFS, alongside the base-case option of a Weibull model for time on treatment (ToT). The resultant combination of curves is presented in the figure below. This plot shows that the EFS and ToT curves cross at approximately [redacted] years, leading to a proportion of patients being progressed or relapsed and still receiving treatment. This is not clinically plausible, and is not aligned with the AGILE study design, which describes continuation with IVO+AZA based on the following: *"*[People] *were to continue to receive therapy with ivosidenib or placebo + azacitidine until death, disease relapse, disease progression, development of unacceptable toxicity (adverse event), confirmed pregnancy, withdrawal by subject, protocol violation, or End of Study."* The crossing of the KM estimates is due to the restricted duration of follow-up available for the EFS endpoint, as compared to ToT.

Inconsistency of EFS and ToT when exponential model selected for EFS

[redacted]

Key: EAG, External Assessment Group; EFS, event-free survival; KM, Kaplan-Meier; ToT, time on treatment.

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

	Summary of company's key points: • The choice of OS model has little impact on results, owing to the cure assumption, but both log-normal and Weibull provide a much better fit to the AGILE data versus exponential. Company aligns with EAG's preference for **Weibull** for **OS**, given feedback from first AC meeting. • The choice of EFS model should be considered in line with the cure assumption, the expected pattern of hazards until this time point, and how this interacts with the estimation of treatment duration. Company maintains its preference for **log-normal** for **EFS**, as this model best reflects the probability of an EFS event over time.
5	**Transfusion costs** The Company would like to clarify that the model is set up based on amount of time patients spend in a particular health state (e.g., event-free and in remission), and so this is why patients on IVO+AZA incur lower costs related to blood transfusions. The model associates health state with transfusion requirement, and so any differences in transfusions between treatment arms are driven by health state occupancy, **not** treatment assignment. Patients on any treatment that are both event-free and in remission are assumed to require fewer transfusions, compared to those patients that are event-free but are not in remission. Transfusion frequency was estimated directly from data collected in the AGILE study (using both treatment arms of the AGILE study), to quantify the expected difference in transfusion frequency for event-free patients according to remission status. The requirement for blood transfusions is expected to increase once patients relapse or experience progression of their disease. However, insufficient data were available from the AGILE study to determine the increase in transfusion frequency once patients relapse or progress, compared to patients that are event-free and not in remission. Therefore, the model assumes that transfusion frequency is the same for relapse or progressed patients and patients that are event-free but not in remission. This was a conservative assumption made due to the absence of data to formally quantify further increases in blood transfusion requirements. To illustrate this, an exploratory analysis has been undertaken which assumes a 50% increase in blood transfusions for all treatment arms for patients that relapse or progress, versus event-free patients that are not in remission. The results of this analysis are provided at the end of this response document. While there are no direct comparisons between IVO+AZA and VEN+AZA, the Company wishes to highlight a supporting piece of analysis that was undertaken at the request of the German Federal Joint Committee (G-BA). In this analysis, transfusion independence (TF-ind) data from the AGILE and VIALE-A studies were compared using a consistent measure (that is, transfusion independence for at least 24 weeks). The analysis showed that 34 of 73 patients (46.6%) on the IVO+AZA arm of the AGILE study had TF-ind (≥24 weeks), whereas in VIALE-A, 64 of 210 patients (35.2%) on the VEN+AZA arm had TF-ind (≥24 weeks). The results for AGILE can be found here, whereas the results for VIALE-A can be found here. In addition, although not a comparative analysis, the company has extracted additional data from the AGILE study concerning transfusion units in Cycle 1 for subjects in the IVO+AZA arm. For IVO+AZA in AGILE, a median of 2 blood units and 2 platelet units were used, which is expected to be lower than what is typically observed for patients receiving VEN+AZA in practice. **Summary of company's key points:** • The economic model includes cost savings associated with IVO+AZA linked to a reduction in blood transfusions, due to better remission rates. • A scenario analysis has been conducted showing that if transfusion requirements increase upon progression or relapse, then cost-effectiveness estimates would be improved. • While incompatible with the economic model, supporting data of transfusion independence further substantiates an expected improvement in terms of a reduced requirement for transfusions for IVO+AZA versus VEN+AZA.

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

6	**Length of stay in hospital following initiation of VEN+AZA** Two sources of hospitalisation length of stay for VEN+AZA were provided: 14 days (based on a study by Othman *et al.*, [2021]) and 32 days (based on a study by Rausch *et al.*, [2021]). As described previously, there are pros and cons associated with each source. Othman *et al.* reflects the experience of UK patients, but specifically during the COVID-19 pandemic (April 2020 to August 2021) during which inpatient resources were critically constrained. Patients included in the study by Othman *et al.* were deemed eligible for intensive treatment, where venetoclax was offered as an alternative therapy according to COVID-19 guidelines that were in place during the pandemic. The NHS temporarily made venetoclax available as an alternative to intensive chemotherapy, with the aim of reducing both mortality (associated with COVID-19) and healthcare resource use (by treating patients in an outpatient rather than inpatient setting). The cohort of patients described by Othman *et al.* are expected to be fitter than the population considered in this appraisal, since these patients were deemed eligible for intensive treatment (where eligibility is determined based on patient fitness). Furthermore, hospital stays during the pandemic are unlikely to reflect current practice, owing to the unprecedented demand on NHS resources during this time (and that the purpose of making venetoclax available during the pandemic was to specifically reduce healthcare resource use). Consequently, the average length of stay in this study (reported as 14 days) is highly likely to be a substantial underestimate of the expected length of stay for a population deemed ineligible for intensive treatment treated in current NHS practice. Rausch *et al.* reflects a pre-pandemic study period (November 2014 to December 2019), though included patients were treated in the US. Despite this, the findings of the study by Rausch *et al.* were not directly influenced by changes in policy that were temporarily imposed during the pandemic. As such, this study is expected to represent a more accurate reflection of both the relevant patient population expected to receive VEN+AZA in practice, as well as how they would be managed without the unprecedented demand on NHS resources imposed by the pandemic. Taking into consideration the pros and cons of each source, in the Company's revised base-case analysis, an average across both sources has been included, representing 23 days for VEN+AZA. This is expected to represent a more realistic estimate of the average duration of hospitalisation for patients initiated with VEN+AZA in current NHS practice. **Summary of company's key points:** • Othman *et al.*, (2021) represents hospitalisation days for a population who temporarily were able to receive venetoclax during the COVID-19 pandemic. This is not expected to represent the population relevant to this appraisal managed in current NHS practice. • Rausch *et al.*, (2014) represents a population more closely aligned to the population relevant to this appraisal, and the findings are not influenced by the COVID-19 pandemic. However, this study was conducted in the US. • The Company's base-case analysis has been updated to use an average across both sources of 23 days for VEN+AZA.
7	**IDH1 mutation testing cost** Based on information received by the Company, following the introduction of IVO+AZA there may need to be an element of service redesign to improve the timeliness of next-generation sequencing (NGS), although this is considered *service redesign* rather than introduction of a new test associated with additional cost. The British Society of Haematology (BSH) consensus on molecular testing does not recommend a polymerase chain reaction (PCR) test and states that reporting of an NGS panel needs to be under 14 days, including IDH1 results as part of a myeloid panel.[14] Therefore, there is no need to include the cost of a PCR test as part of the economic evaluation, and there is also no need to include the cost of NGS since this is already conducted.

