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:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Servier Laboratories:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Leukaemia Care – endorsed by patient expert Charlotte Crowley
   b. Royal College of Pathologists

4. **External Assessment Report** prepared by Peninsula Technology Assessment Group

5. **External Assessment Report – factual accuracy check**

6. **Statements from experts**
   a. Esther Beswick – Patient expert, nominated by Leukaemia Care

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

September 2023

File name	Version	Contains confidential information	Date
Ivosidenib with azacitidine for untreated IDH1-positive acute myeloid leukaemia [ID6198]-doc B	1.0	Yes	04/09/2023

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Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

The overall frequency of IDH1 mutations in AML is only 6-10%, making IDH1 mutation-positive AML a rare disease within a recognized orphan condition.

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 prognostic impact of mIDH1 on patients with AML has been assessed in several studies, but there is no clear evidence for an important difference in prognosis.

AML prognosis worsens with increasing age and is especially poor in the elderly, who represent the majority of patients with AML. Furthermore, elderly patients, who account for the majority of new cases, are often unable to tolerate current regimens, especially intensive regimens, and currently carry a particularly poor prognosis.

Referring to the licensed indication for ivosidenib, about 55-60% of AML patients are ineligible to receive intensive chemotherapy due to age, KPS/ECOG performance status and comorbidities.

Venetoclax + azacitidine is now the standard of care in these patients, and has superseded the use of azacitidine alone. However, neither venetoclax nor azacitidine are specifically indicated for the treatment of mIDH1 AML.

The place in the treatment pathway for ivosidenib is as per the NCCN and ELN guidelines The NCCN guidelines show where the combination of ivosidenib and azacitidine has been included as a category 1 recommendation for newly diagnosed patients harbouring IDH1 mutations who are ineligible for standard intensive induction chemotherapy.

Ivosidenib is the first targeted therapy (with designated EU orphan status) indicated for the treatment of patients with AML and IDH1 mutation who are ineligible for intensive chemotherapy. For the first time, patients now have an opportunity to benefit from a targeted therapy that is highly effective with a favourable safety profile and a positive QoL impact. In addition to the compelling clinical case, the confidential discount on Ivosidenib ensures it is value for money for the NHS. Additionally with around 110 patients eligible for treatment with ivosidenib, the overall budget impact is anticipated to be small.

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1: The Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated IDH1-positive AML when intensive induction chemotherapy is unsuitable	In combination with azacitidine for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy	To align with license
Intervention	Ivosidenib with azacitidine	Ivosidenib with azacitidine	
Comparator(s)	• azacitidine alone for adults who are not eligible for HSCT and have AML with 20% to 30% blasts and multilineage dysplasia • low dose cytarabine • venetoclax with low dose cytarabine if people have over 30% bone marrow blasts • venetoclax with azacitidine	Venetoclax with azacitadine	The following comparators were not deemed relevant to this appraisal: • **AZA:** In TA218 (2011) AZA was recommended for patients with 20-30% blasts. However, in TA765 (2022), VEN+AZA was recommended for both the 20% to 30% and >30% blasts group. VEN+AZA supersedes AZA as standard of care within the NHS and is now considered standard of care (based on clinician feedback and endorsed by ELN and BSH guidelines). • **VEN+LDAC:** Patients in the AGILE study must be deemed able to receive treatment with an HMA (such as AZA), and so VEN+AZA is the relevant comparator regimen. **LDAC:** LDAC is also by VEN+LDAC for anyone with >30% blasts, and is not a relevant comparator given the eligibility criteria for IVO+AZA.
Outcomes	• overall survival • event-free survival • disease-free survival • response rates, including remission • blood transfusion dependence • rate of complete remission and complete remission with	Per scope, excluding 'disease-free survival'	Disease-free survival is not an outcome relevant to the AGILE study, nor the population of patients for whom ivosidenib is indicated.

	partial haematologic recovery • adverse effects of treatment • health-related quality of life.		

B.1.2 Description of the technology being evaluated

Table 2: Technology being evaluated

UK approved name and brand name	Ivosidenib (Tibsovo)
Mechanism of action	Ivosidenib is an inhibitor of mutated IDH1 enzyme. Mutated IDH1 converts alpha- ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG) which blocks cellular differentiation and promotes tumourigenesis in both haematologic and non-haematologic malignancies. The mechanism of action of ivosidenib beyond its ability to suppress 2-HG and impair cellular differentiation is not fully understood across indications
Marketing authorisation/CE mark status	In combination with azacitidine for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy. MHRA granted Marketing authorisation/Orphan designation 05/07/2023
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	In combination with azacitidine for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy.
Method of administration and dosage	500mg once daily (2x 250mg tablets) to be taken orally*
Additional tests or investigations	The use of ivosidenib is conditional on the presence of IDH1 gene mutation. IDH1 gene mutation should be idenfied and is currently tested for via the Myeloid NGS panel already commissioned by NHS England Therefore, diagnostic testing for IDH1 gene mutation should be carried out through an NGS panel, which is already commissioned by NHS England
List price and average cost of a course of treatment	£12,500 per month
Patient access scheme (if applicable)	PAS simple discount

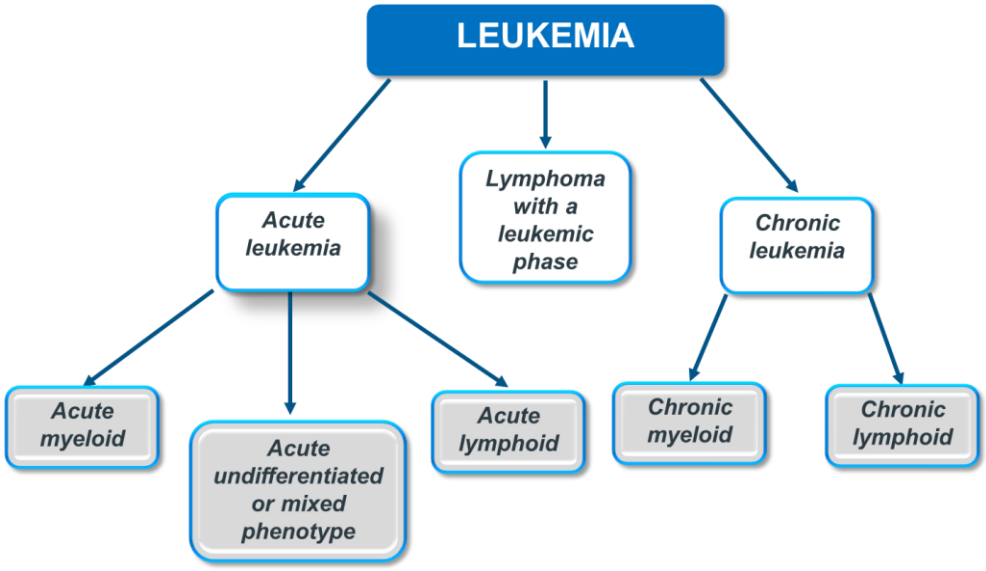
Note: *a dose adjustment needs to be implemented for concomitant azole antifungal use. See section B.3.5

B.1.3 Health condition and position of the technology in the treatment pathway

Disease Overview

Leukaemia is a form of haematological cancer arising from dysfunctional proliferation of progenitor leukocytes. Leukaemia is classified into acute and chronic forms based on growth rate, and further subdivided into myeloid or lymphoid forms based on the source progenitor cell type (Figure 1).

Figure 1: Broad classification of haematological cancers



Source: Juliusson 2021 (1)

Acute myeloid leukaemia (AML) is an aggressive form of blood and bone marrow cancer (2), resulting in rapid disease progression. It is the most common form of leukaemia and accounts for approximately 80% of leukaemia cases diagnosed in adults (3). AML constitutes a diverse range of haematopoietic stem cell disorders arising from aberrant and immature blood cells. This results in haematologic malignancy that manifests itself in the form of anaemia (shortage of red blood cells), leukopenia (shortage of normal white blood cells), neutropenia (shortage of infection-fighting white blood cells called neutrophils), and thrombocytopenia (shortage of blood platelets). AML is characterized by a population of cells developed from extensive and uncontrolled proliferation of myeloid progenitor cells (3).

<u>IDH Mutations in AML</u>

The IDH proteins are critical metabolic enzymes involved in DNA and histones hypermethylation, which can result in altered gene expression, dysregulating oncogenes and tumor-suppressor genes (4). IDH proteins play a role in several types of tumours, and exist as three isoforms: IDH1, IDH2, and IDH3. IDH1 mutation is associated with altering the metabolic functions of myeloblasts and bringing about genetic instability in myeloid

progenitor cells due to accumulation of 2-hydroxyglutarate (2-HG) oncometabolite, which disrupts the normal cellular differentiation mechanism.(5)

Molecular profiling to identify genetic mutations in AML patients are strongly recommended by global guidelines to ensure implementation of suitable treatment strategies.(6–8), and is routinely carried out in NHS practice. Based on a review of the literature, the overall frequency of IDH1 mutations in AML is small, making IDH1 mutation-positive AML a rare disease within a recognized orphan condition.(9) There is a paucity of studies reporting the epidemiology of mIDH1 specifically in newly diagnosed AML patients, or in those who have comorbidities that preclude use of intensive induction chemotherapy. Given the dearth of evidence on mIDH1 prevalence in these AML patients, an mIDH1 prevalence rate of 6% to 10% is assumed in this population.(10) In addition, referring to the licensed indication for ivosidenib, about 55-60% of AML patients are ineligible to receive intensive chemotherapy due to age, KPS/ECOG performance status and comorbidities.(11)

There is mixed evidence concerning the prognostic impact of IDH1m on AML patients in the literature(12–15). The prognostic impact of mIDH1 on patients with AML has been assessed in several studies, but there is no clear evidence for an important difference in prognosis.

A large meta-analysis investigating the prognosis of IDH1 mutations, pooled results from 33 studies reporting the impact of IDH mutations on the outcomes of adults with AML (n = 12,747) from various regions, including Europe. In this analysis, patients with mIDH1 AML were found to have a slightly poorer OS (HR 1.17; p = 0.0047) and event-free survival (EFS; HR 1.29, p = 0.011) compared to those patients without mIDH1 AML. CR rates were also worse in patients with mIDH1 AML (RR 1.21, p = 0.029)(14). A further study corroborated the results reported by the meta-analysis(13).

Wang et al performed a retrospective analysis of common genetic mutations in AML patients aged over 60 years (n = 329) to develop a reliable prediction model for stratifying the risk of elderly patients (108). IDH1 mutations were significantly associated with lower CR (OR = 0.366, p = 0.004) and shorter EFS (HR, 1.702, p = 0.002) and OS (HR = 1.667, p = 0.006)(16). Furthermore, in a pooled analysis of five prospective trials by Acute Myeloid Leukaemia Study Group (AMLSG), mIDH1 was identified as an unfavourable prognostic factor for OS (HR 1.37, p = 0.03) based on data from 37 patients harbouring mIDH1 out of the 875 patients with R/R AML (median age of 55 years) who received the first intensive salvage treatment (17)

However, these results are not consistent with findings of more recent studies in newly diagnosed AML, which did not find IDH1 to be a molecular prognostic factor. Other observational and controlled studies also found that mIDH1 is an unfavourable prognostic factor in AML(18, 19), although the difference in OS between patients with mutant and wild-type IDH1 in some studies lacked statistical significance(15, 20) In the study reported by DiNardo et al, no statistically significant differences in OS were observed in the presence of mIDH1 in either the induction or salvage setting; however, the study acknowledged that the patient characteristics of mutated patients differed in terms of age, FLT-3 mutations,

intermediate-risk cytogenetics, platelet count, bone marrow blast percentage, circulating blasts, and absolute neutrophil count (ANC).

Overall, the balance of evidence suggests that mutations in IDH1 may be associated with inferior responses and worse OS, but this is uncertain and the magnitude of any difference in prognosis is difficult to establish. Three meta-analyses (13, 12, 14) show that the presence of an IDH1 mutation is associated with a worse prognosis compared to wild-type IDH1, but the significance of this is unclear. A more recent development of a prognostic model (21) looking at prediction of survival with lower intensity therapy among older patients with acute myeloid leukaemia, included 89 patients with IDH1 mutation and 139 with IDH2. IDH1 was not shown to be a prognostic factor (HR 0.968, CI 0.747-1.256) whereas IDH2 was shown to have significant prognostic value (HR 0.69, CI 0.549-0.869)(22). This is also reflected in the ELN guidelines, which state that current evidence does not yet warrant the assignment of IDH-1 mutation status to a distinct prognostic group. (7)

Risk Factors

Although the cause of AML is not known, several factors are associated with an increased risk of the disease. Risk factors associated with AML include increasing age, male gender, genetic factors, environmental factors and lifestyle, drugs, chemical exposure, and antecedent blood disorders. Factors such as older age (≥70 years), male gender, presence of comorbidities, ECOG performance status ≥2, intermediate/adverse ELN risk, and hypoalbuminemia have also been associated with increased mortality rate or decreased survival rates (23).

Burden to patients, carers, and society

Epidemiology

The prevalent population was not considered as very few patients in the population were expected to survive beyond a year with existing standard of care.

Table 3 presents the epidemiology inputs used to derive the eligible patient population. These inputs were obtained from the Office of National Statistics (ONS) and the existing epidemiological literature.

Table 3: Epidemiology estimates

Inputs	Value	Source
Total population (over 18 years old) in England, by year	2023: 52,143,000 2024: 52,398,000 2025: 52,656,000 2026: 52,934,000 2027: 53,217,000	ONS Principle Projection(24)
AML incidence rate	4.9 per 100,000 persons	Cancer research UK (23)
% of AML patients with IDH1 mutation	8%	Bullinger (10)
% of patients ineligible standard chemotherapy	55%	Servier (11)

Abbreviations: IDH1, isocitrate dehydrogenase 1; ONS, Office of National Statistics.

This gives an incidence of 110 pts eligible in England for ivosidenib. The incident rate was assumed to remain constant for the time horizon, as according to cancer research UK, incident rates have remained stable over the last decade. Table 4 presents eligible patient population estimates, by year (calculated using the epidemiology inputs provided in Table 3).

Table 4: Calculation of new eligible patients in England, by year

	Current practice	Year 1	Year 2	Year 3	**Year 4**	Year 5
Year	2023	2023	2024	2025	2026	2027
Population (≥18 year) in England	52,143,000	52,143,000	52,398,000	52,656,000	52,934,000	53,217,000
Number with AML	2555	2555	2567	2580	2594	2608
Number with IDH mutation	204	204	205	206	208	209
Number ineligible for intensive chemotherapy	112	112	113	113	114	115

Abbreviations: AML, acute myeloid leukaemia.

Prognosis

Several prognostic factors have been identified in AML. Adverse cytogenetic risk status, advanced age, and comorbidities were found to be the most common risk factors affecting prognostic outcomes in AML patients (25). Many patients and disease-specific factors contribute to the poorer outcomes among elderly patients including poorer ECOG PS at

diagnosis; lower CR rates with intensive chemotherapy; increased early death rates with intensive chemotherapy; an increased incidence of unfavorable cytogenetics; and an increased incidence of sAML, defined as AML arising from an antecedent haematologic disorder such as myelodysplastic syndrome (MDS) or attributable to prior chemotherapy or radiation. These factors lead many clinicians to choose less intensive treatment strategies, which have historically proven less effective at inducing remissions. Similar concerns limit the use of the most effective consolidation strategies when patients do achieve a CR

Diagnosis

Methods used for the diagnosis of AML include consideration of medical history and physical examinations such as blood tests, bone marrow core and aspirate sampling via biopsy. Other procedures include immunophenotyping and cytogenetic and molecular testing. An overview of common diagnostic procedures for AML compiled from recent clinical guidelines is presented in Table 5.

Table 5: Common diagnostic procedures used in AML

Diagnostic procedure	Description
Morphology	Diagnosis of AML based on ≥200 leukocytes on blood smears and 500 nucleated cells on speculated marrow smears. A marrow or blood blast count of ≥20%, except for AML with t (15;17), t (8;21), inv (16), or t (16;16)
Immunophenotyping	Several cell-surface and cytoplasmic markers are indicative of AML, including precursors, granulocytic, monocytic, megakaryocytic, and erythroid markers
Cytogenetics and molecular cytogenetics	Cytogenetic analysis of translocations and inversions is recommended to establish differential diagnosis of "AML with recurrent genetic abnormalities" or "AML with myelodysplasia-related changes" Screening is recommended specifically for gene rearrangements including PML-RARA, CBFB-MYh11, RUNX1-RUNX1T1, and BCR-ABL1
Molecular testing	Screening for gene mutations is recommended for AML diagnosis including NPM1, CEBPA, RUNX1, FLT3, TP53, ASXL1, TET2, WT1, DNMT3A, C-KIT, IDH1, and IDH2
Other information	Demographics and medical history, detailed family history, patient bleeding history, and performance status (ECOG/WHO score)

Abbreviations: AML, acute myeloid leukemia; ASXL1, additional sex combs like 1 transcriptional regulator; BCR-ABL1, breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1 fusion protein (Philadelphia chromosome); CBFB-MYH11, core binding factor beta subunit-myosin heavy chain 11 fusion protein; CEBPA, CCAAT/enhancer binding protein alpha; DNMT3, DNA methyltransferase 3 alpha; ECOG, Eastern Cooperative Oncology Group; FLT3, FMS related tyrosine kinase 3; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; NPM1, nucleophosmin 1; RUNX1-RUNX1T1, runt-related transcription factor 1-RUNX1 translocation partner 1 fusion protein; TET2, tet methyl cytosine dioxygenase 2; TP53, tumor protein 53; WHO, World Health Organization; WT1, Wilms tumor 1
Sources: Adapted from Döhner et al. 2022 (7)

Defining the subset of patients who are not eligible for intensive therapy involves a degree of subjectivity, and criteria are yet to be standardized across or within institutions. Diagnostic procedures to identify the patient population that is ineligible for standard intensive induction chemotherapy usually involve evaluation of physical performance, comorbidities, and cognitive functions. Physical performance is quantitatively evaluated using Eastern Cooperative Oncology Group performance status (ECOG PS). Patients with advanced age typically fall in the category of ineligible for intensive treatment due to poor outcomes,

biologically poor disease prognosis, and higher incidence of high-risk karyotypic abnormalities.

In anticipation of the availability of therapies which target IDH mutations, the 2020 European Society for Medical Oncology (ESMO) guidelines recommend testing for mIDH1 to identify patients who may benefit from these targeted treatments(8). The European LeukemiaNet (ELN) 2022 guidelines recommend screening for mIDH1 with results preferably available in 3 to 5 days. However, the mutation is not included among the genetic abnormalities associated with the ELN 3-group risk stratification (favorable, intermediate, and adverse) as explained in detail in section B1.3.1 (7). In the UK, mIDH1 testing is already a part of routine diagnostic practice, via the myeloid NGS panel.

Unmet need in the treatment of AML

There is an unmet need for an efficacious and tolerable targeted therapy that can improve long term outcomes and HRQoL in 1L AML patients who are ineligible for intensive induction chemotherapy. This is particularly relevant in the elderly population, where increased age is associated with poor prognosis(25) and greater mortality(26).

In this population, five-year survival rates decrease from 41.6% in patients under 65 years to only 5.4% in patients over 65 years (27) These results underscore the fact that AML prognosis worsens with increasing age and is especially poor in the elderly, who represent the majority of patients with AML (median age at diagnosis is approximately 68 years) (28–30). Furthermore, elderly patients, who account for the majority of new cases, are often unable to tolerate current regimens, especially intensive regimens, and currently carry a particularly poor prognosis. The condition is considered to be both, life threatening and chronically debilitating, due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within a few months or less, if left untreated.(31)

Clinical pathway of care

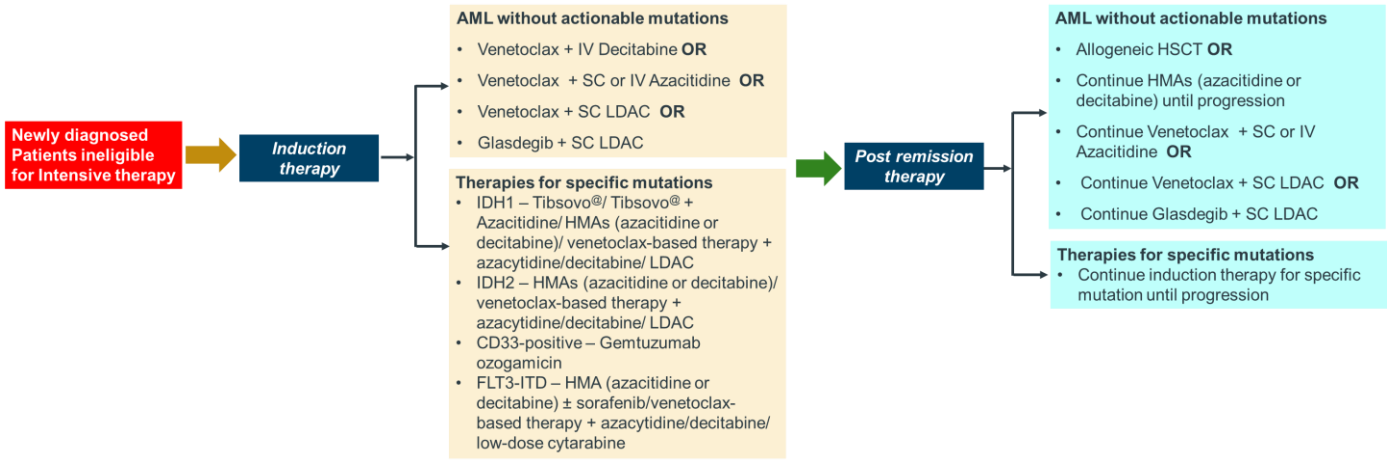
<u>Guidelines</u>

The current NCCN guidelines(32) provide recommendations for induction and post-remission treatment strategies for AML patients ineligible for standard intensive induction chemotherapy (Figure 2). The clinical guidelines define a line of treatment based on the presence or absence of notable genetic mutations. The guidelines recommend treatment with venetoclax, with or without HMAs (such as azacitidine/decitabine) or low-dose cytarabine (LDAC), as first-line (1L) treatment for induction therapy in patients without any known genetic mutations. Alternatively, glasdegib in combination with LDAC is also recommended for these patients; however, as glasdegib is associated with adverse events (AEs), it is more likely to be discontinued(32). Patients with known genetic mutations such as IDH1, IDH2, CD33-positive, or FLT3-ITD are recommended targeted therapies. The preferred treatments for patients with an IDH1 mutation are venetoclax-based therapy (in

combination with azacitidine, or decitabine) or ivosidenib monotherapy/combination with HMA treatment; another recommended therapy for this group is low-intensity therapy with HMAs (azacitidine or decitabine). Recently, the combination of ivosidenib and azacitidine has been included as a category 1 recommendation for newly diagnosed patients harbouring IDH1 mutations who are ineligible for standard intensive induction chemotherapy

Post-remission therapy in patients without any known genetic mutations involves allogenic HSCT or sustained, periodic usage of venetoclax with or without HMAs or LDAC, or glasdegib and LDAC. For patients with an IDH1 mutation, iv treatment is recommended until progression.

Figure 2: NCCN recommendations for the treatment of AML patients ineligible for standard intensive induction chemotherapy



Abbreviations: AML; acute myeloid leukemia; FLT3-ITD, FLT3 internal tandem duplication; G-CSF, granulocyte colony stimulating factor; HMAs, hypomethylating agents; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; IV, intravenous; LDAC, low-dose cytarabine; HSCT, hematopoietic stem cell transplantation; NCCN, national comprehensive cancer network; SC, subcutaneous

Source: NCCN guidelines (2023 v3.0) (12)

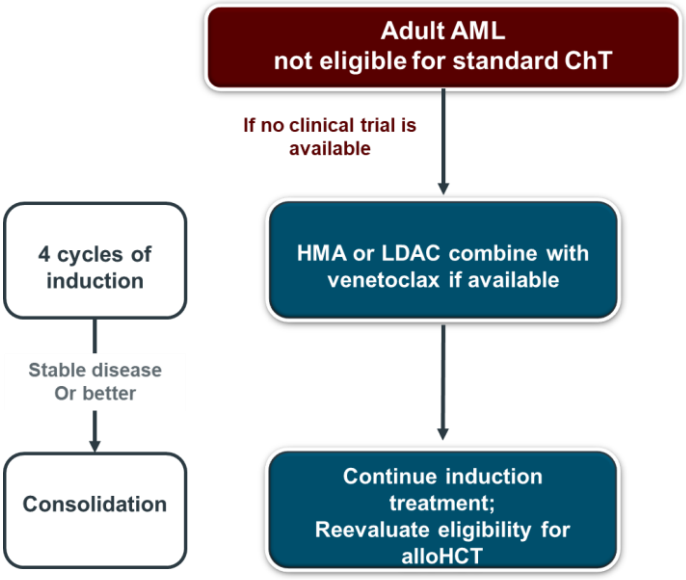
European Leukaemia Guidelines

The European LeukemiaNet (ELN) developed clinical guidelines for the treatment of AML. The current ELN AML clinical guidelines (2022)(7), recommend BSC, low-intensity treatment, or enrolment in clinical trials testing investigational drugs for patients with AML who are ineligible for intensive induction chemotherapy. The guideline states the standard of care is Azacitadine and venetoclax. For patients unable to receive a HMA, LDAC in combination with venetoclax represents an alternative treatment option. For newly diagnosed patients with IDH1 mutation, IDH1 inhibitor ivosidenib plus azacitidine improves EFS, clinical response and median OS, compared to azacitidine plus placebo. Patients with IDH1-mutated AML who are considered too frail to tolerate HMA-based treatment may be offered BSC or monotherapy with targeted IDH1 inhibitors. Furthermore, although allogenic HCT remains a promising post-remission therapy, it is not strongly recommended by the ELN as only a minority of patients are responsive to the therapy. Glasdegib + LDAC is not recommended.

European Society for Medical Oncology (ESMO) Guidelines

The current ESMO guidelines (2020) provide recommendations for induction and consolidation treatment for AML patients ineligible for standard intensive induction chemotherapy (Figure 3)(8)The ESMO guidelines recommend HMAs (first choice) or LDAC combined with venetoclax, if available, for the 1L treatment of patients who are ineligible for standard intensive induction chemotherapy. The guidelines recommend HMA treatment (azacitidine or decitabine; no predictive markers are known to recommend one over the other) in a 5-day schedule, until disease progression has been achieved or intolerance is observed. HMA treatment is discontinued after at least 4 weeks if the patient is unresponsive or no clinical benefit is observed. Given the moderate effects of HMAs, LDAC is considered a suitable alternative to HMA. In patients progressing from myelodysplastic syndrome (MDS) to AML, HMA treatment along with venetoclax, LDAC, or BSC (with either 6-mercaptopurine or low-dose melphalan or hydroxycarbamide) are treatment options if no clinical trial is available. Based on the response to induction therapy, patients can be evaluated for their ability to undergo alloHCT using reduced-intensity conditioning (RIC).

Figure 3: ESMO recommendations for the treatment of AML patients ineligible for standard intensive induction chemotherapy



Abbreviations: AML; acute myeloid leukemia; alloHCT, allogeneic hematopoietic cell transplant; ChT, chemotherapy; ESMO, European society for medical oncology HMA, hypomethylating agents; LDAC, low-dose cytarabine

Source: Adapted from Heuser, 2020 (18)

In England, treatment options for AML include intensive induction chemotherapy followed by consolidation chemotherapy, allogeneic stem cell transplantation, or both; however, not all patients diagnosed are eligible for treatment with intensive chemotherapy due to advanced age, coexisting conditions, and a high incidence of unfavourable genomic features. Instead, historically, the main treatment options for these patients include less intensive regimens with hypomethylating agents such as azacitidine or decitabine, and low-

dose cytarabine. In TA218 (33) azacitadine was recommended for AML only in those with 20-30% blasts. Therefore, low dose cytarabine was used in those with over 30% blasts.

However, in TA765 (34), the committee recommended venetoclax plus azacitidine as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable. This includes those in the 20% to 30% blast group and the over 30% blast group. Therefore, venetoclax plus azacitadine now supersedes azacitidine as standard of care within the NHS. This is now considered standard of care via clinician feedback (35) and endorsed by ELN 2022 guidelines (7) and BSH 2022 good practice guideline (36), leaving azacitdine monotherapy as the treatment choice for MDS /AML patients with a blast level below 20%

In addition, low dose cytarabine monotherapy is also superseded by venetoclax plus azacitdine for anyone with > 30% blasts. As a result of this low dose cytarabine is no longer used in clinical practice.

According to an advisory board run by Servier UK and specific clinician feedback, venetoclax + azacitidine is now the standard of care in these patients, and has superseded the use of azacitidine alone (11, 35). Of note, neither venetoclax nor azacitidine are specifically indicated for the treatment of mIDH1 AML.

The place in the treatment pathway for Ivosidenib is as per the NCCN and ELN guidelines (7) (32). The NCCN guidelines show where the combination of ivosidenib and azacitidine has been included as a category 1 recommendation for newly diagnosed patients harboring IDH1 mutations who are ineligible for standard intensive induction chemotherapy.

B.1.4 Equality considerations

No equality considerations.

B.2 Clinical effectiveness

The only RCT in IDH1m population, AGILE was a Phase III, multicentre, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of ivosidenib + azacitidine compared to placebo + azacitidine in newly diagnosed AML adult patients with an IDH1 mutation who are ineligible for intensive induction chemotherapy. This provides the relevant efficacy and safety data in this population.

AGILE is reflective of and generalisable to patients in UK clinical practice.

The primary efficacy endpoint was met with a significant improvement in EFS demonstrated for patients randomized to the ivosidenib + azacitidine arm relative to the placebo + azacitidine arm (HR = 0.33; 95% CI, 0.16-0.69; p = 0.002).

Median OS follow-up of 28,6 months are available. The analyses showed that the large OS effect was sustained and significantly better for patients randomized to the ivosidenib + azacitidine arm relative to the placebo + azacitidine arm (HR for death = 0.42; 95% CI, 0.27-0.65; p = 0.0001), with a median OS of 29.3 months (95% CI, 13.2-NE months) in the ivosidenib + azacitidine arm and 7.9 months (95% CI, 4.1-11.3 months) in the placebo + azacitidine arm.

The clinical benefit of ivosidenib + azacitidine was supported by improvements in multiple HRQoL domains, including Global Health Status/QoL and functional subscales according to EORTC QLQ-C30. HRQoL improvements were also observed for ivosidenib + azacitidine based on EQ-5D-5L index values.

There is a lack of trial data for the relevant comparators specifically in IDH1 mutated AML, however, indirect treatment comparisons using the most robust data sources and methods possible provide plausible evidence of clinically meaningful improvements in survival outcomes compared with current standard of care (venetoclax + azacitadine.

The findings from the NMA demonstrated that IVO+AZA is associated with improved OS [redacted] and improved EFS [redacted] compared to venetoclax + azacitadine.

The AGILE trial demonstrated that the combination of ivosidenib + azacitidine was associated with AEs similar to those attributed to treatment for AML, although Ivosidenib displays a unique increase in absolute neutrophil count from cycle 1 reducing febrile neutropenia and infections.

According to clinician feedback to the company during a recent advisory board, the neutrophil recovery data seen with ivosidenib + azacitidine would require less monitoring, less in patient days, and reduced blood transfusions, compared to venetoclax +azacitidine, which would have a substantial impact on an elderly persons quality of life due to more time spent away from the hospital.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in October 2021, subsequently updated on 1 February 2023, the clinical SLR identified clinical evidence on current and emergent treatments for newly diagnosed AML patients who are ineligible for intensive chemotherapy. The search aimed to explore the clinical efficacy and safety outcomes of treatment options in patients.

The clinical SLR was conducted in Embase®, MEDLINE® and CENTRAL® using a pre-defined search strategy applying the PICOS terms, publication year and language limits presented in appendix D. The clinical SLR was designed to answer the following research question:

- What are the clinical efficacy and safety outcomes of current treatment options in adults with previously untreated (including secondary) AML?

In addition, recently published SLRs and meta-analyses were checked to ensure all relevant evidence are captured.

In the original SLR, 4,503 references were identified from electronic databases searches conducted on 28th October 2021 (MEDLINE®: 828; Embase®: 2,629; CENTRAL: 1,046). After removal of 1,397 duplicate records, the remaining 3,106 publications were screened. After the title abstract screening, 2,772 references were excluded according to the eligibility criteria and 334 potentially relevant references were retrieved for full-text assessment. During the full-text review, further 150 records were excluded based on PICOS eligibility criteria. Therefore, 184 records were included from full text screening. A hand-search was conducted which included screening of specific conferences, clinical trial registries and reference checks of other reviews. From the hand-search, 50 additional records were identified that met the inclusion criteria.

An SLR update identified 883 additional records between 28th October 2021 and 1st Feb 2023 from electronic databases (Medline®: 109; Embase®: 603; Cochrane®: 171). After removal of 371 duplicate records, the remaining 512 publications were screened. After the title and abstract screening, 444 references were excluded according to the eligibility criteria and 68 potentially relevant references were retrieved for full-text assessment. During the full-text review, a further 23 records were excluded based on PICOS eligibility criteria. Therefore, 45 records were included from full text screening. From the hand-search, 6 additional records were identified that met the inclusion criteria.

After combining the results from the original and updated SLR, 26 unique studies reported in 69 publications were prioritised for data extraction based on study design (RCTs only) and a total sample size of the study above and equal to 20 numbers.

Notably, the eligibility criteria for the SLR conducted is broader than the population relevant to this appraisal (i.e., the SLR covers a broader AML population, and not just those patients with an IDH1 mutation). This broader population was considered appropriate for the purpose of the SLR to ensure no potentially relevant studies were missed (e.g., a study for a broader

AML population that may report subgroup analyses by *IDH1* mutation) and therefore, a full unedited report can be found in the Appendix D. However, aligned with the scope for this submission, the only identified studies considered to be of direct relevance to this appraisal are AGILE (37) and VIALE A (38) (as listed in Table 6).

Results specific to patients with IDH1 mutation are reported only for venetoclax + azacitidine in Dinardo 2020 (VIALE-A) (38)and Pollyea 2022 (pooled data from VIALE-A and a single-arm phase Ib study) (39) but are based on post-hoc subgroup analyses with small sample sizes (specifically <20 IDH1m positive patients were enrolled in the azacitidine arm in VIALE-A, which does not meet the sample size inclusion criterion in the SLR.

Venetoclax, in combination with azacitidine, has demonstrated significant clinical benefit in newly diagnosed AML patients who are ineligible for intensive induction chemotherapy, with an OS of 14.7 months(38). However, venetoclax does not specifically target the IDH1 mutation.(7) For IDH1 mutations, evidence with venetoclax is limited to results from a post hoc analysis, where IDH1m was not a stratification factor, and no reporting of patient baseline characteristics for the IDH1m subgroup, showing a mOS of 10.2 months in 23 patients,(40) compared to a mOS with ivosidenib of 29.3 months in 73 patients.

A recent pooled post-hoc analysis of two trials (Phase 1 and phase III) with Venetoclax confirmed that AML patients with IDH1 and IDH2 mutations do respond to treatment with Venetoclax(39).However, this was mainly driven by the IDH2 mutation with an OS of 24.5 months in the IDH1/2 group, compared to 15.2 months OS in the IDH1 group. In support of this, an American cohort of 331 AML patients treated with venetoclax showed a mOS in IDH1 patients of 13,1 months compared to a mOS of IDH2 patients of 42 months, and a mOS in the overall population of 13,9 months(41).

Table 6: Included studies identified from clinical SLR

Study name (trial name): NCT	Study phase and centres	Patient Population (N)	Treatment/ comparator	Outcomes
AGILE(37) NCT03173248	Phase III Australia, Austria, Brazil, Canada, China, Czechia, France, Germany, Israel, Italy, Japan, Korea, Republic of Mexico, Netherlands, Poland, Russian, Federation, Spain, Taiwan, United Kingdom	Previously untreated patients with *IDH1* Mutation and ineligible for intensive induction chemotherapy (N=146)	Ivosidenib + azacitidine/ Azacitidine + placebo	Primary outcomes: EFS Secondary outcomes: CR rate, OS, CR+CRh rate, ORR, HRQoL, Safety

VIALE-A (38) NCT02993523	Phase III Australia, Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Japan, Norway, Poland, Portugal, Russia, South Africa, South Korea, Spain, Sweden, Taiwan, Turkey, United States	Previously untreated, sAML, ineligible for intensive induction therapy (N=433)	Venetoclax + azacitidine/ Azacitidine + Placebo	Primary outcomes: OS Secondary outcomes: Composite complete remission (CRi), CRh, complete remission by the initiation of cycle 2, red-cell and platelet transfusion independence, composite complete remission, and OS in molecular and cytogenetic subgroups, EFS, measurable residual disease by flow cytometry, and quality of life according to patient-reported outcomes

Abbreviations: Abbreviations: ASC, Active symptom control; CCA, cholangiocarcinoma; mFOLFOX, folinic acid, fluorouracil and oxaliplatin; NR not recorded

B.2.2 List of relevant clinical effectiveness evidence

Table 7: Clinical effectiveness evidence

Study	AG120-C-009 AGILE (Phase 3-pivotal) (37) [NCT03173248]
Study design	Phase 3, multicentre, double-blind, randomized, placebo-controlled study
Population	Previously untreated patients with IDH1 Mutation and ineligible for intensive induction chemotherapy
Intervention(s)	Ivosidenib 500 mg once daily (QD) orally (approximately every 24 hours) during Weeks 1 to 4 in continuous 4-week (28 day) cycles (n = 72) + azacitidine 75 mg/m2/day subcutaneous (SC) or intravenous (IV) for 1 week every 4 weeks until study end
Comparator(s)	Placebo 500 mg QD orally (approximately every 24 hours) during Weeks 1 to 4 in continuous 4-week (28 day) cycles (n = 72) + azacitidine 75 mg/m2/day SC or IV for 1 week every 4 weeks until study end (n = 74)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	• Overall survival • Event-free survival • Response rates, including remission • Blood transfusion dependence • Rate of complete remission and complete remission with partial haematologic recovery • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	• Duration of CR (DOCR) • Duration of CRh (DOCRh) • Duration of response (DOR) • Time to CR (TTCR) • Time to CR +CRh (TTCRh) • Time to response (TTR) • Time to CR +CRi (TTCRi)

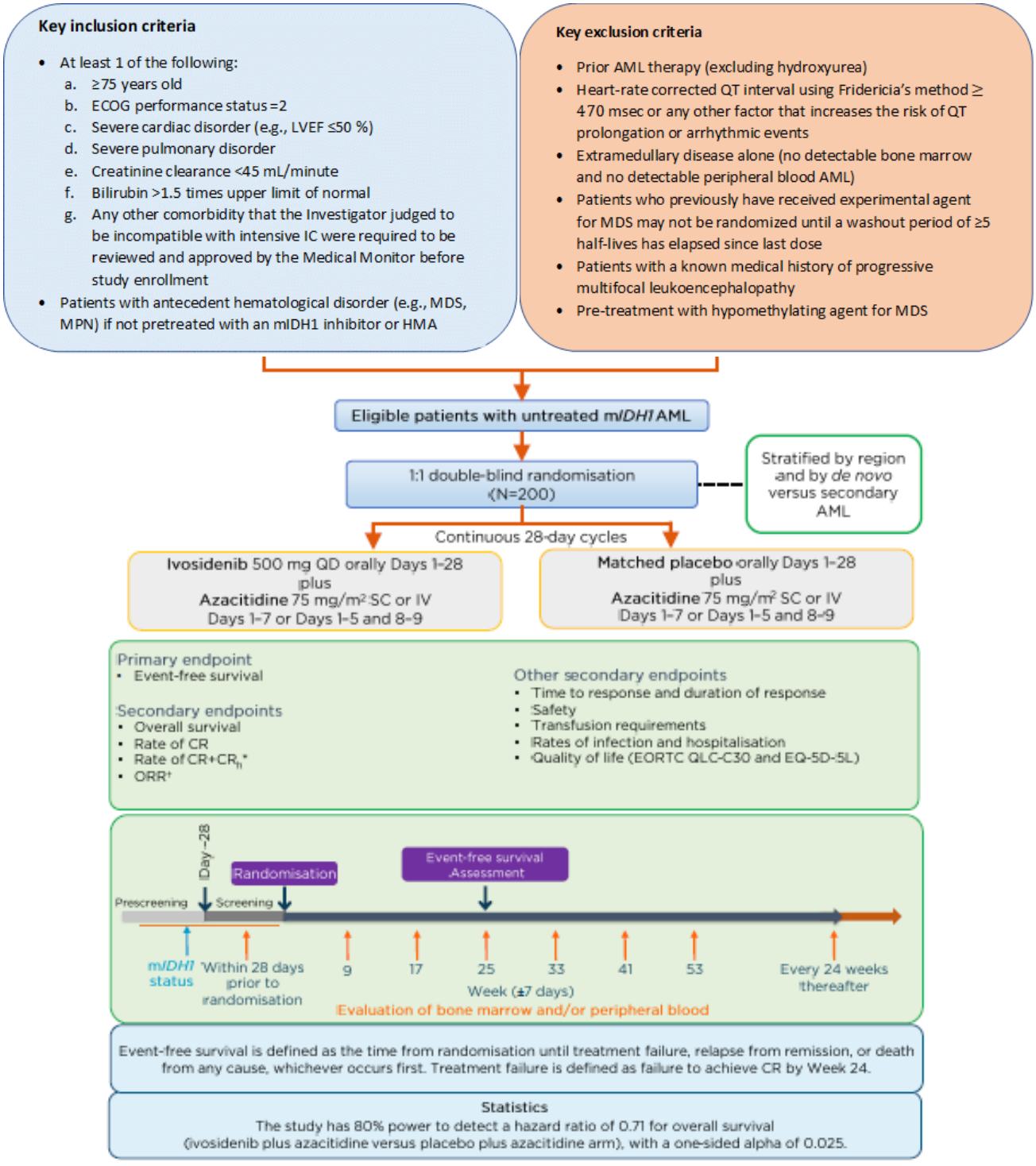
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Study design

AGILE was a Phase 3, multicenter, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of ivosidenib + azacitidine compared to placebo + azacitidine in newly diagnosed AML adult patients with an IDH1 mutation who are ineligible for intensive induction chemotherapy. Patients were randomized 1:1 to receive oral ivosidenib or matched placebo, both administered in combination with subcutaneous (SC) or intravenous (IV) azacitidine. Randomization was stratified by disease status (primary versus secondary AML) and geographic region (US and Canada; Western Europe, Israel, and Australia Japan; and rest of world)

An overview of the AGILE study design is shown in Figure 4.

Figure 4: AGILE study schema



Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRp, complete remission with incomplete platelet recovery; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol-5 dimension 5-level health-related quality of life questionnaire; LVEF, left ventricular ejection fraction; HMA, hypomethylating agent; IDH1, isocitrate dehydrogenase 1; IV, intravenous; MDS, myelodysplastic syndrome; mIDH1, mutant IDH1; MPN, myeloproliferative neoplasms; ORR, Objective response rate; SC, subcutaneous; WHO, World Health Organization; QD, once daily.

Notes: *CRh is defined as CR with partial recovery of peripheral blood counts (<5% bone marrow blasts, platelets >50,000 /μL, and ANC >500 /μL) and will be derived by the sponsor. †Includes CR,CRi/CRp, partial response, and morphological leukemia-free state.

Source: Montesinos et al. (2020)(42)

Study medicines

Ivosidenib or matched placebo, was administered orally, once-daily (QD), combined with azacitidine (75 mg per square meter of body-surface area SC or IV) for 7 days in 28-day cycles. All patients received azacitidine 75 mg/m2/day SC or IV for the first week (seven days) (or on a 5-2-2 schedule) of each 4-week (28-day) cycle in combination with ivosidenib or placebo once-daily (QD) on each day of the 4-week cycle. The same schedule was to be used for each patient throughout the duration of treatment, when possible. Patients were to be treated for a minimum of six cycles of combination therapy unless they experienced relapse after achieving a complete remission (CR), a CR with incomplete hematologic recovery (CRi) (including CR with incomplete platelet recovery [CRp]), or MLFS; disease progression before achieving a CR/CRi (including CRp), or MLFS; unacceptable toxicity; confirmed pregnancy; withdrawal by patient; protocol violation; death; or end of study.

Dose modifications and delays

Ivosidenib or placebo dose modification

Dose modifications of ivosidenib or placebo from 500 mg to 250 mg were permitted in the study for management of AEs. If more than one AE occurred that required a dose modification, on resolution of all AEs to baseline or Grade 1, ivosidenib or placebo was dose-reduced to 250 mg. Re-escalation was allowed with approval from the medical monitor.

Azacitidine dose modification

Patients were monitored for hematologic toxicity and renal toxicity. During study treatment, dosing interruptions or delays or dose modifications were permitted for managing toxicities and/or treatment response. Where a reduced dose of azacitidine demonstrated a benefit then that dose was maintained during subsequent cycles unless toxicity developed. The medical monitor was contacted, when necessary, for guidance on azacitidine dose modification.

Study endpoints

Investigator response assessments per modified International Working Group (IWG) response criteria for AML were used for all efficacy end points, except CR with partial hematologic recovery (CRh), which was derived by the sponsor.

Patients who discontinued treatment without experiencing death, disease relapse, treatment failure, or withdrawal of consent were followed every day 1 (±7 days) of weeks 9, 17, 25, 33, 41, and 53, and every 24 weeks thereafter for EFS until they experienced treatment failure, relapse, death, withdrawal of consent, or until the time when 173 EFS events had occurred or as deemed necessary by the Independent Data Monitoring Committee (IDMC). Patients who were alive after an EFS event were contacted every 8 weeks for survival follow-up until death, withdrawal by patient, loss to follow-up, or until the study was ended by the sponsor.

Primary endpoint

Rationale for primary endpoint change from OS to EFS

OS was originally planned as the primary endpoint. However, encouraging preliminary safety and efficacy data from a previous phase 1 study(43) suggested that an earlier analysis of EFS in AGILE was justified. Based on the recommendation of the IDMC, enrollment into the study was prematurely discontinued. Sample size estimations showed that this change allowed for a smaller (200 versus 398 patients) and more feasible trial in this rare patient population. Furthermore, EFS more accurately describes the contribution of a novel therapy to clinical benefit by removing the potentially confounding effects of post-trial therapies and by capturing TF as an event. Therefore, the protocol was amended with EFS as a primary endpoint, as a meaningful and direct measure of clinical benefit for treatment of patients with AML ineligible for intensive induction chemotherapy. OS was kept as a key secondary endpoint.