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

	In addition, the 2020 European Society for Medical Oncology (ESMO) guidelines recommend testing for mIDH1 to identify patients who may benefit from targeted treatments. The European LeukemiaNet (ELN) 2022 guidelines recommend screening for mIDH1 with results preferably available in 3 to 5 days. In the UK, mIDH1 testing is already a part of routine diagnostic practice, via the myeloid NGS panel. The Company does not consider it appropriate to include the cost of IDH1 mutation testing in its preferred base-case analysis. Furthermore, the Company does not have a cost available to inform the model to consider further analyses including the cost of service redesign. However, the model has been updated to include functionality to produce results including or excluding IDH1 mutation testing, should this be required by the AC. For the cost of an IDH1 test, the same cost as per NICE TA948 (ivosidenib for treating advanced cholangiocarcinoma with an IDH1 mutation after at least 1 therapy) is used (£34), with an assumed incidence of IDH1 mutation of 8% (midpoint of 6-10%). This means that in the scenario with IDH1 mutation costing enabled, an additional cost of £425 is included within the IVO+AZA arm (i.e., 34 / 8%). The results of this analysis are provided at the end of this response. To re-iterate, the Company does not consider this to be an appropriate cost, but a scenario is provided for completeness. **Summary of company's key points:** • The Company does not believe the cost for IDH1 mutation testing should be included within the model, since this is now recommended as part of a routine NGS panel. While there may be a need for service redesign, this does not warrant inclusion of additional MRU costs for a test already routinely funded. • Despite this, the model retains functionality to explore results with and without this cost included. As a proxy, a cost of £34 per test has been included per the only other NICE appraisal which included a cost for identifying IDH1m (TA948: ivosidenib for treating advanced cholangiocarcinoma with an IDH1 R132 mutation after 1 or more systemic treatments).
8	**Concluding remarks** In this response, the Company has endeavoured to address the key outstanding areas of uncertainty highlighted by the AC in the first AC meeting, through providing a combination of further evidence and analyses, alongside added descriptions and clarifications of evidence presented previously. People with IDH1-mutated AML represent a small population for whom treatment options are currently limited, and are not specifically targeted towards the unique characteristics of their disease. Ivosidenib, in combination with azacitidine, represents the first-in-class targeted small-molecule inhibitor of mutant IDH1, representing an important development in the treatment of this patient population; providing clinically relevant improvements in both event-free and overall survival, including an increased probability of achieving remission, compared with current care. On the basis of this, the company asks the AC to reconsider its recommendation to allow access to this drug for this small population.

Insert extra rows as needed

References

1. Institut de Recherches Internationales Servier. A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination With Azacitidine in Subjects ≥ 18 Years of Age With Previously Untreated Acute Myeloid Leukemia With an IDH1 Mutation [Internet]. clinicaltrials.gov; 2024 Mar [cited 2024 Jan 1]. Report No.: NCT03173248. Available from: https://clinicaltrials.gov/study/NCT03173248

2. Pollyea DA, DiNardo CD, Arellano ML, Pigneux A, Fiedler W, Konopleva M, et al. Impact of Venetoclax and Azacitidine in Treatment-Naïve Patients with Acute Myeloid Leukemia and IDH1/2 Mutations. Clin Cancer Res. 2022 Jul 1;28(13):2753–61.

3. Pratz KW, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Döhner H, et al. Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia. American Journal of Hematology. 2024;99(4):615–24.

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

4. Smith BD, Lachowiez CA, Ambinder AJ, Binder G, Angiolillo A, Vestin A, et al. A Comparison of Acute Myeloid Leukemia (AML) Regimens: Hypomethylating Agents Combined with Ivosidenib or Venetoclax in Newly Diagnosed Patients with IDH1 Mutations: A Real-World Evidence Study. In ASH; 2023 [cited 2024 Mar 19]. Available from: https://ash.confex.com/ash/2023/webprogram/Paper173033.html

5. National Institute for Health and Care Excellence (NICE). TA741: Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer [Internet]. prostate cancer. 2021 [cited 2024 Mar 19]. Available from: https://www.nice.org.uk/guidance/ta741/resources/apalutamide-with-androgen-deprivation-therapy-for-treating-hormonesensitive-metastatic-prostate-cancer-pdf-82611309932485

6. National Institute for Health and Care Excellence (NICE). TA666: Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma [Internet]. 2020 [cited 2024 Mar 19]. Available from: https://www.nice.org.uk/guidance/ta666/resources/atezolizumab-with-bevacizumab-for-treating-advanced-or-unresectable-hepatocellular-carcinoma-pdf-82609262480581

7. National Institute for Health and Care Excellence (NICE). TA587: Lenalidomide plus dexamethasone for previously untreated multiple myeloma [Internet]. 2019 [cited 2024 Mar 19]. Available from: https://www.nice.org.uk/guidance/ta587/resources/lenalidomide-plus-dexamethasone-for-previously-untreated-multiple-myeloma-pdf-82607208310213

8. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. New England Journal of Medicine. 2020 Aug 13;383(7):617–29.

9. Lachowiez C, Zettler C, Barcellos A, Belli A, Fernandes L, Hansen E, et al. Treatment Patterns and Real-World Outcomes Of Molecular Subgroups In Patients With Acute Myeloid Leukemia Receiving Frontline Venetoclax-Based Therapy [Internet]. 2023 [cited 2024 Mar 19]. Available from: https://library.ehaweb.org/eha/2023/eha2023-congress/386343/curtis.lachowiez.treatment.patterns.and.real-world.outcomes.of.molecular.html

10. Martinez-Cuadron D. Treatment Outcomes in Unfit Patients with Newly Acute Myeloid Leukemia According to IDH1 Mutational Status: Real World Evidence from the Pethema Epidemiologic Registry. In ASH; 2023 [cited 2024 Mar 19]. Available from: https://ash.confex.com/ash/2023/webprogram/Paper189800.html

11. Servier DATA ON FILE. Overall survival in newly diagnosed acute myeloid leukemia patients with mIDH1 or mIDH2 in the US, from an international real-world database (REAL-IDH) (submitted manuscript). -.

12. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345–77.

13. Scottish Medicines Consortium (SMC). SMC2615 Ivosidenib (Tibsovo) [Internet]. Scottish Medicines Consortium. 2024 [cited 2024 Mar 19]. Available from: https://www.scottishmedicines.org.uk/medicines-advice/ivosidenib-tibsovo-full-smc2615/

14. Mehta P, Telford N, Wragg C, Dillon R, Freeman S, Finnegan D, et al. Recommendations for laboratory testing of UK patients with acute myeloid leukaemia. Br J Haematol. 2023 Jan;200(2):150–9.

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form - Addendum

Addendum

A — **Company's revised base-case analysis**

The Company's revised base-case analysis comprises the following key settings/assumptions:

- Weibull model for OS.
- Log-normal model for EFS.
- Cure point at 3 years, with an SMR of 1.2 applied, and for the (arm-specific) proportion of patients in remission at 3 years (using the EAG's preferred approach).
- NMA results used to inform OS and EFS for VEN+AZA.
- No 'stopping rule' for 'uncured' patients.
- Number of days in hospital for VEN+AZA revised to an average of both sources (23 days).

The corresponding cell ranges and values used for each item in the list above is provided below for completeness. All other settings/assumptions are aligned with the previous base-case analysis.

- Weibull model for OS.
  - con_OS_ivo = "Weibull"
- Log-normal model for EFS.
  - con_EFS_ivo = "Log-normal"
- Cure point at 3 years, with an SMR of 1.2 applied, and for the (arm-specific) proportion of patients in remission at 3 years (using the EAG's preferred approach).
  - con_lts_enable = "Yes"
  - con_lts_time = 3
  - con_lts_arm_spec = "Yes"
  - con_lts_smr = 1.2
- NMA results used to inform OS and EFS for VEN+AZA.
  - con_OS_HR_ven = [redacted]
  - con_EFS_HR_ven = [redacted]
- No 'stopping rule' for 'uncured' patients.
  - con_all_tx_stop = 100
- Number of days in hospital for VEN+AZA revised to an average of both sources (23 days).
  - con_avg_hosp_ven = "Yes"

Revised company base-case analysis (deterministic)

Technologies	Total			Incremental			ICER
	Costs	LYG	QALYs	Costs	LYG	QALYs	
VEN + AZA	[redacted]	3.05	1.96				
IVO + AZA	[redacted]	4.36	[redacted]	[redacted]	1.31	[redacted]	[redacted]

Key: AZA, azacitidine; ICER, incremental cost-effectiveness ratio; IVO, ivosidenib; LYG, life-years gained; OS, overall survival; QALY, quality-adjusted life year; VEN, venetoclax.

Scenario analyses

Section	Scenario	ICER
3	Cure state: 2 year(s), SMR 1.0	[redacted]
3	Cure state: 2 year(s), SMR 1.1	
3	Cure state: 2 year(s), SMR 1.2	
3	Cure state: 2 year(s), SMR 2.0	
3	Cure state: 3 year(s), SMR 1.0	
3	Cure state: 3 year(s), SMR 1.1	
3	Cure state: 3 year(s), SMR 1.2	
3	Cure state: 3 year(s), SMR 2.0	
3	Cure state: 5 year(s), SMR 1.0	
3	Cure state: 5 year(s), SMR 1.1	
3	Cure state: 5 year(s), SMR 1.2	
3	Cure state: 5 year(s), SMR 2.0	
4	OS model: Exponential, EFS model: Exponential	
4	OS model: Weibull, EFS model: Weibull	
4	OS model: Log-normal, EFS model: Log-normal	
4	OS model: Exponential, EFS model: Log-normal	
4	OS model: Exponential, EFS model: Weibull	

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form - Addendum

	6	50% increase in transfusions after relapse or progression		[redacted]
	5	Apply 14 days hospitalisation for VEN+AZA		
	7	Include IDH1 mutation cost		
	Key: AZA, azacitidine; EFS, event-free survival; ICER, incremental cost-effectiveness ratio; IVO, ivosidenib; OS, overall survival; SMR, standardised mortality ratio; VEN, venetoclax.			
B	**Alternative ITC approach** Please see the separate document regarding the alternative ITC approach explored.			

Please return to: **NICE DOCS**

Addendum: Further indirect treatment comparisons (ITC) for IVO+AZA versus VEN+AZA

Background

In the first AC meeting, the outcomes from the network meta-analysis (NMA), comparing IVO+AZA to VEN+AZA were discussed. The AC concluded that based on the 95% credible intervals (CrIs) including 1, there was insufficient evidence to conclude there being a difference in effect between IVO+AZA and VEN+AZA. In this addendum to the Company's response, a description of additional analyses and corresponding results are provided to address the concerns raised by the AC.

Methods

Based on the limitations identified by the AC, the Company sought alternative methodology to generate an indirect treatment comparison (ITC) between IVO+AZA and VEN+AZA. Given that individual-level data are accessible for the AGILE study (of IVO+AZA), but not the VIALE-A study (of VEN+AZA), the Company conducted matching-adjusted indirect comparisons (MAICs) of IVO+AZA (Data cut-off: 30 June 2022) versus VEN+AZA (Data cut-off: 01 December 2021).

Anchored MAICs for OS and EFS were performed in which the baseline characteristics for patients in AGILE were matched to reflect the baseline characteristics of the ITT population in the VIALE-A study and to adjust for all potential imbalances across the study populations, including age, ECOG performance status, proportion of secondary AML, and poor cytogenetic risk.

When matching AGILE against the mIDH1 OS data for VEN + AZA, an unanchored MAIC approach was deemed more robust than an anchored MAIC and therefore the AZA arms from both studies were disregarded given that notable and implausible differences in median OS were observed between the AZA arms of the two key studies consider in this ITC (i.e., AGILE, VIALE-A), which raised concerns about the comparability of the AZA arms (specifically in the IDH1 subgroup). The 2.2 months median OS reported for AZA in VIALE-A was considerably lower than estimates previously reported for AZA in the literature (median OS in control arms of RCTs ranged from 4.1 months in Wei *et al.*, (2021)[1] to 9.6 months in DiNardo *et al.*, (2020)[2].

In total, three MAICs were conducted by the Company:

1. An *anchored* MAIC of *OS* for IVO+AZA versus VEN+AZA using the VIALE-A ITT population.
2. An *anchored* MAIC of *EFS* for IVO+AZA versus VEN+AZA using the VIALE-A ITT population.
3. An *unanchored* MAIC of *OS* for IVO+AZA versus VEN+AZA using the VIALE-A IDH1m subgroup.

Of note, due to a lack of reported baseline characteristics specifically for IDH1 patients in the VIALE-A study, the baseline characteristics for IDH1/2 patients from the Pollyea *et al.*, (2022)[3] study were used as a proxy. The Company urges caution in interpreting the results of the MAICs conducted, given the inherent limitations in the evidence base available to inform these analyses.

The MAICs are provided in this addendum as supportive evidence only. The Company maintains its preference for the NMA results, since the NMA represents a less complex ITC approach which maintains the randomisation of both studies. However, it is hoped undertaking two types of ITC methodologies will enhance the validity and the robustness of the overall finding that there is an expected benefit of IVO+AZA versus VEN+AZA with respect to the OS and EFS endpoints used to inform the cost-effectiveness analysis.

Results

Anchored MAIC of OS (ITT)

An anchored MAIC for OS in which the baseline characteristics for patients in AGILE were matched to reflect the baseline characteristics of the ITT population in the VIALE-A study. The pre- and post-matching baseline characteristics are presented in Table 1 for the base-case MAIC. One scenario analysis was explored adjusting for AML type.

Table 1: Baseline characteristics in the AGILE trial before and after matching to ITT population for OS (anchored MAIC)

Baseline characteristic	AGILE IPD pre-matching	AGILE IPD post-matching	VIALE- A (ITT)
Age (≥75) (%)	56.9	[redacted]	60.6
Sex, Male (%)	54.9	[redacted]	60.1
ECOG (0 or 1) (%)	65.3	[redacted]	55.2
AML type (De novo / Primary) (%)	74.3	[redacted]	75.2
AML type (Secondary) (%)	25.0	[redacted]	24.8
Cytogenetic risk (Intermediate (%)	63.9	[redacted]	62.9
Cytogenetic risk (Poor) (%)	24.3	[redacted]	37.1
Bone marrow blasts (<30%) (%)	19.4	[redacted]	29.2
Bone marrow blasts (≥30-50%) (%)	26.4	[redacted]	21.8

Key: AML, Acute Myeloid Leukaemia; ECOG, Eastern Cooperative Oncology Group; IPD, Individual patient data; ITT, intention-to-treat.

Table 2 summarises the unadjusted and adjusted median OS times (in months) of the AGILE trial and the VIALE-A study. The KM estimates are similar between the base-case and the scenario analysis which were explored before and after matching due to the overlap in the baseline characteristics within the two studies.