EFS: prespecified analysis

The primary objective was to compare EFS between ivosidenib + azacitidine and placebo + azacitidine. EFS was defined as the time from randomization until TF, relapse from remission, or death from any cause, whichever occurred first. TF was defined as failure to achieve CR by Week 24. Patients who did not achieve CR by Week 24 were considered to have had an EFS event at Day 1 of randomization. For patients who achieved CR by Week 24 (responders), the EFS time was the time from randomization to relapse or death, whichever occurred first.

The EFS definition used in AGILE was the newly recommended definition, aligned with FDA guidelines which advise a definition that has a better association with OS than that used in older trials. This definition is different, and also more stringent, than that used in previous AML studies, such as VIALE-A(38).

EFS: sensitivity analysis

An additional post-hoc EFS analysis was also undertaken using a modified definition similar to that used in other AML trials, including VIALE-A(38). In a sensitivity analysis of EFS, EFS was defined as the time from randomization until progressive disease, relapse from CR or CRi, treatment failure, or death from any cause; a definition similar to that used in other recent AML studies(38). Treatment failure was defined as a lack of CR, complete remission with incomplete haematologic recovery, or morphologic clearance of leukaemic cells from the marrow after at least 24 weeks of treatment, whichever is earlier. Treatment failure patients were considered as events at the End of treatment date.

Secondary endpoints

The key secondary objectives were to characterize the safety profile and to compare CR, OS, CRh and objective response rate (ORR) between ivosidenib + azacitidine and placebo

+ azacitidine. Additional secondary objectives included safety and to compare CRi, duration of CR (DOCR), duration of CRh (DOCRh), duration of CRi (DOCRi), time to CR (TTCR), time to CRh (TTCRh) and time to CRi (TTCRi) between ivosidenib + azacitidine and placebo + azacitidine. An overview of the primary and secondary endpoints and their definitions is presented in Table 8.

Table 8: AGILE - Overview of endpoints

Primary endpoint	Definition
EFS	From randomization until treatment failure (TF), relapse from remission, or death from any cause, whichever occurs first*
Secondary endpoints	
CR	Bone marrow blasts <5% and no Auer rods, absence of extramedullary disease, absolute neutrophil count (ANC) ≥1.0 × 109/L [1000/μL], platelet count ≥100 × 109/L [100,000/μL], and independence of red blood cell [RBC] transfusions
OS	The time from date of randomization to the date of death due to any cause)
CR + CRh rate	CRh defined as a CR with partial recovery of peripheral blood counts where ANC is >0.5 × 109/L [500/μL], and platelet count is >50 × 109/L [50,000/μL]; CRh will be derived by the Sponsor
ORR	The rate of CR, CRi (including CRp), PR and MLFS
CR +CRi (including CRp) rate (CRi [including CRp]	All CR criteria except for residual neutropenia where ANC is <1.0 × 10^9/L [1000/μL] or thrombocytopenia where platelet count is <100 × 10^9/L [100,000/μL]; without platelet transfusion for at least one week prior to disease assessment
DOCR	Among patients who achieved CR; DOCRh, among patients who achieved CR or CRh; DOR, among patients who achieved CR, CRi (including CRp), PR, and/or MLFS and DOCRi, among patients who achieved CR or CRi(including CRp)
TTCR	Among patients who achieved CR; TTCRh, among patients who achieved CR or CRh; TTR, among patients who achieved CR, CRi (including CRp), PR, and/or MLFS; and TTCRi, among patients who achieved CR or CRi(including CRp)
IDH1-MC	CR with IDH1-MC is defined as a response of CR where there is no evidence of the IDH1 mutation by molecular techniques to below the level of detection (0.02%-0.04%) for ≥ 1 on-treatment time point(44)
Additional secondary endpoints	Vital signs, and results of ECOG PS, ECG, and echocardiogram (ECHO) or multi-gated acquisition (MUGA) for left ventricular ejection fraction (LVEF) as clinically indicated
	Clinical laboratory assessments (hematology, chemistry, and coagulation)
	AEs, AEs of special interest (AESIs), SAEs, and AEs leading to discontinuation or death
	Concomitant medication use
	Transfusion requirements (platelet and RBC; number of units transfused), rates of infection, days spent hospitalized, and other efficacy and safety measures that are potentially indicative of clinical benefit
Exploratory endpoints	Evaluation of a variety of established and exploratory biomarkers for morphologic, functional, metabolic, and biologic changes over the course of treatment
	EFS post-hoc analysis (defined as the time from randomization until progressive disease (PD), relapse from CR or CRi, TF or death from any cause. TF is defined as failure to achieve CR, CRi or MLFS after 24 weeks of treatment)

Abbreviations: 2-HG, 2-hydroxglutarate; µL, microliter; AE, adverse event; AESI, adverse event of special interest; ANC, absolute neutrophil count; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; DOCR, duration of complete remission; DOCRh, Duration of CR + CRh; DOCRi, duration of CR +CRi(including CRp); DOR, duration of response; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer core Quality of Life Questionnaire; EQ-5D-5L, EuroQol-5 dimension 5-level health-related quality of life questionnaire; EFS, event-free survival; IDH1, Isocitrate dehydrogenase; IDH1-MC , IDH1-mutation clearance L, liter; LVEF, left ventricular ejection fraction; MC, MLFS, morphologic leukemia-free state; MUGA, multi-gated acquisition; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial remission; PS, performance status; QoL, quality of life; RBC, red blood cell; SAE, serious adverse event; TTCR, time to CR; TTCRh, time to CR + CRh; TTCRi, time to CR +CRi(including CRp); TF, Treatment failure TTR, time to response.

Note: * An EFS sensitivity analysis was also completed. EFS is defined as the time from randomization until progressive disease, relapse from CR or Cri, treatment failure, or death from any cause. Treatment failure is defined as failure to achieve CR, Cri, or MLFS after at least 24 weeks of study treatment, whichever is first.

Source: Montesinos et al. 2022 (37)

Patient disposition

Based on the recommendation of the IDMC, further enrollment into the study was prematurely discontinued due to a clinically meaningful difference being observed between treatment arms. As of the primary data cutoff date of March 18, 2021, 146 patients had been randomized: 72 patients to the ivosidenib + azacitidine arm and 74 patients to the placebo + azacitidine arm. Twenty-seven patients in the ivosidenib + azacitidine arm, and 12 patients in the placebo + azacitidine arm, were still receiving treatment as of the primary data cutoff date. Among patients assigned to receive ivosidenib and azacitidine, 25 continued to receive both ivosidenib and azacitidine, one who discontinued ivosidenib continued to receive azacitidine alone, and one who discontinued azacitidine continued to receive ivosidenib alone (27 patients overall in the ivosidenib -and-azacitidine group).

Reasons for treatment discontinuation were similar between the treatment arms, however a numerically higher number of patients discontinued treatment in the placebo + azacitidine arm due to patient withdrawal, clinical progression, or lack of treatment benefit. A total of 106 patients discontinued ivosidenib or placebo: 45 (62.5%) in the ivosidenib + azacitidine arm, and 61 (82.4%) in the placebo + azacitidine arm; the reasons for treatment discontinuation among patients were (by order of frequency) AEs (27.4%), PD (17.1%), patient withdrawal (10.3%), clinical progression (6.2%) or lack of treatment benefit (6.2%), other (4.8%), and death (one patient in the placebo + azacitidine arm), with similar results observed in both treatment arms. The distribution of discontinuation rates due to the reasons above were similar among patients who discontinued their azacitidine treatment (33).

A summary of patient disposition is provided in Figure 5.

Figure 5: AGILE – Screening and randomization

Abbreviations: IWG, International Working Group; wk, week.

Source: Montesinos et al. 2022 (33).

The number of patients analysed per analysis set is provided by treatment arm in Table 9.

Table 9: AGILE – Summary patients per analysis set

Endpoints	Ivosidenib + azacitidine	Placebo + azacitidine	Total
All screened patients, N	-	-	295
FAS, N	72	74	146
SAS, N	71	73	144

Abbreviations: FAS, full analysis set; N, number; SAS, safety analysis set.

Notes: *The denominator used to calculate percentages was the number of patients in the FAS within each column.
All Screened patients: Patients who signed informed consent and were screened.

Source: AGILE CSR – data cutoff date: 18 March 2021 [Data on file](45)

Baseline demographics and disease characteristics

The AGILE treatment arms were balanced with regard to demographics and disease characteristics. The two treatment arms were comprised of a similar proportion of male patients (42 patients [58%] in the ivosidenib + azacitidine arm and 38 patients [51%] in the placebo + azacitidine arm) and age (median age was 76.0 years and 75.5 years, respectively.

In the ivosidenib + azacitidine group, 54 patients (75%) had primary AML and 18 (25%) had secondary AML; in the placebo + azacitidine group, 53 (72%) had primary AML and 21 (28%) had secondary AML. A total of 16 patients (22%) in the ivosidenib + azacitidine group had poor-risk cytogenetic characteristics, as compared with 20 (27%) in the placebo + azacitidine group.

Baseline demographics and disease characteristics are summarized in Table 10.

Table 10: AGILE – patient demographics and baseline characteristics (FAS) primary analysis March 18, 2021)

Endpoints	IVO + AZA (N = 72)	Placebo + AZA (N = 74)	Total (N = 146)
Age (years)			
Median (range)	76.0 (58.0, 84.0)	75.5 (45.0, 94.0)	76.0 (45.0, 94.0)
Age category (years), n (%)			
<75	33 (45.8)	31 (41.9)	64 (43.8)
≥75	39 (54.2)	43 (58.1)	82 (56.2)
Sex, n (%)			
Male	42 (58)	38 (51)	80 (55)
Female	30 (42)	36 (49)	66 (45)
Race or ethnic group, n (%) †			
Asian	15 (20.8)	19 (25.7)	34 (23.3)
White	12 (16.7)	12 (16.2)	24 (16.4)
Black	0	2 (2.7)	2 (1.4)
Other or not reported	45 (62.5)	41 (55.5)	86 (58.9)
ECOG PS, n (%) ‡			
0	14 (19.4)	10 (13.5)	24 (16.4)
1	32 (44.4)	40 (54.1)	72 (49.3)
2	26 (36.1)	24 (32.4)	50 (34.2)

Endpoints	IVO + AZA (N = 72)	Placebo + AZA (N = 74)	Total (N = 146)
Disease history according to investigator, n (%)			
Primary AML	54 (75.0)	53 (71.6)	107 (73.3)
Secondary AML§	18 (25.0)	21 (28.4)	39 (26.7)
History of myeloproliferative neoplasms	4 (5.6)	8 (10.8)	12 (8.2)
World Health Organization classification, n (%)			
AML with recurrent genetic abnormalities	16 (22.2)	24 (32.4)	40 (27.4)
AML with myelodysplasia-related changes	28 (38.9)	26 (35.1)	54 (37.0)
Therapy-related myeloid neoplasms	1 (1.4)	1 (1.4)	2 (1.4)
Cytogenetic risk status, n (%) **			
Favorable	3 (4.2)	7 (9.5)	10 (6.8)
Intermediate	48 (66.7)	44 (59.5)	92 (63.0)
Poor	16 (22.2)	20 (27.0)	36 (24.7)
Bone marrow blast level, median % (range)	54.0 (20.0-95.0)	48.0 (17.0-100)	52.5 (17, 100)

Abbreviations: AML, Acute myeloid leukemia; AZA, azacitidine; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; IVO, ivosidenib; n, number; PS, performance status.

Notes: The intention-to-treat population included all the patients who underwent randomization. Percentages may not total 100 because of rounding.

* IDH1 mutation for these patients was confirmed with local testing.
† Race or ethnic group was reported by the patient. “Other” includes American Indian or Alaska Native and Native Hawaiian or other Pacific Islander.

‡ Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with higher scores indicating greater disability.

§ Patients with secondary AML also included those with treatment-related AML (2 patients [3%] in the ivosidenib + azacitidine group and 1 [1%] in the placebo-and-azacitidine group), those with a history of myelodysplastic syndrome (10 patients [14%] and 12 [16%], respectively), and those with AML due to other causes (2 patients [3%] and none, respectively).

¶ IDH1 variants were determined with the use of the Abbott RealTime IDH1 in vitro polymerase chain reaction assay.

‖ Variant allele frequency in bone marrow aspirates was quantified by next-generation sequencing.

** Cytogenetic risk status was reported as other or missing for 5 patients (7%) in the ivosidenib + azacitidine group and 3 patients (4%) in the placebo-and-azacitidine group.

Source: Montesinos et al. 2022(37) & AGILE CSR – data cutoff date: 18 March 2021 [Data on file] (45)

The patient demographics and baseline characteristics remained largely unchanged in the updated analysis from 30 June 2022.

The most common prior medications used in these patients were antimycotics (49 [34.0%] patients), drugs for peptic ulcer and gastro-esophageal reflux disease (50 [34.7% patients]), other beta-lactam antibacterials (41 [28.5%] patients), anti-thrombotic agents (37 [25.7%] patients), beta-lactam antibacterials, penicillins (36 [25.0%] patients), beta blocking agents (35 [24.3%] patients), quinolone antibacterials (33 [22.9%] patients) and direct-acting antivirals (31 [21.5%] patients). The most common prior procedures recorded for these patients were investigations (28 [19.4%] patients) and surgical and medical procedures (20 [13.9%] patients). There were no clinically meaningful differences between the treatment arms with regard to the type and frequency of prior medications received or procedures conducted (32).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The following analysis sets were defined for AGILE and results for these are included in this dossier:

- **Full analysis set (FAS):** included all patients who were randomized. Patients were classified according to the randomized treatment arm.
- **Safety analysis set (SAS):** included all patients who received at least one dose of the study treatment. Patients were classified according to the treatment received, where treatment received was defined as:
    - The randomized treatment if it was received at least once, or
    - The first treatment received if the randomized treatment was never received.

The FAS was used for all analyses and the safety population used for all safety analyses, unless otherwise specified. To control the overall type I error rate, the fixed-sequence testing procedure was used to adjust for multiple statistical testing of the primary and key secondary efficacy end points. These end points were tested in the following order: EFS, CR, OS, CRh and ORR.

The hazard ratio (HR) between the trial groups was estimated with the use of a Cox proportional hazards model stratified according to geographic region and disease status. A log-rank test with the same stratification factors was used to compare EFS and OS in the trial groups. A Cochran-Mantel-Haenszel test with the same stratification factors was used to compare the incidences of CR, CRh, ORR, transfusion independence and CR with IDH1 mutation clearance between the trial groups. Randomization stratification factors were used in these analyses. Time-to-event end points were estimated with the use of the Kaplan-Meier (KM) method, with point estimates and 95% confidence intervals provided where appropriate. All reported P values are two-sided.

On the basis of the recommendation of the IDMC, whose members noted a difference in the number of deaths favouring ivosidenib + azacitidine, the sponsor and former sponsor discontinued trial recruitment on May 27, 2021. To account for this unplanned analysis, an individual set of group-sequential boundaries was applied separately to the primary and key secondary efficacy end points.

In addition, a number of subgroup analyses were completed. Hazard ratios were calculated from the unstratified Cox regression model, with placebo and azacitidine as the denominator and with two-sided 95% CIs.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Please see Appendix D.

B.2.6 Clinical effectiveness results of the relevant studies

Primary endpoint: EFS

The primary efficacy endpoint was met with a significant improvement in EFS demonstrated for patients randomized to the ivosidenib + azacitidine arm relative to the placebo + azacitidine arm (HR = 0.33; 95% CI, 0.16-0.69; p = 0.002) (Table 11). Because more than half the patients in each group did not have complete remission by week 24 due to the unique definition of EFS, the median EFS was the same in the two groups. The median EFS in the ivosidenib + azacitidine arm was 0.03 months (95% CI, 0.03-11.01 months) and 0.03 months (95% CI, not estimable [NE]) in the placebo + azacitidine arm.

However, the estimated probability that a patient would remain event-free was 40% at 6 months and 37% at 12 months in the ivosidenib + azacitidine group, as compared with 20% at 6 months and 12% at 12 months in the placebo + azacitidine group (no patients in the placebo + azacitidine arm had EFS of ≥24 months by the data cutoff date). The EFS benefit are summarized in Table 11 and a KM plot of EFS is provided in Figure 6.

Table 11: AGILE – Summary of EFS (FAS)

	Ivosidenib + azacitidine (N = 72)	**Placebo + azacitidine (N = 74)**
EFS (months), n (%) *		
Number (%) of events	46 (63.9)	62 (83.8)
Treatment failure	42 (58.3)	59 (79.7)
TF, on treatment >24 weeks without CR	16 (22.2)	11 (14.9)
TF, treatment discontinuation ≤24 weeks without CR	26 (36.1)	48 (64.9)
Relapse	3 (4.2)	2 (2.7)
Death	1 (1.4)	1 (1.4)
Percentiles (95% CI) **		
25th	0.03 (NE, NE)	0.03 (NE, NE)
50th (median)	0.03 (0.03, 11.01)	0.03 (NE, NE)
75th	23.98 (14.78, NE)	0.03 (0.03, 11.30)
Hazard ratio (95% CI) ***		0.33 (0.16, 0.69)
1-sided p-value****		0.0011
EFS rate (%) (95% CI) *****		
1 Day	41.7 (30.2, 52.7)	20.3 (12.0, 30.0)
3 Months	41.7 (30.2, 52.7)	20.3 (12.0, 30.0)
6 Months	39.9 (28.6, 51.0)	20.3 (12.0, 30.0)
9 Months	39.9 (28.6, 51.0)	20.3 (12.0, 30.0)
12 Months	37.4 (25.9, 48.9)	12.2 (4.3, 24.4)
18 Months	33.3 (20.9, 46.2)	6.1 (0.7, 20.9)
24 Months	22.2 (6.6, 43.4)	NE
36 Months	NE	NE

Abbreviations: CI, Confidence interval; CR, complete remission; EFS, event-free survival; FAS, full analysis set; n, number; NE, not estimable; TF, treatment failure.

Notes: *EFS = (Earliest date of TF or relapse or death – date of randomization + 1)/ 30.4375.

** Percentiles are estimated from product-limit (Kaplan-Meier) method. Confidence intervals are calculated from Brookmeyer and Crowley method with log-log transformation.

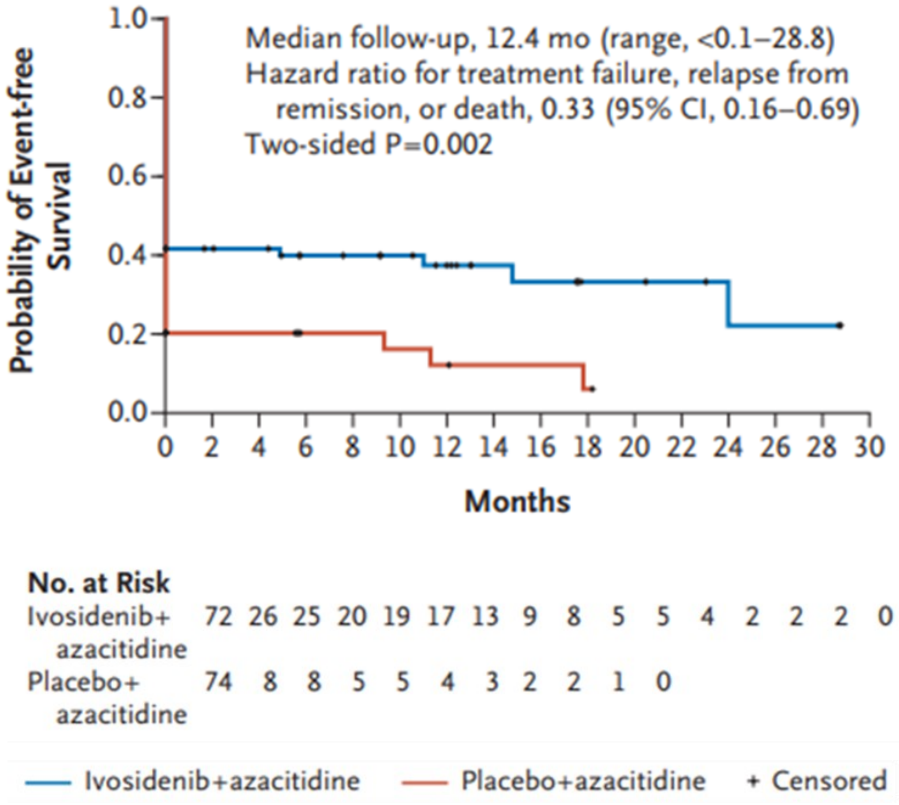
*** Hazard ratio is estimated using a Cox's proportional hazards model stratified by the randomization stratification factors (AML status and geographic region) with placebo + azacitidine as the denominator.

**** P-value is calculated from the one-sided log-rank test stratified by the randomization stratification factors (AML status and geographic region).

***** Event-free survival rate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free survival rates are obtained from the Kaplan-Meier survival estimates. Confidence intervals are calculated using Greenwood's formula and log-log transformation.

Source: Montesinos et al. 2022(37) & adapted from AGILE – data cutoff date: 18 March 2021 [Data on file](45)

Figure 6: AGILE – KM plot of EFS (FAS)



Abbreviations: CI, confidence interval; EFS, event-free survival; FAS, full analysis set; n, number; KM, Kaplan-Meier estimate.

Source: Montesinos et al. 2022(37)

As EFS is a composite endpoint of CR rate by 24 weeks and EFS among patients who achieved CR by 24 weeks, the estimates for each component were summarized. Twenty-seven patients achieved CR by 24 weeks in the ivosidenib + azacitidine arm versus eight patients in the placebo + azacitidine arm. CR rate by 24 weeks was 37.5% (95% CI, 26.4-49.7) in the ivosidenib + azacitidine arm and 10.8% (95% CI, 4.8-20.2) in the placebo + azacitidine arm. Among patients who achieved CR by 24 weeks, median EFS was NE (95% CI, 14.8-NE months) in the ivosidenib + azacitidine arm and 17.8 months (95% CI, 9.3-NE months) in the placebo + azacitidine arm The EFS for patients who achieved CR by 24 weeks is summarized in Table 12.

The 12-month EFS rate was 89.8% (95% CI, 64.3%-97.4%) in the ivosidenib + azacitidine arm versus 60.0% (95% CI, 12.6%-88.2%) in the placebo + azacitidine arm. The EFS rate

at 24 months was 53.2% (95% CI, 8.9%-84.8%) with ivosidenib + azacitidine and was NE in the placebo + azacitidine arm. The durability of the treatment effect was demonstrated in the ivosidenib + azacitidine arm as higher EFS rates at 12, 18, and 24 months (33). The restricted mean survival time (RMST) calculated up to 18.2 months, was 7.1 months in the ivosidenib + azacitidine arm and 3.1 months in the placebo + azacitidine arm. Difference in RMST, calculated by RMST (ivosidenib + azacitidine) – RMST (placebo + azacitidine), was 4.0 months (95% CI, 1.5-6.5 months; one-sided p = 0.0009) (32).

Table 12: AGILE – Summary of EFS for patients who achieved CR by 24 weeks (FAS)

	Ivosidenib + azacitidine (N = 72)	**Placebo + azacitidine (N = 74)**
EFS (months), n (%) *		
Number of patients achieving CR by 24 weeks	27	8
CR rate by 24 weeks, (%)	37.5	10.8
95% CI**	26.4, 49.7	4.8, 20.2
Number of events (%)	4 (14.8)	3 (37.5)
Relapse	3 (11.1)	2 (25.0)
Death	1 (3.7)	1 (12.5)
Percentiles (95% CI) ***		
25th	24.0 (4.9, NE)	11.3 (9.3, 17.8)
50th (median)	NE (14.8, NE)	17.8 (9.3, NE)
75th	NE (24.0, NE)	NE (9.3, NE)
EFS rate (%) (95% CI) ****		
3 Months	100	100
6 Months	95.8 (73.9, 99.4)	100
9 Months	95.8 (73.9, 99.4)	100
12 Months	89.8 (64.3, 97.4)	60.0 (12.6, 88.2)
18 Months	79.9 (46.4, 93.6)	30.0 (1.2, 71.9)
24 Months	53.2 (8.9, 84.8)	NE
36 Months	NE	NE

Abbreviations: CI, Confidence interval; CR, complete remission; EFS, event-free survival; FAS, full analysis set; n, number; NE, not estimable; TF, treatment failure.

Notes: *EFS = (Earliest date of TF or relapse or death – date of randomization + 1)/ 30.4375.

** CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.

*** Percentiles are estimated from product-limit (Kaplan-Meier) method. Confidence intervals are calculated from Brookmeyer and Crowley method with log-log transformation.

**** Event-free survival rate is the estimated probability that a patient will remain event-free up to the specified time point. Event-free survival rates are obtained from the Kaplan-Meier survival estimates. Confidence intervals are calculated using Greenwood's formula and log-log transformation.

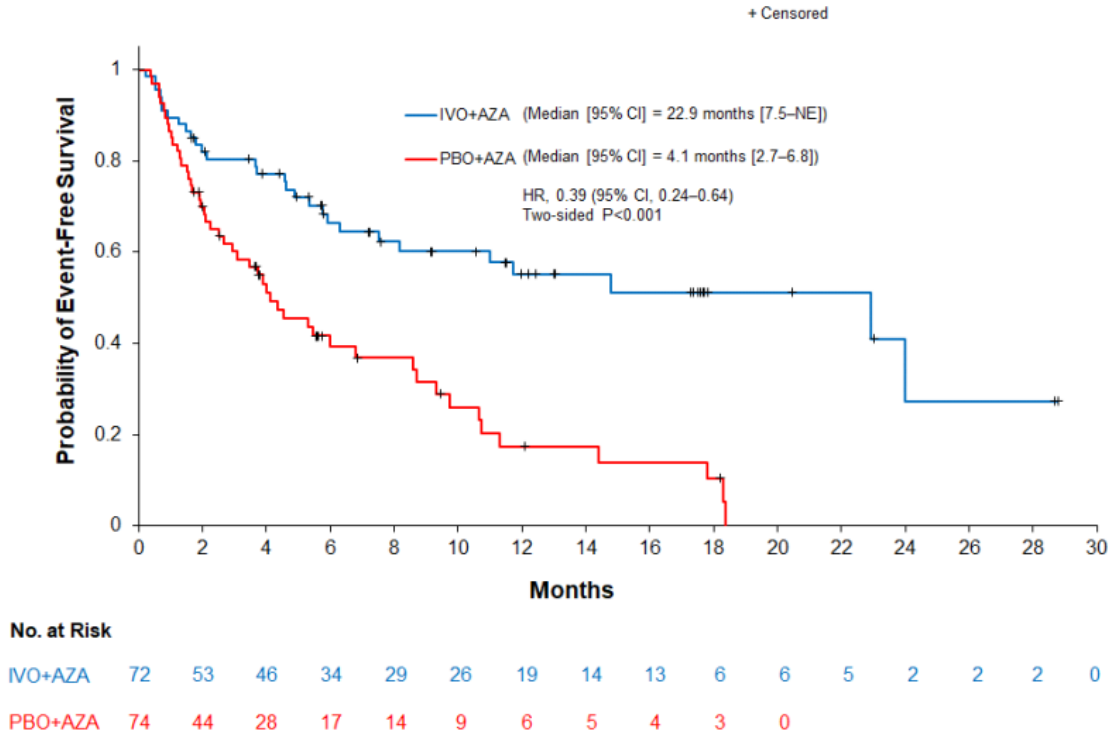
Source: Montesinos et al. 2022 (37) & adapted from AGILE – data cutoff date: 18 March 2021 [Data on file] (45)

EFS sensitivity analysis

When EFS was defined as a lack of CR, Cri, or MLFS after at least 24 weeks of study treatment, the improvement of EFS in the ivosidenib + azacitidine arm was maintained compared with placebo + azacitidine. The median EFS based on this sensitivity analysis was 22.9 months (95% CI, 7.5-NE) with ivosidenib + azacitidine treatment and 4.1 months

(95% CI, 2.7-6.8) with placebo + azacitidine (HR: 0.39; 95% CI, 0.24-0.64; two-sided p<0.001). A KM plot of EFS is provided in Figure 7.

Figure 7: AGILE – EFS with treatment failure defined as failure to achieve CR, CRi, or MLFS after 24 weeks of treatment (FAS; sensitivity analysis)



Abbreviations: AZA, azacitidine; CI, confidence interval; CR, complete remission; Cri, complete remission with incomplete hematologic recovery; FAS, Full-analysis set; HR, hazard ratio; IVO, ivosidenib; MLFS, morphologic leukemia-free state; PBO, placebo.

Notes: A stratified Cox regression model was used to estimate the hazard ratio of event-free survival.

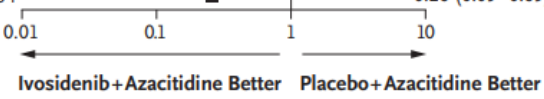
Source: Montesinos et al. 2022 (37)

EFS key subgroup analysis

In general, the EFS benefit associated with ivosidenib + azacitidine, compared with placebo + azacitidine, was consistently observed across all subgroups analyzed (Figure 8).

Figure 8: AGILE – EFS in key subgroups

Subgroup	Ivosidenib+ Azacitidine	Placebo+ Azacitidine	Hazard Ratio for Treatment Failure, Relapse from Remission, or Death (95% CI)
	no. of events/no. of patients		
Overall	46/72	62/74	0.35 (0.18–0.67)
Primary AML on basis of interactive response technologies			
Yes	35/56	46/55	0.33 (0.16–0.69)
No	11/16	16/19	0.32 (0.07–1.56)
Primary AML on basis of investigator from electronic CRF			
Yes	33/54	44/53	0.32 (0.15–0.69)
No	13/18	18/21	0.34 (0.07–1.61)
Region			
United States, Canada, western Europe, Israel, or Australia	30/48	44/50	0.22 (0.09–0.54)
Japan or rest of the world	16/24	18/24	0.73 (0.26–2.08)
Age			
<75 yr	21/33	25/31	0.43 (0.17–1.11)
≥75 yr	25/39	37/43	0.27 (0.10–0.71)
Baseline ECOG performance-status score			
0 or 1	30/46	43/50	0.31 (0.12–0.76)
≥2	16/26	19/24	0.39 (0.14–1.10)
Sex			
Female	19/30	29/36	0.35 (0.12–1.00)
Male	27/42	33/38	0.32 (0.13–0.79)
Race or ethnic group			
White	9/12	10/12	0.72 (0.16–3.20)
Asian	9/15	14/19	0.54 (0.14–2.01)
Other	28/45	38/43	0.21 (0.08–0.54)
Baseline cytogenetic risk status			
Favorable or intermediate risk	30/51	44/51	0.25 (0.11–0.55)
Poor risk	12/16	16/20	0.76 (0.16–3.57)
World Health Organization classification of AML			
AML with recurrent genetic abnormalities	11/16	21/24	0.41 (0.11–1.50)
AML with myelodysplasia-related change	18/28	20/26	0.47 (0.15–1.52)
Therapy-related myeloid neoplasms or AML not otherwise specified	17/28	21/24	0.33 (0.12–0.93)
Baseline white-cell count			
≤5×10^9/liter	33/51	41/49	0.36 (0.16–0.79)
>5×10^9/liter	13/21	21/25	0.35 (0.10–1.21)
Baseline bone marrow blast level			
≤50%	19/30	32/40	0.43 (0.17–1.09)
>50%	26/41	30/34	0.26 (0.09–0.69)



Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; CRF, Case report form; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; no, number.

Notes: Subgroups with five or fewer patients in either group were either pooled with other subgroups or not included. Other race or ethnic group includes Black, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and not reported. Two patients who were classified as having therapy-related myeloid neoplasms were pooled into the subgroup for therapy-related myeloid neoplasms or AML not otherwise specified. A baseline bone marrow blast level of at least 20% was reported for one patient in the ivosidenib + azacitidine group. This patient was not included in the subgroup analyses for baseline bone marrow blast level.

Source: Montesinos et al. 2022 (37)

Secondary endpoint: Overall survival

Overall survival was defined as the time from date of randomization to the date of death due to any cause.

After a median follow-up time of approximately 15 months for both treatment arms, a significant improvement in OS was demonstrated for patients randomized to the ivosidenib + azacitidine arm relative to the placebo + azacitidine arm (HR for death = 0.44; 95% CI, 0.27-0.73; p = 0.001), with a median OS of 24.0 months (95% CI, 11.3-34.1 months) in the ivosidenib + azacitidine arm and 7.9 months (95% CI, 4.1-11.3 months) in the placebo +

azacitidine arm (primary data cutoff date, 18 March 2021). The durability of the treatment effect was demonstrated at 3, 6, 9, 12, 18, and 24 months. A summary of OS data is presented in Table 13. A KM plot of OS is provided in Figure 9.

Table 13: AGILE – Summary of OS (FAS) (primary analysis, 18 March 2021).

	Ivosidenib + azacitidine (N = 72)	**Placebo + azacitidine (N = 74)**
Overall survival (months)		
Number of events (%)	28 (38.9)	46 (62.2)
Number of censored (%)	44 (61.1)	28 (37.8)
Alive	26.4, 49.7	4.8, 20.2
Lost to follow-up	0	1 (1.4)
Withdrawal of consent	6 (8.3)	4 (5.4)
Percentiles (95% CI) *		
25th	5.7 (2.1, 11.3)	2.0 (1.1, 3.1)
50th (median)	24.0 (11.3, 34.1)	7.9 (4.1, 11.3)
75th	34.1 (NE, NE)	18.1 (11.3, NE)
Hazard ratio (95% CI) **	0.44 (0.27, 0.73) 0.001	
Overall survival rate (%) (95% CI) ****		
3 Months	84.2 (73.3, 91.0)	66.6 (54.4, 76.2)
6 Months	72.9 (60.4, 82.0)	56.3 (43.6, 67.3)
9 Months	67.5 (54.4, 77.6)	43.9 (30.9, 56.1)
12 Months	63.4 (49.8, 74.2)	36.9 (24.3, 49.7)
18 Months	60.9 (47.1, 72.2)	26.4 (14.7, 39.6)
24 Months	45.4 (26.8, 62.2)	20.5 (10.0, 33.7)
36 Months	0	NE
Overall survival follow-up time (months) ***		
Median (95% CI)	15.2 (11.2, 19.6)	15.3 (6.8, 24.0)

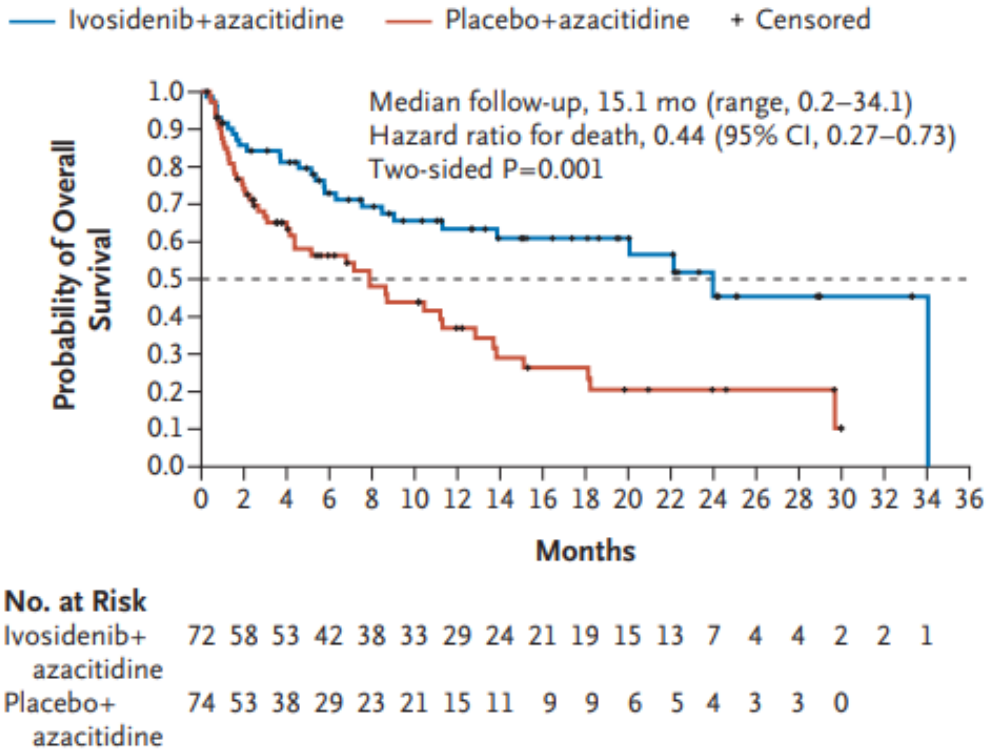
Abbreviations: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; n, number; NE, not estimable; OS, overall survival.

Notes: Percentages are calculated with the number of patients in each column as the denominator.

*Percentiles are estimated from product-limit (Kaplan-Meier) method. Cis are calculated from Brookmeyer and Crowley method with log-log transformation. **Hazard ratio is estimated using a Cox's proportional hazards model stratified by the randomization stratification factors (AML status and geographic region) with placebo + azacitidine as the denominator. *** Two-sided P values were calculated from a Cochran-Mantel-Haenszel test stratified according to the randomization stratification factors (disease status and geographic region). **** OS rate is the estimated probability that a patient will remain alive to the specified time point. OS rates are obtained from the KM survival estimates. Cis are calculated using Greenwood's formula and log-log transformation. ***** OS follow-up time is estimated based on reverse KM method.

Source: Montesinos et al. 2022(37) & adapted from AGILE – data cutoff date: 18 March 2021 [Data on file](45).

Figure 9: AGILE – KM plot of OS (FAS)

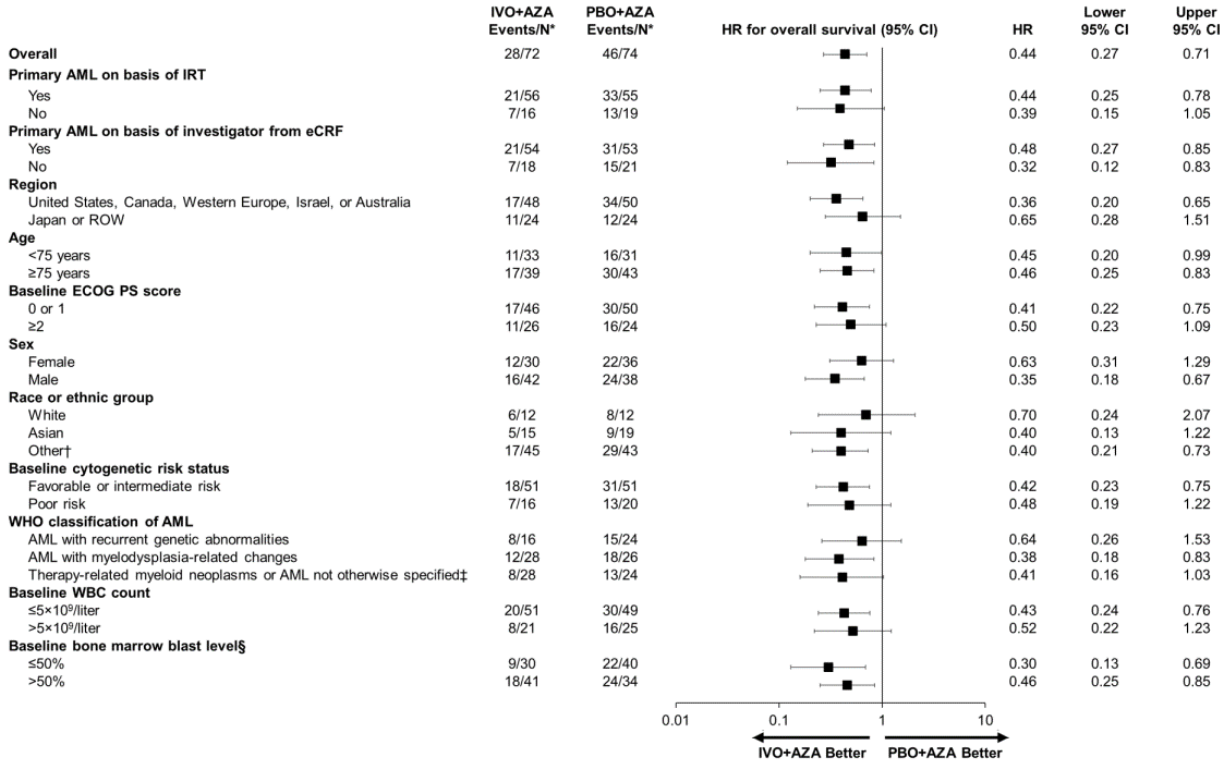


Abbreviations: CI, confidence interval; FAS, full analysis set; KM, Kaplan-Meier estimate; mo, month OS, overall survival.

Source: Montesinos et al. 2022(37).

The OS benefit observed with ivosidenib + azacitidine compared with placebo + azacitidine was generally consistent across patient subgroups, with all point estimates favoring ivosidenib + azacitidine (Figure 10).

Figure 10: AGILE – Forest plot of OS by key subgroup (FAS)



Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group – performance status, eCRF, electronic case report form. FAS, full analysis set; IRT, interactive response technology; HR, Hazard ratio; IVO, ivosidenib; PBO, placebo; OS, overall survival; RWO, rest of the World; WBC, white blood cells; WHO, World Health Organization.

Notes: Hazard ratio is calculated from the unstratified Cox regression model with placebo + azacitidine as the denominator, with two-sided 95% CI. *Subgroups with five or fewer patients in either arm were either pooled with other subgroups or not included. †Includes Black or African American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and not reported.

‡Two patients classified as having therapy-related myeloid neoplasms were pooled into the therapy-related myeloid neoplasms or AML not

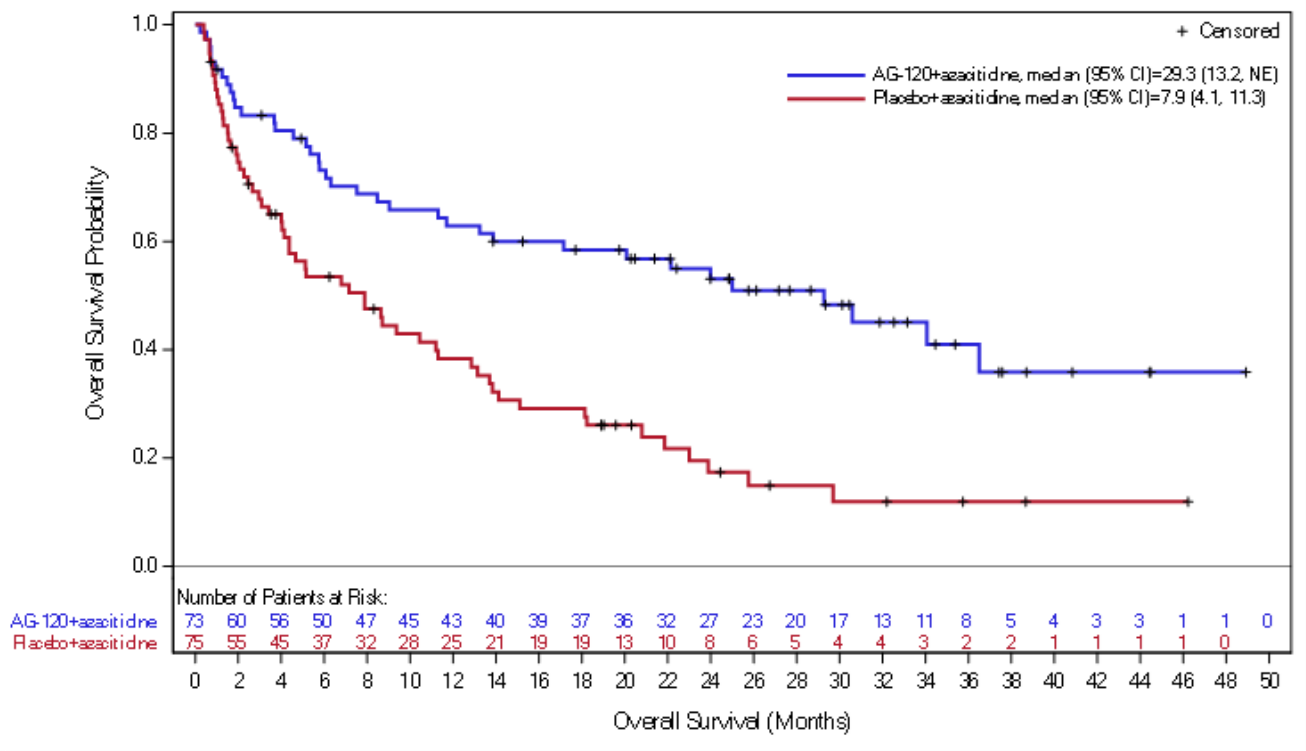
otherwise specified subgroup. §At least 20% of baseline blasts were reported for one patient in the ivosidenib + azacitidine arm. This patient was not included in the subgroup analyses for baseline percentage bone marrow blasts.