Table 2: Median OS times (in months) of AGILE before and after matching to ITT population for OS (anchored MAIC) and VIALE-A – new data cut

Analysis, N/ESS	Trial	Treatment arm	Median OS times (in months) (95% CI)
-	VIALE-A	VEN+AZA	14.7 (12.1, 18.7)
		AZA	9.6 (7.4, 12.7)
Naïve (for BC), N=144	AGILE (unadjusted)	IVO+AZA	29.3 (13.9, NR)
		AZA	7.9 (4.1, 12.8)
BC, ESS=[redacted]	AGILE (adjusted)	IVO+AZA	[redacted]
		AZA	
Naïve (for SA1), N=[redacted]	AGILE (unadjusted)	IVO+AZA	
		AZA	
SA1, ESS=[redacted]	AGILE (adjusted)	IVO+AZA	
		AZA	

Key: AZA, azacitidine; BC, Base case; CI, Confidence interval; ESS, Effective sample size; ITT, Intention to treat; IVO, ivosidenib; OS, Overall survival; SA, Scenario analysis; VEN, venetoclax

The results for this analysis are presented in Figure 1. As can be seen from Figure 1, all point estimates of the HR consistently favour IVO+AZA.

Figure 1: Hazard ratio estimates of OS for ivosidenib + azacitidine compared to venetoclax + azacitidine (all scenario analyses) – Anchored MAIC ITT

[redacted]

Key: CI, Confidence interval; HR, Hazard ratio; OS, Overall survival.

Results were closely aligned with the NMA (OS HR: [redacted]; 95%CI: [redacted]) in the anchored MAIC comparing to the ITT population from VIALE-A (OS HR: [redacted]; 95%CI: [redacted]), thus confirming the expected OS benefit of IVO+AZA relative to VEN+AZA, after adjusting for between-study imbalances in population characteristics.

Anchored MAIC of EFS (ITT)

An anchored MAIC for EFS (using similar EFS definitions between the two studies) in which baseline characteristics for patients in AGILE were matched to reflect the baseline characteristics of the ITT population in the VIALE-A study, was carried out. The pre- and post-matching baseline characteristics are presented in Table 3 for the base-case MAIC. Besides the base-case analysis, two scenario analyses were explored adjusting for sex, and ECOG status (Scenario analysis 1) and adjusting for sex, cytogenetic risk, and ECOG status (Scenario analysis 2).

Table 3: Baseline characteristics in the AGILE trial before and after matching to ITT population for EFS (anchored MAIC)

Baseline characteristic	AGILE IPD pre-matching	AGILE IPD post-matching	Pooled VIALE- A + Phase 1b – (IDH1/2)
Age (≥75) (%)	56.9	[redacted]	60.6
Sex, Male (%)	54.9	[redacted]	60.1
ECOG (0 or 1) (%)	65.3	[redacted]	55.2
AML type (De novo / Primary) (%)	74.3	[redacted]	75.2
AML type (Secondary) (%)	25.0	[redacted]	24.8
Cytogenetic risk (Intermediate (%)	63.9	[redacted]	62.9
Cytogenetic risk (Poor) (%)	24.3	[redacted]	37.1
Bone marrow blasts (<30%) (%)	19.4	[redacted]	29.2
Bone marrow blasts (≥30-50%) (%)	26.4	[redacted]	21.8

Key: AML, Acute Myeloid Leukaemia; ECOG, Eastern Cooperative Oncology Group; IPD, Individual patient data; ITT, intention-to-treat.

Table 4 summarises the unadjusted and adjusted median EFS times (in months) of the AGILE trial and the pseudo-IPD for VIALE-A study. The KM estimates for the base-case and the scenario analyses explored are again very similar before and after population adjustment.

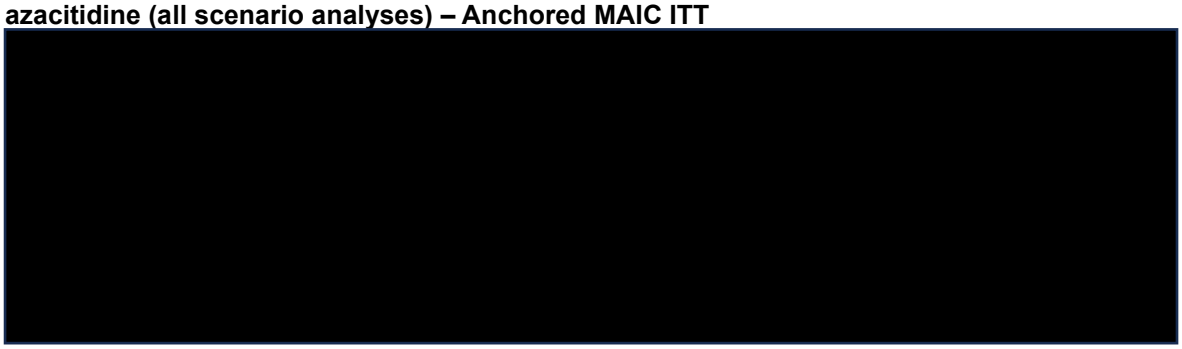
Table 4: Median EFS times (in months) of AGILE before and after matching to ITT population for EFS (anchored MAIC) and VIALE-A

Analysis, N=ESS	Trial	Treatment arm	Median EFS times (in months) (95% CI)
-	VIALE-A	VEN+AZA	9.8 (8.4, 11.8)
		AZA	7.0 (5.6, 9.5)
Naïve (for BC), N=144	AGILE (unadjusted)	IVO+AZA	22.9 (7.5, NR)
		AZA	4.1 (2.7, 8.6)
BC, ESS=[redacted]	AGILE (adjusted)	IVO+AZA	[redacted]
		AZA	
Naïve (for SA1 and SA2), N=[redacted]	AGILE (unadjusted)	IVO+AZA	
		AZA	
SA1, ESS=[redacted]	AGILE (adjusted)	IVO+AZA	
		AZA	
SA2, ESS=[redacted]	AGILE (adjusted)	IVO+AZA	
		AZA	

Key: BC, Base case; CI, Confidence interval; EFS, event-free survival; ESS, Effective sample size; NR, Not reached; SA, Scenario analysis.

The anchored MAIC for EFS showed a statistically significant improvement of EFS for IVO+AZA in all analyses except Scenario 2 (with 95% CI in this case of 1.00), as shown in Figure 2. As EFS is the endpoint considered to report the direct efficacy of combinations without considering potential confounding effects of subsequent treatment, this MAIC showed the superiority of IVO+AZA compared to VEN+AZA.

Figure 2: Hazard ratio estimates of EFS for ivosidenib + azacitidine compared to venetoclax + azacitidine (all scenario analyses) – Anchored MAIC ITT



Key: CI, Confidence interval; EFS, event-free survival; HR, Hazard ratio.

Results were closely aligned with the NMA (EFS HR: [redacted]; 95%CI: [redacted]) in the anchored MAIC comparing to the ITT population from VIALE-A (EFS HR: [redacted]; 95%CI: [redacted]), thus confirming the significant EFS benefit of IVO+AZA relative to VEN+AZA, after adjusting for between-study imbalances in population characteristics.

Unanchored MAIC of OS (IDH1m subgroup)

An unanchored MAIC for OS in which the baseline characteristics for patients in AGILE were matched to reflect the baseline characteristics of the VEN+AZA arm in the IDH1/2 post-hoc subgroup of VIALE-A reported in the Pollyea *et al.* study. For the unanchored MAIC, OS data for VEN+AZA were obtained from the IDH1 sub-population in the VIALE-A study, however, due to lack of baseline characteristics specifically for IDH1 patients, the baseline characteristics for IDH1/2 patients from the Pollyea *et al.* study were used instead. The pre- and post-matching baseline characteristics are presented in Table 5 for the base-case MAIC. Besides the base-case analysis, two scenario analyses adjusted for age and the percentage of bone marrow blasts (Scenario analysis 1) and adjusting for age, ECOG status, and the percentage of bone marrow blasts (Scenario analysis 2).