Source: Montesinos et al. 2022(37)

Updated analysis – data cut-off 30 June 2022

Updated analyses for this endpoint with a data cutoff date of 30 June 2022 and a median OS follow-up of 28,6 months are available. The analyses showed that the large OS effect was sustained and still significantly better for patients randomized to the ivosidenib + azacitidine arm relative to the placebo + azacitidine arm (HR for death = 0.42; 95% CI, 0.27-0.65; p = 0.0001), with a median OS of 29.3 months (95% CI, 13.2-NE months) in the ivosidenib + azacitidine arm and 7.9 months (95% CI, 4.1-11.3 months) in the placebo + azacitidine arm. The durability of the treatment effect was demonstrated up to the last data point, and a probability of survival of 35.8% at 4 years. This constitutes an absolute OS gain of 21.4 months which is considered a meaningful clinical benefit (46). The updated OS data is presented in Figure 11 and Table 14.(46)

Figure 11: Updated AGILE analysis (DCO 30th June 2022) – KM plot of OS (FAS)



Abbreviations: AG-120, ivosidenib; CI, confidence interval; NE, not estimable

Source: Updated AGILE analysis DCO30Jun2022.Data on file ((46))

Table 14: Updated AGILE analysis (DCO 30th June 2022) – Summary of OS (FAS)

	Ivosidenib + azacitidine (N = 73)	Placebo + azacitidine (N = 75)
Overall Survival (months)		
Number (%) of Events	37 (50.7)	58 (77.3)
Number (%) Censored	36 (49.3)	17 (22.7)
Alive	30 (41.1)	9 (12.0)
Lost to Follow-up	0	1 (1.3)
Withdraw by Subject	6 (8.2)	7 (9.3)
Percentiles		
25th Percentile (95% CI)	5.7 (1.8, 11.3)	2.0 (1.2, 3.4)
Median (95% CI)	29.3 (13.2, NE)	7.9 (4.1, 11.3)
75th Percentile (95% CI)	NE (36.5, NE)	20.8 (13.1, 29.7)
Hazard ratio (95% CI)	0.42 (95% CI: 0.27 – 0.65) p<0.0001	
KM Survival Rate (%) (95% CI)		
3 Months	83.3 (72.4, 90.1)	67.8 (55.9, 77.1)
6 Months	73.1 (61.1, 82.0)	53.5 (41.3, 64.1)
9 Months	67.3 (55.0, 76.9)	44.5 (32.7, 55.6)
12 Months	62.9 (50.4, 73.0)	38.3 (27.0, 49.5)
18 Months	58.4 (45.9, 69.0)	29.1 (18.9, 40.1)
24 Months	53.1 (40.4, 64.2)	17.4 (8.9, 28.2)
36 Months	41.0 (26.7, 54.7)	11.9 (4.7, 22.9)
48 Months	35.8 (20.8, 51.2)	NE

Abbreviations: CI, confidence interval; KM, Kaplan-Meier estimate; NE, not estimable

*1-sided p-value

Source: Updated AGILE analysis DCO30Jun2022 Data on file ((46))

Other clinically relevant outcome(s): Secondary endpoint: Subsequent stem cell transplants

At time of the 30 June 2022 data-cut, ivosidenib plus azacitidine also enabled 5 (7%) patients to receive a HSCT compared to 2 (3%) in the placebo plus azacitidine group(46). The OS for patients treated with ivosidenib plus azacitidine who received subsequent HSCT ranged from 27.2 to 44.5 months, compared to 9.4 to 38.7 months among patients treated with placebo + azacitidine. Table 15 shows the type of HSCT and disease status at the time thereof.

Table 15: Updated AGILE analysis – Subsequent stem cell transplant (FAS)

	Ivosidenib + azacitidine n=73	Placebo + azacitidine n=75
Type of HSCT	5 (6.8%)	2 (2.7%)
Allogeneic	5 (6.8%)	2 (2.7%)
Disease status at the time of HSCT	5 (6.8%)	2 (2.7%)
Morphologic CR	3 (4.1%)	2 (2.7%)
PD	2 (2.7%)	0 (0%)
Alive at the data cut off data (30 June 2022)	3 (4.1%)	1 (1.3%)

Abbreviations: CR, complete remission; HSCT, hematopoietic stem cell transplant; PD, progressive disease

Source: Servier Data on File ((46))

Secondary endpoint: Complete remission

The CR rate in the FAS was significantly higher in the ivosidenib + azacitidine arm than in the placebo + azacitidine arm (47.2% [95% CI, 35.3-59.3] versus 14.9% [95% CI, 7.7-25.0]; odds ratio of 4.76 [95% CI, 2.15-10.50]; two-sided p<0.001). Median time to CR was 4.3 months with ivosidenib + azacitidine compared to 3.8 months with placebo + azacitidine

The median duration of CR was not reached with ivosidenib + azacitidine and was 11.2 months (95% CI, 3.2-NE) with placebo + azacitidine. Among patients with CR, the estimated probability that a patient would remain in CR at 12 months was 88% with ivosidenib + azacitidine and 36% with placebo + azacitidine (33). The CR rates are summarized in Table 16.

Table 16: AGILE – Summary of CR (FAS)

	Ivosidenib + azacitidine (N = 72)	Placebo + azacitidine (N = 74)
CR rate, n (%)	34 (47.2)	11 (14.9)
95% CI	(35.3, 59.3)	(7.7, 25.0)
Odds ratio (95% CI); 2-sided p-value		4.76 (2.15, 10.50) <0.001
Median duration of CR (95%CI), month	NE (13.0, NE)	11.2 (3.2, NE)
Median time to CR (range), month	4.3 (1.7, 9.2)	3.8 (1.9, 8.5)

Abbreviations: CI, confidence interval; CR, complete remission; FAS, full analysis set; N, number; NE, not estimated.

Notes: Percentages may not total 100 because of rounding.

Source: Montesinos et al. 2022 (37)

Secondary endpoint: CR + CRh

The CR + CRh rate was significantly higher in the ivosidenib + azacitidine arm than in the placebo + azacitidine arm (52.8% [95% CI, 40.7-64.7] versus 17.6% [95% CI, 9.7-28.2]; odds ratio of 5.01 [95% CI, 2.32-10.81]; two-sided p<0.001) (33). A summary of CR + CRh rates is presented in Table 17.

Table 17: AGILE – Summary of CR + CRh rates (FAS)

	Ivosidenib + azacitidine (N = 72)	Placebo + azacitidine (N = 74)
CR + CRh rate, n (%)	38 (52.8)	13 (17.6)
95% CI	(40.7, 64.7)	(9.7, 28.2)
Odds ratio (95% CI) 2-sided p-value		5.01 (2.32, 10.81) <0.001
Median duration of CR + CRh (95%CI), month	NE (13.0, NE)	9.2 (5.8, NE)
Median time to CR + CRh (range), month	4.0 (1.7, 8.6)	3.9 (1.9, 7.2)

Abbreviations: CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; FAS, full analysis set; n, number; NE, not estimated.

Notes: Two-sided P values were calculated from a Cochran-Mantel-Haenszel test stratified according to the randomization stratification factors (disease status and geographic region).

Percentages may not total 100 because of rounding.

Source: Montesinos et al. 2022(37).

Secondary endpoint: CR + CRi

CR + CRi was achieved in 54.2% (95% CI, 42.0-66.0) of the patients in the ivosidenib + azacitidine arm and 16.2% (95% CI, 8.7-26.6) of the patients in the placebo + azacitidine arm. CR + CRi rate was more than three times higher in the ivosidenib + azacitidine arm than in the placebo + azacitidine arm. CR + CRi was significantly higher in the ivosidenib + azacitidine arm than in the placebo + azacitidine arm (odds ratio of 5.9 [95% CI, 2.69-12.97]; p<0.001). A summary of the CR + CRi outcomes are presented in Table 18.

Table 18: AGILE – Summary of CR + CRi rate (FAS)

	Ivosidenib + azacitidine (N = 72)	**Placebo + azacitidine (N = 74)**
CR + CRi rate, n (%)	39 (54.2)	12 (16.2)
95% CI	(42.0, 66.0)	(8.7, 26.6)
Odds ratio (95% CI)	5.90 (2.69, 12.97)	
1-sided p-value	<0.0001	

Abbreviations: CI, confidence interval; CR, complete remission; Cri, complete remission with incomplete hematologic recovery; FAS, full analysis set; n, number.

Notes: Response was determined according to modified International Working Group criteria. One-sided P values were calculated from a Cochran-Mantel-Haenszel test stratified according to the randomization stratification factors (disease status and geographic region). Percentages may not total 100 because of rounding.

Source: Adapted from AGILE – data cutoff date: 18 March 2021 [Data on file](37).

Objective response

ORR, defined as the rate of CR, CRi (including CRp), PR, and MLFS, was achieved in 62.5% (95% CI, 50.3-73.6) of the patients in the ivosidenib + azacitidine arm and 18.9% (95% CI, 10.7-29.7) of the patients in the placebo + azacitidine arm. ORR was significantly higher in the ivosidenib + azacitidine arm than in the placebo + azacitidine arm (odds ratio of 7.15 [95% CI, 3.31-15.44]; p<0.001). Additionally, seven (9.7%) patients in the ivosidenib + azacitidine arm and 27 (36.5%) in the placebo + azacitidine arm had SD at the time of data cutoff. A summary of ORR is presented in Table 19.

Table 19: AGILE – Summary of ORR (FAS)

	Ivosidenib + azacitidine (N = 72)	**Placebo + azacitidine (N = 74)**
OR rate, n (%)	45 (62.5)	14 (18.9)
95% CI	(50.3, 73.6)	(10.7, 29.7)
Odds ratio (95% CI)	7.15 (3.31, 15.44)	
2-sided p-value	<0.001	

Abbreviations: CI, confidence interval; FAS, full analysis set; n, number; ORR, objective response rate.

Notes: Response was determined according to modified International Working Group criteria. Two-sided P values were calculated from a Cochran-Mantel-Haenszel test stratified according to the randomization stratification factors (disease status and geographic region). Percentages may not total 100 because of rounding.

Source: Montesinos et al. 2022 (37)

Secondary endpoint: Duration of response

DOR

Median DOR was 22.1 months in the ivosidenib + azacitidine arm (95% CI, 13.0-NE) and 9.2 months in the placebo + azacitidine arm (95% CI, 6.6-14.1). The durability of the ivosidenib + azacitidine treatment effect was demonstrated at 9, 12, 18, and 24 months

DOCR

DOCR was defined, for patients who achieved CR, as the time from the first occurrence of CR to confirmed relapse or death due to any cause. Median DOCR was not estimable as of the data cutoff date in the ivosidenib + azacitidine arm and was 11.2 months in the placebo + azacitidine arm (95% CI, 3.2-NE). The durability of the ivosidenib + azacitidine treatment effect was demonstrated at 6, 9, 12, 18, and 24 months

DOCRh

Median DOCRh was NE as of the data cutoff date in the ivosidenib + azacitidine arm and was 9.2 months in the placebo + azacitidine arm (95% CI, 5.8-NE). The durability of the ivosidenib + azacitidine treatment effect was demonstrated at 3, 6, 9, 12, 18, and 24 months.

DOCRi

Median DOCRi was NE as of the data cutoff date in the ivosidenib + azacitidine arm and was 9.2 months in the placebo + azacitidine arm (95% CI, 5.8-NE). The durability of the ivosidenib + azacitidine treatment effect was demonstrated at 6, 9, 12, 18, and 24 months

Secondary endpoint: Time to response

Time to response, defined as TTCR, TTCRh and TTCRi, is reported in Table 20. The median time to first CR was 4.2 months (range, 1.7 to 9.2) in the ivosidenib + azacitidine arm and 3.8 months (range, 1.9 to 8.5) in the placebo + azacitidine arm. The median time to first CR + CRh was 4.0 months (range, 1.7 to 8.6 months) in the ivosidenib + azacitidine arm and 3.9 months (range, 1.9 to 7.2 months) in the placebo + azacitidine arm. The median TTR was 2.1 months (range, 1.7 to 7.5 months) in the ivosidenib + azacitidine arm and 3.7 months (range, 1.9 to 9.4 months) in the placebo + azacitidine arm. The median time to first CR +CRi was 2.8 months (range, 1.7 to 7.2 months) in the ivosidenib + azacitidine arm and 3.8 months (range, 1.9 to 7.2 months) in the placebo + azacitidine arm.

Table 20: AGILE – Summary of time to CR, CR + CRh, first response and CR +CRi (TTCR, TTCRh, TTR, TTCRi) (FAS)

	Ivosidenib + azacitidine (N = 72)	Placebo + azacitidine (N = 74)
Time to CR (months)*		
N	34	11
Mean (SD)	4.5 (1.934)	4.8 (2.294)
Median	4.2	3.8
Min, max	1.7, 9.2	1.9, 8.5
Time to CR + CRh (months)**		
N	38	13
Mean (SD)	4.1 (1.889)	4.2 (1.548)
Median	4.0	3.9
Min, max	1.7, 8.6	1.9, 7.2
Time to first response (months)***		
N	45	14
Mean (SD)	2.8 (1.320)	3.9 (1.985)
Median	2.1	3.7
Min, max	1.7, 7.5	1.9, 9.4
Time to CR +CRi(months)******		
N	39	12
Mean (SD)	3.46 (1.569)	3.9 (1.483)
Median	2.8	3.8
Min, max	1.7, 7.2	1.9, 7.2

Abbreviations: CI, confidence interval; CR, complete remission; CRh, complete remission with partial hematologic recovery; Cri, complete remission with incomplete recovery; FAS, full analysis set; NE, not estimable; SD, standard deviation.

Notes: Percentages are calculated with the number of patients in each column as the denominator. *Time to CR is defined, for patients who achieved CR, as the time from randomization to first occurrence of CR. TTCR (months) = (first date of CR – date of randomization + 1)/30.4375.
Time to CR + CRh is defined, for patients who achieved CR or CRh, as the time from randomization to first occurrence of CR or CRh. TTCRh (months) = (first date of CR or CRh – date of randomization + 1)/30.4375. * Time to first response is defined, for patients who achieved CR, Cri(including CRp), PR or MLFS, as the time from randomization to first occurrence of CR, Cri(including CRp), PR or MLFS. TTR (months) = (first date of CR, Cri(including CRp), PR or MLFS – date of randomization + 1)/30.4375. **** Time to CR + CRiis defined, for patients who achieved CR or Cri(including CRp), as the time from randomization to first occurrence of CR or Cri(including CRp). TTCR (months) = (first date of CR orCRi(including CRp) – date of randomization + 1)/30.4375.

Source: Montesinos et al. 2022(37) & adapted from AGILE – data cutoff date: 18 March 2021 [Data on file](45)

Overall, the median duration of treatment was more than two times longer in the ivosidenib + azacitidine arm (6.0 months [range, 0.1 to 33.5]) than in the placebo + azacitidine arm (2.8 months [range, 0.1 to 19.8])

Secondary endpoint: Haematologic improvement

Analyses were conducted to assess baseline transfusion dependence or independence and post-baseline transfusion dependence or independence in the FAS. Baseline RBC and/or PLT transfusion dependence was similar in the ivosidenib + azacitidine and placebo + azacitidine arms (54.2% versus 54.1%, respectively). Among patients who were transfusion dependent at baseline, a higher proportion who received ivosidenib + azacitidine (18 [46.2%]

patients) experienced RBC and PLT transfusion independence compared with those who received placebo + azacitidine (7 [17.5%] patients) (two-sided p = 0.006). Furthermore, regardless of baseline transfusion status, a greater proportion of patients in the ivosidenib + azacitidine arm (45 [62.5%] patients) experienced RBC and/or PLT transfusion independence compared with the placebo + azacitidine arm (38 [51.4%] patients), however this difference was not statistically significant (two-sided p = 0.21).

Patient-reported outcomes

Baseline EORTC QLQ-C30 scores were available for 69 patients (96%) who received ivosidenib + azacitidine and 66 (89%) who received placebo + azacitidine (34).

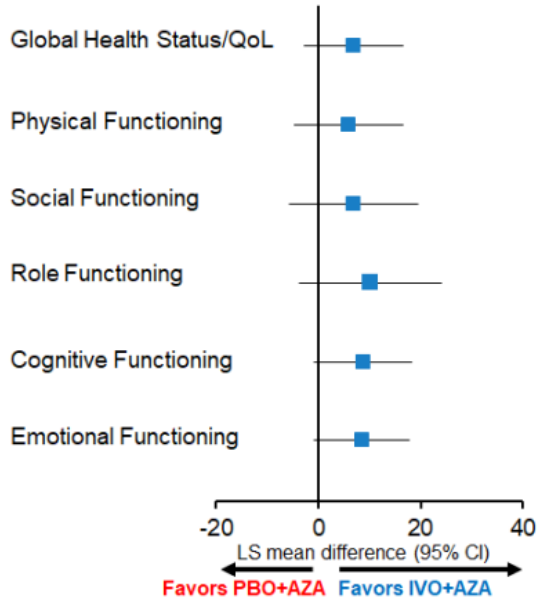
Clinical benefits seen in the ivosidenib + azacitidine arm (e.g., EFS, OS, responses) were supported by improvements in multiple HRQoL domains, including Global Health Status/QoL and Fatigue. Patients in the ivosidenib + azacitidine arm experienced stabilization of HRQoL, and in some cases clinically meaningful improvements, through Day 1 of Cycle 19 (C19D1) compared to the placebo + azacitidine arm(37). Although compliance rates were reasonably high across visits, interpretation of HRQoL data is limited by the decreasing HRQoL sample sizes over time, likely owing to disease progression and treatment discontinuation. In addition, prespecified domains of interest and anchor questions to assess population-specific meaningful change thresholds were not available to indicate conclusively significant and meaningful differences between treatment arms. Finally, p values were not adjusted for multiplicity(37)

EORTC QLQ-C30

A threshold of 10 points was used to interpret group differences and clinically meaningful changes in subscale scores over time. Higher scores in the global and functioning subscales and lower scores in the symptom/single-item subscales indicate better HRQoL (37)

At baseline, the mean scores for EORTC QLQ-C30 subscales were similar between the treatment arms, with no difference of greater than 10 points. Across all subscales of the EORTC QLQ-C30, HRQoL results favored the ivosidenib + azacitidine arm, with no statistically significant or clinically meaningful differences (i.e., difference in subscale score change exceeding 10 points) in favor of the placebo + azacitidine arm at any visits (Figure 12 and Figure 13)(37).

Figure 12: AGILE – EORTC QOQ-C30 Global Health Status/QoL and functional subscales change scores between arms at C5D1 (FAS)

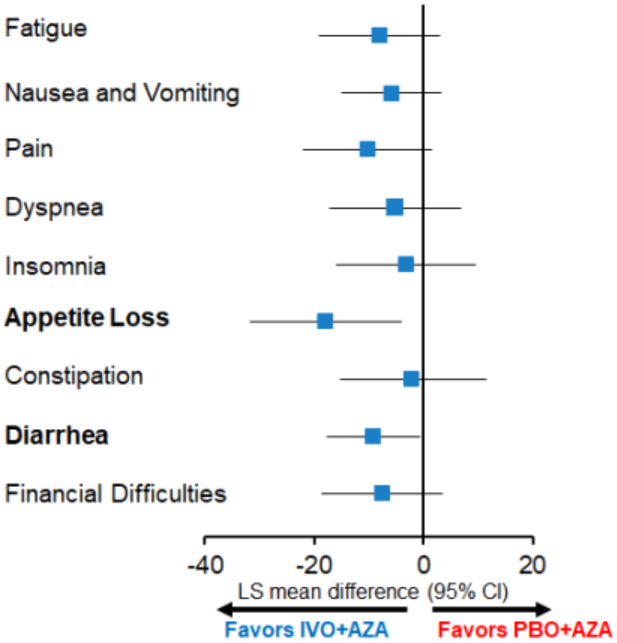


Abbreviations: AZA, azacitidine; C, cycle; D, day; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FAS, full analysis set; IVO, ivosidenib; LS, least squares; n, number; PBO, placebo; QoL, quality of life.

Note: higher scores denote better health status or function.

Source: Montesinos et al. 2022 (37)

Figure 13: AGILE – EORTC QOQ-C30 symptom subscales change scores between arms at C5D1 (FAS)



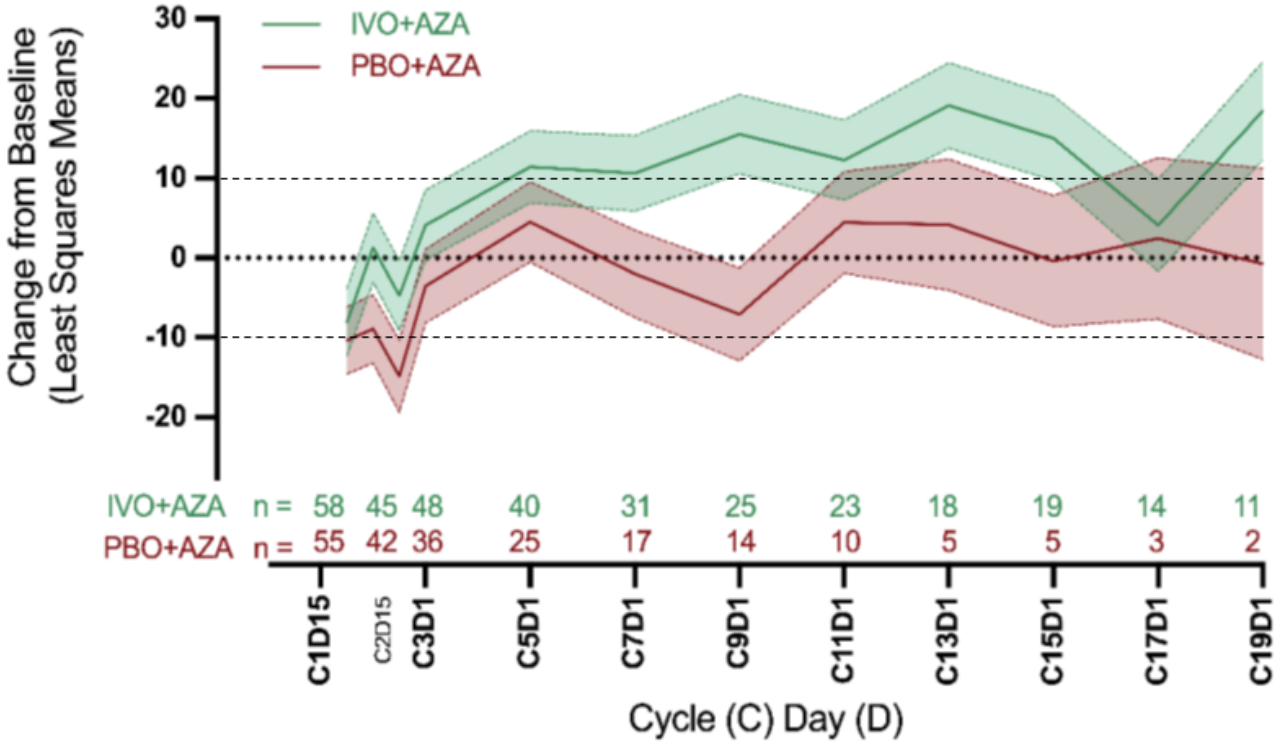
Abbreviations: AZA, azacitidine; C, cycle; D, day; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FAS, full analysis set; IVO, ivosidenib; LS, least squares; PBO, placebo

Note: higher scores denote worse symptoms. Bold text indicates two-sided p<0.05.

Source: Montesinos et al. 2022 (37)

Following an initial, similar decline from baseline to C3D1 in both arms, HRQoL for remaining patients in the ivosidenib + azacitidine arm was similar to baseline or showed improvement across many EORTC QLQ-C30 subscales from C5D1 until C19D1 (after which no placebo + azacitidine HRQoL data were available). The decline was consistent with time to response of about 4 months. Notably, from C5D1 to C19D1, patients in the ivosidenib + azacitidine arm experienced clinically meaningful improvements in the Global Health Status/QoL subscale (exceeding the 10-point threshold) at all visits except C17D1 (Figure 14). In contrast, patients in the placebo + azacitidine arm had no meaningful changes compared to baseline. From baseline through C19D1, the difference in Global Health Status/QoL score changes between arms was significant at C2 (D1, p = 0.0126; D15, p = 0.0225), C7 (p = 0.0261) and C9 (p = 0.0002), with clinically meaningful differences for the ivosidenib + azacitidine arm versus the placebo + azacitidine arm at C2D1 (10.2 point difference), C2D15 (10.1), C7 (12.6), C9 (22.6), C13 (14.9), C15 (15.4) and C19 (19.2) (37, 47)

Figure 14: AGILE – EORTC QOQ-C30 Global Health Status/QoL score change from baseline through C19D1 (FAS)



Abbreviations: AZA, azacitidine; C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FAS, full analysis set; IVO, ivosidenib; n, number; PBO, placebo; QoL, quality of life.

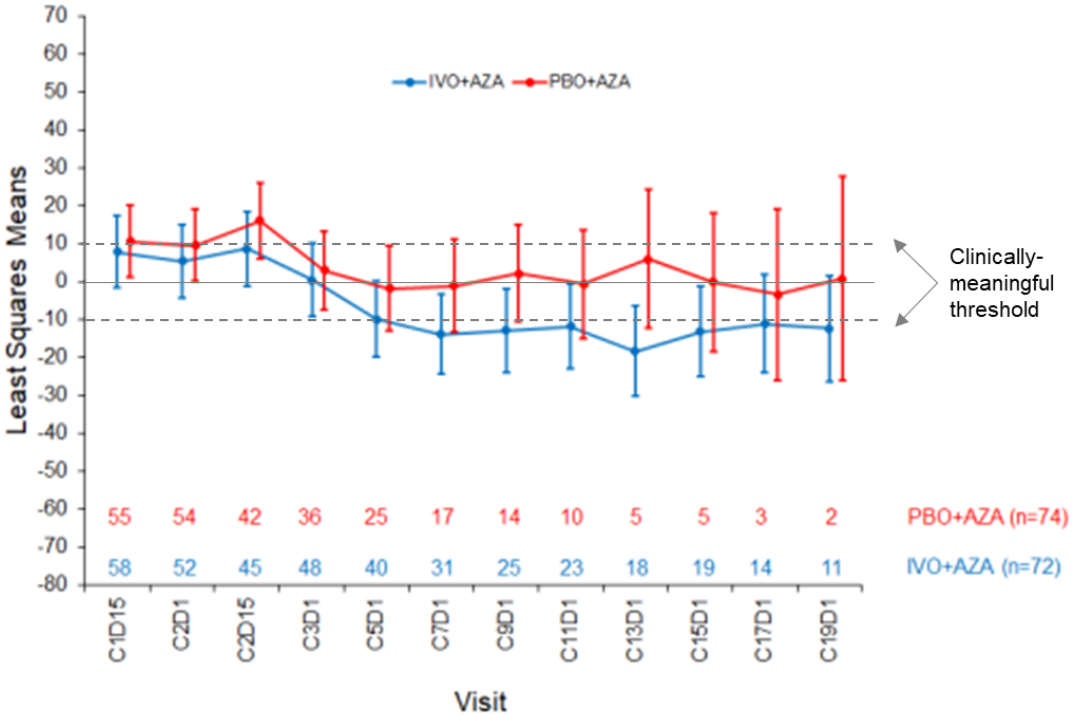
Note: A threshold of 10 points was used to interpret group differences and clinically meaningful changes in subscale scores over time. Higher scores in the global and functioning subscales and lower scores in the symptom/single-item subscales indicate better HRQoL.

Source: Montesinos et al. 2022(37)

Similar trends were observed on the fatigue subscale (Figure 15). From C5D1-C19D1, improvements in the ivosidenib + azacitidine arm were clinically meaningful at all visits

except for C5D1, whereas Fatigue scores were similar to baseline in the placebo + azacitidine arm. The difference between arms was statistically significant at C7 (p = 0.0482), C9 (p = 0.0309), and C13 (p = 0.0147), with clinically meaningful differences for the ivosidenib + azacitidine arm versus the placebo + azacitidine arm at C7 (12.7), 9 (15.0), 11 (11.1), 13 (24.1), 15 (13.1), and 19 (13.1)(37, 47)

Figure 15: AGILE – EORTC QOQ-C30 Fatigue score change from baseline through C19D1 (FAS)



Abbreviations: AZA, azacitidine; C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FAS, full analysis set; IVO, ivosidenib; n, number; PBO, placebo; QoL, quality of life.

Note: A threshold of 10 points was used to interpret group differences and clinically meaningful changes in subscale scores over time. Higher scores in the global and functioning subscales and lower scores in the symptom/single-item subscales indicate better HRQoL.

Source: Montesinos et al. 2022 (37)

In addition, clinically meaningful differences between arms, favoring ivosidenib + azacitidine, in appetite loss and nausea and vomiting symptoms subscales were observed at most visits from C5D1 to C19D1 (284). Scores remained worse than baseline in the ivosidenib + azacitidine and placebo + azacitidine arms for the insomnia and constipation subscales, with meaningful deterioration at multiple visits for both arms.

Patients in the placebo + azacitidine arm generally had EORTC QLQ-C30 scores similar to baseline or worse than baseline. When applying the 10-point threshold across visits, no subscales were improved relative to baseline in the placebo + azacitidine arm. For some subscales, there was clinically meaningful deterioration at most visits between C5D1 and C19D1, including social functioning (C7-C19), nausea and vomiting (C9-C19), insomnia (C7-11, C15-19) and constipation at (C5-9, C13-19)

Score change from baseline for each EORTC QLQ-C30 subscale was analyzed with mixed models for repeated measures. Results favored ivosidenib + azacitidine across all EORTC QLQ-C30 subscales (37)

EQ-5D-5L

A difference from baseline of at least seven points was considered clinically meaningful for EQ-5D-5L VAS scores, and a difference from baseline of at least 0.06 points was considered clinically meaningful for US index values.

HRQoL improvements over time were also observed for ivosidenib based on the summary of EQ-5D-5L VAS scores and index values. Between C5D1 and C19D1, there was clinically meaningful improvement in the ivosidenib + azacitidine arm at most visits compared to baseline (Table 21 and Table 22)).

In comparison, in the placebo + azacitidine arm clinically meaningful improvements from baseline in the VAS scores were only observed at C11, followed by a deterioration of scores at C15, C17 (clinically meaningful) and C19 (Table 21). Clinically meaningful improvement in the index value were observed at C11D1, C13D1, and C19D1 (Table 22) (45)

Table 21: AGILE – EQ-5D-5L VAS scores and change from baseline (FAS)

Visit	Ivosidenib + azacitidine	Placebo + azacitidine
Baseline, mean (SD)	63.01 (20.947). n = 68	62.89 (20.011). n = 66
Change from baseline		
C5D1	**10.56 (22.589). n = 39**	-4.96 (21.143). n = 25
C7D1	**9.45 (16.906). n = 29**	1.63 (19.510). n = 16
C9D1	**10.63 (14.240). n = 24**	-6.64 (24.044). n = 14
C11D1	6.05 (18.248). n = 22	**7.50 (24.001). n = 10**
C13D1	**13.72 (16.153). n = 18**	4.00 (23.313). n = 5
C15D1	**8.53 (19.184). n = 19**	-6.40 (19.527). n = 5
C17D1	**9.36 (23.621). n = 14**	-7.67 (24.786). n = 3
C19D1	**10.27 (21.868). n = 11**	-5.50 (34.648). n = 2

Abbreviations: Cx, cycle x day y; EQ-5D-5L, 5-level EuroQol Five Dimensions Questionnaire; FAS, full analysis set; n, number; SD, standard deviation; VAS, visual analog scale.

Notes: Change from baseline is calculated only for the subjects having observed value at both baseline and post-baseline visits.

Baseline is defined as most recent measurement on or before the date of randomization. If there is no value available on or before the date of randomization, the last measurement on or before the start of study treatment will be used as baseline. Unscheduled visits are excluded from the analysis.
Bold text indicates clinically meaningful difference from baseline (a difference from baseline of at least 7 points for EQ-5D-5L VAS scores was considered clinically meaningful).

Source: Source: Adapted from AGILE - data cutoff date: 18 March 2021 [Data on file](45).

Table 22: AGILE – EQ-5D-5L index values and score change from baseline (FAS)

Visit	Ivosidenib + azacitidine	Placebo + azacitidine
Baseline, mean (SD)	0.7116 (0.27756). n = 68	0.6796 (0.28516). n = 66
Change from baseline		
C5D1	**0.1032 (0.29723). n = 39**	0.0082 (0.23908). n = 25
C7D1	**0.0796 (0.30054). n = 29**	0.0071 (0.25429). n = 16
C9D1	**0.0630 (0.26742). n = 24**	0.0049 (0.26003). n = 14
C11D1	0.0471 (0.27756). n = 22	**0.1046 (0.31273). n = 10**
C13D1	**0.1046 (0.29168). n = 18**	**0.0636 (0.12576). n = 5**
C15D1	0.0526 (0.29660). n = 19	0.0062 (0.15240). n = 5
C17D1	0.0328 (0.30635). n = 14	0.0363 (0.11585). n = 3
C19D1	**0.0626 (0.32590). n = 11**	**0.0995 (0.09405). n = 2**

Abbreviations: Cx, cycle x day y; EQ-5D-5L, 5-level EuroQol Five Dimensions Questionnaire; FAS, full analysis set; n, number; SD, standard deviation.

Notes: Change from baseline is calculated only for the subjects having observed value at both baseline and post-baseline visits.

Baseline is defined as most recent measurement on or before the date of randomization. If there is no value available on or before the date of randomization, the last measurement on or before the start of study treatment will be used as baseline. Unscheduled visits are excluded from the analysis.
Bold text indicates clinically meaningful difference from baseline (a difference from baseline of at least 0.06 points for US index values was considered clinically meaningful).

Source: Source: Adapted from AGILE - data cutoff date: 18 March 2021 [Data on file] (45)

The clinical benefit ivosidenib + azacitidine was supported by improvements in multiple HRQoL domains, including Global Health Status/QoL and functional subscales according to EORTC QLQ-C30. Clinically meaningful improvements were also demonstrated in the Fatigue symptom subscale at most visits. In addition to improvements in both appetite and diarrhoea, HRQoL results also favored ivosidenib + azacitidine over placebo across the remaining symptoms subscales. Patients in the ivosidenib + azacitidine arm experienced stabilization of HRQoL and showed clinically meaningful improvements in Global Health Status/QoL at most visits. HRQoL improvements were also observed for ivosidenib + azacitidine based on EQ-5D-5L index values. Although compliance rates were reasonably high across visits, interpretation of HRQoL data are limited by the decreasing HRQoL sample sizes over time likely due to disease progression and treatment discontinuation (37)

B.2.7 Subgroup analysis

Subgroup analysis are provided in the key results section for EFS and OS in each of the main subgroups.

Provide a summary of the results for the subgroups in appendix E.

B.2.8 Meta-analysis

Ivosidenib + azacitidine has not been investigated with Venetoclax + azacitidine in a head-to-head randomized controlled trial (RCT) and so a network meta-analysis was carried out to provide the indirect comparison (alongside a range of other potential comparators, though none of these were deemed relevant to NHS England practice, as discussed in Section B.1.1 Decision problem). Therefore, only outputs for Ivosidenib + azacitidine and Venetoclax + azacitidine are given.

Full details of this are explored further in section B.2.9

B.2.9 Indirect and mixed treatment comparisons

In appendix D include full details of the methodology for the indirect comparison or mixed treatment comparison.

Venetoclax was recommended by NICE for use within England in combination with azacitadine for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy (34).

The target population for the ITCs was based on the population of the AGILE trial. It included subjects with 1L/treatment naïve/newly diagnosed AML who are unfit/ineligible for intensive chemotherapy. However, due to lack of comparative evidence in the literature for patients specifically with IDH1 mutation status, the target population was not restricted to patients with a confirmed IDH1 mutation. The outcomes considered were overall survival (OS) and event-free survival (EFS), the results of which are then included in the economic analysis.

Ivosidenib + azacitidine has not been investigated with Venetoclax + azacitidine in a head-to-head randomized controlled trial (RCT) and so a network meta-analysis was carried out to provide the indirect comparison (alongside a range of other potential comparators, though none of these were deemed relevant to NHS England practice, as discussed in Section B.1.1 Decision problem). Venetoclax was not approved as a treatment for newly diagnosed AML patients ineligible for intensive induction chemotherapy when the AGILE trial was designed and started. The AGILE trial commenced in June 2017, and the European

Medicines Agency Committee for Medicinal Products for Human Use positive opinion for venetoclax + azacitidine in AML was delivered on 22 April 2021.

Therefore, as venetoclax was not part of the standard of care for the target population it was not included as a comparator treatment in the AGILE trial.

In addition, there is a lack of published data for patients with IDH1m. Furthermore, it appears that historical studies report IDH mutation status in aggregate, combining IDH1 and IDH2. Unlike AGILE's IDH1 genetic alteration-specific cohort, comparison studies included in the NMA enrolled patients with differing genotypic characteristics such as patients with and/or IDH1m/IDH2m within the ITT population. Only four comparative studies reported the baseline IDH1/2m proportions, where the proportion of patients with the IDH1/2m ranged from 15.8% to 25.0% across studies, indicating differences in genetic disposition. Whether or not IDM1m status is an effect modifier for one or more of the comparator treatments is currently unknown (discussed further in Section B.1.3 Health condition and position of the technology in the treatment pathway), and therefore the NMA results should be interpreted within this context. However, given the lack of clear evidence for an important difference in prognosis between IDH1m and IDH1 wild type and the fact that venetoclax is not specifically designed to target IDH1 mutated patients, efficacy between IDH1 mutant and IDH1 wild type patients is not expected to differ. This is reflected in the current ELN guidelines, which state that current evidence does not yet warrant the assignment of IDH-1 mutation status to a distinct prognostic group (7)Therefore, an NMA comparing ivosidenib as studied in a molecularly selected population to venetoclax as studied in a molecularly unselected population was considered justifiable.

An SLR was conducted to identify relevant clinical trials (company sponsored and investigator-initiated) for evidence synthesis of efficacy and safety outcomes of current treatment options in adults with previously untreated (including secondary) AML who are ineligible for intensive chemotherapy. The SLR was conducted using a standardized approach, following the Cochrane Handbook for Systematic Reviews of Interventions and the methods for systematic review specified by National Institute for Health and Care Excellence (NICE) (48, 49). The approach complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(50)

The study eligibility criteria (i.e., inclusion and exclusion criteria) were developed using the Population, Intervention, Comparator, Outcomes, Study design (PICOS) statement, and are shown in the SLR.

The databases searched for the SLR included:

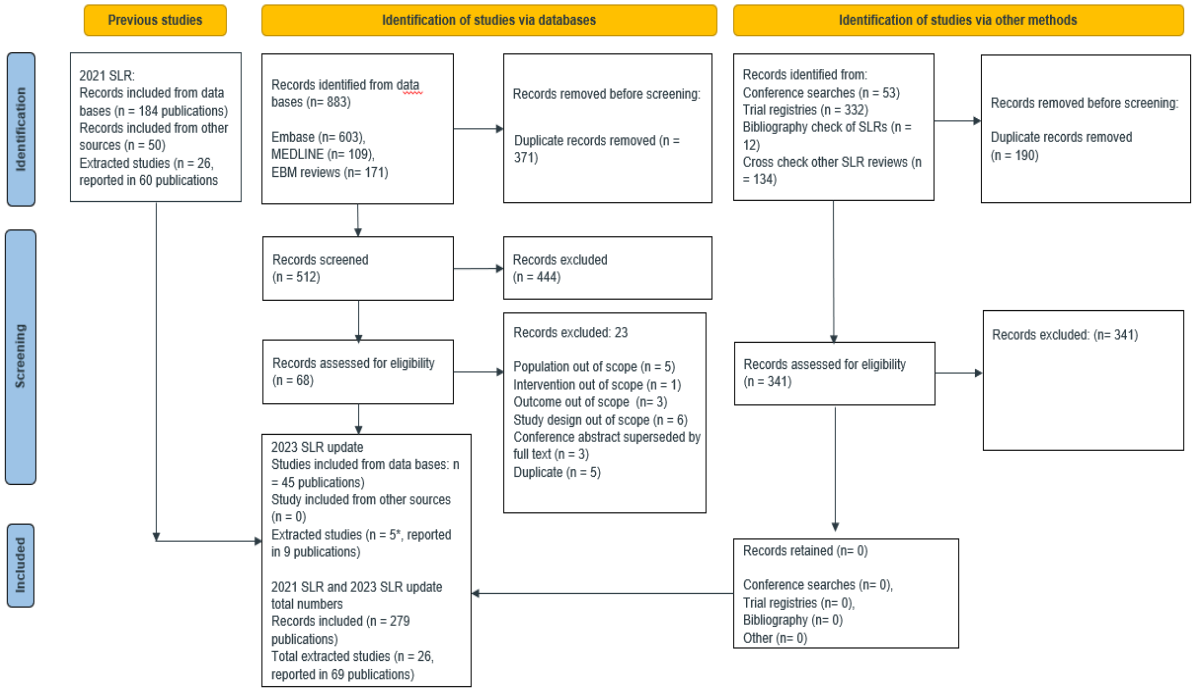
- MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) – 1946 to current
- Embase®– <1974> to current
- Cochrane Central Register of Controlled Trials (CENTRAL) – <1991> to current

The search was conducted on 28th October 2021 through the OVID platform, using the advanced search technique. An update of the SLR search was conducted on 31st of January 2023.

In addition, various oncology conferences were searched to identify abstracts presented between 2019 and 2021, including the American Society of Clinical Oncology (ASCO), American Society of Haematology (ASH), European Haematology Association (EHA), European Society for Medical Oncology (ESMO) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). To ensure all relevant trials are captured, searches of the Clinicaltrials.gov, International Clinical Trials Registry Platform (ICTRP) and Clinicaltrialsregister.eu registries for completed trials were undertaken.

Abstracts were considered for inclusion if they provided additional information or updated outcomes on studies already included based on the original full-text publication. Publications of SLR and meta-analyses were not among the included study designs (as per exclusion criteria), however, they were flagged and consulted for reference list review purposes. An update of the hand search was conducted on 7th February 2023.

Figure 16: PRISMA diagram



Following data extraction, included studies were screened against the following criteria to ascertain eligibility for inclusion in the feasibility assessment:

- Interventions: The respective study had to investigate one of the following agents: HMAs (decitabine or azacitidine), LDAC, venetoclax in combination with other agents, glasdegib in combination with other agents, and best supportive care (BSC) including blood transfusion, etoposide, mercaptopurine, or hydroxyurea. Investigational agents or any treatments not listed above were excluded from the feasibility assessment.

- Sample size: studies with < 20 patients per arm and phase II single-arm studies were excluded from the feasibility, because such studies are expected to yield considerably uncertain estimates and may risk the introduction of unnecessary bias due to quality of conduct issues.

Following screening of the 26 extracted studies against the above criteria, 10 studies were included in the feasibility assessment, including the AGILE study and a recent publication by Pollyea et al.(39) on venetoclax. A list of the studies excluded from the feasibility (based on the criteria described in the two bullet points above) is shown below. It should be noted that apart from AGILE none of the identified studies recruited patients with IDH1 mutations only, but it was decided to include in the evidence base comparative studies irrespective of mutation status if they recruited adults with previously untreated AML who are ineligible for intensive chemotherapy. This is a limitation of the current analyses; however, it was deemed appropriate to be more inclusive in the effort to establish the comparative efficacy of ivosidenib + azacitidine. Results specific to patients with IDH1 mutation are reported only for venetoclax + azacitidine in Dinardo 2020 (VIALE-A) and Pollyea 2022 (pooled data from VIALE-A and a single-arm phase Ib study) but are based on post-hoc subgroup analyses with small sample sizes (specifically <20 IDH1m positive patients were enrolled in the azacitidine arm in VIALE-A, which does not meet the sample size inclusion criterion in the feasibility assessment).

Key considerations in the feasibility assessment included availability of outcomes of interest, study design, characteristics of patient populations, posology of evaluated interventions, definitions, and methods ascertainment of outcomes.

Excluded studies as per above listed criteria are shown in Table 23.

Table 23: Excluded studies

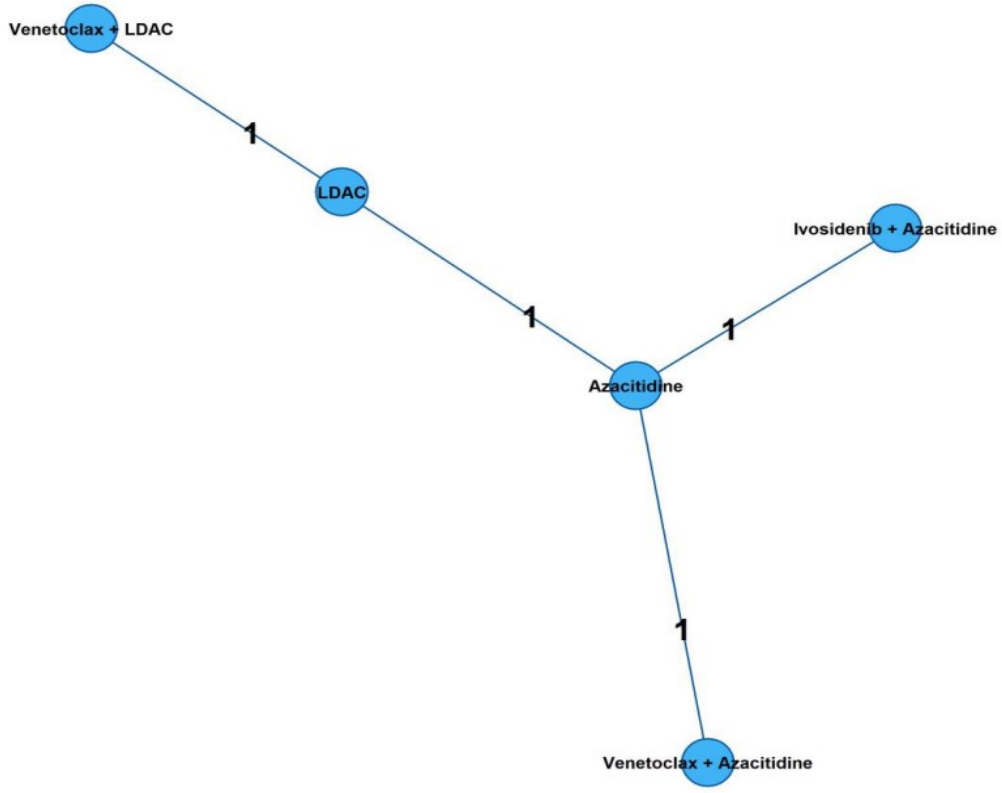
Publication	Intervention/comparator	Sample size
Medeiros 2018	Lenalidomide, Azacitidine+Lenalidomide, Azacitidine	15, 39, 34
Dohner 2014	LDAC, LDAC+Volasertib	45, 42
Harousseau 2009	Tipifarnib, BSC	228, 229
Zeidan 2019	Azacitidine+Durvalumab, Azacitidine	64, 65
Amadori 2016	Gemtuzumab Ozogamicin, BSC	118,119
Burnett 2013	LDAC, Clofarabine	176, 171
Kantarjian 2021	Decitabine/Sapacitabine, Decitabine	241, 241
Yamauchi 2021	Venetoclax+LDAC, Placebo+LDAC	18, 9
DiNardo 2021	Enasidenib+Azacitidine, Azacitidine	3, 3, 68, 33
Roboz 2019	Guadecitabine, Azacitidine or Decitabine or Low dose Ara-C	408, 407
Lubbert 2019	Decitabine, Decitabine+Valproate, Decitabine+ATRA, Decitabine+Valproate+ATRA	47, 57, 46, 50
Sekeres 2013	Lintuzumab+LDAC, Placebo + LDAC	107, 104
Dohner 2021	Volasertib+LDAC, Placebo+LDAC	444, 222
Burnett 2015	LDAC, Sapacitabine	73, 70
NA	LDAC+GRASPA, LDAC	NR
NA	AZD1152 (baracertib), LDAC	NR

For EFS, the network of evidence is presented in Figure 17 although again only ivosidenib + azacitidine versus venetoclax + azacitidine was considered.