Table 5: Baseline characteristics in the AGILE trial before and after matching to IDH1 population for OS (unanchored MAIC)

Baseline characteristic	AGILE IPD pre-matching	AGILE IPD post-matching	Pooled VIALE- A + Phase 1b – (IDH1/2)
Age (≥75) (%)	54.2	[redacted]	65.4
ECOG (0 or 1) (%)	62.5	[redacted]	56.8
Bone marrow blasts (<30%) (%)	18.1	[redacted]	17.3
Bone marrow blasts (≥30-50%) (%)	22.2	[redacted]	24.7

Key: ECOG, Eastern Cooperative Oncology Group; IPD, Individual patient data; ITT, intention-to-treat.

Table 6 contains the median OS times (in months) of the AGILE trial before and after matching and also of the pseudo-individual patient data (IPD) of VIALE-A per scenario analysis.

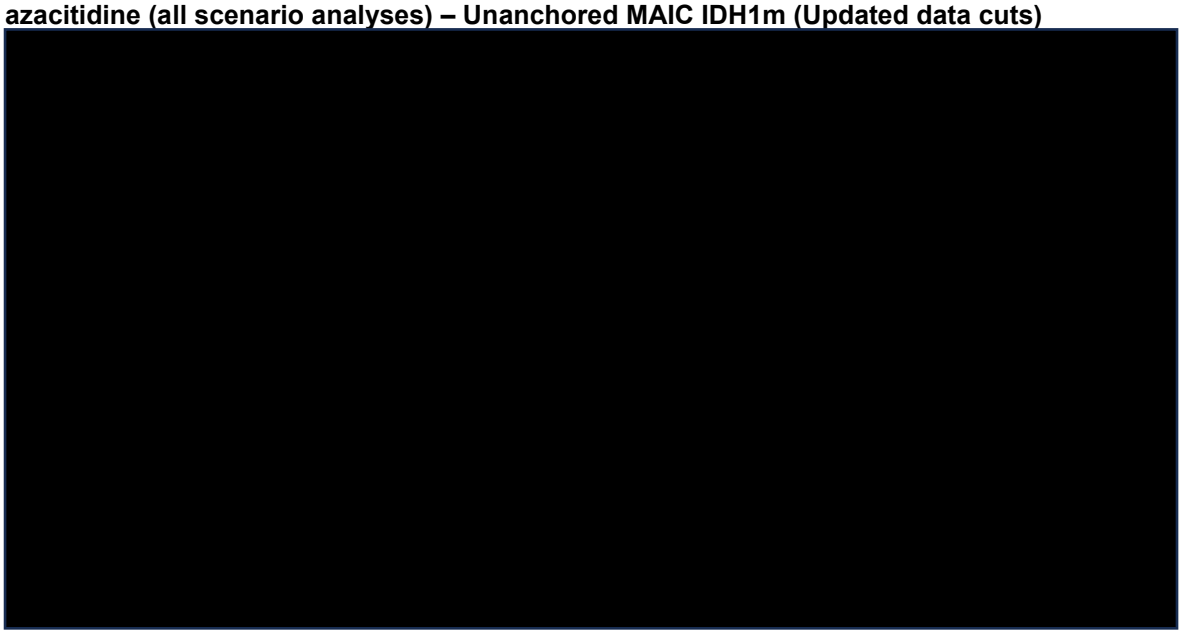
Table 6: Median OS times (in months) of AGILE before and after matching to IDH1 population for OS (unanchored MAIC) and VIALE-A

Analysis, N/ESS	Trial	Treatment arm	Median OS times (in months) (95% CI)
-	VIALE-A	VEN+AZA	10.2 (3.2, 31.1)
Naïve, N=71	AGILE (unadjusted)	IVO+AZA	29.3 (17.1, NE)
BC, ESS=[redacted]	AGILE (adjusted)	IVO+AZA	[redacted]
SA1, ESS=[redacted]		IVO+AZA	[redacted]
SA2, ESS=[redacted]		IVO+AZA	[redacted]

Key: BC, Base case; CI, Confidence interval; ESS, Effective sample size; NR, Not reached; OS, Overall survival; SA, Scenario analysis.

Results from the unanchored MAIC are presented in Figure 3, matching the AGILE trial to IDH1 population of the VIALE-A study using the baseline characteristics from pooled VIALE-A and phase Ib study reported by Pollyea *et al*. The point estimates, while uncertain, show a statistically significant improvement that consistently favours IVO+AZA.

Figure 3: Hazard ratio estimates of OS for ivosidenib + azacitidine compared to venetoclax + azacitidine (all scenario analyses) – Unanchored MAIC IDH1m (Updated data cuts)



Key: CI, Confidence interval; HR, Hazard ratio; OS, Overall survival.

Conclusions

Both types of ITC, NMA (respecting the randomisation) and MAIC (addressing differences in prognostic factors) are consistent and therefore underpin the expected benefit of IVO+AZA versus VEN+AZA in terms of EFS and OS. In view of the comparable results for the NMA and MAIC (after matching), the documented differences in baseline characteristics (age, cytogenetic risk, ECOG) had only little impact on the relative effect estimates. The consistency of the results, all in favour of IVO+AZA, whichever methods were used and confirms the validity of the ITC and the robustness of the results in this rare patient population. A summary of the ITC results is provided in Table 7.

Table 7: Summary of results comparing ITC methods

Method	**NMA**	**MAIC (anchored)**	**MAIC (unanchored)**
Population	**ITT**	**ITT**	**IDH1 population**
OS			
IVO+AZA vs. VEN+AZA	[redacted]	[redacted]	[redacted]
EFS			
IVO+AZA vs. VEN+AZA	[redacted]	[redacted]	-

Key: AZA, azacitidine; EFS, event-free survival; ITC, indirect treatment comparison; IVO, ivosidenib; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; OS, overall survival; VEN, venetoclax; vs., versus.

References

1. Wei AH, Panayiotidis P, Montesinos P, Laribi K, Ivanov V, Kim I, et al. 6-month follow-up of VIALE-C demonstrates improved and durable efficacy in patients with untreated AML ineligible for intensive chemotherapy (141/150). Blood Cancer J. 2021 Oct 1;11(10):163.

2. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. New England Journal of Medicine. 2020 Aug 13;383(7):617–29.

3. Pollyea DA, DiNardo CD, Arellano ML, Pigneux A, Fiedler W, Konopleva M, et al. Impact of Venetoclax and Azacitidine in Treatment-Naïve Patients with Acute Myeloid Leukemia and IDH1/2 Mutations. Clin Cancer Res. 2022 Jul 1;28(13):2753–61.

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 20 March 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Leukaemia Care

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 20 March 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	No change from submission earlier in the process
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 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	We urge the committee to come to a conclusion based on the available evidence for this submission. There are very few effective treatments for those who cannot have chemotherapy and therefore there is an urgent need for further treatment options to become available.
2	We ask the committee to consider if any of its remaining uncertainties can be addressed by use of the CDF.
3	We welcome the committee acknowledgement that a proportion of AML patients can be cured.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 20 March 2024. Please submit via NICE Docs.

4	We urge the committee to be more willing to accept uncertainties in this case, given a comparison directly to venetoclax was not available at the time the trial was set up.
5	We would like to see more information regarding the issue of scaling up IDH testing. Our clinical engagement elsewhere in the UK suggested this should be relatively easy and we ask that the committee requests further detail on costs from NHS England.
6	We are disappointed that the committee do not consider this to meet the severity modifier. We feel the modifier disadvantages older people at the end of life, even though a terminal illness is inherently a severe and life threatening situation.
7	The section of the document discussing costs of hospital stays fails to mention the clinical viewpoint on this question. Our clinical advice suggests that multiple and frequent hospital stays are a leading challenge due to side effects from venetoclax. We would like to see further clinical input on this point.

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 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) 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 draft guidance document, please submit these separately.

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

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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 20 March 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Jazz Pharmaceuticals

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 20 March 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A – no funding received
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A – no links to or funding from the tobacco industry
Name of commentator person completing form:	[redacted]

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	Section 3.1 states that 'ivosidenib is an oral treatment that can be taken at home'. There is potential for this statement to be misleading. Ivosidenib is administered concurrently with subcutaneous azacitidine, which is not a homebased treatment in most cancer centres. The

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 20 March 2024. Please submit via NICE Docs.

	statement should be amended to clarify how it is administered, or 'where home treatment is provided' be added to the sentence.
2	
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) 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 draft guidance document, please submit these separately.

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

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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 20 March 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AbbVie Ltd

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 20 March 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	NA – Manufacturer of Venetoclax
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** 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	Section 3.13 states that the "*choice of modelled hospitalisation days was the main driver of its claim that using ivosidenib would lead to cost savings related to health care expenditure*"

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 20 March 2024. Please submit via NICE Docs.

	AbbVie agree with the EAG and Committee that 14 days for the venetoclax plus azacitadine (VenAza) hospital stay is the more appropriate length. We consider the Othman paper a more appropriate source for this data given it is UK Real World Evidence on the use of VenAza and Venetoclax plus Low Dose Cytarabine as an alternative to intensive chemotherapy during the COVID pandemic. It includes 301 patients coming from 65 NHS hospitals so is considered representative of UK practise.
2	Section 3.6 states that the company stated "*that because venetoclax was not designed to specifically target IDH1, its efficacy is not expected to be different in people who have the mutation and those who do not*" We disagree with this statement as many therapies can show increased efficacy in mutational subgroups despite not being designed to specifically target that mutation.
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) 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 draft guidance document, please submit these separately.

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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 20 March 2024. Please submit via NICE Docs.

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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 20 March 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	N/A

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 20 March 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
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 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	**Comment on section 3.6 (Committee-discussion, Network meta-analysis)** I am commenting as the clinical expert present at the meeting. Since the meeting, we have performed further analysis of a large cohort of patient treated with venetoclax + azaciditine during the coronavirus pandemic (n=587). This cohort is the same as the Othman reference cited in the report, which was a conference abstract of an earlier data

NICE National Institute for Health and Care Excellence

Ivosidenib with azacitidine for untreated acute myeloid leukaemia with an IDH1 R132 mutation [ID6198]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 20 March 2024. Please submit via NICE Docs.

	cut. In the final data cut of this cohort the median overall survival was 13.6 months. 45 patients had IDH1 mutations and we could not detect a difference in survival in this group compared to patients without this mutation on multivariable analysis (HR 0.84 95% CI 0.5 - 1.4). This manuscript is currently being prepared for submission and I'm very happy to share a copy in confidence if that would be helpful.

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 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) 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 draft guidance document, please submit these separately.

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

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

Ivosidenib with azacitidine for untreated IDH1-positive acute myeloid leukaemia [ID6198]

A Single Technology Appraisal

Addendum #1

EAG ACD Response
March, 2024

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School South Cloisters St Luke's Campus Heavitree Road Exeter EX1 2LU
Authors	**Maxwell S. Barnish**[1] **Brian O'Toole**[1] **Elham Nikram**[1] **Justin Matthews**[1] **Sophie Robinson**[1] **Ahmed Abdelsabour**[1] **Steven Knapper**[2] **Edward C.F. Wilson**[1] [1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter [2] School of Medicine, Cardiff University, Cardiff
Correspondence to	Dr Maxwell S. Barnish 3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; m.s.barnish@exeter.ac.uk
Source of funding	This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR 136108.

Declared competing interests of the authors	None
Acknowledgments	The authors acknowledge the administrative support provided by Mrs Sue Whiffin and Ms Jenny Lowe (both PenTAG).
Rider on responsibility for document	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors
This addendum is linked to EAG report	Barnish MS, et al. Ivosidenib with azacitidine for untreated IDH1-positive acute myeloid leukaemia [ID5198]: A Single Technology Appraisal. Peninsula Technology Assessment Group (PenTAG), 2023.
Copyright	

1. INTRODUCTION

The purpose of this addendum is to provide the EAG's response to the company's ACD response ahead of AC2.

2. RESPONSES TO COMPANY COMMENTS

2.1. Comment 1: Relative effect of IVO+AZA vs VEN+AZA

The company supplied evidence from additional indirect treatment comparisons (ITCs). At AC1, the committee decided that, since the 95% credible intervals from the presented ITCs included 1, there was insufficient evidence to conclude that there was a difference in effect between IVO+AZA and VEN+AZA. The committee requested a scenario analysis including a hazard ratio of 1 (i.e. zero difference in treatment effect between IVO+AZA and VEN+AZA).

The company declined to undertake the analysis and sought alternative methodology to generate an ITC between IVO+AZA and VEN+AZA. The company conducted a MAIC analysis between these treatment regimens, since individual patient data were available for the AGILE study (of IVO+AZA), but not the VIALE-A study (of VEN+AZA).

Anchored MAIC analyses were conducted in which the baseline characteristics for participants in AGILE were matched to reflect the ITT population in VIALE-A. The company said that this adjusted for all potential imbalances across the studies, including age, ECOG performance status, proportion of secondary AML, and poor cytogenetic risk. Anchored MAIC analyses were conducted separately for the EFS and outcomes.

An unanchored MAIC analysis was also conducted for OS in the IDH1m subgroup. The company considered this to be more robust than an anchored MAIC in this subgroup because of 'notable and implausible' differences in median OS between the AZA arms for the IDH1m subgroup in these two studies, which the EAG understands to refer to the observed results (2.2 months vs 7.9 months). The EAG notes that an anchored MAIC makes the strong assumption of 'conditional constancy of absolute effects' and therefore the 'weighting model must include every effect modifier and prognostic variable' (TSD 18, p35[1]). The EAG anticipates that, were all such variables correctly included, the adjusted placebo arm outcomes would be similar, but has not seen evidence to support that. Also, the unanchored MAIC used a reduced covariate set (age, ECOG, bone marrow blasts) compared to the anchored, despite the more stringent modelling requirements. Finally, it remains uncertain whether any other, possibly unobserved, prognostic and effect modifier variables might have been omitted, given that all are required by the assumption. For this reason, the EAG believes the unanchored MAIC results as presented are of limited value.

A summary of the company's ITC results can be found in Table 1. This includes the NMA from the original company submission. In the ITT population, the results for the NMA and anchored MAIC for OS are very similar, both showing that the confidence intervals cross 1 . For EFS, the results are very similar too. In the NMA, the credible intervals cross 1, [redacted]. The EAG considered this not to make a material difference to the interpretation of the findings.

Table 1. Summary of results comparing ITC methods

Method	NMA	MAIC (anchored)	MAIC (unanchored)
Population	ITT	ITT	IDH1 population
OS			
IVO+AZA vs. VEN+AZA	[redacted]	[redacted]	[redacted]
EFS			
IVO+AZA vs. VEN+AZA	[redacted]	[redacted]	-

Source: Company addendum, Table 7.

Key: AZA, azacitidine; EFS, event-free survival; ITC, indirect treatment comparison; IVO, ivosidenib; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; OS, overall survival; VEN, venetoclax; vs., versus.