The network consists of four studies reporting estimates for five interventions:

- Dinardo 2020 (22): Venetoclax + azacitidine and azacitidine
- Dombret 2015 (27): Azacitidine and LDAC
- Wei 2021 (28): Venetoclax + LDAC and LDAC
- AGILE (20, 21): Ivosidenib + azacitidine and azacitidine

Figure 17: Network diagram (event-free survival)



The network of evidence for OS with new data cut from AGILE (30 June 2022; median follow-up 28.6 months) and VIALE-A (01 December 2021; median follow-up: 43.2 months) is presented below. However, due to the population and standard of care in England, only ivosidenib + azacitidine versus venetoclax + azacitidine was considered.

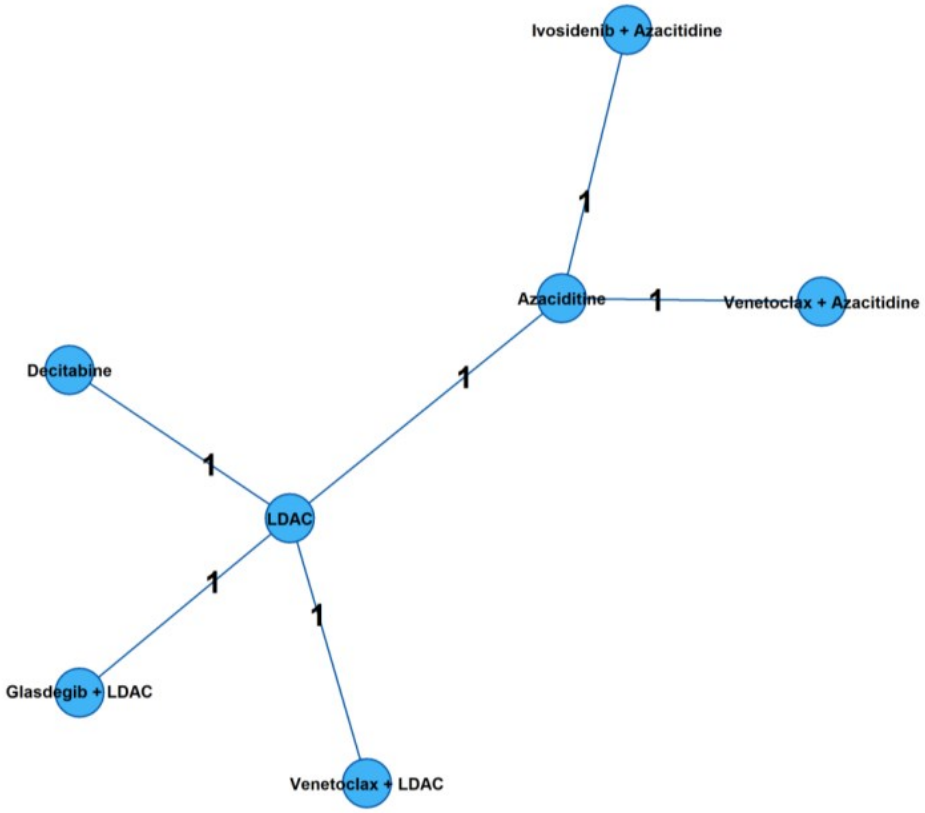
The network consists of six studies reporting estimates for seven interventions. The following studies contribute to the network:

- Dinardo 2020 (22): Venetoclax + azacitidine and azacitidine
- Heuser 2021 (24): Glasdegib + LDAC and LDAC
- Kantarjian 2012 (25): Decitabine and LDAC
- Dombret 2015 (27): Azacitidine and LDAC

- Wei 2021 (28): Venetoclax + LDAC and LDAC
- AGILE (20, 21): Ivosidenib + azacitidine and azacitidine

A network diagram is presented in Figure 18.

Figure 18: Network diagram (overall survival)



The Risk of Bias-2 (RoB-2) tool (revised tool for assessing risk of bias in randomised trials) (35) was used for the risk of bias assessment in the studies, as explained in Table 24.

- Several included studies were marked with some concerns due to their open-label design and lack of allocation concealment.
- Risk of bias for Pollyea 2022 study was not evaluated as the study was suggested to be included by Servier due to reporting results specific to patients with IDH1 mutation. However, the Pollyea 2022 results are based on a post-hoc analysis from a pooled data from Phase Ib study with VIALE-A trial (Phase III). Due to the pooling of the two studies randomization was not preserved, whereas different venetoclax dosages were lumped in the intervention arm in Pollyea, hence raising concerns on several risk of bias categories, and not included in the NMA.

Table 24: RoB-2 tool for assessing risk of bias in randomised trials

Study	Author	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
VIALE-A	Dinardo, 2020	LR	LR	LR	LR	LR	LR
BRIGHT AML 1003	Cortes, 2019/ Heuser 2021	SC	SC	LR	SC	LR	SC
DACO-016	Kantarjian 2012	LR	SC	LR	SC	LR	SC
AZA-AML-001	Dombret, 2015	LR	LR	LR	LR	LR	LR
VIALE-C	Wei, 2020	LR	LR	LR	LR	LR	LR
VIALE-A + Phase1b	Pollyea, 2022	NA	NA	NA	NA	NA	NA
AGILE	Montesinos 2022	LR	LR	LR	LR	LR	LR

Abbreviations: LR, low risk; NA, not available; NR, Not reported; SC, some concerns.

Both fixed effects (FE) and random effects (RE) models were considered for each analysis. The binomial random effects model employed in the analyses are presented below. A fixed effects model was obtained if σ^2 equalled zero.

Bayesian random effects network meta-analysis model for binary outcomes

$$r_{jk} \sim Binomial\ (p_{jk}, n_{jk})$$

$$\log\ it\ (p_{jk}) = \begin{cases} \mu_{jb} & b = A,B,C,.... \quad if\ k = b \\ \mu_{jb} + \delta_{jbk} & \text{if } k \text{ alphabetic ally after } b \end{cases} \qquad \text{(Likelihood)}$$

$$\delta_{jbk} \sim Normal(d_{bk}, \sigma^2) = Normal(d_{Ak} - d_{Ab}, \sigma^2)$$

$$d_{AA} = 0 \qquad \text{(Random effects model)}$$

$$\mu_{jb} \sim Normal(0, 0.001)$$

$$d_{Ak} \sim Normal(0, 0.001) \qquad \text{(Prior distributions)}$$

$$\sigma \sim Uniform(0, 2)$$

Where:

j	=	study
b	=	control group, can be treatment *A, B, C*
k	=	treatment group, can be *B, C, D*
r_{jk}	=	number of events observed for the treatment k in study j
p_{jk}	=	probability of an event for treatment k in study j
n_{jk}	=	number of subjects for treatment k in study j
μ_{jb}	=	log odds of an event for 'baseline' treatment b in study j
δ_{jbk}	=	log odds ratio for treatment k relative to treatment b in study j
d_{bk}	=	pooled log odds ratios of an event with treatment k relative to treatment b
σ^2	=	between study variance or 'heterogeneity parameter'
d_{Ak}	=	pooled log odds ratio of an event with treatment k versus A
d_{Ab}	=	pooled log odds ratio of an event with treatment b versus A

Both results from the fixed and random effect models were run. However, only one model was chosen to draw any inferences. The Deviance Information Criterion (DIC) was reported to choose the appropriate model for the data. The DIC provides a measure of model fit that penalises model complexity – lower values of the DIC suggest a more parsimonious model; however, differences of less than three are not considered to be important.(51) To assess model fit we additionally considered an absolute measure of fit: the total residual deviance. The value of total residual deviance was compared to the number of independent data points

to check whether model fit can be improved. As a rule, each data point should contribute about one to the posterior mean deviance, hence these two values should be very close in the presence of a model that is a good predictor.

Following the feasibility assessment, meta-regression was not carried out to adjust for differences in study level effect modifiers due to lack of data.

Table 25: Assessment of heterogeneity

Study	Study-design (Crossover: Yes/No)	Blinding	Trial phase
AGILE	Randomized, 1:1 Cross-over following unblinding	Double-blind	Phase III
VIALE-A	Randomized, 2:1 Crossover: No	Double-blind	Phase III
BRIGHT AML 1003	Randomized Crossover: No	Open-label	Phase II
DACO-016	Randomized 1:1 Crossover: Yes	Open-label	Phase III
AZA-AML-001	Randomized 1:1 Crossover: No	Open-label	Phase III
VIALE-C	Randomized 2:1 Crossover: No	Double-blind	Phase III

Table 26: Key features of included studies

Criterion	AGILE	AZA-AML 001	VIALE-C	VIALE-A	BRIGHT AML 1003	DACO-016
Age	Aged ≥18 years	Aged ≥ 65 years	Aged ≥18 years	Aged ≥18 years	Aged ≥ 55 years	Aged ≥ 65 years
AML diagnosis	Patients with previously untreated AML, defined according to WHO criteria. Patients who met at least 1 of the following criteria defining ineligibility for intensive IC (see footnote*)	Newly diagnosed AML patients. Patients who were not considered eligible for hematopoietic stem cell transplantation	Previously untreated AML who were ineligible for intensive chemotherapy	Previously untreated AML according to WHO criteria	Newly diagnosed, previously untreated AML or high-risk and who were ineligible for IC	Diagnosed with AML with a life expectancy of at least 12 weeks
ECOG	ECOG PS score of 0 to 2	ECOG scores ≤2	ECOG score: a. of 0 to 2 for patients ≥75 years of age; or b. of 0 to 3 for patients between 18 to 74 years of age	ECOG score: a. 0 to 2 for patients ≥ 75 years of age; OR b. 0 to 3 for patients ≥ 18 to 74 years of age	ECOG score = 0 or 1 who met ≥1 other inclusion criteria	ECOG score of 0 to 2
Prior treatment (Exclusion criteria)	Had received any prior treatment for AML with the exception of non-oncolytic treatments to stabilize disease such as hydroxyurea or leukapheresis	Patients could not have received prior decitabine, azacitidine, or cytarabine treatment; prior AML therapy (except hydroxyurea, which was allowed up to 2 weeks before the screening haematologyy sample was taken); or any experimental drug within 4 weeks of starting study treatment.	Not investigated	Previous receipt of any hypomethylating agent, venetoclax, or chemotherapy for myelodysplastic syndrome was exclusionary.	Patients with leukocytes >=30×109/L at study entry were excluded. Patients with active malignancy were excluded, with the exception of basal cell carcinoma, non-melanoma skin cancer, and cervical carcinoma in situ.	Patients must not have had previous chemotherapy (except hydroxyurea) for any myeloid disorder or used experimental drugs for 4 weeks prerandomization, been candidates for bone marrow or stem-cell transplantation for 12 weeks prerandomization, or received radiotherapy for extramedullary disease for 2

						weeks prerandomization
Lack of fitness (Exclusion criteria)	Had significant active cardiac disease within 6 months prior to the start of study treatment, including congestive heart failure, myocardial infarction, unstable angina, and/or stroke.	Other malignancies; or uncontrolled systemic infection.	Cardiac history of congestive heart failure Any other comorbidity ECOG 2 to 3	Aged ≥75 years or if they had at least one of the following coexisting conditions: - A history of congestive heart failure or an ejection fraction of 50% or less or chronic stable angina - ECOG 2 or 3	Patients with active malignancy were excluded, with the exception of basal cell carcinoma, non-melanoma skin cancer, and cervical carcinoma in situ; other prior or concurrent malignancies were considered on a case-by-case basis. Other exclusion criteria included a recent myocardial infarction, congenital long QT syndrome, Torsade de Pointes, clinically significant ventricular arrhythmias within 6 months of study entry, or corrected QT (QTc) interval >470 ms using Fridericia's formula (QTcF).	Exclusion criteria included acute promyelocytic leukemia, t (8;21) or inv (16) karyotype abnormalities, CNS leukemia, active systemic malignancies, unstable angina or New York Heart Association class 3/4 congestive heart failure, inaspirable bone marrow, comorbidities or organ dysfunction, uncontrolled active infection, or HIV

Abbreviations: IC, Induction Chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; AML, Acute Myeloid Leukaemia; QT, haematopoietic stem cell transplantation; CNS, Central Nervous System; ULN, Upper Limit Normal; QT, Q-wave and T-wave; HIV, Human Immunodeficiency Virus

Note: *a. ≥75 years old; b. ECOG PS = 2; c. Severe cardiac disorder; d. Severe pulmonary disorder; e. Creatinine clearance <45 mL/minute; f. Bilirubin >1.5 times the upper limit of normal (× ULN); g. Any other comorbidity that the Investigator judged to be incompatible with intensive IC.

Table 27: Baseline characteristics of included studies

Study	AGILE		AZA-AML 001		VIALE-C		VIALE-A		BRIGHT AML 1003		DACO-016	
Treatment Arm	IVO+ AZA	PBO+ AZA	AZA	CCR	VEN+ LDAC	PBO+ LDAC	VEN+ AZA	PBO+ AZA	Glasdegib +LDAC	LDAC	Decitabine	Supportive care or cytarabine
Population for baseline characteristics (N)	72	74	240	245	143	68	286	145	78	38	242	243
Median age, years (range)	76.0 (58.0 - 84.0)	75.5 (45.0 - 94.0)	75.0 (64.0 - 91.0)	75.0 (65.0 - 89.0)	76.0 (36.0 - 93.0)	76.0 (41.0 - 88.0)	76.0 (49.0 – 91.0)	76.0 (60.0 – 90.0)	77.0 (64.0 – 92.0)	76.0 (58.0 – 83.0)	73.0 (64.0 – 89.0)	73.0 (64.0 – 91.0)
Male, n/N (%)	42 (58.3)	38 (51.4)	139 (57.7)	149 (60.3)	78 (55.0)	39 (57.0)	172 (60.1)	87 (60.0)	59 (76.0)	23 (61.0)	137 (56.6)	151 (62.1)
ECOG 0-1, n (%)	46 (63.8)	50 (67.6)	NR (NR)	NR (NR)	74 (51.0)	34 (50.0)	157 (54.9)	81 (56.0)	36 (46.0)	20 (53.0)	184 (76.0)	183 (75.3)
ECOG 2, n (%)	26 (36.1)	24 (32.4)	55 (22.8)	58 (23.2)	63 (44.0)	25 (37.0)	129 (45.1) †	64 (44.0) †	41(53.0)	18 (47.0)	58 (24.0)	60 (24.7)
Primary/ de novo AML, n(%)	54 (75.0)	53 (71.6)	NR (NR)	NR (NR)	85 (59.0)	45 (66.0)	214 (75.0)	110 (76.0)	38 (49.0)	18 (47.0)	155 (64.0)	157 (64.6)
Cytogenetic risk: intermediate, n (%)	48 (66.7)	44 (59.5)	155 (64.3)	160 (64.5)	90 (63.0)	43 (63.0)	182 (64.0) ‡	89 (61.0) ‡	49 (63.0)	29 (37.0)	152 (63.1)	154 (63.6)
Cytogenetic risk: poor, n (%)	16 (22.2)	20 (27.0)	85 (35.3)	85 (34.4)	47 (33.0)	20 (29.0)	104 (36.0)	56 (39.0)	29 (37.0)	17 (45.0)	87 (36.1)	87 (36.1)
Median bone marrow blasts (95% CI)	54.0 (32.0 - 75.0)	48.0 (33.0 – 70.0)	70.0 (2.0 -100.0)	72.0 (2.0 -100.0)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	41.5 (16.0 – 99.0)	48.3 (13.0 – 95.0)	NR (NR)	NR (NR)
IDH1, n (%)	70 (97.2)	73 (98.7)	NR (NR)	NR (NR)	21 (19.0)	12 (23.0)	61 (25.0) §	28 (22.0) •	19 (24.3)	6 (15.8)	NR (NR)	NR (NR)
IDH2, n (%)	NR (NR)	NR (NR)	NR (NR)	NR (NR)							NR (NR)	NR (NR)

Abbreviations: Eastern Cooperative Oncology Group; NR, Not reported; IDH, isocitrate dehydrogenase; IVO, Ivosidenib; AZA, Azacitidine; PBO, Placebo; VEN, Venetoclax; LDAC, Low-dose cytarabine; CCR, Combined Conventional Care; BSC, Best Standard Care; AML; Acute Myeloid Leukaemia

† Defined as low/intermediate; ‡ Cytogenic risk intermediate is defined as intermediate I and II; ▪ Only includes patients with ECOG 0; * ECOG 2 -3; ᵛ total of 81 IDH1/2 patients due to some patients having both IDH1/2 mutations. ‖ total of 28 IDH1/2 patients due to some patients having both IDH1/2 mutations. § Out of 245 patients. • Out of 127 patients.

Overall, the feasibility assessment identified several limitations for an indirect comparison:

- None of the comparator studies were conducted in the target population (IDH1m).
- In studies reporting mutation subgroup data, IDH1 is based on post hoc analyses with small patient numbers, with IDH1 not being a stratification factor.
- Population baseline characteristics for the IDH1 subgroup are not available for venetoclax + azacitidine (i.e., DiNardo 2020, Pollyea 2022), whereas the IDH1/2 baseline characteristics in Pollyea are unbalanced between treatment arms.
- Notable differences in placebo arm rates are observed across placebo-controlled studies (i.e., AGILE and the IDH1m subgroup from VIALE-A as reported in Pollyea 2022), which raise concerns about outcome homogeneity.

For the reasons listed above, therefore, these studies were not included.

The feasibility assessment identified heterogeneity in the analysis populations arising from a lack of published subgroup data for patients with IDH1m, modest heterogeneity in other patient demographic and disease characteristics (gender, type of AML diagnosis, cytogenic risk, ECOG performance status and median bone marrow blast), differences in placebo arm rates across placebo-controlled studies, and differences in the definition of EFS. However, it should be recognised that for the purposes of generating a comparison of ivosidenib + azacitidine and venetoclax + azacitidine in the cost-effectiveness model, a comparable definition is needed which is aligned with the cost-effectiveness model structure, and so the definition of EFS applied in VIALE-A is used in the model.

Results of NMA

Overall Survival

An indirect comparison was required to compare both IVO+AZA and AZA to VEN+AZA. An NMA was carried out using a fixed effects model to generate an HR for the outcome of OS. Consequently, the output from the NMA were used to inform estimates of OS for VEN+AZA by applying the HR to the selected survival curve for the IVO+AZA arm.

Compared with VEN+AZA, the findings from the NMA demonstrated that IVO+AZA is associated with improved OS (HR = [redacted]). This result is summarised in Table 28, alongside the 95% CrI.

Table 28: Network meta-analysis output for OS used within the cost-effectiveness analysis

Comparison and outcome	Median	95% CrI
OS: IVO+AZA versus VEN+AZA	[redacted]	[redacted]

Key: AZA, azacitidine; CrI, credible interval; IVO, ivosidenib; OS, overall survival; VEN, venetoclax.

Note: The cost-effectiveness model uses outputs from a fixed-effects model, as the deviance information criteria estimates were comparable between fixed effects and random effects models, but the fixed effects model is a more parsimonious model with fewer assumptions.

Event-free survival

An ITC was required to compare both IVO+AZA to VEN+AZA. An NMA was carried out using a fixed effects model to generate an HR for the outcome of EFS. Consequently, the output from the NMA were used to inform estimates of EFS for VEN+AZA by applying the HR to the selected survival curve for the IVO+AZA arm.

Compared with VEN+AZA, the findings from the NMA demonstrated that IVO+AZA is associated with improved EFS (HR = [redacted]). This result is summarised in Table 29, alongside the 95% CrI.

Table 29: Network meta-analysis output for EFS used within the cost-effectiveness analysis

Comparison and outcome	Median	95% CrI
EFS: IVO+AZA versus VEN+AZA	[redacted]	[redacted]

Key: AZA, azacitidine; CrI, credible interval; EFS, event-free survival; IVO, ivosidenib; VEN, venetoclax.

Note: The cost-effectiveness model uses outputs from a fixed-effects model, as the deviance information criteria estimates were comparable between fixed effects and random effects models, but the fixed effects model is a more parsimonious model with fewer assumptions.

Uncertainties in the indirect and mixed treatment comparisons

Results from the analysis of OS and EFS suggested that ivosidenib + azacitidine improves both of these outcomes relative to the comparator of primary relevance to this appraisal: venetoclax + azacitidine. One of the main limitations of the NMA analyses is heterogeneity in the analysis populations arising from a lack of published data for patients with IDH1m outside the AGILE study. Unlike AGILE's IDH1 genetic alteration-specific cohort, the VIALE-A study enrolled patients with differing genotypic characteristics within the ITT population. However, since IDHm is not expected to be a treatment effect modifier for venetoclax, the findings from the NMA are considered suitable for decision making (and inclusion within the cost-effectiveness model).

B.2.10 Adverse reactions

Safety

The AGILE trial demonstrated that the combination of ivosidenib + azacitidine was associated with AEs similar to those attributed to treatment for AML.

Adverse events

Overall, the incidence of any grade AE reported in each arm was comparable, occurring in 70 of 71 patients (99%) treated with ivosidenib + azacitidine and 73 of 73 patients (100%) in the placebo + azacitidine arm. The incidence of Grade ≥3 AEs

reported in each arm were also very similar with 66 of 71 patients (93%) treated with ivosidenib + azacitidine and 69 of 73 patients (94.5%) in the placebo + azacitidine arm

Grade ≥3 AE's that occurred in more than 15% of the patients in both the ivosidenib + azacitidine arm and the placebo + azacitidine arm included febrile neutropenia (28% and 34%, respectively), anemia (25% and 26%), neutropenia (27% and 16%), thrombocytopenia (24% and 21%) and pneumonia (23% and 29%)

Infection events were reported at a higher incidence for any grade, Grade ≥3, serious, and those leading to death in the placebo + azacitidine arm compared with ivosidenib + azacitidine. Infections of any grade were reported in 28.8% patients in the ivosidenib + azacitidine arm and 49.3% patients in the placebo + azacitidine arm. Grade ≥3 infections were reported in 21.1% patients in the ivosidenib + azacitidine arm and 30.1% patients in the placebo + azacitidine arm. A summary of common and Grade ≥3 adverse events is presented by preferred term in Table 30.

Table 30: AGILE – Summary of adverse events (SAS)

Event	Ivosidenib + azacitidine (N = 71) n (%)		Placebo + azacitidine (N = 73) n (%)	
	Any grade	Grade 3+	Any grade	Grade 3+
Any TEAE	70 (98.6)	66 (9.03)	73 (100.0)	69 (94.5)
Hematologic adverse events	55 (77.4)	50 (70.4)	48 (65.7)	47 (64.3)
Anemia	22 (31.0)	18 (25.4)	21 (28.8)	19 (26.0)
Febrile neutropenia	20 (28.2)	20 (28.2)	25 (34.2)	25 (34.2)
Neutropenia	20 (28.2)	19 (26.8)	12 (16.4)	12 (16.4)
Thrombocytopenia	20 (28.2)	17 (23.9)	15 (20.5)	15 (20.5)
Leukocytosis	8 (11.3)	0	1 (1.4)	0
Nonhematologic adverse events	-	-	-	-
Nausea	30 (42.3)	2 (2.8)	28 (38.4)	3 (4.1)
Vomiting	29 (40.8)	0	19 (26.0)	1 (1.4)
Diarrhea	25 (35.2)	1 (1)	26 (35.6)	5 (7)
Pyrexia	24 (33.8)	1 (1)	29 (39.7)	2 (3)
Constipation	19 (26.8)	0	38 (52.1)	1 (1)
Pneumonia	17 (23.9)	16 (23)	23 (31.5)	21 (29)
QT interval prolonged on ECG	14 (20)	7 (10)	5 (7)	2 (3)
Insomnia	9 (12.3)	1 (1)	9 (12.3)	0
Asthenia	24 (32.9)	0	24 (32.9)	5 (6.8)
Hypokalemia	11 (15.5)	2 (2.8)	21 (28.8)	6 (8.2)
Decreased appetite	19 (26.0)	1 (1.4)	19 (26.0)	6 (8.2)
Dyspnea	11 (15.5)	1 (1)	9 (12.3)	3 (4)
Differentiation syndrome	10 (14.1)	3 (4)	6 (8.2)	3 (4)
Pain in extremity	10 (14.1)	1 (1)	3 (4.1)	1 (1)
Fatigue	9 (12.7)	2 (3)	10 (13.7)	2 (3)
Hematoma	9 (12.7)	0	1 (1.4)	0
Edema peripheral	8 (11.3)	0	16 (21.9)	1 (1)

Event	Ivosidenib + azacitidine (N = 71) n (%)		Placebo + azacitidine (N = 73) n (%)	
	Any grade	Grade 3+	Any grade	Grade 3+
Platelet count decreased	8 (11.3)	6 (8.5)	6 (8.2)	6 (8.2)
Arthralgia	8 (11.3)	0	3 (4.1)	0
Headache	8 (11.3)	0	2 (2.7)	0
Bleeding	29 (41)	4 (6)	21 (29)	5 (7)
Infections	20 (28.8)	15 (21.1)	36 (49.3)	22 (30.1)

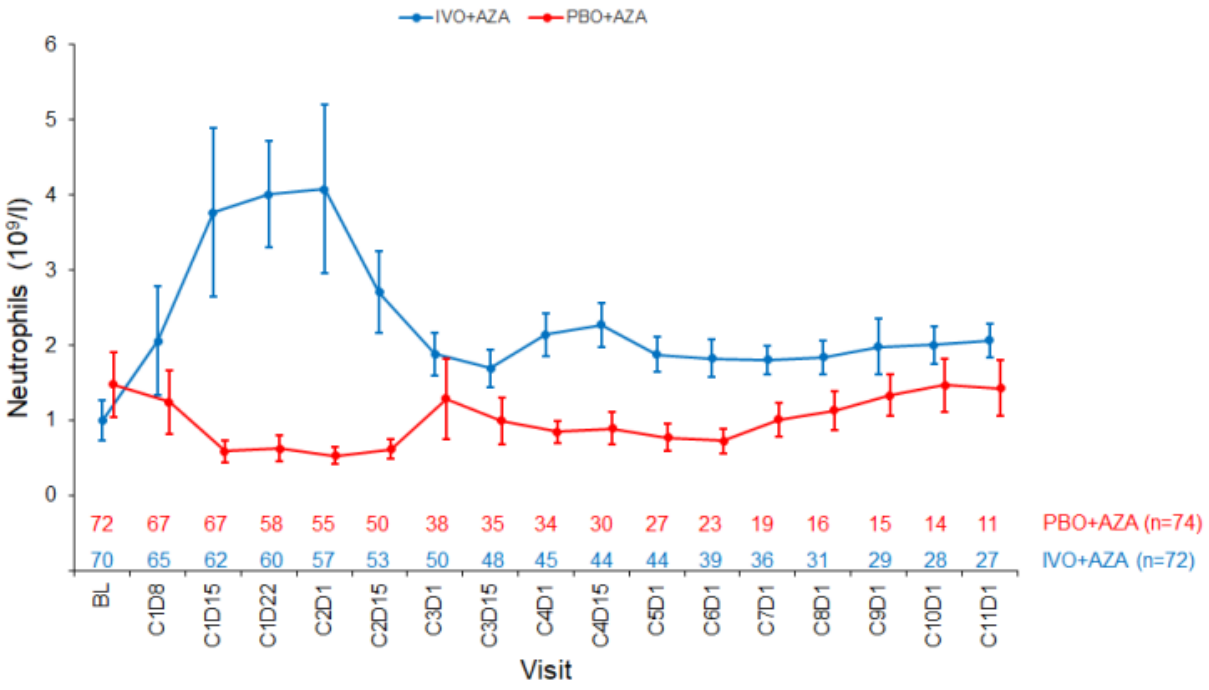
Abbreviations: ECG, electrocardiography; n, number; SAS, safety analysis set; TEAE, treatment emergent adverse events

Notes: The safety population included all the patients who received at least one dose of a trial agent. Events listed are those of any grade that occurred in at least 10% of the patients in the ivosidenib + azacitidine group.

Source: Montesinos et al. 2022 (37) & adapted from AGILE – data cutoff date: 18 March 2021 [Data on file](45).

Consistent with improved infection rates versus placebo + azacitidine, an increase in absolute neutrophil count from baseline was noted only with ivosidenib + azacitidine over time, particularly during the first cycle of treatment. Absolute neutrophil count change from baseline through C11D1 among patients in the ivosidenib + azacitidine arm compared with those in the placebo + azacitidine arm is shown in Figure 19, showing that neutrophil counts recover and stabilize in patients treated with ivosidenib + azacitadine.

Figure 19: AGILE – Change in absolute neutrophil count from baseline with IVO+AZA compared with PBO+AZA



Abbreviations: AZA, azacitidine; BL, baseline; CxDy, cycle x day y; IVO, ivosidenib; n, number; PBO, placebo.

Source: Montesinos et al. 2022 (37)

Bleeding events were more frequent with ivosidenib + azacitidine than with placebo + azacitidine (41% versus 29%)

Serious adverse events

Serious adverse events (SAEs) were reported in fewer patients (49 of 71 patients; 69.0%) in the ivosidenib + azacitidine arm compared with the placebo + azacitidine arm (60 of 73 patients; 82.2%).

Treatment discontinuation and dose interruption

The incidence of adverse events leading to treatment discontinuations of the combination treatment was similar between arms (19 [26.8%] patients versus 19 [26.0%] patients in the ivosidenib + azacitidine and placebo + azacitidine arms, respectively). TEAEs leading to dose reductions of both study drugs were infrequent in the ivosidenib + azacitidine arm (4 [5.6%] patients), while no dose reductions occurred in the control arm. Adverse events leading to dose interruptions of both study medications occurred in 37 patients (52.1%) in the ivosidenib + azacitidine arm and in 28 patients (38.4%) in the placebo + azacitidine arm. The most common adverse events leading to drug interruption included neutropenia (23% with ivosidenib + azacitidine and 4% with placebo + azacitidine), febrile neutropenia (10% and 8%, respectively), and pneumonia (8% and 7%) (33).

Ten (14.1%) patients in the ivosidenib + azacitidine arm had AEs that led to death, while 21 (28.8%) patients had an AE leading to death in the placebo + azacitidine arm. A summary of serious adverse events is presented in Table 31.

Table 31: AGILE – Summary of serious adverse events (SAS)

N (%) of patients	Ivosidenib + azacitidine (N = 71), n (%)	Placebo + azacitidine (N = 73), n (%)
Any adverse events	70 (98.6)	73 (100.0)
Serious adverse events*	49 (69.0)	60 (82.2)
Febrile neutropenia	17 (23.9)	20 (27.4)
Pneumonia	14 (19.7)	16 (21.9)
Differentiation syndrome	6 (8.5)	1 (1.4)
Pyrexia	4 (5.6)	3 (4.1)
Adverse events of special interest†		
Differentiation syndrome	10 (14.1)	6 (8.2)
QT prolongation	7 (9.9)	3 (4.1)
Electrocardiogram QT prolonged	7 (9.9)	2 (2.7)
Syncope	0	1 (1.4)
Leukocytosis	0	0
Adverse events of special interest leading to treatment discontinuation		
Differentiation syndrome	0	1 (1.4)
Treatment-related adverse events‡	42 (59.2)	36 (49.3)
Nausea	17 (23.9)	12 (16.4)
Vomiting	14 (19.7)	8 (11.0)

N (%) of patients	Ivosidenib + azacitidine (N = 71), n (%)	Placebo + azacitidine (N = 73), n (%)
Neutropenia	10 (14.1)	4 (5.5)
Serious treatment-related adverse events*	16 (22.5)	9 (12.3)
Febrile neutropenia	5 (7.0)	5 (6.8)
Adverse events leading to treatment discontinuation	19 (26.8)	19 (26.0)
Hematologic adverse events leading to treatment discontinuation	3 (4.2)	0
Febrile neutropenia	1 (1.4)	0
Neutropenia	1 (1.4)	0
Thrombocytopenia	1 (1.4)	0
Adverse events leading to treatment interruption	37 (52.1)	28 (38.4)
Hematologic adverse events leading to treatment interruption§	23 (32.4)	8 (11.0)
Neutropenia	16 (22.5)	3 (4.1)
Febrile neutropenia	7 (9.9)	6 (8.2)
Thrombocytopenia	5 (7.0)	1 (1.4)
Leukopenia	3 (4.2)	0
Anemia	1 (1.4)	0
Pancytopenia	1 (1.4)	0
Adverse events leading to dose reduction	4 (5.6)	0
Neutropenia	3 (4.2)	0
Thrombocytopenia	1 (1.4)	0
Adverse events leading to death	10 (14.1)	21 (28.8)

Abbreviations: n, number; SAS, safety analysis set.

Notes: *Serious adverse events reported in at least 5% of patients in the ivosidenib +azacitidine arm and their corresponding frequencies in the placebo + azacitidine arm are shown.

†All adverse events of special interest reported are shown. The following were considered adverse events of special interest: QT prolongation (Grade 3 and higher), leukocytosis (Grade 3 and higher), and isocitrate dehydrogenase differentiation syndrome (Grade 2 and higher).

‡Treatment-related adverse events reported in at least 10% of patients in the ivosidenib +azacitidine arm and their corresponding frequencies in the placebo + azacitidine arm are shown.

§Hematologic adverse events reported in at least 1% of patients in the ivosidenib + azacitidine arm and their corresponding frequencies in the placebo + azacitidine arm are shown.

Source: Montesinos et al. 2022 (37)

Adverse events of special interest

Differentiation syndrome

The percentage of patients with differentiation syndrome of any grade was 14.1% (10 patients) with ivosidenib + azacitidine treatment and 8.2% (six patients) with placebo + azacitidine. The majority of differentiation syndrome AEs in the ivosidenib + azacitidine arm were Grade 2 (seven [9.9%] patients), with only three (4.2%) patients experiencing a grade 3 event. In the placebo + azacitidine arm, three patients (4.1%) experienced a grade 2 AE, two (2.7%) patients experienced a Grade 3 event and one (1.4%) experienced a Grade 4 event (Table 32). Serious AEs of differentiation

syndrome were reported in six (8.5%) patients in the ivosidenib + azacitidine arm and one (1.4%) patient in the placebo + azacitidine arm.

All cases were managed with glucocorticoids, diuretics, and hydroxyurea. The median time to onset of investigator-reported differentiation syndrome of any grade in the ivosidenib + azacitidine group was 19.5 days (range, 3.0 to 33.0). No deaths due to differentiation syndrome were noted in either group.

QT prolongation

Adverse events of QT interval prolonged on ECG of any grade were reported in 14 (19.7%) patients in the ivosidenib + azacitidine arm compared to five (6.8%) of patients in the placebo + azacitidine arm. The frequency of grade ≥3 QT prolongation was 9.9% (seven patients) with ivosidenib + azacitidine compared to 4.1% (three patients) with placebo + azacitidine. All QT prolongation AEs were Grade 3 events (Table 32).

Leukocytosis

Leukocytosis was reported in eight (11.3%) patients in the ivosidenib + azacitidine arm and one (1.4%) patient in the placebo + azacitidine arm. There were no grade ≥3 AEs of leukocytosis reported in either arm. None of the events of leukocytosis were assessed as serious (Table 31).

Table 32: AGILE – Summary of adverse events of special interest (SAS)

	Ivosidenib + azacitidine (N = 71), n (%)	**Placebo + azacitidine (N = 73), n (%)**
Differentiation syndrome		
Any grade n (%)	10 (14.1)	6 (8.2)
Grade 2 n (%)	7 (9.9)	3 (4.1)
Grade 3 n (%)	3 (4.2)	2 (2.7)
Grade 4 n (%)	0	1 (1.4)
Grade 5 n (%)	0	0
Grade ≥3 n (%)	3 (4.2)	3 (4.1)
QT prolongation		
Any grade n (%)	7 (9.9)	3 (4.1)
Grade 2 n (%)	-	-
Grade 3 n (%)	7 (9.9)	3 (4.1)
Grade 4 n (%)	0	0
Grade 5 n (%)	0	0
Grade ≥3 n (%)	7 (9.9)	3 (4.1)

Abbreviations: n, number; SAS, safety analysis set.

Notes: The denominator used to calculate percentages is N, the number of patients in the SAS within each treatment group.

Patients with multiple adverse events within an AESI group are counted only once in that AESI group.

The following are considered AESIs: QT prolongation (Grade 3 and higher), Leukocytosis (Grade 3 and higher), and differentiation syndrome (Grade 2 and higher).

Source: Adapted from AGILE – data cutoff date: 18 March 2021 [Data on file](45).

B.2.11 Ongoing studies

No ongoing studies

B.2.12 Interpretation of clinical effectiveness and safety evidence

Venetoclax, in combination with azacitidine, has demonstrated significant clinical benefit in newly diagnosed AML patients who are ineligible for intensive induction chemotherapy, with an OS of 14.7 months(38). However, Venetoclax does not specifically target the IDH1 mutation.(7) For IDH1 mutations, evidence with venetoclax is limited to results from a post hoc analysis, where IDH1m was not a stratification factor, and no reporting of patient baseline characteristics for the IDH1m subgroup, showing a mOS of 10.2 months in 23 patients,(40) compared to a mOS with ivosidenib of 29.3 months in 73 patients.

Table 33: Median OS and median follow-up for Ivosidenib and Venetoclax in AGILE and VIALE-A studies, respectively

	Ivosidenib + azacitidine (March 2021) IDH1 only	**Ivosidenib + azacitidine (June 2022) IDH1 only**	**Venetoclax + azacitidine (January 2020) Broad population[(40)]**	**Venetoclax + azacitidine (December 2021) Broad population**
Median Follow-up (months)	15.1	28.6	20.5	43.2
mOS (months)	24.0 (11.3, 34.1)	29.3 (13.2-NE)	14.7 (11.9, 18.7) 10.2 (2.3, -) only IDH1	14.7 (12.1, 18.7) 10.2 only IDH1[(40)]*

Note: *All patients included in the IDH1subgroup of VIALE-A treated with venetoclax+azacitidine (n=23), had an event by Month 27, thus mOS is not expected to be different at the most recent data-cut

A recent pooled post-hoc analysis of two trials (Phase 1 and phase III) with Venetoclax confirmed that AML patients with IDH1 and IDH2 mutations do respond to treatment with Venetoclax(39).However, this was mainly driven by the IDH2 mutation with an OS of 24.5 months in the IDH1/2 group, compared to 15.2 months OS in the IDH1 group. Clinician feedback to the company during a recent advisory board supports the belief that the IDH2 population responds better to venetoclax than the IDH1 population(11). In support of this, an American cohort of 331 AML patients treated with venetoclax showed a mOS in IDH1 patients of 13,1 months compared to a mOS of IDH2 patients of 42 months, and a mOS in the overall population of 13,9 months(41). This data clearly supports the need for a better management of the condition of mIDH1 patients, and the clear difference observed with mIDH2 patients when treated by Venetoclax. Therefore, despite the advances observed with the availability of venetoclax, there remains an unmet need for a targeted, efficacious, and tolerable therapy that can improve clinical outcomes in this patient population, as seen with a 29.3 month mOS

with ivosidenib. Ivosidenib is the only drug specifically developed in the IDH1 mutated AML population and therefore is the only drug evaluated in a randomised, double-blind, multicentre, placebo-controlled Phase 3 study in this mIDH1 population.

Additional clinical benefits

Neutrophil count

Ivosidenib displays a unique increase in absolute neutrophil count from cycle 1 reducing febrile neutropenia and infections. This significant clinical benefit of ivosidenib + azacitidine compared to venetoclax + azacitidine is the difference in the recovery of the absolute neutrophil count after the initiation of the treatment. This recovery leads to a lower level of febrile neutropenia and from there to a lower percentage of infections. This is of particular importance for patient management as patients with febrile neutropenia at a high risk of complications should be hospitalised and treated without delay with broad spectrum antibiotics according to the 2016 ESMO guidelines on Management of febrile neutropenia(52)

In the AGILE study, an increase in absolute neutrophil count from baseline was noted only with ivosidenib + azacitidine over time, particularly during the first cycle of treatment (Figure 20). On the other hand, an analysis of the neutrophil count change from baseline was performed for VIALE-A showing a reduction in the neutrophil count from baseline across the entire first cycle of treatment for venetoclax + azacitidine (Figure 21).

According to clinician feedback to the company during a recent advisory board, the neutrophil recovery data seen with ivosidenib + azacitidine would require less monitoring, less in patient days, and reduced blood transfusions, compared to venetoclax +azacitidine, which would have a substantial impact on an elderly persons quality of life due to more time spent away from the hospital(11)

Figure 20: Mean change in neutrophil count from baseline with IVO+AZA versus PBO+AZA

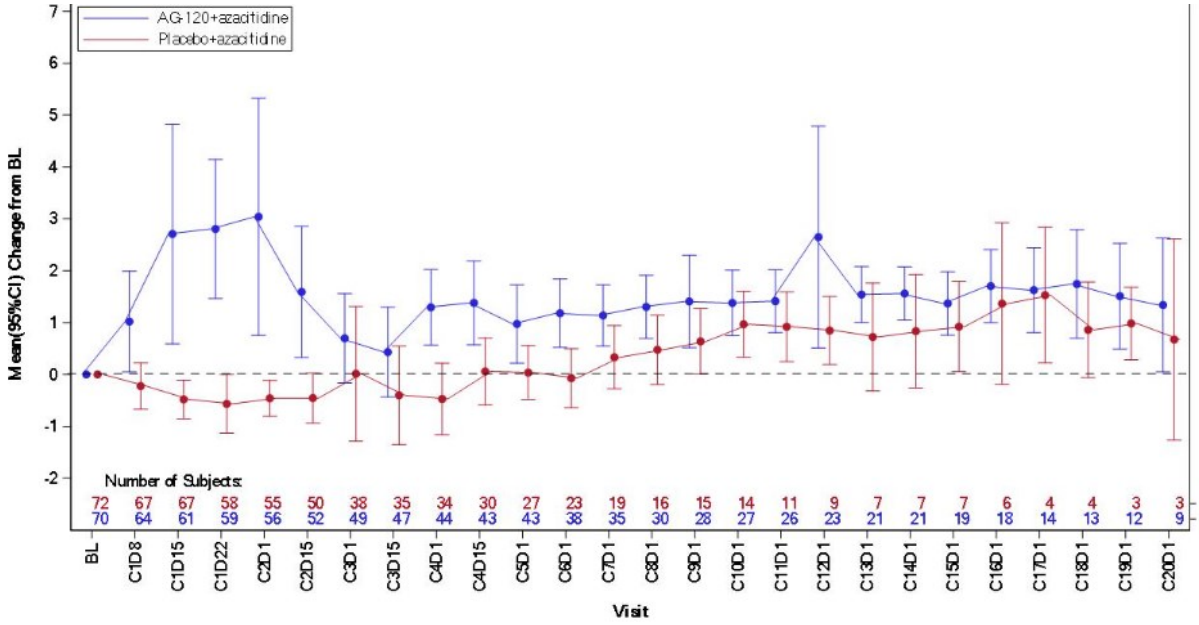
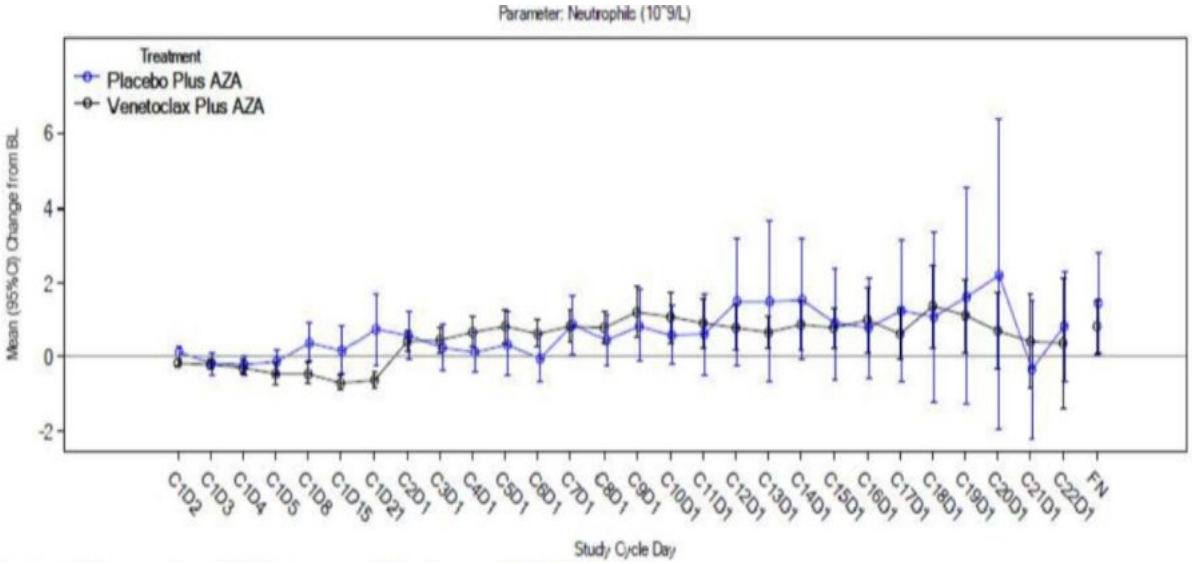


Figure 21: Mean change in neutrophil count from baseline with VEN+AZA versus PBO+AZA



Source: Venetoclax CDER Approval Package; CDER, 2020

When considering febrile neutropenia in the clinical studies, results from AGILE showed a unique situation as the rate of febrile neutropenia in this study was lower in the active arm compared to the control group (28% vs. 34%). Ivosidenib, through its specific mechanism of action that restores the normal differentiation of the blast, is able to lead to an increase in neutrophil count within the first cycle. This increase has been translated in a reduction in febrile neutropenia and infections compared to azacitidine. In contrast, in VIALE-A the rate of febrile neutropenia was higher in the venetoclax + azacitidine group than in the control group (42% vs. 19%).