The company stated that these additional analyses were not intended to inform any specific modelling analyses, as the company still believes that the NMA as submitted to AC1 provides the most robust available evidence to address relative efficacy. Instead, the company intended these additional ITC results to provide supportive information to aid with interpretation and address the committee's concerns regarding the relative efficacy of IVO+AZA and VEN+AZA.

The EAG considered the different ITC methods in the ITT population to not offer meaningfully different results, and agrees with the company that the NMA is the most reliable analysis. As such, the EAG considered that its concerns regarding the relative efficacy of IVO+AZA and VEN+AZA have not been resolved (these can likely only be resolved with additional data). Nevertheless, the EAG agrees with the company that absence of evidence is not evidence of absence of effect, and notes that that point estimate hazard ratios from the NMA are all below 1 (Table 1). The balance of probabilities would be in favour of there being some treatment effect, but chance cannot be adequately ruled out as explaining this finding. However, a scenario with a HR of 1 would provide a 'worst case scenario' limit which the EAG believes to be potentially informative for the committee and so presented the results of that analysis in this addendum (Section 3).

2.2. Comment 2: Evidence for IDH1 mutation as a treatment effect modifier for VEN+AZA

The EAG agrees with the company that there is no conclusive evidence that IDH1 mutation is a treatment effect modifier. In the VIALE-A study there is superficial evidence of a stronger treatment effect in the IDH1m subgroup (see DiNardo et al [2] fig 3). This was further discussed in the EAG report pp70-71 which concluded that there is not strong statistical support for effect modification.

The company's response states that the recent results in the updated publication on VIALE-A (Pratz et al[3]) 'further demonstrate that IDH1 is not a treatment effect modifier'. The EAG notes that the updated information includes that the median OS in the IDH1 subgroup is 10.2 months, compared to 14.7 months in the ITT, and Pratz et al. report a point estimate of HR = 0.28 among the IDH1 patients, compared to HR=0.58 in the ITT. The EAG believes the situation is maintained, in which there is a suggestion that treatment effectiveness differs in the IDH1m subgroup, but without any strong statistical support. The EAG does not see there has been a 'demonstration' of no effect modification by IDH1. The company argues that the IDH2 subgroup effect (median OS 19.9 months) is the 'driver' of the observed IDH1/2 subgroup differences, which the EAG believes is not relevant.

The company carried out a MAIC restricted to the IDH1m subgroup from the VIALE-A trial (see Comment 1). While in principle this could account for effect modification by IDH1 status, and for further differences in prognostic and effect modifiers between the trials, the EAG argues that the requirements of an 'unanchored' MAIC are very strong and have not been met in that analysis.

The EAG also re-iterates the clinical advice it received, taking account of treatment mechanisms, that there is no anticipated difference in treatment effect for the IDH1m subgroup.

The EAG was not able to assess the three further sources of evidence presented by the company due to time limitations.

2.3. Comment 3: Scenarios exploring the cure assumption

The company's base case assumed that those in the remission health state are functionally cured after 3 years. As the hazard of mortality remained above that of the general population at the end of the trial, the committee requested scenarios with a cure assumption at 2, 3 and 5

years, with SMRs of 1.1, 1.2 and 2 applied. The company submitted analyses as requested as well as a set of scenarios at an SMR of 1, comprising a total of 12 scenarios with a company preferred base case implementing a cure at 3 years with an SMR of 1.2. The company stated that there is no clear evidence in favour of a particular SMR, but that 1.2 was accepted in a previous appraisal (TA765).

The company also modified the model such that only those patients achieving CR/CRi were moved to the cured health state, rather than all patients in the EFS state. This meant 96.9% of IVO+AZA patients in the EFS state were moved to the cured state at 3 years and 90.6% in the VEN+AZA arm.

The EAG thanks the company for providing the additional analyses and agrees with the approach to moving only patients with CR/CRi to the cured state in both arms, if the committee decides a cure assumption is valid. The company presented the results of its analysis in its ACD response. The EAG applied the same scenario set to its own base case, shown in Table 5 (based on PAS discount for ivosidenib and list prices for other drugs). A repeated analysis including PAS discounts for all drugs is in the confidential appendix to this addendum.

The EAG is not able to argue for the merit of one scenario over another, save for the observation that the hazard of mortality at trial end was higher than for the general population (but uncertain), and that a flattening of the curve is not necessarily indicative of a cure due to small numbers at risk: the confidence intervals at the end of the observed data will be very wide. The addition of an SMR to those in the cured state provides a compromise allowing for increased mortality despite the ‘cure’ definition.

2.4. Comment 4: Curve selection

The committee questioned the company’s choice of the log-normal curve for OS and EFS for IVO+AZA. At AC1 the EAG preferred Weibull for both OS and EFS. The committee considered that the exponential may produce more clinically plausible estimates in the longer term.

The company responded that it felt the exponential provided a poor fit to the observed data for OS. Whilst the EAG agrees with this observation, the key issue is whether the long term extrapolations (beyond the observed data) are clinically plausible: a good fit to the observed data can generate highly implausible longer term predictions, and vice versa. As the EAG stated in its report (EAG report, P91), 2 of 3 clinicians consulted by the company felt the Weibull and exponential curves produced more plausible (long term) OS estimates. The EAG notes that

the company's preferred base case for OS is now the Weibull, consistent with the EAG's previously preferred base case. The EAG is not able to recommend between the Weibull and exponential.

For EFS, the company prefers to retain the log normal on that grounds that it better characterises the observed hazard through time than the Weibull. Again, whilst the EAG agrees with this observation, it reiterates its point about the need to generate plausible long term extrapolations, and, as stated in its report (p86), clinical opinion to the EAG was that the "EFS estimates produced for IVO+AZA appeared to lack clinical plausibility… a Weibull parametric curve appeared more reasonable". The EAG therefore considers either the Weibull or exponential to be more appropriate.

2.5. Comments 5-7: Cost assumptions

The committee was concerned that the company's claim that using IVO+AZA would lead to cost savings related to healthcare expenditure was not supported by the evidence or explained well enough. This related specifically to blood transfusion costs and length of hospital stay.

The company responded with additional justification for transfusion costs and length of stay. The company's post-AC1 base case no longer makes a claim for cost savings. However, a breakdown of costs by category and arm are in Table 2. The major difference is in medical resource use, with the company estimating a cost of £97,094 in the IVO+AZA arm vs £119,240 in the VEN+AZA arm. This difference mostly disappears in the EAG's base case (£121,351 vs £125,845), and is almost entirely driven by the assumed survival function for EFS (log-Normal for company, Weibull for EAG). The Weibull leads to a higher proportion of patients in the progressed state compared with log-Normal, which is associated with a higher cost than the EFS.

Table 2 Breakdown of costs, Company and EAG base cases

	Company			EAG		
Item	**IVO + AZA**	**VEN + AZA**	**AZA**	**IVO + AZA**	**VEN + AZA**	**AZA**
Drug	[redacted]	[redacted]	£6,322	[redacted]	[redacted]	£6,322
Admin	£25,342	£15,402	£9,855	£25,273	£15,507	£9,855
MRU	£97,094	£119,240	£88,636	£121,251	£125,845	£88,636
AEs	£1,032	£1,643	£954	£1,032	£1,643	£954
EOL	£5,159	£5,274	£5,498	£5,206	£5,320	£5,498

Total	[redacted]	[redacted]	**£111,265**	[redacted]	[redacted]	**£111,265**

With respect to IDH1 mutation testing cost, the company argued that this should be excluded on the grounds of this requiring a service redesign rather than introduction of a new test at additional cost. However, as per the committee's request, the company calculated a scenario with a cost of £34 per test (equating to £425 per patient entering the model pathway, assuming an 8% prevalence = £34/0.08).