Blood transfusions and hospitalisations

Burden of disease is high, primarily due to prolonged hospitalizations and high rates of infectious complications (53). Treating AML is also associated with a considerable clinical burden, with patients requiring frequent hospitalizations and extensive use of hospital resources. Hospitalizations can have a substantial detrimental impact on the physical and psychosocial well-being of patients ineligible for intensive chemotherapy(53).

Ivosidenib is expected to reduce burden on hospital capacity, primarily by the reduced need for red blood cell and plasma transfusions. Among patients who were transfusion dependent at baseline, a higher proportion who received ivosidenib + azacitidine (18 [46.2%] patients) experienced RBC and PLT transfusion independence compared with those who received placebo + azacitidine (7 [17.5%] patients) (two-sided p = 0.006). The cost-effectiveness model developed to inform this submission illustrates how this finding leads to important cost savings related to reduced healthcare expenditure (discussed further in Section B.3).

In general, elderly AML patients (≥60 years) require more inpatient care and a longer length of hospital stay, and this incurs greater outpatient resource utilization than younger patients(<60 years).(54, 55)

Retrospective analysis with venetoclax shows that patients were hospitalized for a median of 32 days during the 1st cycle.(56) The British Society of Haematology (BSH) good practice paper states that patients on venetoclax should be admitted at least for 5 days and in some cases it will be necessary to admit patients until count recovery after cycle 1(36), which would support the figure in the retrospective analysis(56)

Further analysis for venetoclax hospitalisations was also conducted among those patients who were eligible for intensive chemotherapy, showing a median duration of 14 days(57). However, as these patients were a population deemed eligible for intensive treatment for AML where venetoclax was offered as an alternative according to the NICE Covid AML guidelines, it should be noted that these patients would be a cohort that would be fitter than Intensive Chemotherapy ineligible patients and their outcomes cannot be used as a surrogate for performance in the population relevant to this appraisal, particularly regarding hospitalisation. Further, there is enriched enrolment of NPM1 patients, who have favorable outcomes regardless of treatment.

In addition, this analysis was conducted during COVID; this likely underreports hospitalization events and duration due to COVID pressures, and cannot be considered as representative of current treatment patterns.

In contrast, analysis from the AGILE trial(58) shows a median of [redacted] bed days with ivosidenib + azacitadine during the first cycle, aligning with clinician feedback that they would expect hospital days to be a lot lower with ivosidenib + azacitadine compared to venetoclax + azacitadine.

Quality of life

At present, available treatments generally maintain quality of life rather than improving it(59). To this point, in the main publications reporting the pivotal study of venetoclax, the authors state that “No differences were observed between the two treatment groups with respect to quality-of-life measures”(60, 61). Although a secondary analysis of VIALE-A and VIALE-C HRQoL data showed a significantly longer TTD for patients receiving combination venetoclax compared with placebo + azacitidine or LDAC for all patient reported outcomes (PRO) measures (including HRQoL) (269), it is worth noting that there were several limitations to the analysis.

Firstly, the primary analysis of the VIALE-A results did not assess improvement of HRQoL from baseline but rather utilized an indirect way via the time to deterioration and the reliability of such a method is questioned by the authors. Secondly, it is subject to bias as it significantly depends on the EFS/OS improvement, indeed, when patients had an event (e.g., death, progression, relapse), HRQoL data were not collected anymore, favoring the arm with the longer EFS/OS (in the case of VIALE-A the venetoclax + azacitidine arm). A limitation identified by the authors is that the primary analysis did not assess improvement of HRQoL from baseline.

However, as seen in in Section B.2.6, quality of life was reported to improve with ivosidenib treatment over time.

Adverse events of special interest

The main AEs of special interest seen with Venetoclax are serious infections, including sepsis with fatal outcome. Furthermore, tumour lysis syndrome (TLS) was reported in three patients (1%) who received venetoclax combination therapy, compared to none in the comparator group(38). TLS is a concern as it may cause renal failure, resulting in death (38)

Differentiation syndrome has been reported following treatment with ivosidenib. Differentiation syndrome may be life-threatening or fatal if not treated. It is associated with rapid proliferation and differentiation of myeloid cells. Differentiation syndrome of any grade occurred in 14.1% (10/71) of patients who received ivosidenib plus azacitidine and 8.2% (6/73) of those who received placebo plus azacitidine(37). Patients must be informed of signs and symptoms of differentiation syndrome, be advised to contact their physician immediately if these occur and the need to carry the Patient Alert Card with them at all times, that is provided by the company.

B.3 Cost effectiveness

Ivosidenib (in combination with azacitidine, IVO+AZA) is a novel and clinically effective, targeted treatment option for untreated *IDH1*-positive acute myeloid leukaemia (AML). The safety and efficacy of IVO+AZA was investigated in AGILE (a global, multicentre, randomized, double-blind, placebo-controlled phase III study), which demonstrated a statistically significant improvement in event-free survival (EFS) and overall survival (OS), compared with azacitidine alone (AZA).

In practice, patients with previously untreated *IDH1*-positive AML that are eligible to receive a hypomethylating agent (such as AZA) are expected to receive venetoclax + azacitidine (VEN+AZA), in line with NICE TA765. However, VEN+AZA is not specifically indicated for patients with an *IDH1* mutation, and at the time the AGILE study was conducted this was not the standard of care. As such, the modelling approach relies on an indirect comparison between IVO+AZA and VEN+AZA, made possible by using data available from the VIALE-A clinical trial (though this is not in an *IDH1*-specific population).

The base case modelling approach, including cost inputs and utility values is consistent with the NICE reference case, and broadly consistent with methods accepted in TA765 for VEN+AZA. However, a different model structure was necessary to facilitate a comparison between IVO+AZA and VEN+AZA using available evidence for both treatments. The most clinically plausible extrapolations of EFS and OS data were selected for the base case analysis, and extensive scenario analyses were presented to test methodological uncertainty (with only a small impact to cost-effectiveness results). Parametric uncertainty was tested in deterministic one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA).

In the base case analysis, IVO+AZA dominates VEN+AZA (i.e., provides more QALYs at a reduce overall cost). IVO+AZA therefore represents a cost-effective use of NHS resources for patients with untreated *IDH1*-positive AML.

B.3.1 Published cost-effectiveness studies

Identification of published cost-effectiveness studies

Please see Appendix D for details.

Summary of identified cost-effectiveness studies

In summary, there has been one published cost-effectiveness study of IVO+AZA, compared with AZA alone (62) which is summarised in Table 34. Of note, this study has limited relevance to this appraisal owing to the choice of comparator (i.e., AZA, not VEN+AZA – choice of comparator discussed further in Section B.3.2) and the US payer perspective taken. Therefore, a *de novo* model was developed to inform this submission.

Table 34: Summary list of published cost-effectiveness studies

Study (lead author)	Year	Summary of model	QALYs	Costs	ICER (per QALY gained)
Bewersdorf	2022	PartSA	IVO+AZA: 1.30 AZA: 0.35	IVO+AZA: $403,062 AZA: $161,887	$252,782

Key: AZA, azacitidine; ICER, incremental cost-effectiveness ratio; IVO, ivosidenib; PartSA, partitioned survival analysis; QALYs, quality-adjusted life years.

B.3.2 Economic analysis

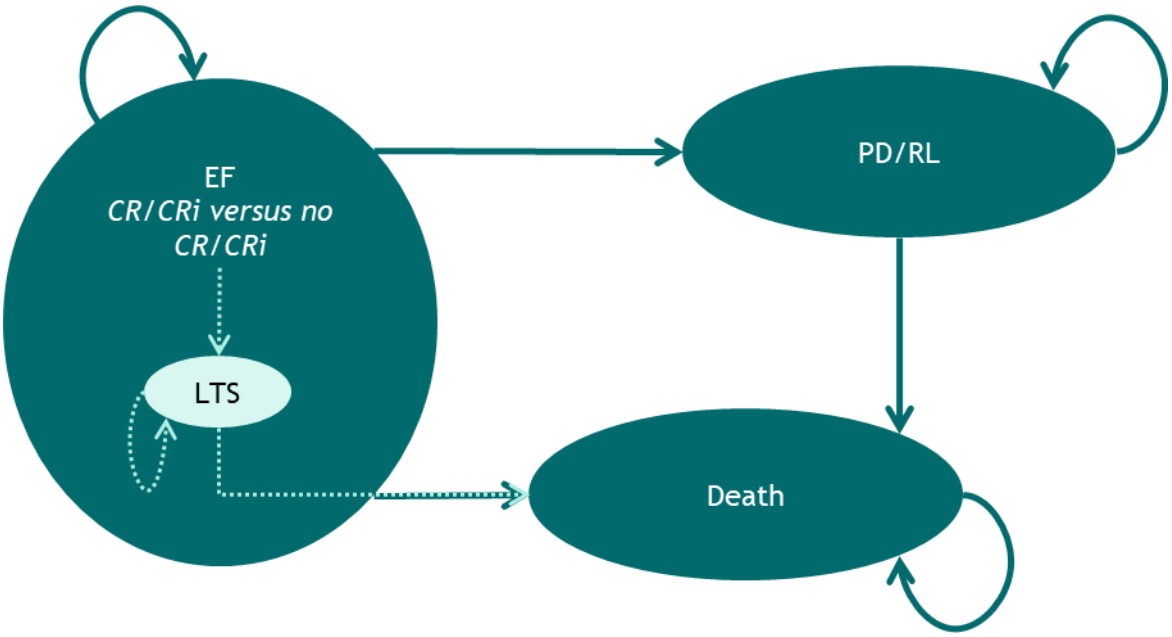
Model structure

The economic evaluation takes the form of a cost-utility analysis, using a cohort-based model developed in Microsoft Excel®. The model adopts a three-state partitioned survival analysis (PartSA) structure, with health states centred around the primary endpoint from the AGILE study (event-free survival, EFS), and overall survival (OS). The three over-arching health states are: event-free (EF), progressed disease or relapse (PD/RL), and dead. However, to account for the impact of achieving CR/CRi and to capture the expected long-term survival outcomes for patients that remain event-free for several years, the model includes the following modifications to a traditional three-state model:

- The EF state is further partitioned into the estimated proportion of patients with CR/CRi versus those without CR/CRi. In the base-case analysis, CR/CRi affects utility values and resource use, which are discussed in turn throughout the ‘Data collection’ sub-section.
- In previous AML models of venetoclax, patients that remain EF for an extended time period are expected to have a life expectancy per the age- and sex-adjusted general population. In the base-case analysis (aligned with NICE TA765, (34) patients that remain in the EF state at 3 years are assumed to be long-term survivors and enter a parallel health state in which they are no longer at risk of disease progression or relapse and follow a survival trajectory based on life tables, discussed further in Section B.3.3.

A summary of the model schematic is provided in Figure 22.

Figure 22: Model schematic



Key: CR/CRi, complete remission or complete remission with incomplete count recovery; EF, event-free; LTS, long-term survival; PD, progressed disease; RL, relapsed.

A PartSA-based model was chosen for the following key reasons:

- Allows for transparent integration of the primary endpoint from AGILE to be integrated without the need to perform any post-hoc adjustments (e.g., breaking down EFS events to inform transitions to separate PD or relapse health states, which would require estimation based on small sample sizes).
- Time-to-event data from AGILE are sufficiently mature, allowing for survival extrapolations to be reliably estimated, with the ability to also consider alternative parametric models.
- Enables the incorporation of outputs from the ITC to compare IVO+AZA and AZA with VEN+AZA, through the specification of HRs for OS and EFS.
- A PartSA model structure has been used in several published cost-effectiveness analyses in a similar setting, including the identified published cost-effectiveness analysis of IVO+AZA (62)(63–65).

A summary of the main features of the economic analysis is provided in Table 35.

Table 35: Features of the economic analysis

Factor	Previous evaluation	Current evaluation	
	TA765	**Chosen values**	**Justification**
Model structure	Cohort level Markov model.	Cohort level hybrid PartSA and Markov model.	Based on (i) limited reporting of the model structure used to inform TA765(34) (due to redaction of key elements in the appraisal papers), and (ii) unavailability of patient-level data to inform transitions for VEN+AZA, a PartSA-based model was developed instead of the cohort-level Markov model used to inform TA765. Further benefits of specifying this alternative model structure include the ability to explore structural uncertainty (by enabling/disabling specific elements) and enabling the integration of results from an indirect comparison based on comparable endpoints (namely, EFS and OS).
Time horizon	Lifetime (40 years).	Lifetime (25 years).	Mean age of cohort upon model entry is approximately 75 years, and so a time horizon of 25 years was deemed sufficiently long to capture the full extent of both costs and effects. Different time horizons explored in sensitivity analysis.
Cycle length	28 days, with half-cycle correction.	28 days, with half-cycle correction.	In line with NICE reference case. 28 days is aligned with the duration of a treatment cycle for both IVO+AZA and VEN+AZA.
Discount rate	3.5% for both costs and effects.	3.5% for both costs and effects.	In line with the NICE reference case. In the results provided, LYs are undiscounted for ease of interpretation (but can be discounted in the economic model submitted alongside this dossier).
Treatment waning effect?	Not captured explicitly.	Not captured explicitly.	No treatment waning effect was captured within the model as long-term extrapolations are adjusted to account for long-term survivors. No difference in survival estimated for patients that enter the 'LTS' state.
Source of utilities	Estimated from EQ-5D-5L data collected in the VIALE studies, cross-walked to EQ-5D-3L using the van Hout *et al.*, (2012) algorithm.	Estimated from EQ-5D-5L data collected in the AGILE study, cross-walked to EQ-5D-3L using the Hernández-Alava *et al.*, (2018)(66) algorithm.	In line with the NICE reference case. For completeness, utility values from TA765 are redacted, and used the now superseded crosswalk algorithm by van Hout *et al.*, (2012)(67). Therefore, alternative utility values are explored from the literature, but it is not possible to use values from TA765.
Source of costs	• MIMS • eMIT • NHS NCC • National Tariff System (2016-17, 20-21) • NICE TA642 & TA451	A range of standard reference sources, including BNF, NHS NCC, and eMIT. Where unavailable from these sources, published literature or previous NICE appraisals are cited and justified.	In line with the NICE reference case.

Key: AZA, azacitidine; BNF, British National Formulary; EFS, event-free survival; eMIT, electronic market information tool; IVO, ivosidenib; LTS, long-term survival; LY(s), life-year(s); MIMS, Monthly Index of Medical Specialities; NCC, National Cost Collection; NHS, National Health Service; OS, overall survival; PartSA, partitioned-survival analysis; VEN, venetoclax.

Patient population

A summary of the baseline patient characteristics used to inform the cost-effectiveness model are provided in Table 36. Characteristics were aligned with the AGILE study population. Mean age and the proportion of female patients were used in the model to calculate age- and sex-matched general population mortality rates and to age adjust utility values. Weight and body surface area (BSA) were used to calculate drug acquisition costs for treatments with a weight- or BSA-based dosing regimen.

Table 36: Patients characteristics used in the economic model

Characteristic	Input value	Source
Mean age (years)	74.84	AGILE
Proportion female (%)	45.21	AGILE
Mean body weight (kg)	71.17	AGILE
Mean body surface area (m^2)	1.78	AGILE

Key: AZA, azacitidine; IVO, ivosidenib; NR, not reported; VEN, venetoclax.
Note: Body weight data was missing for n=1 patient in AGILE; body surface area data was missing for n=2 patients in AGILE.

Of note, the model assumes all patients have an *IDH1* mutation, as this is aligned with the marketing authorisation for IVO+AZA (68). However, some input sources (e.g., inputs extracted from the VIALE-A study) reflect populations that are not exclusively *IDH1* mutation positive.

Intervention technology and comparators

Intervention

The intervention considered in this submission is IVO+AZA. IVO+AZA is incorporated into the analysis according to its anticipated marketing authorisation and in line with the decision problem described in Section B.1.1.

IVO is an oral, potent, targeted inhibitor of mutated *IDH1*, administered at a dose of 500mg once daily in continuous 28-day cycles. AZA is a hypomethylating agent, administered either intravenously (IV) or subcutaneously (SC) at a dose of 75mg/m^2 for days 1 to 7 in continuous 28-day cycles. Treatment with IVO+AZA is continued until relapse, disease progression, unacceptable toxic effects, or death.

Further details about IVO+AZA, including information about the AGILE trial and marketing authorisation status, are provided in Section B.1.1 and Appendix C.

Comparator

The final scope issued by NICE highlights four potential comparators to IVO+AZA:

- Venetoclax with azacitidine (VEN+AZA)
- Azacitidine (AZA, if not eligible for hematopoietic stem cell transplantation [HSCT] and have AML with 20-30% blasts and multilineage dysplasia)

- Venetoclax with low dose cytarabine (VEN+LDAC, if >30% blasts)
- Low dose cytarabine (LDAC)

Taking each of these comparators in turn:

VEN+AZA

NICE TA765 recommended VEN+AZA within its marketing authorisation, as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable (34). This recommendation does not differentiate patients by blast count, as the final guidance explicitly states: *"… the committee recommended* [VEN+AZA] *as an option for untreated* [AML] *in adults when intensive chemotherapy is unsuitable. This includes those in the 20% to 30% blast group and the over 30% blast group."*

This recommendation is also aligned with clinician feedback obtained by Servier(35)), and is endorsed by ELN 2022 guidelines, (7)and BSH 2022 good practice guideline (36); the latter explicitly stating: *"The new standard therapy for older AML patients considered unfit for intensive chemotherapy is* [VEN+AZA]*"* Therefore, VEN+AZA represents the standard of care in NHS practice for this patient population, and is a relevant treatment to compare to IVO+AZA.

AZA

The comparator arm in the AGILE study is AZA. At the time the AGILE study was designed (study start date: 26 June 2017), VEN (in combination with either AZA or LDAC) was not available for patients with previous untreated AML, and therefore AZA represented the standard of care for this patient population. Since this time, VEN+AZA has been established as the standard of care in this patient population, and so use of AZA monotherapy has been superseded (supported also by clinical feedback provided to Servier (35)). Consequently, AZA is not considered a relevant comparator in this appraisal.

VEN+LDAC

VEN+LDAC was recommended as part of NICE TA787, specifically for patients with over 30% blasts (69). The final guidance explains that the choice between AZA and LDAC (given in combination with VEN) would be based on individual choice for patients and clinicians. The ELN 2022 guidelines state: *"For patients unable to receive a hypomethylating agent (HMA),* [LDAC] *in combination with* [VEN] *represents an alternative treatment option." (7)* Consequently, VEN+LDAC does not represent a relevant comparator to IVO+AZA since by definition, patients in the AGILE study must be deemed able to receive treatment with an HMA (such as AZA).

LDAC

As with VEN+AZA versus AZA, and noting the eligibility criteria for the AGILE study for patients to receive IVO+AZA, the availability of VEN is expected to have

superseded the use of LDAC monotherapy, and all patients treated with IVO+AZA must be deemed able to receive treatment with an HMA, and so LDAC is not considered a relevant comparator in this appraisal.

In summary, the comparator considered in this submission is VEN+AZA, which represents the current standard of care in this patient population (despite VEN+AZA not being specifically indicated for a population with *IDH1*-mutated AML). The model provided alongside this submission includes a comparison to AZA (given data were available from the AGILE study), but this is not considered a relevant comparator in NHS practice, and so results are not presented in this submission. Both VEN+LDAC and LDAC are not considered relevant comparators, owing mostly to the fact that patients must be able to receive treatment with an HMA in order to receive IVO+AZA, and therefore LDAC±VEN is not discussed further throughout the remainder of the submission.

B.3.3 Clinical parameters and variables

Survival extrapolations and health state transitions

As described previously, the model makes use of survival extrapolations based on data collected as part of the AGILE study for IVO+AZA, with an indirect comparison used to generate corresponding extrapolations for VEN+AZA. Further details concerning the AGILE study are provided in Section B.2, as well as further information concerning the ITC with VEN+AZA.

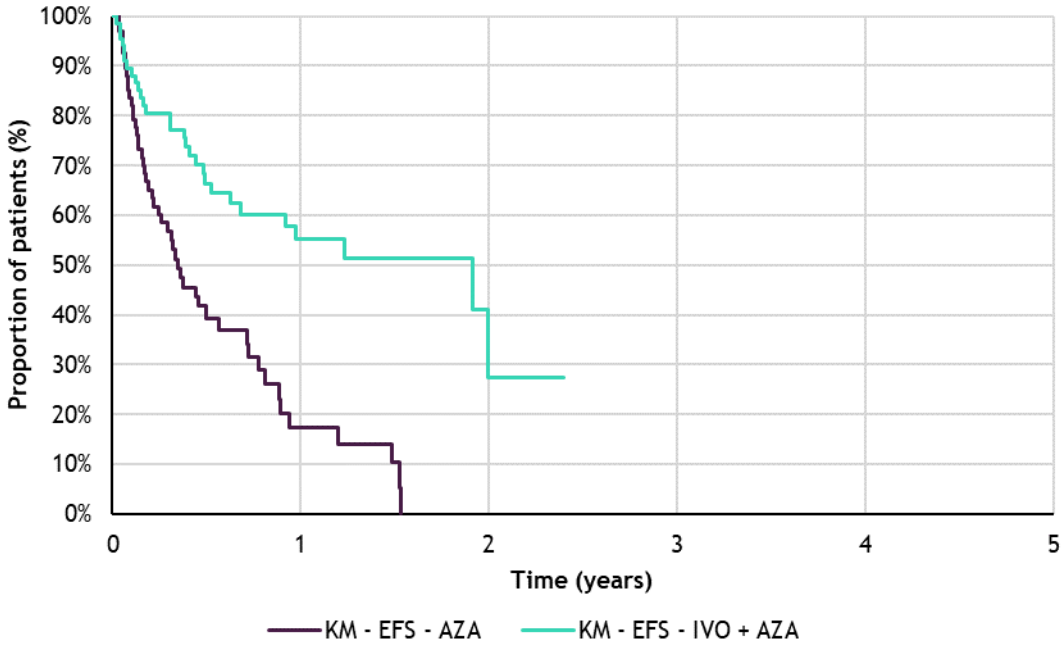
In the following sub-section, curve fits are presented for IVO+AZA, VEN+AZA, and AZA. While AZA is not considered a relevant comparator, these estimates are provided for completeness, as visualisation of these estimates may help with contextualising estimates for both IVO+AZA and VEN+AZA.

Event-free survival

IVO+AZA and AZA

For IVO+AZA and AZA, EFS was estimated using patient-level data available from the AGILE study. Independent parametric models were fitted to produce extrapolations of EFS over the time horizon of the cost-effectiveness model. Kaplan-Meier (KM) estimates of EFS from AGILE are presented in Figure 23. Please note: the definition used for EFS within the cost-effectiveness model is different to the definition used for the primary endpoint in AGILE, where EFS was defined as the time from randomization until PD, relapse from CR or CRi, treatment failure (failure to achieve CR, CRi, or morphologic leukaemia-free state [MLFS] after at least 24 weeks of study treatment), or death from any cause. This was to ensure alignment with the definition of EFS used in the VIALE-A study (which forms the basis of the ITC against VEN+AZA).

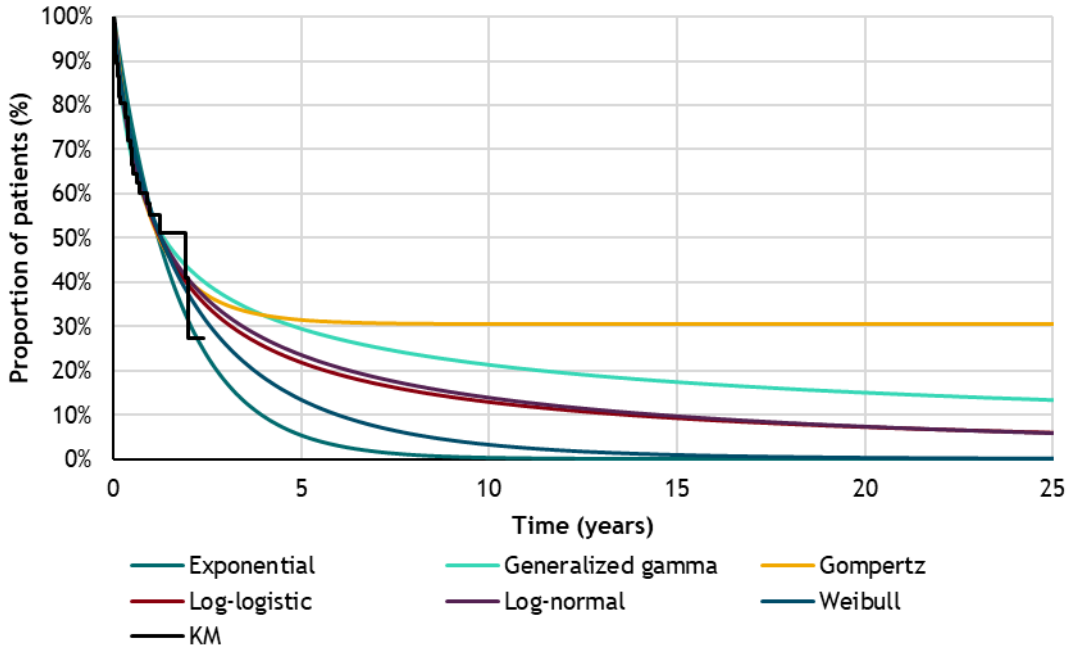
Figure 23: KM estimates of EFS from AGILE



Key: AZA, azacitidine; EFS, event-free survival; IVO, ivosidenib; KM, Kaplan-Meier.

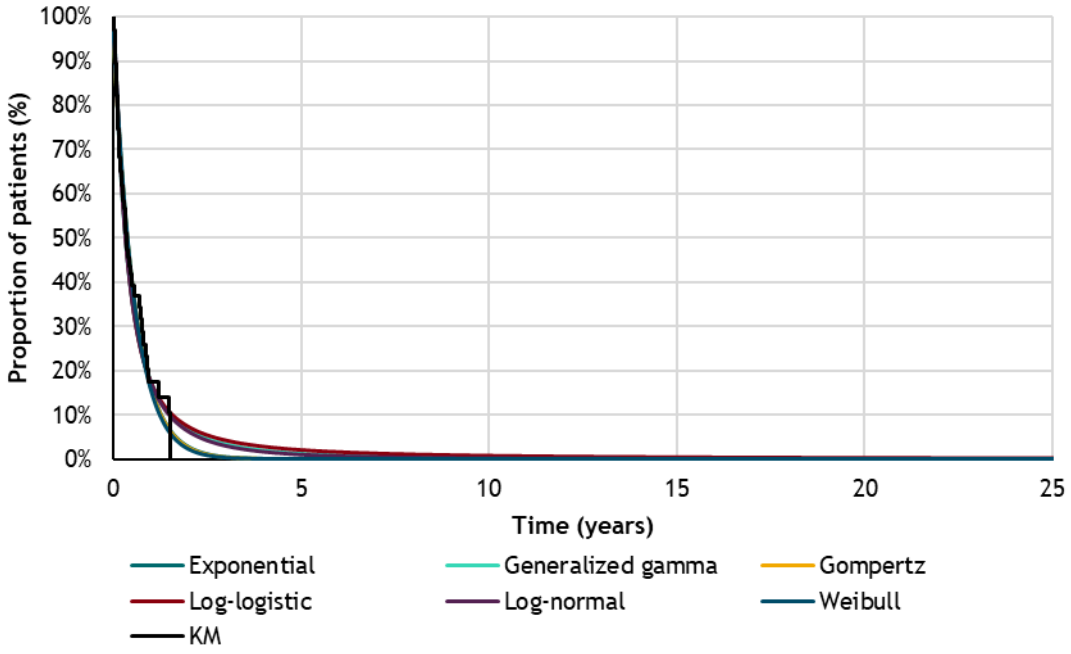
The fitted parametric models for the IVO+AZA and AZA arms are provided in Figure 24 and Figure 25, respectively. Please note that these extrapolations are unadjusted models that do not account for the possibility of 'crossing' the OS curve, which is addressed later in this sub-section. The corresponding statistical goodness-of-fit scores for the models fitted to each arm are provided in Table 37.

Figure 24: Parametric models for EFS – IVO+AZA



Key: AZA, azacitidine; EFS, event-free survival; IVO, ivosidenib; KM, Kaplan-Meier.

Figure 25: Parametric models for EFS – AZA



Key: AZA, azacitidine; EFS, event-free survival; KM, Kaplan-Meier.

Table 37: Statistical goodness-of-fit scores for the EFS models

Model	IVO+AZA		AZA	
	AIC	BIC	AIC	BIC
Exponential	235.04	237.31	286.81	**289.12**
Generalized gamma	233.15	239.98	286.97	293.88
Gompertz	233.99	238.55	288.81	293.41
Log-logistic	233.21	237.76	288.33	292.94
Log-normal	**231.63**	**236.18**	**284.99**	289.60
Weibull	234.05	238.61	288.65	293.26

Key: AIC, Akaike's information criterion; AZA, azacitidine; BIC, Bayesian information criterion; EFS, event-free survival; IVO, ivosidenib.
Note: The lowest scores are highlighted in bold print in the table above (with lower scores indicating a superior goodness of fit).

In the base-case analysis, a log-normal model was selected for IVO+AZA. The log-normal model provided the best statistical fit (except from BIC, though the difference between the best- and second best-fitting model was 0.48 points) and produces extrapolations that are appear reasonable. The exponential and Gompertz models produced extrapolations that were deemed too pessimistic and too optimistic, respectively by clinician feedback to the company (35)In a cost-effectiveness analysis by Pratz *et al.*, (2022) based on the VIALE-A study, the Gompertz model was selected for patients treated with VEN+AZA, whereas an exponential model was selected for patients treated with AZA (63). As noted above, the Gompertz model was deemed to be unrealistic in the context of this study for the IVO+AZA arm, hence the log-normal model was preferred. The remaining models that were deemed

potentially plausible (generalised gamma, log-logistic, and Weibull) were explored within sensitivity analysis.

VEN+AZA

An ITC was required to compare both IVO+AZA and AZA to VEN+AZA. Full details of the approach taken to generate the ITC are provided in Section B.2. However, for brevity, an NMA was carried out using a fixed effects model to generate an HR for the outcome of EFS. Consequently, the output from the NMA were used to inform estimates of EFS for VEN+AZA by applying the HR to the selected survival curve for IVO+AZA.

Compared with VEN+AZA, the findings from the NMA demonstrated that IVO+AZA is associated with improved EFS (HR = [redacted]). This result is summarised in Table 38, alongside the 95% CrI, and the resultant extrapolation used to inform the cost-effectiveness analysis is provided in Figure 26.

Table 38: Network meta-analysis output for EFS used within the cost-effectiveness analysis

Comparison and outcome	Median	95% CrI
EFS: IVO+AZA versus VEN+AZA	[redacted]	[redacted]

Key: AZA, azacitidine; CrI, credible interval; EFS, event-free survival; IVO, ivosidenib; VEN, venetoclax.
Note: The cost-effectiveness model uses outputs from a fixed-effects model, as the deviance information criteria estimates were comparable between fixed effects and random effects models, but the fixed effects model is a more parsimonious model with fewer assumptions.

Figure 26: Estimated EFS curve for VEN+AZA

Key: AZA, azacitidine; EFS, event-free survival; HR, hazard ratio; IVO, ivosidenib; VEN, venetoclax.

Capping of EFS by OS

To ensure no patients were simultaneously modelled to be 'event-free' via EFS and 'dead' via OS, the selected projection of EFS was capped by the selected projection of OS. The OS models are presented separately in the 'OS' sub-section.

Base-case estimates for event-free survival

The base-case projections of EFS are provided for each treatment arm in Figure 27, accounting for the previously described adjustments.

Figure 27: Base-case EFS extrapolations – all arms

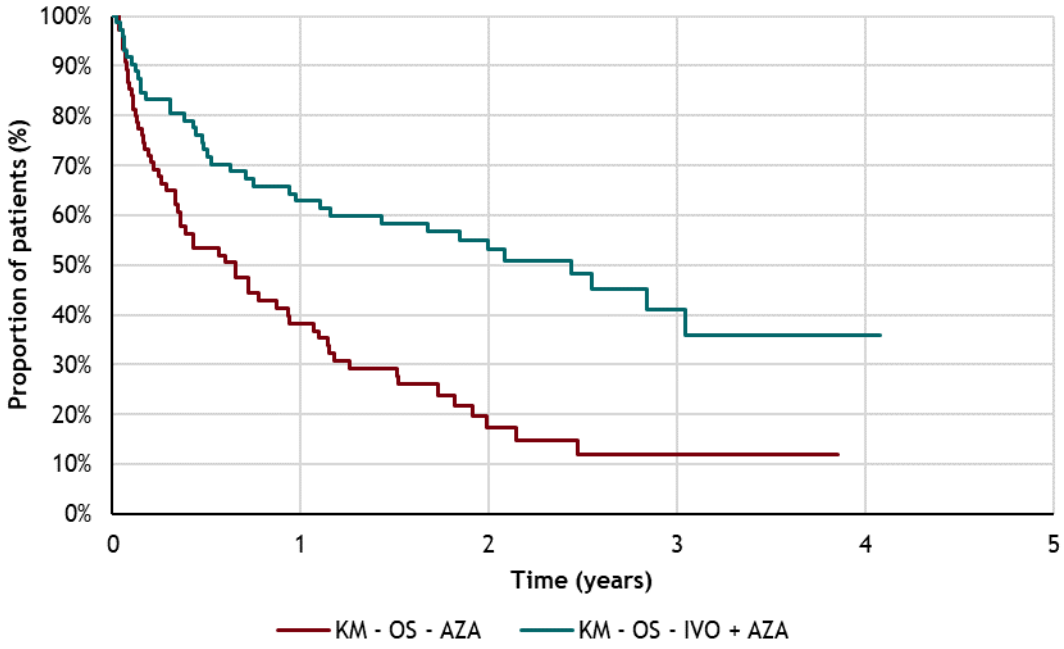
Key: AZA, azacitidine; EFS, event-free survival; IVO, ivosidenib; VEN, venetoclax.

Overall survival

IVO+AZA and AZA

For IVO+AZA and AZA, OS was estimated using patient-level data available from the AGILE study. Independent parametric models were fitted to produce extrapolations of OS over the time horizon of the cost-effectiveness model. KM estimates of OS from AGILE are presented in Figure 28.

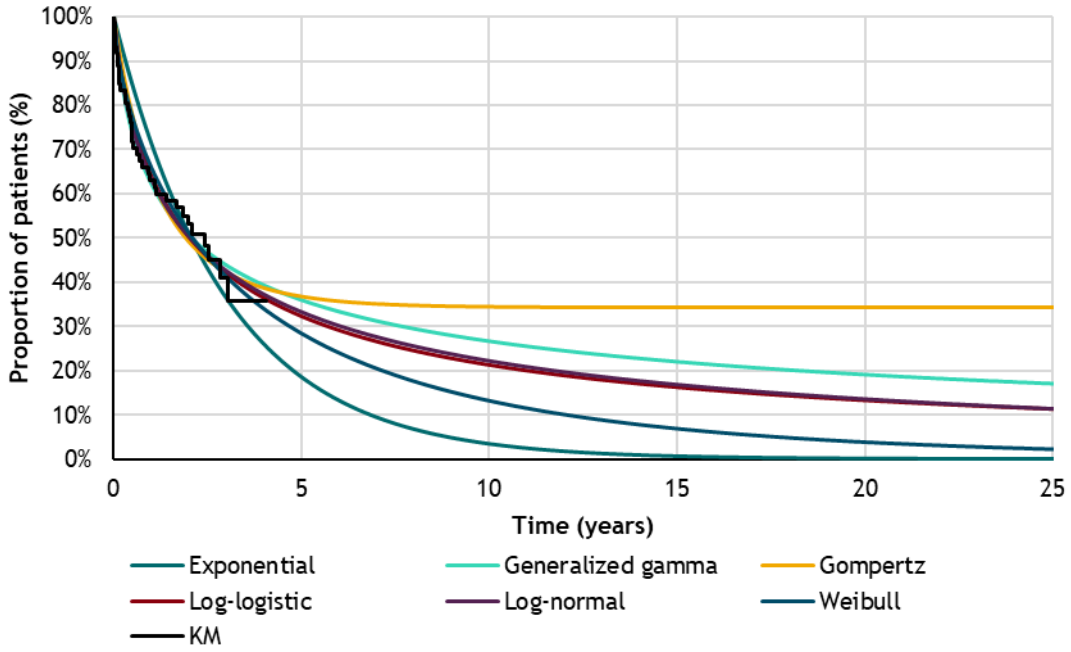
Figure 28: KM estimates of OS from AGILE



Key: AZA, azacitidine; IVO, ivosidenib; KM, Kaplan-Meier; OS, overall survival.

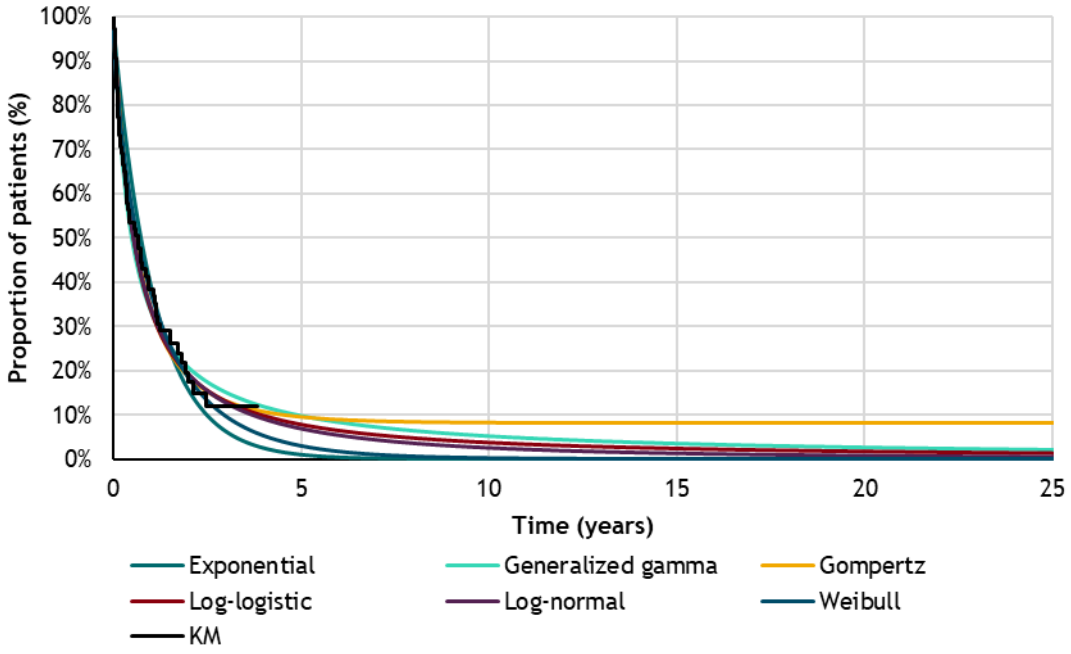
The fitted parametric models for the IVO+AZA and AZA arms are provided in Figure 29 and Figure 30, respectively. Please note that these extrapolations are unadjusted models that do not account for background mortality which is addressed later in this sub-section. The corresponding statistical goodness-of-fit scores for the models fitted to each arm are provided in Table 39.

Figure 29: Parametric models for OS – IVO+AZA



Key: AZA, azacitidine; IVO, ivosidenib; KM, Kaplan-Meier; OS, overall survival.

Figure 30: Parametric models for OS – AZA



Key: AZA, azacitidine; KM, Kaplan-Meier; OS, overall survival.

Table 39: Statistical goodness-of-fit scores for the OS models

Model	IVO+AZA		AZA	
	AIC	BIC	AIC	BIC
Exponential	340.28	342.57	415.81	418.13
Generalized gamma	333.49	340.37	407.02	413.98
Gompertz	335.84	340.42	410.50	415.14
Log-logistic	333.61	338.19	409.19	413.82
Log-normal	**331.88**	**336.46**	**406.03**	**410.67**
Weibull	334.54	339.12	412.99	417.62

Key: AIC, Akaike's information criterion; AZA, azacitidine; BIC, Bayesian information criterion; IVO, ivosidenib; OS, overall survival.
Note: The lowest scores are highlighted in bold print in the table above (with lower scores indicating a superior goodness of fit).

In the base-case analysis, a log-normal model was selected for both treatment arms. The log-normal model provided the best statistical fit to both arms, yielded plausible extrapolations according to clinician feedback to the company (35), and was the model selected to inform the majority of transitions to death in NICE TA765 of VEN+AZA, and was selected to inform the VEN+AZA arm of a cost-effectiveness analysis by Pratz *et al.*, (2022) based on the VIALE-A study. (34, 63)

VEN+AZA

An indirect comparison was required to compare both IVO+AZA and AZA to VEN+AZA. Full details of the approach taken to generate this indirect comparison are provided in Section B.2. However, for brevity, an NMA was carried out using a fixed effects model to generate an HR for the outcome of OS. Consequently, the

output from the NMA were used to inform estimates of OS for VEN+AZA by applying the HR to the selected survival curve for the IVO+AZA arm.

Compared with VEN+AZA, the findings from the NMA demonstrated that IVO+AZA is associated with improved OS (HR = [redacted]). This result is summarised in Table 40, alongside the 95% CrI, and the resultant extrapolation used to inform the cost-effectiveness analysis is provided in Figure 31.

Table 40: Network meta-analysis output for OS used within the cost-effectiveness analysis

Comparison and outcome	Median	95% CrI
OS: IVO+AZA versus VEN+AZA	[redacted]	[redacted]

Key: AZA, azacitidine; CrI, credible interval; IVO, ivosidenib; OS, overall survival; VEN, venetoclax.
Note: The cost-effectiveness model uses outputs from a fixed-effects model, as the deviance information criteria estimates were comparable between fixed effects and random effects models, but the fixed effects model is a more parsimonious model with fewer assumptions.

Figure 31: Estimated OS curve for VEN+AZA

Key: AZA, azacitidine; IVO, ivosidenib; HR, hazard ratio; OS, overall survival; VEN, venetoclax.

Background mortality adjustment

Within the model, age- and sex-adjusted general population mortality estimates were also produced based on population-level statistics from the Office for National Statistics (24). At each model cycle, the implied hazard of death was checked against the projected hazard of death from the chosen OS model – if the extrapolated hazard was lower than that of the age- and sex-adjusted general population, the hazard was instead taken from the life table estimates. Owing to the starting age of the cohort (close to 75 years of age, see Table 36), this approach

ensures that background mortality rates serve as the minimum estimated hazard of death for the population under consideration.

Long-term survivors

A recent data cut from the AGILE trial (June 2022) demonstrated a plateau in the IVO+AZA OS, which implies potential to 'cure' the target AML patients by providing sustained survival benefit. Thus, similar to TA765 of VEN+AZA to NICE, the base-case analysis assumed that patients who received IVO+AZA and remained 'event-free' for 36 months entered a cure state. (34) The use of a 'cure state' is common practice for economic evaluations supporting HTA submissions in cancers where long-term survival has been evidenced for those that achieve CR.

When the cure assumption is considered, patients who remained in the EFS state beyond the cure point (36 months in the base-case analysis) were assumed to be cured. Cured patients were assumed to experience similar survival outcomes as the general UK population (age- and gender-specific cohorts). Furthermore, cured patients were assumed to no longer receive the primary treatment, hence drug acquisition, drug administration and concomitant medication costs were not applied to patients in the cure state. Cured patients had similar health state utility and medical resource use cost incurred as EFS patients with complete remission.

Clinician feedback obtained to inform this submission highlighted that while the plausibility of the various input parameters to inform a 'cure state' in a non-intensively treated AML population was subject to uncertainty, there should be no difference in what is assumed to apply for patients on IVO+AZA or VEN+AZA if both patients are otherwise in the same health state (35).

To appropriately account for a proportion of long-term survivors, the model base-case analysis imposes a 'cure point' at 3 years, for all treatment arms (aligned with TA765) (34). At this landmark time, all patients residing in the 'EF' health state transition to the 'LTS' (long-term survival) health state. In this health state, patients are no longer permitted to transition to the 'PD/RL' health state as they are assumed to no longer be at risk of progression or relapse. Accordingly, OS from this timepoint onwards is based on population-level life tables. Patients that are alive at 3 years but reside within the 'PD/RL' health state are assumed to follow the unadjusted survival model.

The model includes the ability to apply custom standardised mortality ratios (SMRs) to adjust the risk of death beyond 3 years for 'LTS' and 'PD/RL' patients. In the base-case analysis, SMRs of 1 are assumed to apply for both extrapolations, though alternative values are explored in sensitivity analysis (alongside specification of alternative timepoints from which 'EF' patients transition to 'LTS'). A sensitivity analysis is also provided where the OS estimates are not adjusted to account for long-term survivors, but cost and utility implications are retained.

Base-case estimates for overall survival

The base-case projections of OS are provided for each treatment arm in Figure 32, accounting for the background mortality and long-term survivor adjustments (including notably the 'cure point' which applies at 3 years in the base-case analysis). Please note: the slight 'bump' in the curve at 3 years is due to the specification of the 'cure point'.

Figure 32: Base-case OS extrapolations – all arms

Key: AZA, azacitidine; IVO, ivosidenib; OS, overall survival; VEN, venetoclax

IVO+AZA and AZA

For IVO+AZA and AZA, ToT was estimated using patient-level data available from the AGILE study. Independent parametric models were fitted to produce extrapolations of ToT over the time horizon of the cost-effectiveness model. KM estimates of ToT from AGILE are presented in Figure 33.

Figure 33: KM estimates of ToT from AGILE

Key: AZA, azacitidine; IVO, ivosidenib; KM, Kaplan-Meier; ToT, time on treatment.

The fitted parametric models for the IVO+AZA and AZA arms are provided in Figure 34 and Figure 35, respectively. The corresponding statistical goodness-of-fit scores for the models fitted to each arm are provided in Table 41.

Figure 34: Parametric models for ToT – IVO+AZA

Key: AZA, azacitidine; IVO, ivosidenib; KM, Kaplan-Meier; ToT, time on treatment.

Figure 35: Parametric models for ToT – AZA

Key: AZA, azacitidine; KM, Kaplan-Meier; ToT, time on treatment.