The company argued that the source used by the EAG for length of stay (Othman et al.[4]) represented a time period during the COVID-19 pandemic when resources were severely constrained, as well as modification of treatment patterns making venetoclax available as an alternative to intensive chemotherapy. The company therefore claims it reflects an artificially low length of stay compared with routine practice. The Rausch et al.[5] study is from 2014-2019, prior to the pandemic, and whilst is a US setting, the company considers this more representative of treatment patterns compared with the Othman study. The company's base case represented a compromise for length of stay in the VEN+AZA arm between the EAG's preference (14 days) and the company's previous base case (32 days), i.e. 23 days.

2.6. Additional comments from the EAG

The EAG maintains its position that all relevant comparators should be included in the analysis, and that frequency of use is not an appropriate justification for exclusion. The analysis should therefore comprise a fully incremental analysis of IVO+AZA vs VEN+AZA vs AZA.

2.7. Summary of changes to Company base case

The committee and company's preferred assumptions are in Table 3. Briefly, differences of opinion remain between the company and committee over functional form for EFS in the IVO+AZA arm, length of stay for VEN+AZA and inclusion of IDH1 testing costs.

Table 3 Committee and Company Preferred Assumptions

Assumption	Committee preference	Company preference	EAG preference	Agreement
OS, IVO+AZA	Weibull or exponential	Weibull	Weibull or exponential	**NA**
EFS, IVO+AZA	Weibull or exponential	Log normal	Weibull or exponential	**No**
Cure point & SMR	Various scenarios	3 year, 1.2 SMR No stopping rule for non CR/CRi	As per committee	**NA**
Relative Dose Intensity	100% for VEN and IVO	100% for VEN and IVO	100% for VEN and IVO	**Yes**
CR/CRi	Informed by NMA	Informed by NMA	Informed by NMA	**Yes**
Length of Stay	14 days for VEN+AZA	23 days for VEN+AZA & IVO+AZA	14 days for VEN+AZA	**No**
Cost of rapid testing for IDH1	Include	Exclude	Include	**No**

3. EAG ADDITIONAL ANALYSES AND REVISED BASE CASE

The company's revised base case reports an incremental comparison between IVO+AZA and VEN+AZA alone. As stated above, the EAG considers AZA monotherapy a valid comparator and therefore presents the company revised base case including AZA. In all scenarios, comparators are presented in order of increasing cost to facilitate fully incremental analysis.

The EAG is not able to argue in favour of a cure assumption or the specifics thereof, or between exponential and Weibull functions for survival curves. The EAG therefore defines a nominal base case as assuming Weibull functions, the company's base case cure assumptions (3 years with 1.2 SMR), and inclusion of the committee's preferences regarding length of stay and IDH1 testing costs.

Table 4 reports the company revised base case (albeit fully incremental analysis). Subsequent rows (2-4) show the individual impact of adding the committee's preferences regarding length of stay, cost of rapid testing, and assuming a Weibull distribution for EFS. Row 5 is the EAG's (nominal) base case, merging 2-4 together. Following this, scenarios are presented as variants of 5, firstly assuming a hazard ratio of 1 between IVO+AZA and VEN+AZA (i.e. no treatment effect), secondly assuming exponential functions for OS and EFS in IVO+AZA and finally excluding the cure assumption. Table 5 shows the impact of the various scenarios considered by the company regarding cure and SMR as variants on the EAG base case (row 5 of Table 4) and presents fully incremental ICERs against the next-best non-dominated option.

Use of a 14 day LoS vs 23 days for VEN+AZA has zero impact on the fully incremental ICER as VEN+AZA is extendedly dominated. However, this approximately doubles the pairwise ICER. Assuming no difference in treatment effect between IVO+AZA and VEN+AZA yields an ICER of [redacted]. As stated previously, the EAG believes this to represent an upper, pessimistic bound, and the balance of probabilities favours a positive treatment effect. The ICER is highly sensitive to cure assumptions, lying within NICE's upper limit of £30,000/QALY only when the cure assumption is triggered at less than 3 years.

Table 4 Company and Committee/EAG preferred base case and scenarios (deterministic analyses)

Assumption	Comparator	Total Costs	Total QALYs	ICERs	Notes
1. Company revised base-case	AZA	£111,265	0.84		(OS Weibull, EFS Log-normal)
	VEN+AZA	£160,209	1.96	Extendedly dominated	
	IVO+AZA	[redacted]	[redacted]	[redacted]	
2. 14 day LoS for VEN+AZA	AZA	£111,265	0.837		As (1) but 14 day LoS for VEN+AZA
	VEN+AZA	£153,039	1.959	Extendedly dominated	
	IVO+AZA	[redacted]	[redacted]	[redacted]	
3. Include IDH1 testing	AZA	£111,265	0.837		As (1) but including cost of IDH1 testing
	VEN + AZA	£160,209	1.959	Extendedly dominated	
	IVO + AZA	[redacted]	[redacted]	[redacted]	
4. EFS Weibull (IVO+AZA)	AZA	£111,265	0.837		As (1) but Weibull EFS
	VEN + AZA	£174,241	1.776	Extendedly dominated	
	IVO + AZA	[redacted]	[redacted]	[redacted]	
5. EAG base case	AZA	£111,265	0.837		(2), (3) and (4) in aggregate.
	VEN + AZA	£167,070	1.776	Extendedly dominated	
	IVO + AZA	[redacted]	[redacted]	[redacted]	
6. HR = 1, IVO+AZA v VEN+AZA	AZA	£111,265	0.837		Variant on (5)
	VEN + AZA	£166,836	2.676	£30,222	
	IVO + AZA	[redacted]	[redacted]	[redacted]	
7. OS & EFS exponential (IVO+AZA)	AZA	£111,265	0.837		Variant on (5)
	VEN+AZA	£161,184	1.410	Extendedly dominated	
	IVO+AZA	[redacted]	[redacted]	[redacted]	
8. No cure assumption	AZA	£115,408	0.786		Variant on (5)
	VEN+AZA	£183,697	1.494	£96,381	
	IVO+AZA	[redacted]	[redacted]	[redacted]	

Table 5 Scenario analyses on time to cure and SMR (EAG base case, list prices for comparators)

SMR \ time to cure	2 years	3 years	5 years	No cure*
1.0	[redacted]	[redacted]	[redacted]	[redacted]
1.1	[redacted]	[redacted]	[redacted]	[redacted]
1.2	[redacted]	[redacted]	[redacted]	[redacted]
2.0	[redacted]	[redacted]	[redacted]	[redacted]

* SMR not applicable for no cure scenarios

4. REFERENCES

1. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE; 2016.
2. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med 2020;**383**(7):617-29. DoI: 10.1056/NEJMoa2012971
3. Pratz KW, Jonas BA, Pullarkat V, et al. Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia. Am J Hematol 2024;**99**(4):615-24. DoI: 10.1002/ajh.27246
4. Othman J, Amer M, Amofa R, et al. Venetoclax with Azacitidine or Low Dose Cytarabine As an Alternative to Intensive Chemotherapy in Fit Adults during the COVID19 Pandemic: Real World Data from the UK National Health Service. Blood 2021;**138**(Supplement 1):2321-21. DoI: 10.1182/blood-2021-149685
5. Rausch CR, DiNardo CD, Maiti A, et al. Venetoclax Dosing in Combination with Antifungal Agents: Real World Experience in Patients with Acute Myeloid Leukemia. Blood 2019;**134**(Supplement_1):2640-40. DoI: 10.1182/blood-2019-131988