Table 41: Statistical goodness-of-fit scores for the ToT models

Model	IVO+AZA		AZA	
	AIC	BIC	AIC	BIC
Exponential	365.97	368.25	**398.20**	**400.50**
Generalized gamma	354.13	360.96	401.48	408.39
Gompertz	356.92	361.47	400.15	404.76
Log-logistic	353.84	358.39	405.46	410.07
Log-normal	**352.19**	**356.75**	404.52	409.13
Weibull	355.28	359.83	400.13	404.74

Key: AIC, Akaike's information criterion; AZA, azacitidine; BIC, Bayesian information criterion; IVO, ivosidenib; ToT, time on treatment.
Note: The lowest scores are highlighted in bold print in the table above (with lower scores indicating a superior goodness of fit).

In the base-case analysis, a Weibull model was selected for IVO+AZA. The Weibull model was selected based on it providing statistical goodness-of-fit scores that were similar to the best-fitting models for each arm, and a reasonable visual fit to the KM estimate of ToT for each arm of the AGILE study. For the VEN+AZA arm, it was necessary to fit an exponential model, though as can be seen from Figure 34 and Table 41, the exponential model does not appear to provide a good fit to the IVO+AZA arm.

VEN+AZA

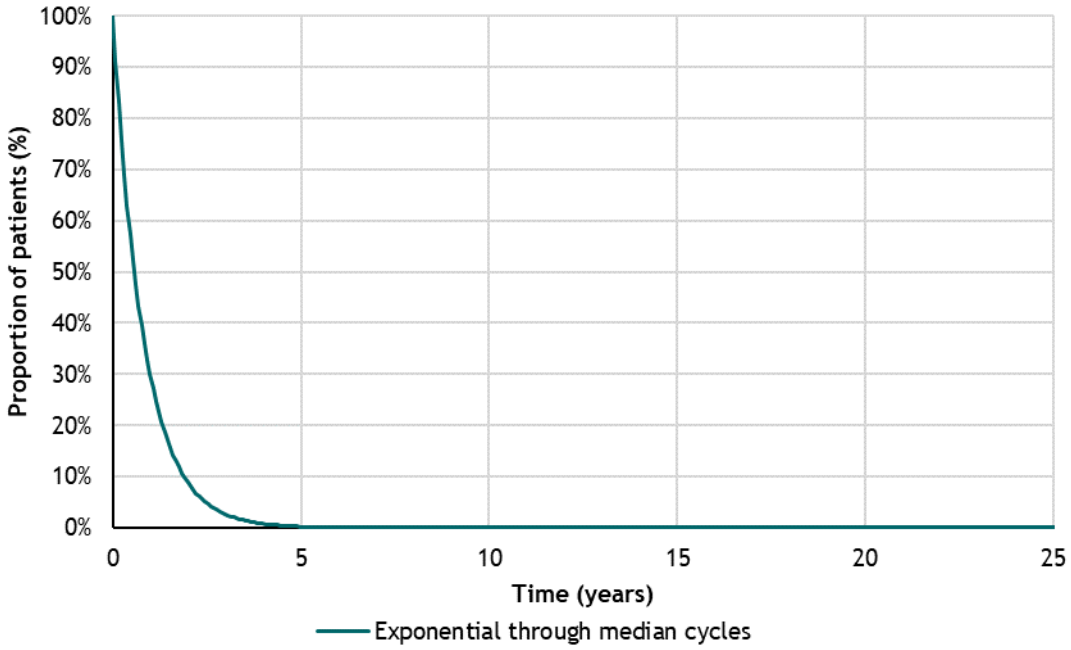
For VEN+AZA, two options were included in the cost-effectiveness model to estimate ToT:

- Option 1: An exponential model was fitted to align with the reported mean number of treatment cycles for VEN+AZA in VIALE-A (10.76 cycles) to produce a ToT curve (63).
- Option 2: Apply an arbitrary HR against the EFS curve to produce a proxy ToT curve.

For the base-case analysis, Option 1 was preferred given that this makes use of data from the VIALE-A study. The mean number of cycles, 10.76, was converted to a median duration of treatment based on the following formula, with the resultant ToT curve provided in Figure 36:

$$\frac{\ln 2}{\left(\frac{1}{10.76 \times 4}\right)} \approx 29.83\ weeks$$

Figure 36: Estimated ToT curve for VEN+AZA



Key: AZA, azacitidine; ToT, time on treatment; VEN, venetoclax.

Assumed maximum ToT

Across all treatment arms, it was considered unlikely that patients would continue treatment beyond 3 years, in keeping with the expectation that by this time, most patients would have either experienced disease progression/relapse, or if still in an EFS state may be considered long-term survivors, for which further treatment would not be required. As such, a further adjustment was applied in the model base-case analysis to stop all treatment at 3 years.

Base-case estimates for ToT

The base-case projections of ToT are provided for each treatment arm in Figure 37, including the cap at 3 years for all treatments.

Figure 37: Base-case ToT extrapolations – all arms

Key: AZA, azacitidine; IVO, ivosidenib; ToT, time on treatment; VEN, venetoclax.
Note: Due to the specification of a 4-weekly model cycle, the 2-year assumed maximum treatment duration is applied in the first cycle after 3 years, which is at 3.07 years.

Adverse reactions

In order to capture the cost and utility implications associated with adverse events (AEs), the rate of AE occurrence was also included within the model. AEs were included within the model if they occurred at Grade 3 or 4. Two options are included within the model to determine which Grade 3 or 4 AEs are modelled, based on the proportion of patients affected in the AGILE or VIALE-A studies:

- **Option 1:** AEs that occur in at least 10% patients in either treatment arm of AGILE or the VEN+AZA arm of VIALE-A.
- **Option 2:** AEs that occur to at least 5% patients in either treatment arm of AGILE or the VEN+AZA arm of VIALE-A, plus differentiation syndrome (DS) as an AE of particular interest.

For the VEN+AZA arm, reported AE frequencies were extracted from the VIALE-A study (38). No formal adjustment was applied to the AE rates to account for differences between the AGILE and VIALE-A studies. The three most common Grade 3 or 4 AEs on the comparator arm of VIALE-A (AZA) were thrombocytopenia (38%), neutropenia (28%), and anaemia (20%), and the corresponding rates for the AZA arm in AGILE were 21%, 16%, and 26%, respectively.

A summary of the AEs included within the model for each arm are provided in Table 42. The AEs highlighted are included only for Option 2. All other values are included for both Option 1 and Option 2.

Table 42: Adverse events included within the cost-effectiveness model

Adverse event	IVO + AZA	AZA	VEN + AZA
Anaemia	25.40%	26.00%	26.10%
Bacteraemia	0.00%	2.70%	44.20%
Decreased appetite	1.40%	8.20%	4.20%
Diarrhoea	1.40%	6.80%	4.60%
Electrocardiogram QT prolonged	9.90%	2.70%	NR
Febrile neutropenia	28.20%	34.20%	41.70%
Hypokalaemia	2.80%	8.20%	10.60%
Hyponatraemia	4.20%	6.80%	NR
Hypotension	0.00%	5.50%	NR
Other infections (excluding pneumonia)	45.00%	42.50%	43.80%
Leukopenia	7.00%	2.70%	20.50%
Neutropenia	26.80%	16.40%	42.00%
Neutrophil count decreased	8.50%	6.80%	NR
Platelet count decreased	8.50%	8.20%	NR
Pneumonia	22.50%	28.80%	19.80%
Pulmonary embolism	5.60%	1.40%	NR
Sepsis	2.80%	8.20%	NR
Thrombocytopenia	23.90%	20.50%	44.50%
Differentiation syndrome	4.20%	4.10%	NR

Key: AZA, azacitidine; IVO, ivosidenib; NR, not reported; VEN, venetoclax.
Note: Unreported values are assumed to be zero. Values highlighted in blue are not included if the model is set to only include AEs that occurred in at least 10% patients in either treatment arm of AGILE or the VEN+AZA arm of VIALE-A.

The unit costs and disutility values used to inform the cost and utility implications of AE occurrence within the model are discussed separately in the sub-sections that follow.

B.3.4 Measurement and valuation of health effects

Identification of health-related quality-of-life studies

Please see Appendix H for details.

Health-related quality-of-life data from clinical trials

In the AGILE study, EuroQoL Five-dimension five-level (EQ-5D-5L) data were collected, and so it was deemed possible to obtain utility values from the AGILE trial using a United Kingdom (UK) value set for implementation in the cost-effectiveness analysis. First, it was necessary to define time-period definitions for the analysis. All EQ-5D responses collected in AGILE were considered to have been collected within one of the time-periods defined in Table 43.

Table 43: Time-period definitions for EQ-5D responses

Definition for model	Definition in AGILE
Baseline	Cycle 1 Day 1 before the start of study treatment. If no value was available on or before the date of randomization, the last measurement

Definition for model	Definition in AGILE
	on or before the start of study treatment was considered as the baseline.
EFS (with CR/CRi as the best response)	Time from randomization until progressive disease, relapse from CR or CRi, treatment failure defined as failure to achieve CR, CRi, or MLFS after at least 24 weeks of study treatment or death from any cause, with the state of CR/CRi as the best response as assessed by investigators using the IWG Response Criteria for AML.
EFS (without CR/CRi as the best response)	Time from randomization until progressive disease, relapse from CR or CRi, treatment failure defined as failure to achieve CR, CRi, or MLFS after at least 24 weeks of study treatment or death from any cause without the state of CR/CRi as the best response as per the IWG Response Criteria for AML.
PD/RL	The phase following relapse from remission or disease progression

Key: AML, acute myeloid leukaemia; CR/CRi; complete remission or complete remission with incomplete count recovery; EFS, event-free survival; IWG, International Working Group; MLFS, morphologic leukaemia-free state; PD/RL, progressed disease or relapse.

The event-free status variable was defined by comparing a patient's "date of clinical event (death, disease progression, relapse, or treatment failure)" and their EQ-5D assessment date. If an EQ-5D assessment occurred after the date of treatment failure, the assessment was a "progressive disease / relapse" assessment. Otherwise, the status variable took the value "event-free". The pre-progression value was also stratified by whether the assessment occurred at baseline or not. For records where the date of progression or relapse was missing, the date of death / censoring was used as a proxy for the date of progression.

The CR / CRi variable is a binary variable to record if a patient ever reached CR or CRi (including CRp) during trial follow-up. For records where the "best response" data was missing, it was assumed that the patient did not reach CR or CRi.

Overall, 890 observations were recorded from 142 patients. The breakdown of responses by health state definition is provided in Table 44.

Table 44: EQ-5D assessments recorded for each health state

Value	IVO + AZA (N = 512)	AZA (N = 378)	Total (N = 890)
Baseline	68	66	134
EFS	385	258	643
EFS (CR/CRi)	298	94	392
EFS (No CR/CRi)	87	164	251
PD/RL	59	54	113

Key: AML, acute myeloid leukaemia; AZA, azacitidine; CR/CRi; complete remission or complete remission with incomplete count recovery; EFS, event-free survival; IVO, ivosidenib; PD/RL, progressed disease or relapse.

Since health-related quality of life data from the AGILE study were collected using the EQ-5D-5L descriptive system, utility values needed to be calculated by mapping the -5L descriptive system data onto the -3L value set for the UK. To do this, the 'crosswalk' approach developed by Hernández-Alava *et al.*, (2018) was used (66).

The mapped EQ-5D-3L utility values were then analysed using univariate and multivariate model structures and clustering by time-periods. Given that patients may

provide multiple assessments within the same time-period, a Mixed Model for Repeated Measures (MMRM) was tested. This model allows for the considerations of repeated EQ-5D-3L measurements at a patient level given that patients may provide several assessments during the study follow-up period.

The variables that were considered of most interest include EFS states, CR/CRi as the best response, and treatment arm. In addition to the inclusion of individual variables in the model, interactions between variables were also assessed for their impact, such as the interaction of treatment arm and EFS status. If the coefficients on interaction terms were not statistically significant, the interactions were excluded from the models. A stepwise approach was used to assess the model fitting and select the final model based on AIC estimates.

Table 45 presents the final MMRM coefficients. On average, compared to patients who have CR/CRi as the best response and are on treatment, patients who do not have CR/CRi as the best response were estimated to have a utility score reduction by 0.140, those who have PD/RL a score decreased by 0.035, and those no longer on treatment a score decreased by 0.073. The AIC of the final model is -264.918, whereas a model including treatment arm had an AIC of -262.967 (and so the final model was preferred over the model including treatment arm).

Table 45: EQ-5D-3L index scores, MMRM results, final model

Variable	β	95% CI	t	p-value
Intercept	0.769	(0.711, 0.827)	25.974	<0.001
EFS status: PD/RL	-0.035	(-0.082, 0.012)	-1.477	0.140
Best response: No CR/CRi	-0.140	(-0.214, -0.065)	-3.690	<0.001
Treatment status: Discontinued	-0.073	(-0.131, -0.015)	-2.776	0.013

Key: CI, confidence interval; CR/CRi; complete remission or complete remission with incomplete count recovery; EFS, event-free survival; PD/RL, progressed disease or relapse.

The resultant utility values used to inform the cost-effectiveness analysis are provided in Table 46. For the purpose of generating these utility values, patients in the 'PD/RL' health state were assumed to have No CR/CRi as their best response to treatment. Patients residing in the 'LTS' health state are assumed to have the same utility value as patients in the 'EF, CR/CRi' health state. For patients that are no longer receiving treatment in either the 'EFS' or 'PD/RL' health states, a disutility of 0.073 is applied for the duration of the model cycle, per the regression output in Table 45.

Table 46: Health state utility values estimated from the AGILE study

Adverse event	Mean	Source
EFS, CR/CRi	0.769	Analysis of AGILE patient-level data
EFS, no CR/CRi	0.629	Analysis of AGILE patient-level data
PD/RL	0.594	Analysis of AGILE patient-level data

Key: CR/CRi; complete remission or complete remission with incomplete count recovery; EFS, event-free survival; PD/RL, progressed disease or relapse; SE, standard error.

Utility values from the published literature

From the systematic literature review (see Appendix H), a range of alternative utility values were identified. Two studies were deemed suitable sources of utility values for consideration within sensitivity analysis, for the following reasons:

- Coyle *et al.*, (2020) (70): This study was cited by Bewersdorf *et al.*, (2022) to inform their cost-effectiveness analysis of IVO+AZA versus AZA from a US payer perspective.
- Pratz *et al.*, (2022) (63): This study reports utility values estimated from the VIALE-A study (of VEN+AZA), which is the study used to inform the ITC.

The corresponding values from the Coyle *et al.*, (2020) and Pratz *et al.*, (2022) studies are presented in Table 47.

Table 47: Health state utility values from the literature

Adverse event	Mean	95% CI
Coyle *et al.*, (2020)		
AML in remission	0.751	(0.676, 0.826)
Relapsed AML	0.675	(0.608, 0.743)
Pratz *et al.*, (2022)		
EFS, CR/CRi	0.796	(0.774, 0.818)
EFS, no CR/CRi	0.787	(0.765, 0.809)
PD	0.723	(0.694, 0.752)

Key: CI, confidence interval; CR/CRi; complete remission or complete remission with incomplete count recovery; EFS, event-free survival; PD, progressed disease; SE, standard error.

Estimation of patients with and without CR/CRi, within the EFS state

Owing to the specification of the PartSA model structure, it was necessary to further subdivide the EFS state by 'CR/CRi' versus 'No CR/CRi'. However, since CR/CRi status can change over time, the following approach was taken:

- For the first two model cycles (t=0 and t=4 weeks), it was assumed that no patients are in CR/CRi. The first recorded CR/CRi in AGILE occurred between 4 and 8 weeks.
- From cycle 2 (t=8 weeks) it was considered plausible that patients could achieve CR/CRi. However, by approximately cycle 12 (t=44 weeks), estimates were based on few patients and the proportion appeared to be approximately stable. Therefore, a simple second-order polynomial was fitted within Excel to the raw data using data between cycles 2 and 12.
- For all further cycles (i.e., cycle 13 onwards), the proportion of CR/CRi patients within the EF state was assumed to remain static (i.e., last observation carried forward was assumed).

For the VEN+AZA arm, the following estimation approach was taken:

- In AGILE, the CR/CRi rate was estimated to be 54.2% for IVO+AZA and 16.2% for AZA.
- In VIALE-A, the CR/CRi rate was estimated to be 66.4% for VEN+AZA and 28.3% for AZA.
- Using these estimates, an estimate for VEN+AZA aligned with the AGILE study was produced:

$$Rate_{AZA\ in\ AGILE} \times \frac{Rate_{VEN+AZA\ in\ VIALE-A}}{Rate_{AZA\ in\ VIALE-A}} = 16.2\% \times \frac{66.4\%}{28.3\%} = 38.0\%$$

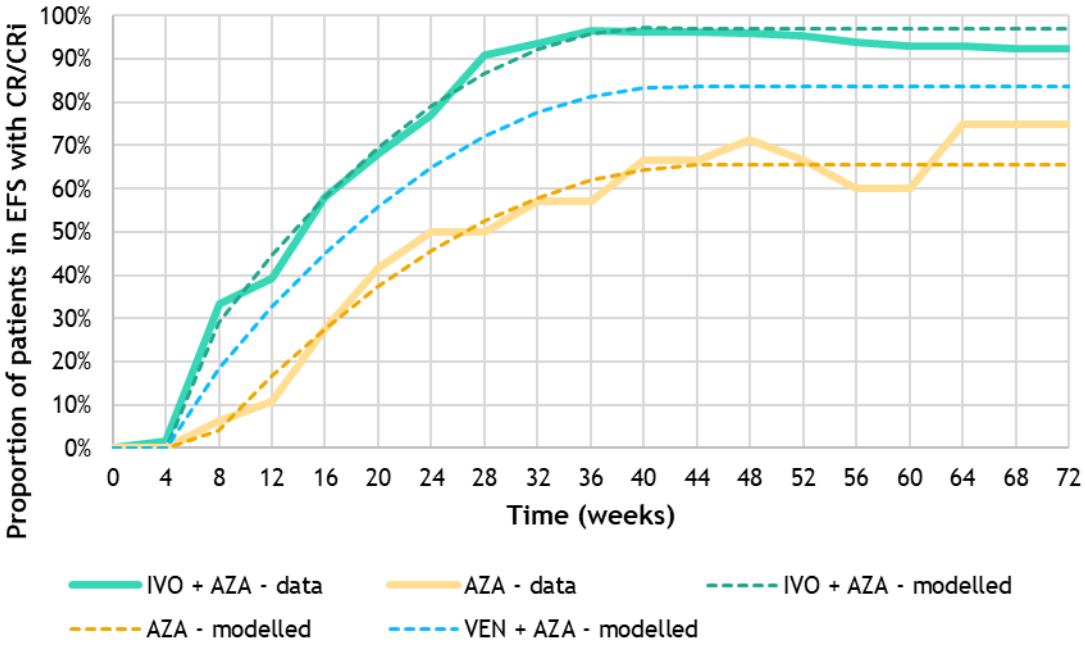
- Then, the estimated CR/CRi rate for VEN+AZA of 38.0% was represented as a weighted average of the AGILE estimates for IVO+AZA and AZA:

$$Rate_{VEN+AZA\ proxy\ in\ AGILE} = Rate_{IVO+AZA\ in\ AGILE} \times p + Rate_{AZA\ in\ AGILE} \times (1-p)$$

- Solving for p yielded a value of 57.4%, and so the estimated proportion of 'EF' patients on the VEN+AZA arm with CR/CRi was estimated as a weighted average of the IVO+AZA and AZA arms using this value.

The fitted and raw estimates of the proportion of 'EF' patients separated by 'CR/CRi' versus 'No CR/CRi' is provided in Figure 38.

Figure 38: Estimation of CR/CRi versus No CR/CRi within the EFS state by arm



Key: AZA, azacitidine; CR/CRi, complete remission or complete remission with incomplete count recovery; EFS, event-free survival; IVO, ivosidenib; VEN, venetoclax.

Adverse reactions

To capture the impact of AEs on patient utility, the model includes AE-related disutilities that are applied based on the frequency of occurrence. The included AE

disutilities are summarised in Table 48. All AE disutilities were assumed to last for a duration of 28 days (i.e., one treatment cycle). The impact of AEs on patient utility was applied as a one-off QALY loss in the first model cycle.

Table 48: Adverse event disutilities

Adverse event	Disutility	Source
Anaemia	-0.090	Beusterien *et al.*, (2010)(71)
Bacteraemia	0	Assumption
Decreased appetite	-0.176	Wehler *et al.*, (2018)(72)
Diarrhoea	0	Wehler *et al.*, (2018)(72)
Electrocardiogram QT prolonged	0	Assumption
Febrile neutropenia	-0.09	Nafees *et al.*, (2008)(73)
Hypokalaemia	0	Assumption
Hyponatraemia	0	Assumption
Hypotension	-0.020	Neumann *et al.*, (2017)(74)
Other infections (excluding pneumonia)	-0.218	Wehler *et al.*, (2018)(72)
Leukopenia	-0.090	Nafees *et al.*, (2008)(73)
Neutropenia	-0.090	Nafees *et al.*, (2008)(73)
Neutrophil count decreased	-0.090	Assume same as neutropenia
Platelet count decreased	-0.090	Assume same as leukopenia
Pneumonia	-0.218	Wehler *et al.*, (2018)(72)
Pulmonary embolism	-0.218	Wehler *et al.*, (2018)(72)
Sepsis	-0.090	Nafees *et al.*, (2008)(73)
Thrombocytopenia	-0.218	Assume same as infection
Differentiation syndrome	-0.090	Beusterien *et al.*, (2010)(71)

Age adjustment

Age-related utility decrements were included in the model to account for the natural decline in quality of life associated with age. Utility values from the general population at each age were calculated using the algorithm by Ara & Brazier, (2010). The utility multiplier was the calculated per increase in age and applied in each cycle throughout the model time horizon.

$$General\ population\ utility\ value = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2$$

Health-related quality-of-life data used in the cost-effectiveness analysis

In the base-case analysis, utility values derived from the AGILE study were used to inform each of the modelled health states. Scenario analyses exploring alternative utility values from the literature were also explored. Table 49 summarises the utility values included within the base-case cost-effectiveness analysis.

Table 49: Summary of utility values for cost-effectiveness analysis

State	Utility value	Reference in submission	Justification
EFS, CR/CRi	0.769	Section B.3.4, page 102	Estimated from regression fitted to data from the AGILE study
EFS, no CR/CRi	0.629		
PD/RL	0.594		
Off treatment decrement	-0.073		
LTS	0.769		Assumption

Adverse event	Disutility value	Reference in submission	Justification
Anaemia	-0.090	Section B.3.4, page 105	Disutility values taken from published literature (limited evidence specific to an AML population).
Bacteraemia	0		
Decreased appetite	-0.176		
Diarrhoea	0		
Electrocardiogram QT prolonged	0		
Febrile neutropenia	-0.09		
Hypokalaemia	0		
Hyponatraemia	0		
Hypotension	-0.020		
Other infections (excluding pneumonia)	-0.218		
Leukopenia	-0.090		
Neutropenia	-0.090		
Neutrophil count decreased	-0.090		
Platelet count decreased	-0.090		
Pneumonia	-0.218		
Pulmonary embolism	-0.218		
Sepsis	-0.090		
Thrombocytopenia	-0.218		
Differentiation syndrome	-0.090		

Key: CR/CRi, complete remission or complete remission with incomplete count recovery; EFS, event-free survival; LTS, long-term survival; PD/RL, progressed disease or relapse.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Identification of costs and healthcare resource data

Identification of studies concerning healthcare resource use and cost data were considered as part of the broader economic evidence SLR, details of which are provided in Appendix G.

Intervention and comparators' costs and resource use

Unit drug costs

The unit costs for IVO, AZA, and VEN are presented in Table 50. A patient access scheme (PAS) discount of [redacted]% is included for IVO. There is an existing PAS discount for VEN, though the volume of discount offered is confidential, and therefore is not known to Servier to inform the model.

Table 50: Unit drug costs

Treatment	Units (mg)	Pack size	Pack cost	Source
Ivosidenib	250	60	List: £12,500.00 With PAS: £[redacted]	Servier
Azacitidine	100	1	£45.16	eMIT (2023)
Venetoclax	100	7	£299.34	BNF (2023)

Key: BNF, British National Formulary; eMIT, electronic market information tool; PAS, patient access scheme.

Regimen costs

Using the unit costs shown in Table 50, as well as the PAS discount proposed for IVO, each regimen was dosed according to its SmPC for costing within the cost-effectiveness analysis:

- **IVO+AZA:** IVO 500mg on days 1-28 + AZA 75mg/m^2 either IV or SC on days 1-7 of each 28-day cycle.
- **VEN+AZA:** VEN 400mg on days 1-28 + AZA 75mg/m^2 either IV or SC on days 1-7 of each 28-day cycle.

However, two adjustments were made in light of expected 'real-world' dosing:

- The doses of IVO and VEN were adjusted to account for concomitant azole use (discussed further later in this sub-section). However, in brief, the dose accounting for concomitant azole use equates to 250mg for IVO (instead of 500mg), and 100mg for VEN (instead of 400mg).
- The SmPC for VEN+AZA includes dosing of VEN on days 1-28 of each cycle. However, in TA765, the committee heard from clinical experts that for Cycle 2 onwards, patients may instead receive treatment with VEN only on days 1-14 of each cycle. Therefore, the base-case analysis assumes 1-28 day dosing for Cycle 1, and 1-14 day dosing for Cycle 2+.

For AZA, based on the distribution of BSA of the AGILE study population, it was estimated that 1.30% of patients would require 1 x 100mg vial, and 98.70% of patients would require 2 x 100 mg vials, and so a weighted average of 1.99 vials was applied within the model. The relative dose intensity (RDI) for VEN+AZA was not available, so it was assumed that the RDI estimates for this regimen would be similar to IVO+AZA in the AGILE study.

Dose adjustments due to concomitant azole use

The clinical trial protocol for AGILE states that concomitant use of drugs with a potential for QT prolongation, such as azoles, were to be avoided and replaced with alternative treatments (75). However, despite this, data from AGILE on concomitant medication showed that for the pooled arms, more than half of the patients (53.5%) received concomitant azole during study treatment. Dose modifications of IVO or placebo from 500 mg to 250 mg were permitted in the study for management of AEs but no dose reductions were recommended in protocol for concomitant QT prolonging or CYP3A4 inhibiting drugs. However, as dose reductions are recommended according to the IVO SmPC for patients receiving concomitant azoles, the dosing for real-world patients receiving concomitant azoles is expected to be different to the dosing as observed in the AGILE study. It is important to note that such a difference in dosing is supported by clinical expert opinion.

IVO is metabolised in the liver by CYP3A4, therefore coadministration of moderate to strong CYP3A4 inhibitors might affect IVO pharmacokinetics (PK). PK studies show

the area-under-the-curve (AUC) of IVO is increased by 169% when co-administered with itraconazole and by 73% with concomitant fluconazole (76). The concomitant administration of azoles showed the steady state clearance of IVO was reduced with concomitant azoles which lead to AUC increased by 60% and Cmax increased (77). Therefore, based on the use of azoles in AGILE and the aforementioned PK studies, it is expected that concomitant azole usage results in increased drug exposure of IVO, and that consequently dosing in a real-world setting may be different to that in the clinical trial (as it is recommended based on the PK data to reduce the dose to 250 mg).

The FDA states that concomitant strong/moderate CYP3A4 inhibitors voriconazole, fluconazole, and posaconazole increased IVO AUC by approximately 60% (78). The EHA consensus statement on prophylaxis guidelines states that when IVO is administered in combination therapy, as is the case here, there is a strong recommendation for antifungal prophylaxis (79). Overall, in AML, antifungal prophylaxis is recommended with moderate strength in most settings, and strongly recommended if the novel AML agent is administered in combination with intensive induction chemotherapy. It specifically states that for IVO, lestaurtinib, quizartinib, and VEN, it is 'moderately recommended' to adjust the dose of the antileukemic agent during administration of triazoles, the recommended dose of IVO being reduced from 500 to 250 mg per day. This is aligned with clinician feedback to the company that PK data and dose reduction with VEN and an azole antifungal may have set a precedent moving forward for other new therapies (35).

In addition, the SmPC (see Appendix C) states that if a moderate to strong antifungal is used in combination with IVO, the dose should be reduced to 250mg of IVO. The EPAR (see Appendix C) states that no formal interaction study of IVO with moderate CYP3A4 inhibitor was conducted. However, the PBPK model predicted an AUC ratio of 1.90. In absence of formal DDI study conducted with fluconazole, as a conservative measure, and also taking into consideration the safety profile of IVO, in case of concomitant treatment with moderate CYP3A4 inhibitor, IVO exposure increase is considered to be within two-fold. Therefore, the SmPC proposed posology to be reduced by two-fold with safety monitoring is supported in case of concomitant treatment with a moderate or strong CYP3A4 inhibitor.

Clinicians have also advised Servier that if PK studies are available, it is reasonable to assume a similar relationship for the dose and efficacy of IVO compared to VEN, when co-prescribed with an azole, and if the SmPC states a dose reduction to 250mg for IVO with an azole, then that is a reasonable assumption to make. The clinical experts also explained that they would expect the proportion to be co-prescribed an azole between IVO+AZA and VEN+AZA patients to be the same as there is no reason why it should be different.

Concomitant azole use was costed in the model using the price of posaconazole 100mg gastro-resistant tablets from eMIT (£180.57 for a pack of 96 x 100 mg tablets). Based on a recommended daily dose of 300 mg per day (Dennis *et al.*, [2022]), patients co-prescribed an azole incur an additional cost of £158.00 per 28-day model cycle (36).

In the base-case analysis, it is assumed that all patients receive concomitant azole treatment in practice, for both modelled treatment arms. This is aligned with TA765 guidance, which reports that the average dose of VEN in practice is expected to be 100 mg, rather than 400 mg (34). Concomitant azole use affects the dosing of IVO and VEN, but not the AZA component of each regimen. For IVO, the recommended dose reduces from 500 mg to 250 mg if used alongside an azole. For VEN, the recommended dose reduces from 400 mg to 100 mg.

The resultant costs per treatment cycle for each regimen, including costs for concomitant azoles, are presented in Table 51.

Table 51: Regimen costs for IVO+AZA and VEN+AZA (including azoles)

Label		Dose	Units per admin	RDI (%)	Cost per cycle	
Regimen	Treatment				Treatment	Regimen
IVO+AZA	IVO	250 mg*	1.00	89.21	[redacted]	[redacted]
	AZA	75 mg/m^2	1.99	85.85	£539.26	
	Posaconazole	300 mg	1.00	100.00	£158.00	
VEN+AZA	VEN	100 mg*	1.00	89.21	£534.08	£1,231.33
	AZA	75 mg/m^2	1.99	85.85	£539.26	
	Posaconazole	300 mg	1.00	100.00	£158.00	

Key: AZA, azacitidine; IVO, ivosidenib; RDI, relative dose intensity; VEN, venetoclax.
Note: *The target doses for IVO and VEN are 500 mg and 400 mg, respectively. However, due to concomitant azole use, the average dose costed within the model for these treatments are 250 mg and 100 mg, respectively.

Administration

Both IVO and VEN are administered orally daily, and so no administration cost is assigned to these treatments specifically. However, AZA can be administered either via IV or SC. For both IVO+AZA and VEN+AZA, AZA is administered for 7 days in 28-day cycles. In the base-case analysis, it is assumed that all administrations of AZA are SC, but a cost of £381.97 was applied for the cost of both an IV and an SC administration, based on NHS National Cost Collection (2020/21) data, code SB12Z (Daycase, Deliver Simple Parenteral Chemotherapy at First Attendance).

Hospitalisation costs for first cycle

Real-world data concerning the use of VEN+AZA was published by Raush *et al.*, (2021), suggesting that patients treated with VEN+AZA spend a median of 32 days in the hospital during the first cycle of treatment (56). Therefore, the cost-effectiveness analysis includes the cost of 32 days in hospital for patients that initiate treatment with VEN+AZA during the first model cycle. For IVO+AZA, an equivalent cost is applied based on analysis of data from the AGILE study. In AGILE, hospital

days during days 1–28 averaged [redacted]% of days alive for IVO+AZA, and so the following formula was used to estimate the average length of stay in the first cycle:

[redacted]

As discussed in Section B.2.12 of this submission, another study by Othman *et al.*, (2021) also describes the average length of hospital stay for real-world AML patients treated with VEN. While this study was carried out in the UK (as opposed to the US population described by Rausch *et al.*), the population considered by Othman *et al.* were patients that were deemed eligible for intensive treatment, where VEN was offered as an alternative therapy according to COVID-19 guidelines that were in place during the pandemic. The NHS temporarily made VEN 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 COVID-19 pandemic are unlikely to reflect current practice, owing to the unprecedented demand on NHS resources during this time (and that the purpose of making VEN 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, and so the study by Rausch *et al.* is considered more suitable.

Electrocardiogram costs for IVO

Patients receiving IVO+AZA may require additional electrocardiogram (ECG) monitoring, due to risk of QTc prolongation. The unit cost of an ECG applied in the model is £162.46 (taken from NHS National Cost Collection [2020/21] - Electrocardiogram Monitoring or Stress Testing, outpatient procedures, medical oncology [EY51Z]). In practice, it is expected that an ECG would be performed once every 3 months, but at initiation of treatment the model assumes three ECGs would be carried out in the first month of treatment (in line with the SmPC for IVO, see Appendix C).

Health-state unit costs and resource use

Red blood cell and platelet transfusions

Transfusion costs were included within the model, with frequencies associated with each health state. Unit costs were sourced from the NHS Blood & Transplant: Blood

and Components Price List (2021/22), shown in Table 52. Frequencies were based on a post-hoc analysis of AGILE to estimate the monthly transfusion units by CR/CRi status, shown in Table 53. For the 'PD/RL' health state, transfusion frequencies for the 'No CR/CRi' health state were assumed to apply. For the 'LTS' health state, no transfusions were assumed to be required.

Table 52: Transfusion unit costs

Item	Cost	Source
RBC	£145.99	BC001 – Standard Red Cells. NHS Blood & Transplant: Blood and Components Price List (2021/22)
Platelet	£222.94	BC044/BC045 – Platelets, Aphresis (1 ATD) or Platelets, Pooled (1 ATD). NHS Blood & Transplant: Blood and Components Price List (2021/22)

Key: ATD, adult therapeutic dose; NHS, National Health Service; RBC, red blood cell.

Table 53: Transfusion monthly frequencies

Item	EFS – CR/CRi	EFS – No CR/CRi	PD/RL	LTS
RBC	0.89	5.89	5.89	0
Platelet	1.52	7.20	7.20	0
Source	Analysis of AGILE patient-level data		Assumption	

Key: CR/CRi, complete remission or complete remission with incomplete count recovery; EFS, event-free survival; LTS, long-term survival; PD/RL, progressed disease or relapse; RBC, red blood cell.

Adverse reaction unit costs and resource use

AE costs were sourced from the NHS National Cost Collection database (2021/21). Unless stated otherwise, costs were assumed to be non-elective, short stay (NES), and a weighted average across CC scores was estimated based on included currency codes. Currency codes are aligned with those specified in NICE TA765, unless stated otherwise (34). The included AE costs are summarised in Table 54.

Table 54: Adverse event costs

Adverse event	Cost	Source
Anaemia	£542.77	SA08G, SA08H, SA08J
Decreased appetite	£0.00	Assumed zero
Diarrhoea	£582.14	FD01A-FD01J, not same as TA765 (AE not included)
Electrocardiogram QT prolonged	£38.18	NICE TA526, uplifted via PSSRU inflation indices (assumed 2016/17 cost). Not same as TA765 (AE not included)
Febrile neutropenia	£571.91	KC05J-KC05N
Hypokalaemia	£731.49	Assume same as sepsis
Hyponatraemia	£571.91	Assume same as fatigue
Hypotension	£571.91	Assume same as fatigue
Other infections (excluding pneumonia)	£571.91	Assume same as fatigue
Leukopenia	£582.14	Assume same as diarrhoea
Neutropenia	£699.05	Assume same as thrombocytopenia
Neutrophil count decreased	£699.05	Assume same as thrombocytopenia
Platelet count decreased	£699.05	Assume same as thrombocytopenia
Pneumonia	£699.05	Assume same as thrombocytopenia

Adverse event	Cost	Source
Pulmonary embolism	£668.60	DZ11K-DZ11N, DZ11P-DZ11V. Not same as TA765 (different currency codes as previous code no longer specific to pneumonia)
Sepsis	£731.49	WJ06A-WJ06H, WJ06J. Not same as TA765 (broader range of currency codes)
Thrombocytopenia	£699.05	SA12G, SA12H, SA12J, SA12K
Differentiation syndrome	£1,355.84	NICE TA526, uplifted via PSSRU inflation indices (assumed 2016/17 cost). Not same as TA765 (AE not included)

Key: AE, adverse event; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit.

Subsequent therapies

After progression or relapse, a small proportion of patients may be eligible to receive gilteritinib, but this is contingent upon patients harbouring both an *IDH1* and *FLT-3* mutation. Patients would otherwise receive hydroxycarbamide/hydroxyurea. The derivation of these costs to inform the model is provided in Table 55.

The co-mutation rate is estimated to be approximately 15%, which is approximately half the mutation rate for an all-comers AML population (estimated to be approximately 30%). As such, the proportion of patients assumed to be eligible for gilteritinib is 50% of the value used to inform NICE TA765 of VEN+AZA in an all-comers AML population (34).

Table 55: Derivation of subsequent therapy costs

Item	Value	Source
Gilteritinib		
Cost per pack	£14,188	BNF (2023)
Dose per administration	120 mg	
Administrations per cycle	28	
Cost per cycle	£14,188	Calculation
Average duration of treatment	4.14 months	Perl *et al.*, (2019)* (80)
Total cost for course of treatment	£63,846	Calculation
Hydroxycarbamide/hydroxyurea		
Cost per pack	£10.47	BNF (2023)
Dose per administration	1,779 mg	Based on target dose of 25 mg/kg
Administrations per cycle	28	
Cost per cycle	£142.17	Calculation
Average duration of treatment	4.14 months	Assumed same as gilteritinib
Total cost for course of treatment	£640	Calculation

Key: BNF, British National Formulary.
Note: * The median duration of exposure to gilteritinib and chemotherapy was 18 weeks (interquartile range, 9 to 34) and 4 weeks (interquartile range, 4 to 4), respectively.

In NICE TA765, 5% of VEN+AZA patients were estimated to be eligible for gilteritinib upon progression or relapse (34). Therefore, for an *IDH1* population, it is estimated that 2.5% of VEN+AZA patients would be eligible for gilteritinib based on the above mentioned co-mutational rate for *FLT-3* and *IDH1*. For IVO+AZA, eligibility is assumed to be similar per VEN+AZA, and so an estimated 2.5% is also applied.

Therefore, upon progression or relapse, a cost of £2,220 is incurred for the VEN+AZA and IVO+AZA arms.

End-of-life care

For completeness, terminal care costs were also included within the cost-effectiveness analysis. A one-off cost is applied on the cycle in which patients die, reflecting the expected costs incurred at the end of life for cancer patients. No AML-specific cost was identified, and so in lieu of this a study by Round *et al.*, (2015) was used to inform the analysis (81). Round *et al.* present the mean estimated cost of death per patient for four cancer types: breast, colorectal, lung, and prostate cancer; across four categories: health care, social care, charity care, and informal care. The costs for health and social care were considered relevant to the perspective of the cost-effectiveness analysis, summing to a total of £6,083. This cost was uplifted using inflation indices reported in the Unit Costs of Health and Social Care 2022 Manual, and so a final cost of £6,774.39 is applied to all patients upon death. Since all patients incur this cost, the only difference reflected by the model across treatment arms is due to the specification of a 3.5% annual discount rate for costs.

B.3.6 Severity

This technology does not meet the criteria for a severity weight (see Table 56).

Table 56: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
7.29 (based on the QALY shortfall calculator by Schneider *et al.*, 2021; assuming 45% female aged 75 years at baseline)	VEN+AZA: 2.17 (obtained from the cost-effectiveness model base-case analysis)	Absolute: 5.12 Proportional: 70.22% QALY weight: x 1

Key: AZA, azacitidine; QALY, quality-adjusted life year; VEN, venetoclax.

B.3.7 Uncertainty

IDH1 mutations are rare, occurring in 6-10% of patients with AML (10). Therefore, with the exception of the AGILE study, there is a dearth of evidence in an *IDH1*-mutated specific population to inform the cost-effectiveness analysis developed for this submission. This is most evident when considering the indirect comparison to VEN+AZA, which relies on the full population from the VIALE-A study. The impact of *IDH1* mutation on outcomes for patients treated with VEN+AZA is not fully understood which is not possible to address with current evidence, and so this remains an uncertainty inherent within the analysis presented in this submission.

B.3.8 Summary of base-case analysis inputs and assumptions

Base-case inputs

A summary of variables applied in the economic model are presented in Table 57.

Table 57: Summary of variables applied in the economic model

Parameter	Value	Distribution	Lower bound	Upper bound
Model settings (Section B.3.2)				
Time horizon (years)	25	Not varied	-	-
Model cycle length (weeks)	4	Not varied	-	-
Annual discount rate: Costs	3.50%	Not varied	-	-
Annual discount rate: LYs	0.00%	Not varied	-	-
Annual discount rate: QALYs	3.50%	Not varied	-	-
Age (mean, years)	74.84	Normal	73.73	75.94
Proportion female (%)	45.21%	Beta	37.23%	53.30%
Weight (mean, kg)	71.17	Normal	68.83	73.51
BSA (mean, m²)	1.78	Normal	1.75	1.82
Treatment costs (Section B.3.5)				
Drug cost: Ivosidenib (250 mg)	£12,500.00	Not varied	-	-
Drug cost: Azacitidine (100 mg)	£45.16	Normal	£44.90	£45.42
Drug cost: Venetoclax (100 mg)	£299.34	Not varied	-	-
Drug cost: Posaconazole (96 x 1mg)	£180.57	Normal	£176.55	£184.58
Administration costs (Section B.3.5)				
Administration cost: IV	£207.59	Normal	£166.90	£248.28
Administration cost: SC	£207.59	Normal	£166.90	£248.28
Healthcare resource use costs (Section B.3.5)				
HCRU cost: Haematologist visits	£200.81	Normal	£161.45	£240.17
HCRU cost: Nurse visits	£26.00	Normal	£20.90	£31.10
HCRU cost: General practitioner visits	£42.00	Normal	£33.77	£50.23
HCRU cost: ED visits	£278.10	Normal	£223.59	£332.61
HCRU cost: Hospitalisation days	£796.69	Normal	£640.54	£952.84
HCRU cost: Imaging procedures	£117.51	Normal	£94.48	£140.54
HCRU cost: Bone marrow biopsy	£752.46	Normal	£604.98	£899.94
HCRU cost: Lumbar puncture	£752.46	Normal	£604.98	£899.94
HCRU cost: ICU stay	£2,137.87	Normal	£1,718.85	£2,556.88
HCRU frequency (EF, CR/CRi): Haematologist visits	1.00	Normal	0.80	1.20
HCRU frequency (EF, CR/CRi): Nurse visits	0.00	Normal	0.00	0.00
HCRU frequency (EF, CR/CRi): General practitioner visits	0.00	Normal	0.00	0.00
HCRU frequency (EF, CR/CRi): ED visits	0.00	Normal	0.00	0.00
HCRU frequency (EF, CR/CRi): Hospitalisation days	0.00	Normal	0.00	0.00
HCRU frequency (EF, CR/CRi): Imaging procedures	0.00	Normal	0.00	0.00

HCRU frequency (EF, CR/CRi): Bone marrow biopsy	0.00	Normal	0.00	0.00
HCRU frequency (EF, CR/CRi): Lumbar puncture	0.00	Normal	0.00	0.00
HCRU frequency (EF, CR/CRi): ICU stay	0.00	Normal	0.00	0.00
HCRU frequency (EF, No CR/CRi): Haematologist visits	2.63	Normal	2.11	3.15
HCRU frequency (EF, No CR/CRi): Nurse visits	2.77	Normal	2.23	3.31
HCRU frequency (EF, No CR/CRi): General practitioner visits	1.67	Normal	1.34	2.00
HCRU frequency (EF, No CR/CRi): ED visits	0.27	Normal	0.22	0.32
HCRU frequency (EF, No CR/CRi): Hospitalisation days	1.03	Normal	0.83	1.23
HCRU frequency (EF, No CR/CRi): Imaging procedures	0.00	Normal	0.00	0.00
HCRU frequency (EF, No CR/CRi): Bone marrow biopsy	0.71	Normal	0.57	0.85
HCRU frequency (EF, No CR/CRi): Lumbar puncture	1.07	Normal	0.86	1.28
HCRU frequency (EF, No CR/CRi): ICU stay	0.18	Normal	0.14	0.22
HCRU frequency (PD/RL): Haematologist visits	2.79	Normal	2.24	3.34
HCRU frequency (PD/RL): Nurse visits	3.05	Normal	2.45	3.65
HCRU frequency (PD/RL): General practitioner visits	1.67	Normal	1.34	2.00
HCRU frequency (PD/RL): ED visits	0.58	Normal	0.47	0.69
HCRU frequency (PD/RL): Hospitalisation days	2.13	Normal	1.71	2.55
HCRU frequency (PD/RL): Imaging procedures	0.57	Normal	0.46	0.68
HCRU frequency (PD/RL): Bone marrow biopsy	0.32	Normal	0.26	0.38
HCRU frequency (PD/RL): Lumbar puncture	0.16	Normal	0.13	0.19
HCRU frequency (PD/RL): ICU stay	0.22	Normal	0.18	0.26
ECG cost (IVO + AZA)	£162.46	Normal	£130.62	£194.30
ECG initiation (IVO + AZA)	3.00	Normal	2.41	3.59
ECG ongoing (IVO + AZA)	0.25	Normal	0.20	0.30
Bed days - initiation (IVO + AZA)	[redacted]	Normal	[redacted]	[redacted]
Bed days - initiation (VEN + AZA)	[redacted]	Normal	[redacted]	[redacted]
Adverse event frequency (Section B.3.3)				
AE frequency (IVO + AZA): Anaemia	25.40%	Beta	20.59%	30.53%
AE frequency (IVO + AZA): Decreased appetite	0.00%	Beta	0.00%	0.00%
AE frequency (IVO + AZA): Diarrhoea	0.00%	Beta	0.00%	0.00%
AE frequency (IVO + AZA): Electrocardiogram QT prolonged	0.00%	Beta	0.00%	0.00%
AE frequency (IVO + AZA): Fatigue	0.00%	Beta	0.00%	0.00%
AE frequency (IVO + AZA): Febrile neutropenia	28.20%	Beta	22.84%	33.88%
AE frequency (IVO + AZA): Hypokalaemia	2.80%	Beta	2.28%	3.37%
AE frequency (IVO + AZA): Hyponatraemia	0.00%	Beta	0.00%	0.00%
AE frequency (IVO + AZA): Hypotension	0.00%	Beta	0.00%	0.00%
AE frequency (IVO + AZA): Other infections (excl. pneumonia)	16.90%	Beta	13.72%	20.34%

AE frequency (IVO + AZA): Leukopenia	7.00%	Beta	5.69%	8.43%
AE frequency (IVO + AZA): Neutropenia	26.80%	Beta	21.71%	32.21%
AE frequency (IVO + AZA): Neutrophil count decreased	0.00%	Beta	0.00%	0.00%
AE frequency (IVO + AZA): Platelet count decreased	0.00%	Beta	0.00%	0.00%
AE frequency (IVO + AZA): Pneumonia	25.40%	Beta	20.59%	30.53%
AE frequency (IVO + AZA): Sepsis	0.00%	Beta	0.00%	0.00%
AE frequency (IVO + AZA): Thrombocytopenia	23.90%	Beta	19.38%	28.73%
AE frequency (IVO + AZA): Differentiation syndrome	0.00%	Beta	0.00%	0.00%
AE frequency (VEN + AZA): Anaemia	26.10%	Beta	21.15%	31.37%
AE frequency (VEN + AZA): Decreased appetite	0.00%	Beta	0.00%	0.00%
AE frequency (VEN + AZA): Diarrhoea	0.00%	Beta	0.00%	0.00%
AE frequency (VEN + AZA): Electrocardiogram QT prolonged	0.00%	Beta	0.00%	0.00%
AE frequency (VEN + AZA): Fatigue	0.00%	Beta	0.00%	0.00%
AE frequency (VEN + AZA): Febrile neutropenia	41.70%	Beta	33.65%	49.97%
AE frequency (VEN + AZA): Hypokalaemia	10.60%	Beta	8.61%	12.76%
AE frequency (VEN + AZA): Hyponatraemia	0.00%	Beta	0.00%	0.00%
AE frequency (VEN + AZA): Hypotension	0.00%	Beta	0.00%	0.00%
AE frequency (VEN + AZA): Other infections (excl. pneumonia)	43.80%	Beta	35.32%	52.46%
AE frequency (VEN + AZA): Leukopenia	20.50%	Beta	16.63%	24.66%
AE frequency (VEN + AZA): Neutropenia	42.00%	Beta	33.89%	50.33%
AE frequency (VEN + AZA): Neutrophil count decreased	0.00%	Beta	0.00%	0.00%
AE frequency (VEN + AZA): Platelet count decreased	0.00%	Beta	0.00%	0.00%
AE frequency (VEN + AZA): Pneumonia	19.80%	Beta	16.06%	23.82%
AE frequency (VEN + AZA): Sepsis	0.00%	Beta	0.00%	0.00%
AE frequency (VEN + AZA): Thrombocytopenia	44.50%	Beta	35.88%	53.29%
AE frequency (VEN + AZA): Differentiation syndrome	0.00%	Beta	0.00%	0.00%
Adverse event costs (Section B.3.5)				
AE cost: Anaemia	£542.77	Normal	£436.39	£649.16
AE cost: Decreased appetite	£0.00	Normal	£0.00	£0.00
AE cost: Diarrhoea	£582.14	Normal	£468.04	£696.24
AE cost: Electrocardiogram QT prolonged	£38.18	Normal	£30.70	£45.66
AE cost: Fatigue	£571.91	Normal	£459.82	£684.00
AE cost: Febrile neutropenia	£731.49	Normal	£588.12	£874.86
AE cost: Hypokalaemia	£571.91	Normal	£459.82	£684.00
AE cost: Hyponatraemia	£571.91	Normal	£459.82	£684.00
AE cost: Hypotension	£571.91	Normal	£459.82	£684.00
AE cost: Other infections (excl. pneumonia)	£582.14	Normal	£468.04	£696.24

AE cost: Leukopenia	£699.05	Normal	£562.04	£836.06
AE cost: Neutropenia	£699.05	Normal	£562.04	£836.06
AE cost: Neutrophil count decreased	£699.05	Normal	£562.04	£836.06
AE cost: Platelet count decreased	£699.05	Normal	£562.04	£836.06
AE cost: Pneumonia	£668.60	Normal	£537.55	£799.64
AE cost: Sepsis	£731.49	Normal	£588.12	£874.86
AE cost: Thrombocytopenia	£699.05	Normal	£562.04	£836.06
AE cost: Differentiation syndrome	£1,355.84	Normal	£1,090.10	£1,621.58
End-of-life costs (Section B.3.5)				
EOL cost: Round et al. (2015) - health	£4,254.00	Normal	£3,420.23	£5,087.77
EOL cost: Round et al. (2015) - social	£1,829.00	Normal	£1,470.52	£2,187.48
Health state utility values (Section B.3.4)				
HSUV regression: Intercept	0.769	Multivariate normal	0.711	0.827
HSUV regression: EFS status	-0.035	Multivariate normal	-0.082	0.012
HSUV regression: Best response	-0.140	Multivariate normal	-0.214	-0.065
HSUV regression: Treatment status	-0.073	Multivariate normal	-0.131	-0.015
HSUV: EFS, CR/CRi	0.000	Beta	0.000	0.000
HSUV: EFS, no CR/CRi	0.000	Beta	0.000	0.000
HSUV: PD/RL	0.000	Beta	0.000	0.000
Adverse event utility decrements (Section B.3.4)				
AE disutility: Anaemia	0.090	Beta	0.034	0.169
AE disutility: Decreased appetite	0.000	Beta	0.000	0.000
AE disutility: Diarrhoea	0.176	Beta	0.113	0.250
AE disutility: Electrocardiogram QT prolonged	0.000	Beta	0.000	0.000
AE disutility: Fatigue	0.000	Beta	0.000	0.000
AE disutility: Febrile neutropenia	0.090	Beta	0.073	0.108
AE disutility: Hypokalaemia	0.000	Beta	0.000	0.000
AE disutility: Hyponatraemia	0.000	Beta	0.000	0.000
AE disutility: Hypotension	0.020	Beta	0.000	0.104
AE disutility: Other infections (excl. pneumonia)	0.218	Beta	0.164	0.277
AE disutility: Leukopenia	0.090	Beta	0.073	0.108
AE disutility: Neutropenia	0.090	Beta	0.073	0.108
AE disutility: Neutrophil count decreased	0.090	Beta	0.073	0.108
AE disutility: Platelet count decreased	0.090	Beta	0.073	0.108
AE disutility: Pneumonia	0.218	Beta	0.164	0.277
AE disutility: Sepsis	0.218	Beta	0.164	0.277
AE disutility: Thrombocytopenia	0.090	Beta	0.042	0.154

AE disutility: Differentiation syndrome	0.218	Beta	0.177	0.262
AE duration: Anaemia	28	Normal	23	33
AE duration: Decreased appetite	28	Normal	23	33
AE duration: Diarrhoea	28	Normal	23	33
AE duration: Electrocardiogram QT prolonged	28	Normal	23	33
AE duration: Fatigue	28	Normal	23	33
AE duration: Febrile neutropenia	28	Normal	23	33
AE duration: Hypokalaemia	28	Normal	23	33
AE duration: Hyponatraemia	28	Normal	23	33
AE duration: Hypotension	28	Normal	23	33
AE duration: Other infections (excl. pneumonia)	28	Normal	23	33
AE duration: Leukopenia	28	Normal	23	33
AE duration: Neutropenia	28	Normal	23	33
AE duration: Neutrophil count decreased	28	Normal	23	33
AE duration: Platelet count decreased	28	Normal	23	33
AE duration: Pneumonia	28	Normal	23	33
AE duration: Sepsis	28	Normal	23	33
AE duration: Thrombocytopenia	28	Normal	23	33
AE duration: Differentiation syndrome	28	Normal	23	33
General population utility - coefficients (Section B.3.4)				
Male	0.02121	Not varied	-	-
Age	-0.00026	Not varied	-	-
Age²	-0.00003	Not varied	-	-
Constant	0.95086	Not varied	-	-
Indirect treatment comparison (Section B.3.3)				
OS HR: IVO + AZA versus VEN + AZA	[redacted]	Drawn from posterior	[redacted]	[redacted]
EFS HR: IVO + AZA versus VEN + AZA	[redacted]	Drawn from posterior	[redacted]	[redacted]
ToT: VEN + AZA, median duration (weeks)	29.83	Normal	23.99	35.68

Key: AE, adverse event; AZA, azacitidine; BSA, body surface area; CR/CRi, complete remission or complete remission with incomplete count recovery; ECG, electrocardiogram; ED, emergency department; EFS, event-free survival; EOL, end of life; HCRU, healthcare resource use; HR, hazard ratio; ICU, intensive care unit; IV, intravenous; IVO, ivosidenib; LY, life-year; PD/RL, progressed disease or relapse; SC, subcutaneous; ToT, time on treatment; QALY, quality-adjusted life year; VEN, venetoclax.

Base-case assumptions

Table 58 presents a summary of key modelling assumptions.

Table 58: Summary of key modelling assumptions

Assumption	Description	Justification
Economic analysis (Section B.3.2)		
Time horizon	25 years constitutes a lifetime horizon.	Approximately 99% of the modelled cohort have entered the 'Dead' state by 25 years, across both treatment arms.
Cycle length	A 28-day cycle length with half-cycle correction.	Aligned with treatment cycle length.
Long-term survivors	No risk of progression or relapse after 3 years in EFS for either treatment arm.	Aligned with clinical opinion regardless long-term outcomes for patients that remain event-free for 3 years and aligned with accepted approach in NICE TA765.
Clinical parameters and variables (Section B.3.3)		
OS, EFS, and ToT for IVO+AZA	Log-normal curves selected for OS and EFS, Weibull selected for ToT. Alternative parametric models tested in scenario analysis.	Based on a combination of clinical plausibility of extrapolations, statistical goodness-of-it and visual fit. Model for ToT (Weibull) is similar to the model required for VEN+AZA (exponential) due to limited reporting.
ITC generalisability	Indirect comparison of IVO+AZA to VEN+AZA assumed to be generalisable to an *IDH1* population.	There is no reliable evidence for an *IDH1* population treated with VEN+AZA that could be used to inform the model. Therefore, the relative effects from the full population in VIALE-A were assumed to be generalisable.
Duration of treatment with VEN+AZA	Average number of treatment cycles from VIALE-A used to inform an exponential model for ToT.	This approach was deemed preferable over assuming all EF patients were on treatment, which would likely over-estimate drug costs for VEN+AZA.
Measurement and valuation of health effects (Section B.3.4)		
Utility for LTS	The utility for patients in LTS was assumed to be the same as the utility for EFS – CR/CRi.	It is expected that utility for LTS patients would be similar to, or possibly slightly greater than, utility for patients in EFS with CR/CRi.
Utility for PD/RL	PD/RL patients assumed to have CR/CRi as best response for estimating utility value.	Some patients that move to PD/RL may have temporarily achieved a CR/CRi, though this is not expected to materially influence their utility after progression or relapse.
Missing response data	Missing response was assumed to not achieve CR/CRi.	It was considered more likely that a missing response measure would be associated with non-response, versus response.
Duration of AEs	All AE disutilities were assumed to last for 28 days.	Aligned with TA765, as a pragmatic assumption given limited data. Different durations would likely have a small impact on results.
AE disutilities	Some AE disutilities assumed to be same as 'similar' events.	Approach broadly aligned with TA765, but with some pragmatic assumptions made on the basis of plausibility and to align with other sources where reported.
Cost and healthcare resource use identification, measurement, and valuation (B.3.5)		
RDI	RDI for components of VEN+AZA assumed to be the same as IVO+AZA.	RDI data for VEN+AZA are not reported, and so it was considered reasonable that these estimates would be similar to IVO+AZA.
Azole-related dosing	Dosing for IVO and VEN to reflect concomitant azole use	Dosing for IVO and VEN is expected to be impacted by concomitant use of azoles, per the SmPC for each product. The model

Assumption	Description	Justification
		therefore accounts for these adjustments, based on consensus reached in TA765.
AZA administration	All AZA administrations assumed to be SC	The same cost is applied in the model for SC or IV administration, but clinical opinion suggests SC is generally preferred in practice.
ECG frequency for IVO	Three ECGs in the first month of treatment, with an ECG expected to be performed every 3 months.	Three ECGs in first month is aligned with the SmPC. Regular ECGs is aligned with clinical opinion.
Transfusion frequencies	Transfusion frequency for PD/RL was assumed to be the same as EFS – No CR/CRi. For LTS, no transfusions were assumed.	No data for PD/RL or LTS states, so aligned with expectation. PD/RL expected to have transfusion frequency in excess of the EFS No CR/CRi group, but assuming same is likely conservative. By definition, LTS patients are not expected to require any further transfusions.
AE costs	Some AE costs assumed to be same as 'similar' events	Pragmatic assumption given limited data and a relatively small impact on results.
Subsequent therapies	2.5% of patients on either arm assumed to be eligible for gilteritinib upon progression.	Co-mutation rate (*FLT3* and IDH1) is estimated to be approximately half of the mutation rate for an all-comers population. Therefore, the estimated proportion of patients eligible for gilteritinib in TA765 (5%) was halved for an *IDH1* mutation population.

Key: AE, adverse event; AZA, azacitidine; EFS, event-free survival; *FLT3*, fms-like tyrosine kinase 3; *IDH1*, Isocitrate dehydrogenase 1; ITC, indirect treatment comparison; IVO, ivosidenib; LTS, long-term survivors; OS, overall survival; PD/RL, progressed disease or relapse; RDI, relative dose intensity; SmPC, summary of product characteristics; TA, technology appraisal; ToT, time on treatment; VEN, venetoclax.

B.3.9 Base-case results

Base case deterministic results are presented in Table 59, with net-health benefit (NHB) results provided in Table 60 (at willingness-to-pay [WTP] thresholds of £20,000 and £30,000 per QALY gained). These results demonstrate that IVO+AZA provides more QALYs (+[redacted]) with an incremental cost of -£[redacted], giving a dominant result (i.e., more QALYs at a reduced cost).

Table 59: Base-case results (deterministic)

Technologies	Total			Incremental			
	Costs	LYG	QALYs	Costs	LYG	QALYs	ICER
VEN + AZA	£190,639	4.26	2.17				
IVO + AZA	[redacted]	5.97	[redacted]		1.71	[redacted]	Dominant

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 60: Net health benefit (deterministic)

Technologies	Total		Incremental			
	Costs	QALYs	Costs	QALYs	NHB at £20,000	NHB at £30,000
VEN + AZA	£190,639	2.17				
IVO + AZA	[redacted]					

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

The corresponding probabilistic results are presented in Table 61 (base-case) and Table 62 (NHB), respectively. These results are broadly aligned with the deterministic results. Further details about the probabilistic analysis are provided in Section B.3.11).

Table 61: Base-case results (probabilistic)

Technologies	Total			Incremental			
	Costs	LYG	QALYs	Costs	LYG	QALYs	ICER
VEN + AZA	£193,209	4.31	2.18				
IVO + AZA	[redacted]	5.94	[redacted]		1.62	[redacted]	Dominant

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 62: Net health benefit (probabilistic)

Technologies	Total		Incremental			
	Costs	QALYs	Costs	QALYs	NHB at £20,000	NHB at £30,000
VEN + AZA	£193,209	2.18				
IVO + AZA	[redacted]					

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Please refer to Appendix J for a summary of the clinical outcomes from the model, as well as disaggregated results of the base-case incremental cost-effectiveness analysis.

B.3.10 Exploring uncertainty

Sensitivity analysis approach

A range of sensitivity analyses were undertaken to assess the structural and parameter uncertainty inherent within the cost-effectiveness model. These comprised of three forms of sensitivity analysis:

- A deterministic, one-way sensitivity analysis (OWSA), which involves individually varying each parameter at its lower and upper bounds and recording the impact on the model results.
- A series of deterministic scenario analyses (ScA), which encompass a range of alternative model settings and assumptions (e.g., alternative choices of survival model for a given outcome).
- A probabilistic sensitivity analysis (PSA), which involves simultaneously varying all parameters associated with parameter uncertainty over a sufficiently large number of iterations and recording the impact on results.

A summary of the model inputs, the corresponding choices of distribution, and quantified uncertainty are provided in Table 57. The inclusion/exclusion of parameters within the sensitivity analyses, and the choice of distribution for specific parameters were selected based on the following convention:

- Fixed parameters are not varied within the OWSA or PSA (e.g., a list price for a branded medicine).
- Where uncertainty measures were available (e.g., standard deviations and standard errors), these were used to populate the model. Given the model adopts a cohort-level structure, standard errors were used to reflect the uncertainty for the cohort.
- Wherever uncertainty information was unavailable, parameters were varied based on an assumed (and arbitrary) standard error equivalent to 10% of the mean input value.
- Proportions and health state utility values were varied according to a Beta distribution, to ensure sampled values fall within the bounds of 0 and 1. Disutilities were varied via a Beta distribution on the absolute scale, and then converted back to a disutility, to ensure values are strictly negative. Coefficients from the utility regression analysis are varied according to a multivariate Normal distribution.
- HRs outputted by the NMA were sampled according to draws from the posterior distribution, given that a Bayesian NMA was used to inform the cost-effectiveness model. Any assumed HRs not obtained from the NMA were varied according to a lognormal distribution.
- All other parameters, including costs, were sampled according to a Normal distribution, based on the role of the Central Limit Theorem. Costs were not varied using a Gamma distribution since the submitted model reflects the average costs incurred by the cohort, not the individual. Misspecification of a Gamma distribution for costs would erroneously reflect a skew in the distribution for the average cost incurred by the cohort.

Probabilistic sensitivity analysis

The PSA was run for 5,000 iterations, after which relatively small fluctuations in the mean incremental net monetary benefit (INMB) were noted, as shown in Figure 39 (please note PSA iterations are presented on a log scale).

Figure 39: PSA convergence

Key: INMB, incremental net monetary benefit; PSA, probabilistic sensitivity analysis.

The mean results of the PSA are presented earlier in Table 61, showing similar results to the deterministic base-case analysis (presented in Table 59). The corresponding PSA scatterplot is presented in Figure 40, and a cost-effectiveness acceptability curve (CEAC) presented in Figure 41. At a WTP threshold of £30,000 per QALY gained, there is a(n) [redacted]% probability that IVO+AZA may be considered a cost-effective treatment option, compared to VEN+AZA.

Figure 40: PSA scatterplot

Key: k, thousand(s); PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Figure 41: Cost-effectiveness acceptability curve

Key: AZA, azacitidine; IVO, ivosidenib; k, thousand(s); VEN, venetoclax; WTP, willingness-to-pay.

Deterministic sensitivity analyses

One-way sensitivity analysis

The results of the OWSA are presented as a tornado diagram in Figure 42. The results of this analysis are presented with the outcome of INMB, at a WTP threshold of £30,000 per QALY gained.

Figure 42: Tornado diagram

Key: AZA, azacitidine; CR/CRi, complete remission or complete remission with incomplete count recovery; EF, event free; EFS, event-free survival; HR, hazard ratio; HCRU, healthcare resource use; INMB, incremental net monetary benefit; IV, intravenous; IVO, ivosidenib; k, thousand(s); LB, lower bound; PD/RL, progressed disease or relapse; UB, upper bound; VEN, venetoclax.

The results of the OWSA suggest that the most influential parameters were those related to the ITC between IVO+AZA and VEN+AZA, as well as the estimated duration of treatment for VEN+AZA. The 95% CrI for the OS and EFS HRs both include 1 (95% CrI for EFS: [0.36-1.07]; OS: [0.46-1.18]), which is to be expected with the uncertainty inherent within the ITC (due to relatively small sample sizes in each study). For the OS HR, the lower bound (i.e., using an HR of 0.46) yields a lower INMB. This is because OS and EFS are varied independently within the OWSA, and the inverse of the HR is applied to generate an OS curve for the VEN+AZA arm. As such, the lower bound of the HR yields a lower OS curve for VEN+AZA (i.e., fewer LYs and fewer QALYs) but leaves EFS for VEN+AZA unchanged. The impact on cost-effectiveness results is therefore explained by the high medical resource use costs associated with the ‘PD/RL’ health state.

It should be noted that the OWSA only considers parameter uncertainty for model inputs that can be varied in isolation of all other model inputs (even with caveats, such as varying OS independently of EFS, and vice versa). Therefore, the results of the OWSA should be interpreted with caution, and the series of deterministic

scenario analyses may better represent the uncertainty in the base-case model results (which are described in the sub-section that follows).

Scenario analysis

The results of the scenario analyses are provided in Table 63.

Table 63: Scenario analysis results

#	Label	ICER
-	*Base-case analysis*	Dominant
1	Time horizon, 15 years	[redacted]
2	Time horizon, 20 years	
3	Discount rates, 1.50%	
4	Discount rates, 6.00%	
5	Curve fit: IVO + AZA OS, Generalised gamma	
6	Curve fit: IVO + AZA OS, Log-logistic	
7	Curve fit: IVO + AZA OS, Weibull	
8	Curve fit: IVO + AZA EFS, Generalised gamma	
9	Curve fit: IVO + AZA EFS, Log-logistic	
10	Curve fit: IVO + AZA EFS, Weibull	
11	Curve fit: IVO + AZA ToT, Exponential	
12	Curve fit: IVO + AZA ToT, Log-logistic	
13	Curve fit: IVO + AZA ToT, Log-normal	
14	Long-term survival timepoint: 2 year(s)	
15	Long-term survival timepoint: 4 year(s)	
16	Long-term survival %: 80%	
17	Long-term survival %: 90%	
18	Long-term survival SMR: 1.1	
19	Long-term survival SMR: 1.2	
20	Long-term survival SMR: 2	
21	Non-LTS SMR: 1.1	
22	Non-LTS SMR: 1.2	
23	Apply LTS state for costs and utilities only	
24	Use HR against EFS for VEN+AZA ToT: 1.1	
25	Use HR against EFS for VEN+AZA ToT: 1.2	
26	Remove concomitant azole costs and dosing adjustments	
27	Remove subsequent treatment costs	
28	Utility source: Coyle (2020)	
29	Utility source: Pratz (2022)	
30	AE inclusion criteria: 5% cut off and consider DS	
31	VEN dosing every 28 days for all cycles	

Key: AZA, azacitidine; DS, differentiation syndrome; EFS, event-free survival; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IVO, ivosidenib; SMR, standardised mortality ratio; OS, overall survival; ToT, time on treatment; VEN, venetoclax.

The scenarios which had the greatest impact on results were the scenarios involving changing OS or EFS, and removing the concomitant azoles from the model. Changing the EFS curve to Weibull (Scenario #10) has a notable impact on the results of the model, since this also impacts the proportion of patients that enter the LTS state (and so in turn also impacts OS). Removing the azole costs and dosing adjustments (which is unlikely to reflect real-world practice, Scenario #26) results in the increased costs for both IVO and AZA, which due to the differential modelled ToT between arms also has a marked impact on results. However, across the majority of

scenarios, IVO+AZA remains dominant compared to VEN+AZA, and across all scenarios the ICER does not exceed £30,000.

B.3.11 Subgroup analysis

There are no subgroup analyses considered within the cost-effectiveness analysis.

B.3.12 Benefits not captured in the QALY calculation

While the QALY calculation captures the majority of direct health effects on patients, the model developed to inform this submission does not fully reflect all expected benefits of IVO+AZA. For example, the model does not capture any benefits to caregivers through improved health-related quality of life of patients, or through reduced time spent attending hospital appointments for blood transfusions. Less time in hospital is expected to reduce the anxiety, time and cost pressures associated with visiting hospitals. For carers, this may also mean taking less time away from work and other usual activities.

B.3.13 Validation

Internal validation of the cost-effectiveness analysis demonstrated that modelled median OS and EFS estimates closely reflected outcomes from AGILE, with expected differences compared to the VIALE-A study for VEN+AZA given differences in the AZA arm versus the AGILE study (see Appendix J).

Prior to submission, the cost-effectiveness model was quality assured as part of the internal processes of the external analysts who built the model. As part of this quality-control process, the model was reviewed for potential coding errors, inconsistencies, and the plausibility of inputs by an economist who was not involved in the model development process. The review comprised of a sheet-by-sheet check and a checklist (based on publicly available and peer review checklists). Examples of the basic validity checks followed included:

- Extreme value testing (e.g., how do results change if the time horizon is set to be as short or as long as possible?)
- Logical relationship testing (e.g., if intervention drug costs are increased, do total costs in the intervention arm increase, and is the impact on the ICER in line with expectations?)
- Consistency checks (e.g., is an input parameter value in one cell reflected elsewhere/used consistently throughout the model?)

Key model assumptions were also validated by UK clinical experts (35) including:

- Determination of the most relevant comparator in UK practice (i.e., VEN+AZA)
- Dosing for IVO and AZA based on the use of concomitant azoles

- The plausibility of parametric survival models, including long-term survivor assumptions
- Health care resource use estimates

B.3.14 Interpretation and conclusions of economic evidence

To determine the cost-effectiveness of IVO+AZA versus VEN+AZA, a de novo cost-effectiveness analysis was undertaken, from the perspective of the NHS and PSS. The cost-effectiveness analysis was informed primarily by data collected in the AGILE study of patients newly diagnosed *IDH1*-mutated AML who were ineligible for intensive induction chemotherapy. The AGILE study was a Phase III, international, randomised controlled trial, enrolling patients across 155 active sites in 20 countries. While there are some differences between the trial and real-world populations, the patient group enrolled within the AGILE study is expected to be representative of the patient population for whom treatment would be indicated for in NHS practice.

The model used to inform the cost-effectiveness analysis adopts a flexible structure such that alternative parametric models, settings, and assumptions can be explored in order to understand parameters of greatest importance, and to address uncertainty in results. Aligned with the previous NICE submission of VEN+AZA in AML (TA765), the model includes the expectation that patients that are 'event-free' by a given landmark (base-case: 3 years) are unlikely to experience disease progression or relapse. The model includes a range of sensitivity analyses to assess the impact of key features, including the choice of utility values and survival extrapolations.

As with any cost-effectiveness analysis, the model is not without limitations. A key limitation of the cost-effectiveness analysis is the need to rely on an ITC of IVO+AZA against VEN+AZA. Data concerning the efficacy of VEN+AZA are available via the VIALE-A study, though this was not conducted in a specific *IDH1*-mutated population. As such, the 'true' impact of *IDH1* mutation status on outcomes for patients treated with VEN+AZA remains unknown. Despite this, the extensive sensitivity analyses carried out demonstrate the robustness of the base-case results, indicating that IVO+AZA is associated with relatively low incremental costs, with a highly clinically meaningful life-year and QALY gain.

In conclusion, the cost-effectiveness analysis demonstrates that IVO+AZA provides both a clinically- and cost-effective treatment option for untreated *IDH1* mutated AML patients who are ineligible to receive intensive chemotherapy. IVO represents the first *IDH1* inhibitor recommended for approval in Europe for this patient population. It is estimated that less than 10% of AML patients have an *IDH1* mutation, and so IVO represents a valuable, targeted treatment option for this small patient population, through extending survival and improving health-related quality of life. Furthermore,

by reducing hospital stays and the need for red blood cell and plasma transfusions, IVO is also expected to reduce burden on hospital capacity.

B.5 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Summary of Information for Patients (SIP)

Sept, 2023

File name	Version	Contains confidential information	Date
ID6198_Ivosidenib_AML_SIP	1.0	No	04/09/2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Ivosidenib (Tibsovo®).

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Ivosidenib, used in combination with azacitidine (a type of chemotherapy drug) is indicated for the treatment of adults with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation (i.e., a specific type of genetic mutation) who are not eligible to receive standard induction chemotherapy. This submission covers the full licensed population.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The marketing authorisation for ivosidenib was approved on 5th July 2023.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

None.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
AML is an aggressive form of blood and bone marrow cancer, resulting in rapid disease progression. It is the most common form of leukaemia and accounts for approximately 80% of leukaemia cases diagnosed in adults. Although the cause of AML is not known, several factors are associated with an increased risk of the disease. Risk factors associated with AML include increasing age, male gender, genetic factors, environmental factors and lifestyle, drugs, chemical exposure, and pre-existing blood disorders. There are an estimated 2555 new cases of AML each year in England, on average. IDH1 mutations are a specific mutation detected in around 8% of AML cases. Also, around 55% of people are deemed to be ineligible for intensive chemotherapy. As ivosidenib is to be used in only patients with an IDH1 mutation and when they are ineligible to receive intensive chemotherapy, there are an estimated 112 people who could be treated with ivosidenib each year (2555 x 8% x 55%). The burden of AML is high, primarily due to the amount of time people spend in hospital and high rates of infectious complications. Hospital stays can have a substantial detrimental impact on the wellbeing of patients. Treating AML is also associated with a considerable clinical burden, with people requiring extensive use of healthcare and hospital resources (such as needing blood transfusions).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
People are diagnosed with AML based on the following: • Consideration of medical history • Physical examination • Blood tests • Biopsy (i.e., extraction of tissue for further investigation) Some people also undergo other procedures, such as immunophenotyping (to measure specific proteins that are expressed by cancer cells), cytogenetic testing (examination of chromosomes to determine abnormalities), and molecular testing (further laboratory testing to check for certain genes, proteins, or other molecules that might influence diagnosis and treatment decisions). To be treated with ivosidenib, patients must have an IDH1 mutation. In the UK, establishing whether a patient has an IDH1 mutation is an established part of routine diagnostic practice.

2c) Current treatment options:

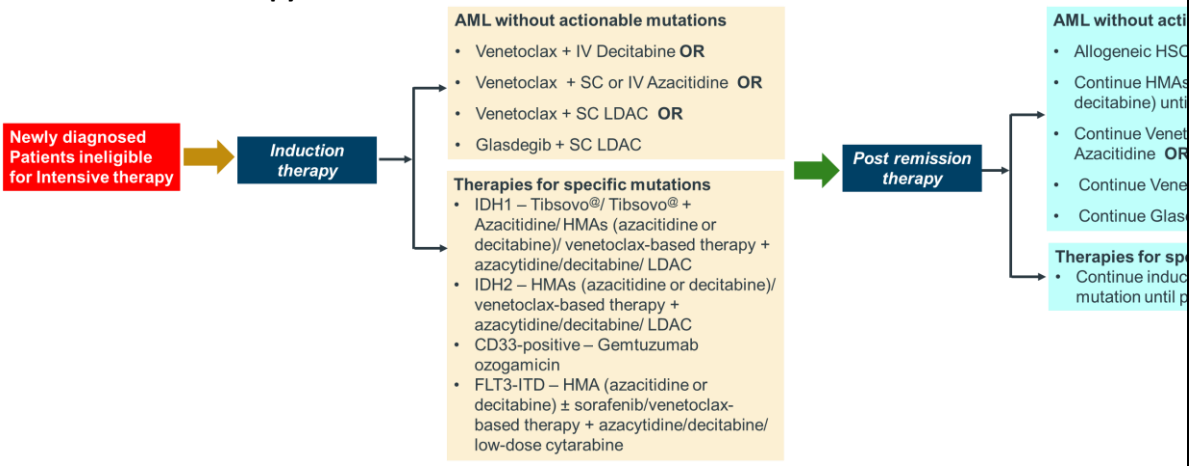
The purpose of this section is to set the scene on how the condition is currently managed: • What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Treatment for patients with newly diagnosed AML who are eligible for standard intensive chemotherapy consists of three phases induction, post-remission, and consolidation. The aim of the induction phase is to induce remission by eradicating as many cancer cells as possible. In newly diagnosed AML, the preferred primary induction treatment is intensive chemotherapy. However, intensive induction chemotherapy may not be suitable due to factors such as advanced age and pre-existing comorbidities.

Patients that are not eligible to receive intensive chemotherapy are typically treated with low intensity therapies or are enrolled in clinical trials. Current treatment options for AML patients with an IDH1 mutation who are not considered suitable for intensive induction chemotherapy in England is venetoclax in combination with azacitidine.

NCCN recommendations for the treatment of AML patients ineligible for standard intensive induction chemotherapy



Abbreviations: AML; acute myeloid leukemia; FLT3-ITD, FLT3 internal tandem duplication; G-CSF, granulocyte colony stimulating factor; HMAs, hypomethylating agents; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; IV, intravenous; LDAC, low-dose cytarabine; HSCT, hematopoietic stem cell transplantation; NCCN, national comprehensive cancer network; SC, subcutaneous

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

In general, elderly AML patients (≥60 years) require more inpatient care and a longer length of hospital stay, and this incurs greater outpatient resource utilization than younger patients. (<60 years)(1, 2)

An online survey-based study suggested that, for patients, a decrease in duration of hospitalization was the attribute they valued most highly, followed by average QoL (increase from 50 to 85 on a 100-point QoL scale) and chance of 2-year OS. Based on these findings, the author's estimated that patients were willing to accept a decrease in 2-year OS, or an increase in risk of serious infections, to decrease time spent hospitalized (from 6 weeks to 2 weeks)(3)

An advisory board was carried out in March 2022 between Servier and the Acute Leukaemia Association Network (ALAN), with 6 patients/carer representatives, including 3 from the UK. Symptoms that matter most can differ greatly between individuals and cycles of treatment. Fatigue/exhaustion was highlighted as a major symptom that interferes with everyday activities and tasks. Loss of mobility was reported as being the main burdensome physical symptom at a later age. Physical symptoms can impact people emotionally (mental health), and emotional symptoms can impact people physically

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6898885/?report=printable

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Ivosidenib is an oral medicine (taken as a tablet) with a first-in-class mode of action, which is used to treat specific cancers that contain a mutated (changed) gene that makes a protein known as IDH1, which plays an important role in making energy for cells. When the IDH1 gene is mutated, the IDH1 protein is changed and does not function properly, and this results in changes in the cell which can lead to the development of cancer. Ivosidenib blocks the mutated form of the IDH1 protein and helps to slow or stop the cancer from growing. Therefore, ivosidenib provides an important treatment option for a relatively small number of patients that have AML with an IDH1 mutation. For this group of patients, there is a substantial unmet need for effective and well tolerated treatments which extend survival.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.
Response: Ivosidenib is used in combination with another drug called azacitidine , as studies were carried out in combination with this..

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Ivosidenib has the advantage of being an oral treatment, which is especially pertinent in the post COVID-19 pandemic world. The daily dose is 500mg once daily , which corresponds to 2x 250mg tablets to be taken orally. Treatment should be continued for as long as clinical benefit is observed, or until treatment is no longer tolerated by the patient.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
The only randomised controlled trial (i.e., study that compares ivosidenib against another treatment) in an IDH1 mutated AML population is called 'AGILE'. AGILE is a multicentre, randomized placebo-controlled phase III study to evaluate ivosidenib in combination with azacitidine for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation who are not eligible to receive standard induction chemotherapy. More information about the AGILE study can be found by search the clinicaltrials.gov website, using the identifier: NCT03173248.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition. In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.
There is an unmet need for an effective and tolerable targeted therapy that can improve long term outcomes and HRQoL in AML patients with an IDH1 mutation who are ineligible for intensive induction chemotherapy. This is particularly relevant in the elderly population, where increased age is associated with poor prognosis. Ivosidenib is the only targeted treatment for patients with an IDH1 mutation in AML, and specifically patients have less transfusions and hospitalisation days compared to currently available treatments, as well as longer overall survival.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used

does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The AGILE trial showed clinically meaningful improvement in certain aspects of quality of life; whereas at present, available treatments generally maintain quality of life rather than improving it. In addition, fewer hospitalisation days have an impact on the quality of life for both patients and their families.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Ivosidenib can cause QTc interval prolongation which can cause irregular heartbeats. Therefore, patients will need to have regular electrocardiograms to monitor their heartbeat

Ivosidenib can cause differentiation syndrome in patients with AML. This is a condition that affects blood cells and may be life threatening if not treated. Seek urgent medical attention if patients have any of the following symptoms after taking ivosidenib:

- Fever
- Cough
- Trouble breathing
- Rash
- Decreased urination
- Dizziness or light headedness
- Rapid weight gain
- Swelling of the arms or legs

Patients should carry the provided alert card with them at all times as it contains important information about what to do for them and the health care professional.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Ivosidenib increases survival compared to current treatments, while balancing this against potential toxicities (i.e., side effects). It has lower transfusion rates and hospitalisations, especially pertinent in the elderly population. The cytotoxic side effects of current treatments are large and therefore, where there is a targeted treatment against an actionable mutation (in this case, IDH1), this should be preferred.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Ivosidenib can cause QTc interval prolongation or differentiation syndrome in patients with AML. This means that patients will need to have regular electrocardiograms to monitor their heartbeat, and that patients should seek urgent medical attention if any of the following symptoms are observed after taking ivosidenib:

- Fever
- Cough
- Trouble breathing
- Rash
- Decreased urination
- Dizziness or light headedness
- Rapid weight gain
- Swelling of the arms or legs

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

An economic model was developed in Microsoft Excel to demonstrate the cost-effectiveness of ivosidenib + azacitidine (IVO+AZA) for IDH1m AML. The model captures health states based on being 'event-free' or 'post-event', which is aligned with the primary measure of treatment effect in the AGILE clinical study: event-free survival. An 'event' covers both relapses and progressions, and so 'post-event' is described as 'progressed disease or relapse'. Being event-free is associated with better quality of life, reduced reliance upon blood transfusions, and better survival.
IVO+AZA is modelled to extend life via survival curves fitted to data from the AGILE study, which are used to determine how long patients are expected to be event-free for, and how long they are expected to survive. As the trial does not provide survival estimates over a full lifetime horizon, the model includes projections of event-free and overall survival beyond the available survival data (i.e., after approximately 4 years).

IVO+AZA is expected to lead to improvements in quality of life because of more time spent 'event-free', and a reduced reliance upon blood transfusions (relative to the comparator treatment). Measuring patient quality of life is challenging because it is not an objective measure (like survival time, for example), but the model makes use of data collected as part of the AGILE study. Therefore, while the model may not fully reflect all differences in quality of life, it is expected that the main differences required for decision making are captured.
The new treatment, IVO, is associated with increased drug costs, but reduced time spent in hospital and reduced need for blood transfusions; compared with the comparator treatment. As the comparator treatment is also given in combination with AZA, no major difference in receiving treatment is expected.
All economic models reflect a simplification of reality, and are therefore subject to a degree of uncertainty. The model relies on a number of assumptions concerning long-term benefits, but is aligned with the assumptions previously used to inform NICE's assessment of the comparator treatment. Alternative settings and assumptions have been explored as part of the modelling work, and results have been presented as part of the submission. The model does not capture any benefits to caregivers through improved health-related quality of life of patients, or through reduced time spent attending hospital appointments for blood transfusions.
The health effects captured within the analysis are a combination of quantity of life and quality of life (known in economic modelling as quality-adjusted life years [QALYs]). A QALY of 1 is equivalent to a person living for 1 year while feeling in 'perfect health'. In terms of results, the model projects approximately 20.5 months of survival benefit for patients receiving IVO+AZA, with a QALY gain of approximately 1.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Ivosidenib is an oral innovative treatment with a first-in-class mode of action. It represents a step change in treatment as it is the first medicine available for AML patients with an IDH1 mutation.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
None.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information about the AGILE clinical trial: https://www.nejm.org/doi/full/10.1056/NEJMoa2117344 Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Katz LM, Howell JB, Doyle JJ, Stern LS, Rosenblatt LC, Piech CT et al. Outcomes and charges of elderly patients with acute myeloid leukemia. Am J Hematol 2006; 81(11):850–7.
2. Kumar AJ, Henzer T, Rodday AM, Parsons SK. Risk factors for length of stay and charge per day differ between older and younger hospitalized patients with AML. Cancer Med 2018; 7(6):2744–52.
3. Zhou M, Yang H, Song Y, Marshall DA, Griffin JD, Saini L et al. Patient and Physician Preferences for Treatment of Newly Diagnosed Acute Myeloid Leukemia (AML) in Patients Not Candidates for Intensive Chemotherapy. Blood 2021; 138(Supplement 1):4047.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

September 2023

File name	Version	Contains confidential information	Date
1D6198 Ivosidenib clarification letter v0.1CM	V1	Yes	13/10/2023

Section A: Clarification on effectiveness data

Literature searches

A1. PRIORITY QUESTION. Note this question also applies to section B. In line 19 of each of the search strategies, [Appendix D, pages 473 onwards] the population facet of the search has been narrowed to include only articles that specifically mention first line/treatment naïve/untreated in the database record (essentially the title and abstract of the article). This seems a risky strategy as it is very possible that articles might not mention these terms in the title/abstract and relevant papers might be missed. Please can you explain how this strategy was decided on and how you have mitigated the high risk of missing relevant articles in these systematic reviews? (See an example at question A6 below on the AZA-001 trial paper which appears to have been missed from the searches for this reason.)

The population facet is in line with the target population. It was carefully constructed to exclude other/ irrelevant indications such as r/r AML, MDS etc and thereby balance the sensitivity and specificity of the search. The specific approach adopted (as described below) has been used in previous systematic literature reviews of clinical efficacy and safety submitted as part of NICE appraisals; there hence is precedent of this approach being accepted.

The following search terms were applied: “(first line or 1st line or 1LOT or first time or treatment naive or front line or naive or untreated or ((new$ or initial$) adj3 diagnos$) or ((initial$ or first or naive or primary or induction) adj3 (therapy or treatment))).mp.”

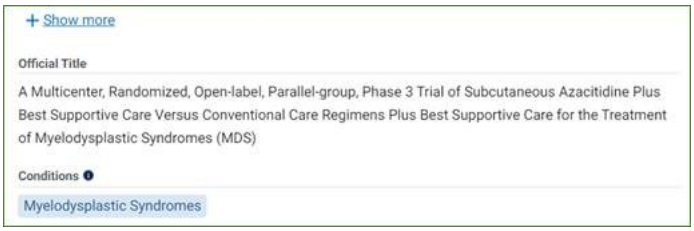
The “mp” free text term was applied, which searches for keywords at the maximum levels, not just the title and abstract. For the full-text articles that are available on Ovid, the 'mp' term enables searching of search terms in multiple fields (mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word).

Electronic searches were also supplemented with hand searches. These were undertaken in CT.gov (International Clinical Trials Registry Platform and

Clinicaltrialsregister.eu/) using the following search terms, however, the trial mentioned at query A6 (AZA-001: NCT00071799) was not identified as the indication is indexed as Myelodysplastic Syndrome (MDS).

Acute myeloid leukemia
AML
ANLL
Erythroleukemia or erythroleukaemia
granulocytic sarcoma
acute panmyelosis and myelofibrosis
sAML
AML-MRC
tAML
diguglielmo
erythremic myelos
Secondary acute myeloid leukemia

Screenshot of Clinical trial.gov: https://clinicaltrials.gov/study/NCT00071799



Screenshot of ICTRP: https://trialsearch.who.int/Trial2.aspx?TrialID=NCT00071799

A2. Note this question also applies to section B. Several of the search strategies [Appendix D. p473 onwards] exclude conference abstracts published between 2011-2015. Please can you explain the reasons for this?

As outlined in the methods of our SLR (Appendix D), conference proceedings for the past 5 years (from original SLR Date 2020) were considered.
Servier don't have access to the full Venetoclax TA765 Appendix D. However, the ERG report (pg 48 of ERG) states "Searches were
performed in a range of databases and included a search of HTA websites and conference abstracts for the period 2017-2020."
Therefore, Servier believes that 5 years timeframe for conference proceedings is acceptable and in keeping with standard practice for HTA

A3. Please provide details of the search strategies used to gather evidence for the NMA [described in Appendix D, second version, p11].

Search strategies used for the NMA are identical to those used for the SLR

Clinical data

A4. PRIORITY QUESTION: For results of the AGILE trial please provide revised doc B figs 6, 7, 9, and 11 to show 95% confidence band around KM curves

Please see the requested figures below.

Figure 1: Revised CS Figure 6

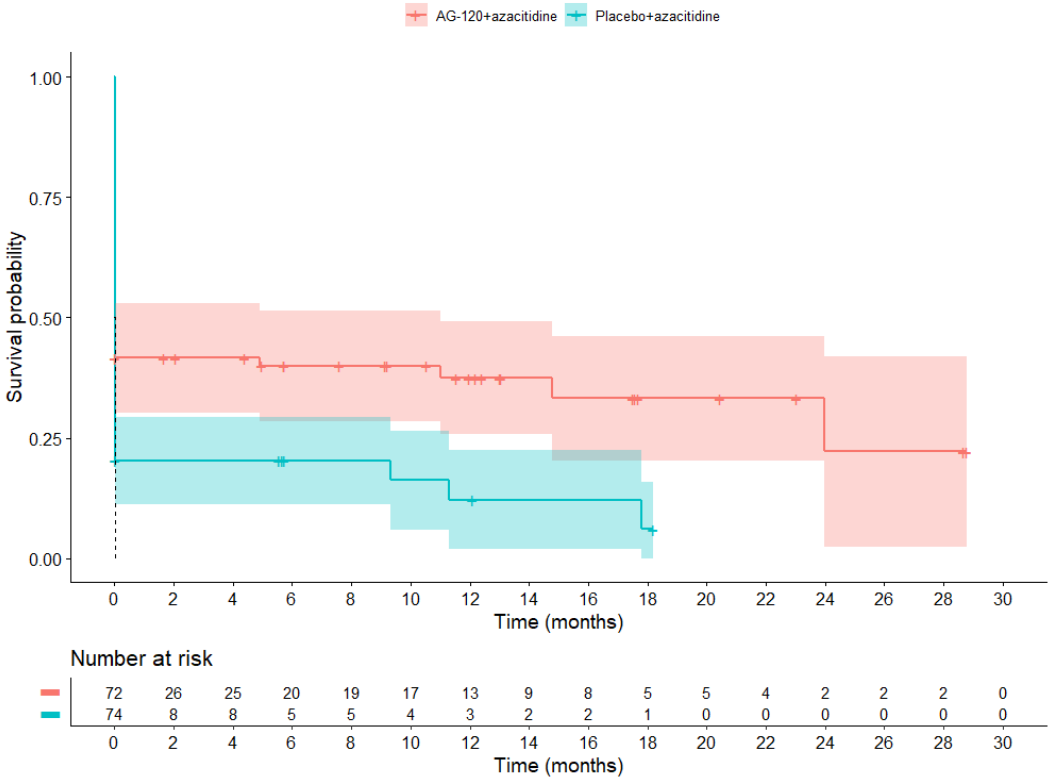


Figure 2: Revised CS Figure 7

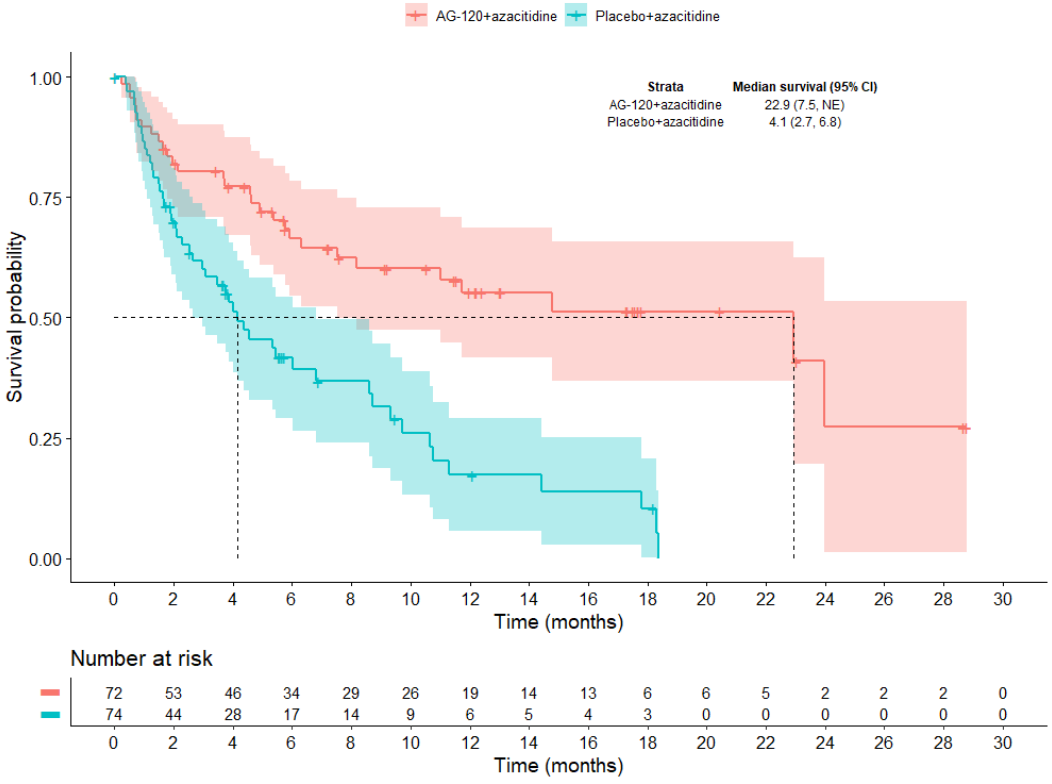


Figure 3: Revised CS Figure 9

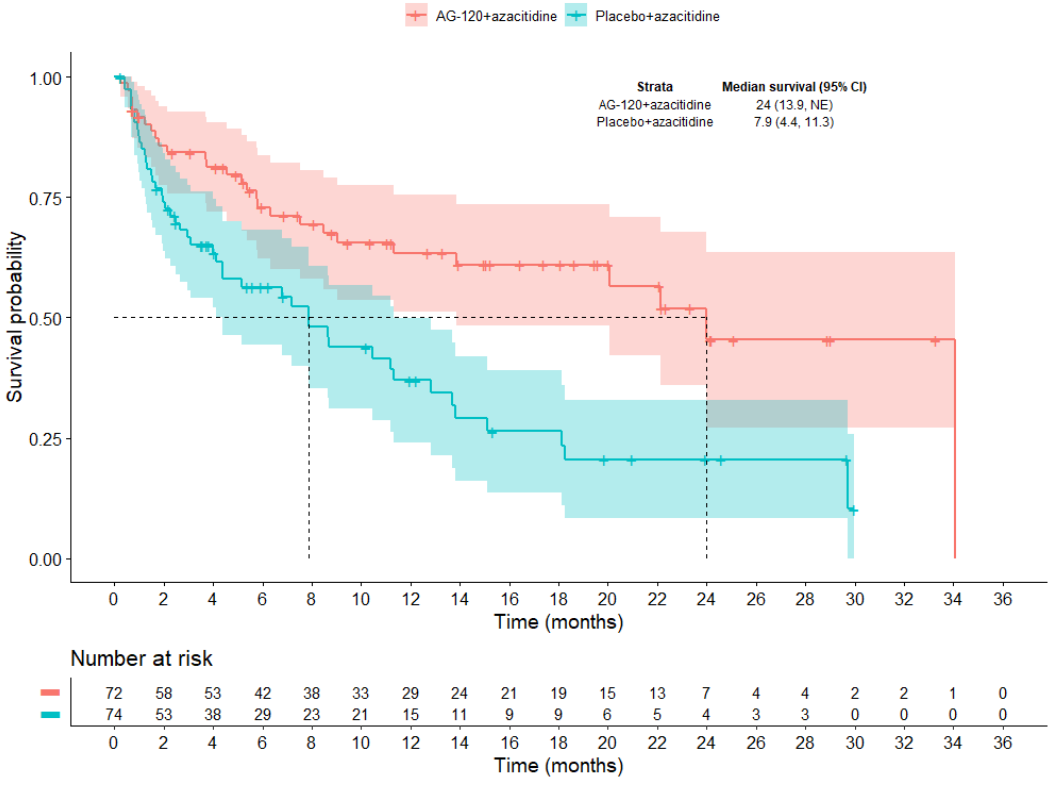
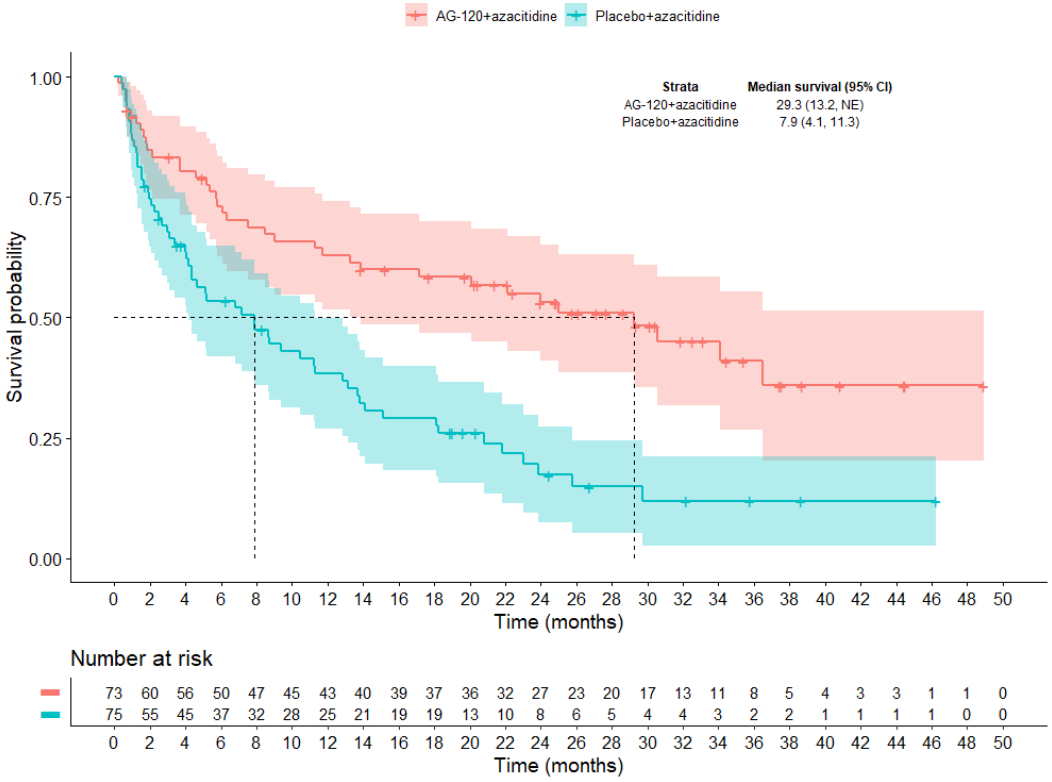


Figure 4: Revised CS Figure 11



A5. Please explain the immediate drop of EFS curve in doc B fig 6.

In AGILE, EFS, was defined as the time from randomisation until treatment failure, relapse from remission, or death from any cause, whichever occurs first. Treatment failure is defined as failure to achieve CR by Week 24. Patients that experienced the event before week 24 were recorded as having the event on Day 1 which accounts for the immediate drop in the curve.

This definition of EFS was defined and aligned according to FDA guidance due to improved association with Overall survival – As outlined in publication 'Response rate, Event free survival and overall survival in Newly Diagnosed Acute Myeloid Leukaemia; US FDA; Patient level analysis JCO 2021' https://pubmed.ncbi.nlm.nih.gov/34890212/

A6. The AZA-001 trial (Fenaux et al. 2010 Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *Blood* 2015; 126:291-299) is missing from list of included (or excluded) studies. Please justify this or

otherwise incorporate it into the results. (See also question A1 above concerning the structure of the literature searches.)

This study was identified, however, for a different publication titled "Santini V, Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Silverman LR, List A, Gore SD, Seymour JF, Backstrom J, Beach CL. Management and supportive care measures for adverse events in patients with myelodysplastic syndromes treated with azacitidine*. Eur J Haematol. 2010 Aug;85(2):130-8. doi: 10.1111/j.1600-0609.2010.01456.x. Epub 2010 Apr 12". The publication by Santini et al was captured in the Ovid search but was excluded at TIAB stage as it did not match the PICOS (exclusion reason: population; study population of original publication was MDS. See further detail in response to A1.

The publication by Fenaux et al, was not retrieved from the database searches as it does not mention the target population according to the search criteria. However, even if it had been identified it would have been excluded at TIAB stage as it did not meet the PICOS criteria of ineligibility for IC.

The original study by Fenaux,2007 was a randomised phase III trial of Azacitidine Vs Conventional Care Regimens -CCR (A mixture of BSC, LDAC and intensive chemotherapy) in high risk MDS and CMML. At a later stage, 32% of the population in this study were later reclassified as AML. A sub group analysis of these patients was undertaken and presented in the AZA-001- AML analysis by Fenaux et al, in 2009 . Within this AML subgroup analysis 86 % of patients were deemed ineligible to intensive chemotherapy and the comparator arm also contained a mixture of BSC, non intensive treatment for AML but also intensive chemotherapy too. However, no subgroup data was provided for the IC-ineligible population. In addition, the blast level included was only 20-30% blasts.

Network Meta Analysis

A7. PRIORITY QUESTION: Please provide the objective definitions (blasts, platelet counts etc.) of CR, CRi and CRh used in AGILE.

CR is defined as: bone marrow blasts< 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count (ANC) > 1.0 × 109/L (1000/μL); platelet count > 100 × 109/L (100,000/μL); and independence of red cell transfusions.
CRh is defined as a CR with partial recovery of peripheral blood counts where ANC is >0.5 × 109/L [500/μL], and platelet count is >50 × 109/L[50,000/μL]
CRi [including CRp] is defined as all CR criteriaexcept for residual neutropenia where ANC is <1.0 × 109/L [1000/μL] or thrombocytopenia where platelet count is <100 × 109/L [100,000/μL];

Please also confirm that for the outcome EFS within the NMA the AGILE trial adopted the updated definition for sensitivity analysis: 'time from randomization until progressive disease, relapse from CR or CRi, treatment failure, or death from any cause' (doc B, p28).

Yes. For consistency across trials in the network (i.e. VIALE-A), similar EFS definitions used in the NMA (i.e. AGILE EFS sensitivity analysis definition used).

A8. Appendix D [ITC] section 5.1.4 states that 'analyses consisted of binary (CR, CR + CRi, TI) and continuous (hazard rates for OS and EFS) outcomes. A binomial model with a logit link function was employed for binary outcomes and a normal model with an identity link function was employed for continuous outcomes'

A model for binomial random effects is shown in Table 9. Please supply the equivalent table for the continuous outcomes.

We do not have a table for the continuous outcomes. However, for continuous outcomes the meta-analysis model for logit link in Table 9, now becomes a Normal generalised linear model (GLM) taking the form:

$$g(\gamma) = \theta_{jk} = \mu_j + \delta_{jbk} I_{\{k \neq 1\}}$$

Where g is the identity link function and θ_{jk} is the linear predictor of the treatment effect in arm k or trial j. As before, μ_j are the trial-specific baseline effects in trial j, treated as unrelated nuisance parameters. The δ_{jbk} are the trial-specific treatment

effect of the treatment in arm k relative to the control treatment in arm b $(b = 1)$ in that trial, and $\delta_{jbk} \sim Normal(d_{bk}, \sigma^2)$ as in Table 9."

This approach is aligned with the NICE DSU guidance on evidence synthesis.

A9. Table 7 of Appendix D [ITC] gives information on binary outcomes (CR, CRi etc). Please also supply the time of assessment for the binary outcomes in each study.

In the AGILE study, all subjects had the extent of their disease assessed by bone marrow aspirate (and biopsy if standard of care) and peripheral blood samples at Screening and within 1 week prior to Day 1 (±3 days) of Weeks 5, 13, 21, and every 8 weeks thereafter (Weeks 29, 37, etc.); at End of Treatment (EOT); as dictated by physical exam and/or blood counts; and/or any time that disease progression is suspected.

In VIALE -A – Bone marrow assessments were performed at screening, at the end of cycle 1, and every three cycles thereafter until two consecutive samples confirmed a complete remission or a complete remission with incomplete haematologic recovery. Disease assessments were performed with the use of the modified International Working Group response criteria for AML.20. We do not have the information on bone marrow aspirate vs bone marrow biopsies.

Survival Analysis

A10. PRIORITY QUESTION: Please provide plots showing hazard curves for all fitted parametric models for figs 24, 25, 29 and 30 in doc B section 3.3, also overlaying the observed hazard function in each. (The latter can be calculated for example with muhaz package in R).

Please see the requested smoothed hazard plots in Figure 5 to Figure 8. Smoothed hazard estimates can vary depending on the approach used to estimate them. For

this reason, we have provided smoothed hazard estimates using two different packages in R: (i) 'muhaz', and (ii) 'bshazard'.
https://cran.rproject.org/web/packages/muhaz/muhaz.pdf

https://cran.r-project.org/web/packages/bshazard/bshazard.pdf

The muhaz package uses kernel methods, whereas the bshazard package uses B-splines. For both methods, estimates were produced using the full range of follow-up data (for consistency across both methods of estimating hazards). However, hazard estimates produced where the number of patients still at risk is small should be interpreted with caution.

Figure 5: Hazard plots: OS for IVO+AZA (models shown in CS Figure 24)

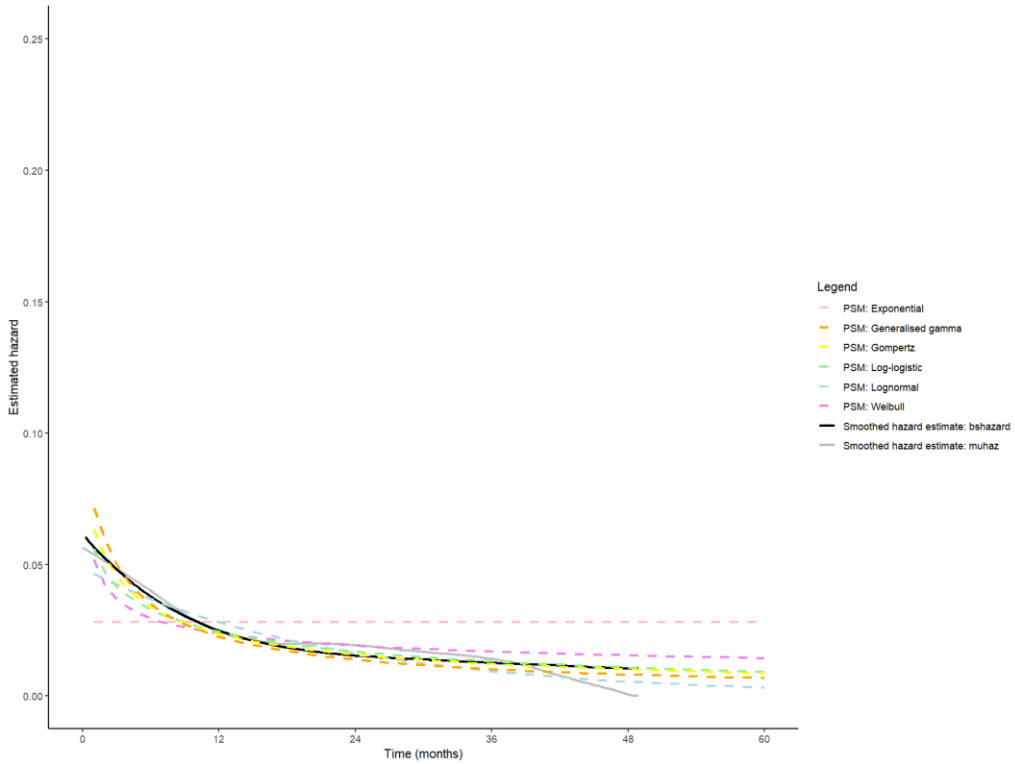


Figure 6: Hazard plots: OS for AZA (models shown in CS Figure 25)

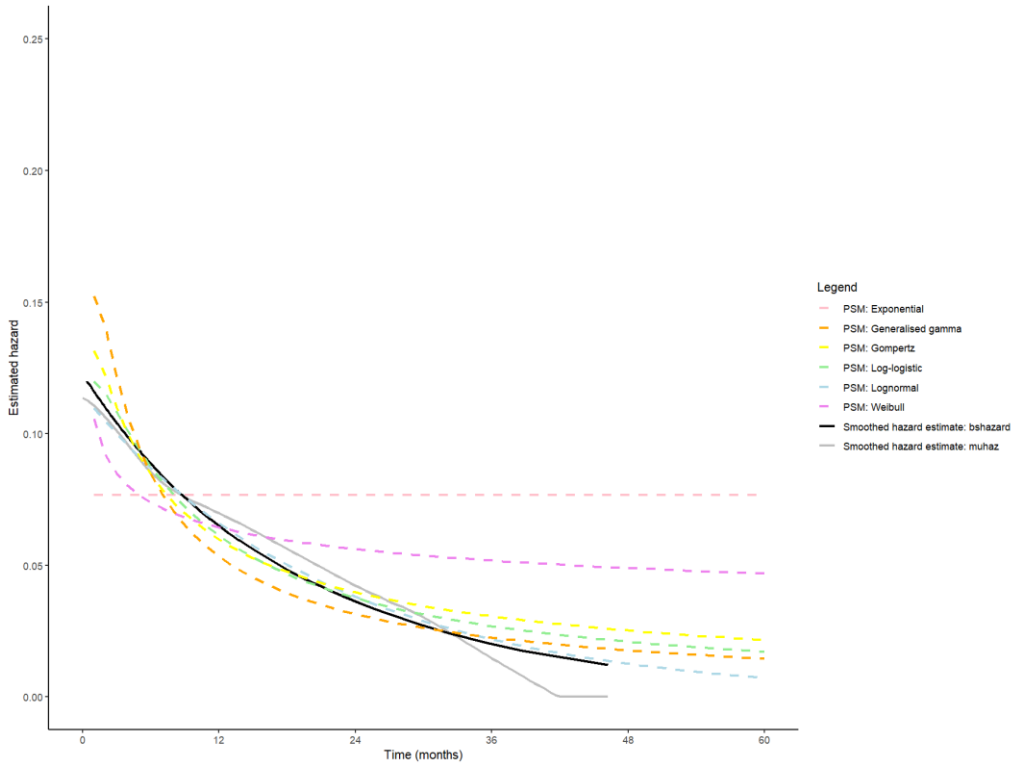


Figure 7: Hazard plots: EFS for IVO+AZA (models shown in CS Figure 29)

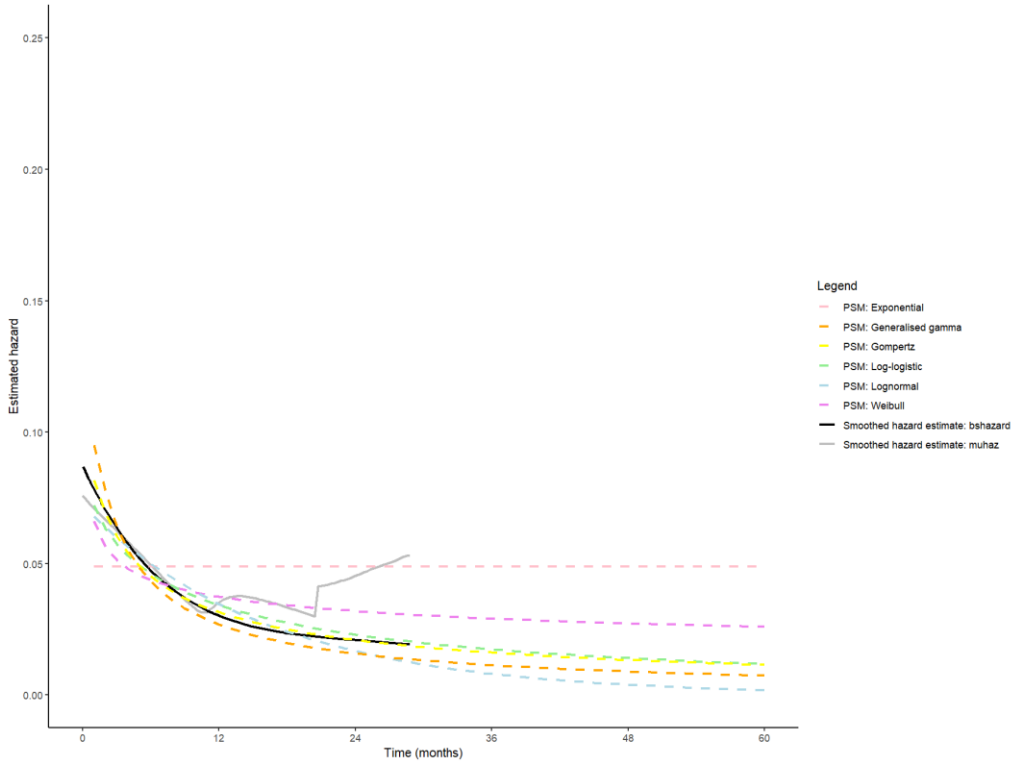
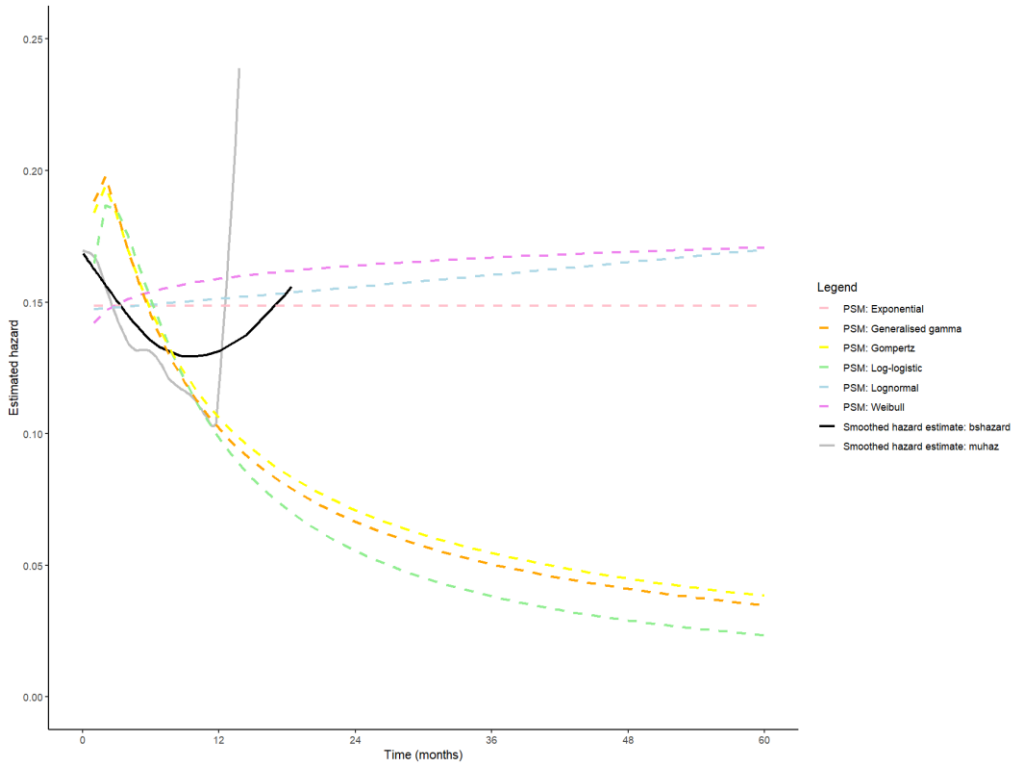


Figure 8: Hazard plots: EFS for AZA (models shown in CS Figure 30)



Section B: Clarification on cost-effectiveness data

Clinical data used in the economic analysis

B1. The EAG understand that the primary clinical data source used to estimate the treatment effectiveness of IVO+AZA in the economic model was from AGILE (based on the data-cut March 18, 2021). However, as part of the NMA and in order to estimate the comparative effectiveness of VEN+AZA, the EAG noted that a more recent data cut from AGILE (June 2022) was used. Is the EAG's understanding correct? If so, please provide additional clarity (and justification) surrounding the use of different data cuts.

Table 1 presents a summary of which data cuts are used to inform each time-to-event endpoint used in the previously submitted cost-effectiveness model. The data cuts described in Table 1 also apply to the NMA for OS and EFS.

Table 1: Data cuts used to inform the model for each time-to-event endpoint (original)

Endpoint	Data cut	Rationale
OS	June 2022	Final analysis – most up-to-date data for OS
EFS	March 2021	Primary data cut – no further EFS data collected beyond this time
ToT	October 2021	Safety update – provided additional data versus primary data cut

Key: EFS, event-free survival; OS, overall survival; ToT, time on treatment.

When checking the data cuts used to inform the model to answer this question, we identified ToT data in the June 2022 data cut, and so an update to the October 2021 estimates has been carried out and included within the model submitted alongside this response. Therefore, Table 2 presents a summary of which data cuts are used to inform each time-to-event endpoint used in the updated cost-effectiveness model.

Table 2: Data cuts used to inform the model for each time-to-event endpoint (update)

Endpoint	Data cut	Rationale
OS	June 2022	Final analysis – most up-to-date data for OS
EFS	March 2021	Primary data cut – no further EFS data collected beyond this time
ToT	June 2022	Final analysis – most up-to-date data for ToT

Key: EFS, event-free survival; OS, overall survival; ToT, time on treatment.

Since the update of this endpoint impacts the base-case analysis of the model, we have provided a set of revised base-case results at the end of this response. Please see ‘Appendix: Revised base-case analysis’.

Definition of EFS used in the model

B2. The EAG note that the definition of EFS used within the model is different to the definition used in the AGILE study. Please clearly state the difference in EFS definition used in AGILE versus the EFS definition used in the model.

Furthermore, please comment on the potential cost effectiveness implications of using the modelled definition of EFS compared to using the AGILE definition.

Table 3 presents a summary of the differences between the EFS definition used in the primary endpoint of AGILE and the secondary endpoint of VIALE-A. Please see our response to A5 and the publication by Norsworthy *et al.*, (2022) https://pubmed.ncbi.nlm.nih.gov/34890212/ for a more detailed history behind the specification of the EFS endpoint in the AGILE study.

Table 3: Comparison of event-free survival definitions in AGILE and VIALE-A

Study	AGILE	VIALE-A
Endpoint type	Primary	Secondary
Definition of event-free survival	Time from randomization until treatment failure (i.e., the patient did not have complete remission by week 24), relapse from remission, or death from any cause, whichever occurred first	Time from randomization to disease progression, treatment failure (failure to achieve complete remission or <5% bone marrow blasts after at least six cycles of treatment), confirmed relapse, or death.
Further notes	Treatment failure applies on Day 1, even if this is determined at week 24	Treatment failure applies at the time of completing at least six cycles of treatment
Source	Montesinos *et al.*, (2022)	DiNardo *et al.*, (2020)

If the EFS definition per the primary endpoint of AGILE was used in the cost-effectiveness model, this would artificially assign some patients to the progressed disease or relapsed health state earlier than they should be defined as such. From a practical perspective, any survival models fitted to EFS according to the primary endpoint from AGILE would either be unrealistic (if including events on Day 1), or would need to be re-based from Day 1. If the models were fitted to re-based data, the resulting number of patients in the IVO+AZA arm would be small – a total of n=26 patients have an EFS time of greater than 1 day using the primary endpoint definition, and of these, only n=4 events were recorded, meaning the remaining n=22 patients are censored. It is not possible to determine how EFS for VEN+AZA would differ when changing the endpoint definition.

B3. It would be helpful if you could provide a scenario analysis which uses the definition of EFS as outlined in the AGILE study, within the economic model.

Unfortunately, we cannot provide this scenario. As explained above in our responses to A5 and B2, it is not possible to generate a comparison of EFS between the AGILE and VIALE-A study populations, using the definition specified as the primary endpoint in the AGILE study. Furthermore, the endpoint description itself involves using a post-baseline measure to determine health state occupancy at baseline which is not suitable for incorporation within our model (i.e., any patients that did not achieve CR by week 24 were considered to have had an EFS event on day 1).

Modelling of complete remission/complete remission with incomplete count recovery (CR/CRi)

B4. Please provide further clarification surrounding the nested 'CR/CRi' and 'No CR/CRi' health states that are contained within the broader EFS state. The EAG noted that the proportion of CR/CRi patients within the EFS state was assumed to remain static after week 13. Was this assumption supported by clinical opinion and/or clinical trial evidence?

Here, the proportion with CR/CRi is assumed to be the same as the previous model cycle from cycle 13, not week 13. Cycle 13 is 48 weeks (i.e., approx. 1 year, and the model cycle following week 44). This assumption was based on the data from AGILE, as shown in CS Figure 38 (where the proportion of patients in EFS with CR/CRi is broadly stable from week 44).

B5. Could you please confirm the CR/CRi proportions used in the model for the IVO+AZA and the VEN+AZA treatment arms and the sources for these. Please also provide additional clarity surrounding the CR/CRi calculation approach for VEN+AZA outlined on p.103 of the submission. Further justification and rationale for undertaking this approach would be helpful. Please also provide additional clarity surrounding the estimation of the CR/CRi proportion in the IVO+AZA arm.

The proportion of patients in CR/CRi between baseline and week 72 were estimated in 4-weekly intervals using patient-level data from AGILE, via a simple count approach (i.e., denominator = number of patients in EFS, numerator = number of

patients in EFS and in CR/CRi). However, for VEN+AZA, we do not have access to patient-level data from VIALE-A, and it is important to account for the difference in the proportion of patients that achieved CR/CRi in the AZA arm of the AGILE study versus the AZA arm of the VIALE-A study.

To obtain an estimate of the proportion of patients in CR/CRi over time for VEN+AZA, we took the approach described in Section B.3.4 of the CS (under the sub-heading 'Estimation of patients with and without CR/CRi, within the EFS state), starting at the bottom of page 101). This analysis was performed to obtain an estimate for VEN+AZA that falls between the IVO+AZA and AZA arms of the AGILE study, since the relative proportions of CR/CRi from the AGILE and VIALE-A studies suggest that while more patients on VEN+AZA achieved CR/CRi in VIALE-A compared with IVO+AZA patients in AGILE, the CR/CRi rate for AZA was notably higher in VIALE-A compared with AGILE (16.2% in AGILE versus 28.3% in VIALE-A). This expectation of the VEN+AZA estimate falling between IVO+AZA and AZA is consistent with the other outcomes explored via the ITC (such as OS and EFS).

It is recognised that CR/CRi is an important determinant of health-related quality of life for people with AML (for example, in TA765 utility values were separately estimated for 'remission' versus 'non-remission'). However, it is challenging to capture differences in utility for patients with CR/CRi versus those without CR/CRi since patients achieve remission after baseline, and some patients may only be in CR/CRi for a relatively short period of time. Therefore, the overall approach to capturing differences in utility by CR/CRi within the EFS health state was designed to be a simple but transparent approach using the available data from AGILE and reported summary data from VIALE-A.

B6. Could you please explain why the proportion of patients experiencing CR/CRi used in the base case was not directly taken from the AGILE study (for the IVO+AZA arm) and from the published study Pratz et al for the VEN+AZA arm?

The cost-effectiveness model uses data from the AGILE and VIALE-A studies to estimate the proportion of patients that achieved CR/CRi for IVO+AZA and VEN+AZA, respectively. For AGILE, estimates were derived from the patient-level data from AGILE, with a resulting number of patients being n=39 patients (54.2%) on

IVO+AZA achieving CR/CRi (versus n=12 [16.2%] on the AZA arm). Please note that this number is different to the value reported in Table 2 of the pivotal study publication by Montesinos *et al.*, (2022) of n=38 because this study publication reports the proportion of patients that achieved CR/CR**h**, not CR/CR**i**. https://www.nejm.org/doi/full/10.1056/NEJMoa2117344

For VEN+AZA, the VIALE-A pivotal study publication by DiNardo *et al.*, (2020) states: *"The incidence of complete remission was higher with* [VEN+AZA] *than with* [AZA] *(36.7% vs. 17.9%; P<0.001), as was the composite complete remission (complete remission or complete remission with incomplete hematologic recovery) (66.4% vs. 28.3%; P<0.001)"*. https://www.nejm.org/doi/full/10.1056/NEJMoa2012971 Here, the values of 66.4% and 28.3% for VEN+AZA and AZA (respectively) were extracted, which correspond to the values from AGILE noted above. Please note that the study by Pratz *et al.*, (2022) is a published cost-effectiveness analysis which uses data from the VIALE-A study, but does not consider a comparison to IVO+AZA, nor does it reflect the patient population of direct relevance to this appraisal (i.e., patients with IDH1-mutant AML).https://pubmed.ncbi.nlm.nih.gov/35696071/

The CR/CRi rate in VIALE-A for the AZA arm was close to double the rate seen in the AGILE study (28.3% in VIALE-A compared with 16.2% in AGILE), and so to account for this difference within the cost-effectiveness model, the CR/CRi rate for VEN+AZA was estimated based on the following formula:

$$VEN + AZA_{AGILE\ proxy} = \frac{VEN + AZA_{VIALE-A}}{AZA_{VIALE-A}} \times AZA_{AGILE} = \frac{66.4\%}{28.3\%} \times 16.2\% = 38.0\%$$

If the CR/CRi rate for AZA was identical across both studies, no adjustment would have been made. If the unadjusted rate from VIALE-A was used, this would ignore the difference in populations across the VIALE-A and AGILE studies (e.g., patients in the AGILE study all have IDH1-mutated disease).

Modelled utility

B7. The EAG note that in the model a utility decrement of -0.073 is applied to patients who are considered 'off treatment'. It is not clear how this is specifically applied. Please elaborate. Does the model assume that a

proportion of patients in the EFS state discontinue treatment i.e. is the decrement applied to patients 'off treatment' within the EFS state? Furthermore, does the off treatment utility decrement only apply to patients who stop treatment due to adverse events or is this applied to patients who discontinue for any reason?

The model includes different utility values that are based on a combination of the following:

- Progressed disease or relapse (i.e., post event)
- Remission or no remission (CR/CRi)
- Treatment discontinuation

The decrement for PD/RL is applied only to patients that reside in the PD/RL health state. The decrement for No CR/CRi is applied only to patients that are either in the EFS with No CR/CRi health state or the PD/RL health state. The decrement for treatment discontinuation is applied to patients that are off treatment in any health state apart from the LTS health state (where it is assumed that patients have a utility value as per the EFS CR/CRi health state, without any decrements applied).

Decrements for patients being off treatment are applied in a separate column in the patient flow sheets (please see column AQ in the model patient flow sheets to see which health state are affected by this utility decrement).

For completeness, answers to the specific questions raised are provided below:

Does the model assume that a proportion of patients in the EFS state discontinue treatment i.e. is the decrement applied to patients 'off treatment' within the EFS state?

Based on the estimated time on treatment curve, the model estimates that some patients in EFS may have discontinued treatment. For these patients, the decrement for 'off treatment' is applied.

Furthermore, does the off treatment utility decrement only apply to patients who stop treatment due to adverse events or is this applied to patients who discontinue for any reason?

This decrement is applied for discontinuation due to any reason except for entry to the LTS health state.

Model structure

B8. The EAG note that a partitioned survival model was chosen as the preferred modelling approach. For validation purposes (and if possible) could you please provide the results using a Markov model approach.

As described in the CS (please see Table 35 in Document B), we are unfortunately unable to re-create a state-transition model as per the structure used to inform TA765. This is because we do not have access to either the patient-level data from the VIALE-A study or sufficient summary statistics to enable estimation of transition probabilities.

In terms of specifying a different type of Markov model (e.g., one in which health state may be defined based on EFS with and without CR/CRi, PD/RL, LTS, and Dead), we also consider this infeasible owing to the number of patients in the AGILE study (n=72 for the IVO+AZA arm), compared with the number of transitions that would need to be populated. This is complicated further by considering some transitions would not be permitted within a fully Markov framework. For example, patients can transition from EFS No CR/CRi to EFS CR/CRi and then back to EFS No CR/CRi, but cannot then return to EFS CR/CRi once more. In addition, transitions from EFS to PD/RL do not appear constant based on the EFS Kaplan-Meier estimate and best-fitting parametric models (see CS Figures 23, 24, and 25; as well as Table 37).

It is, however, possible within the current model structure to select a variety of different survival models for each of the time-to-event endpoints, including the exponential model. We would however strongly urge caution with this specification of the model using potentially implausible extrapolations, since (for example) the exponential models were shown to provide a poor visual and statistical fit to the data from the AGILE study (most notably, the OS estimate for IVO+AZA).

B9. In Table 35, the modelling approach is described as a 'cohort level hybrid PartSA and Markov model. The EAG note that state occupancy for EFS and OS

is determined by survival curves (via a PartSA approach). What element of this model is considered to follow a Markov approach?

The EAG is correct to highlight that the model primarily adopts a PartSA structure. However, we included two modifications to the model structure which we felt warranted describing the model as a hybrid of a PartSA and a Markov model. These modifications were (i) for the utility values by CR/CRi, and (ii) the transition to long-term survival (which technically means some patients transition via a probability to a different health state at a given point in time).

These are the only elements that are not aligned with a 'standard' PartSA model, and we have no objection to the model being described as a PartSA given that the core model structure follows this approach. However, we hope this explanation clarifies why we described the model as a hybrid of a PartSA and a Markov model.

B10. The EAG note that the model incorporates a cured health state 'LTS' (long-term survival). Please clarify why you opted to explicitly use a 'cure' health state as opposed to using a mixture cure modelling approach to extrapolate long term survival?

The cost-effectiveness model includes an assumption that people that remain event-free for 3 years are considered functionally cured in practice (i.e., that the excess mortality attributed to their disease is effectively zero). As can be seen from the available data from the AGILE study (e.g., see CS Figures 23 and 38), there are no patients still at risk for EFS at 3 years, with only n=8 patients still at risk for OS at 3 years. Therefore, rather than relying solely upon a fitted survival model to determine long-term outcomes, we opted instead to use a model-based assumption that allows for stress-testing estimated survival outcomes. This approach is consistent with the application of a 'cure' state in TA765 of VEN+AZA. Furthermore, there are difficulties that would be introduced when attempting to draw a comparison to VEN+AZA using a mixture-cure model for IVO+AZA (e.g., determining for how long the hazard ratio should be applied for). For these reasons, we did not consider using MCMs for extrapolating survival.

B11. On p.93 of the submission, it is stated that at the 3-year landmark time point all patients residing in the EFS health state transition to the LTS health

state. Does this mean that patients in the EFS state at 3 years with No CR/CRi will be considered functionally cured?

The cost-effectiveness model makes a simplifying assumption that all patients in EFS at 3 years would transition to LTS. The EAG correctly highlights that this would include patients with CR/CRi and patients without CR/CRi. As noted in response to B10 above, we unfortunately do not have sufficiently long follow-up to determine the proportion of patients with CR/CRi in EFS at 3 years, and so we assumed that the proportion of patients in CR/CRi from week 44 would remain approximately constant for the remainder of the model.

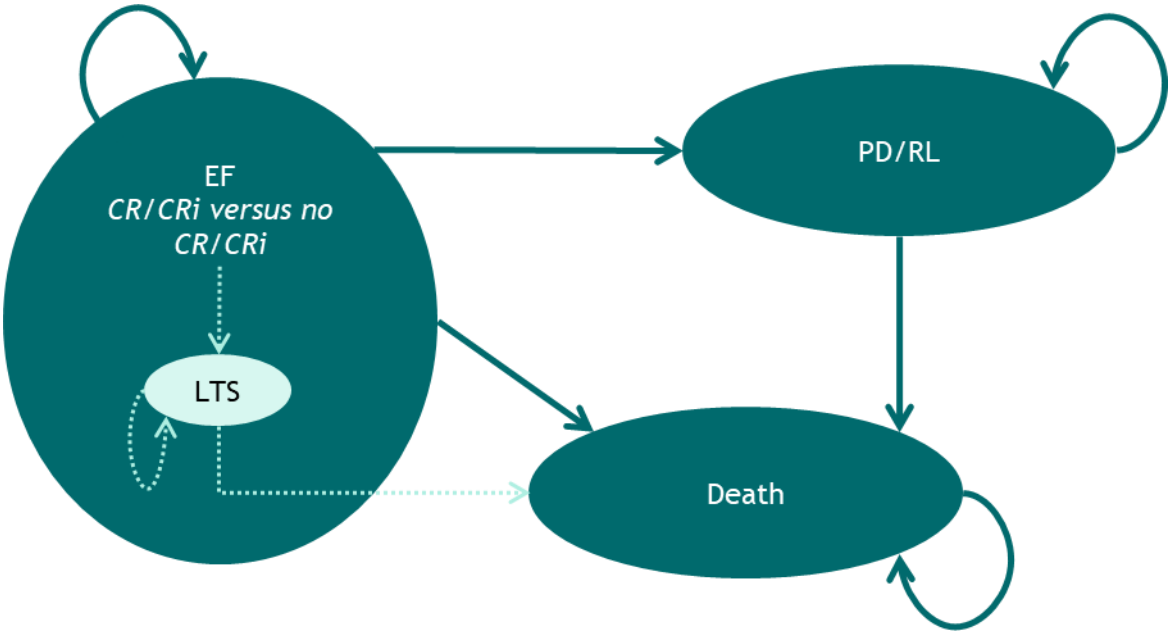
In reality, it is expected that patients in EFS without CR/CRi are much more likely to experience disease progression or relapse and transition out of the EFS state between week 44 and week 156 (i.e., 3 years), versus patients with CR/CRi. While there are no data from the AGILE study to substantiate this expectation, this means that by the time the LTS assumption applied the vast majority of patients in EFS are expected to also be in CR/CRi. However, since the model assumes that the CR/CRi proportion would be constant (in the absence of data), this approach likely under-estimates the average utility for an EFS patient from week 44 to week 156.

Should the EAG wish to consider alternative analyses, it is possible to set the proportion of patients that transition from EFS to LTS at 3 years to a value less than 100% (see cell range 'con_lts_prop'). However, this functionality applies to both the IVO+AZA and VEN+AZA arms, and so to facilitate a comparison using the precise proportion estimated to be in CR/CRi at 3 years, it may be necessary to run the model twice (once using a value of 96.9% [reflective of IVO+AZA], and once using a value of 83.6% [reflective of VEN+AZA]).

B12. Based on the model diagram, the EAG note that the model structure does not allow patients with CR/CRi and no CR/CRi to move directly into the death health state i.e. it appears that patients in the EFS health state must first move into the LTS health state before moving to the death state. Please confirm if this is correct? If so, is this assumption supported by clinical opinion?

The model diagram includes two arrows overlayed on top of each other, which is intended to demonstrate that patients can move to death either from the LTS health

state or from the broader EF health state. Please see below a revised diagram where these arrows have been separated for transparency:



B13. Please clarify how background mortality has been incorporated into the model? The EAG note that background mortality has been captured for patients in the LTS health state, however it is unclear how background mortality has been applied to all patients.

For the non-LTS health states, at each model cycle, the probability of either an OS or an EFS event is taken as the maximum of either the fitted model or the estimated risk of death in the general population. For EFS, this may over-estimate the risk of an EFS event in the long-term, since not all EFS events are deaths. However, disabling this adjustment has no impact on the base-case cost-effectiveness results since general population adjustment only applies at a time point after 3 years, at which point no patients reside in the EFS state (all patients will have either died, progressed/relapsed, or entered the LTS health state).

Modelled treatment discontinuation

B14. Please provide further clarity on how treatment discontinuation was incorporated within the model (particularly during years 1-3). What proportion

of patients were assumed to stop treatment in both arms? What sources were used to inform treatment discontinuation rates?

Treatment discontinuation was informed by estimating a time on treatment curve using data from the AGILE study (for IVO+AZA). Ultimately, all patients stop treatment eventually, but this curve determine the proportion of patients expected to remain on treatment for each model cycle. For completeness, time on treatment was defined as:

$$Time\ on\ treatment\ (in\ days) = Treatment\ end\ date - treatment\ start\ date + 1\ day$$

Patients were considered as an 'event' if they had permanently discontinued treatment, or 'censored' if treatment was ongoing. For the IVO+AZA arm, n=[redacted] of the n=72 patients exposed to treatment had discontinued at data cut-off, meaning that n=[redacted] patients were censored.

For VEN+AZA, a published estimate of the mean duration of treatment was identified from the Pratz *et al.* cost-effectiveness analysis (citing the VIALE-A study), which was used to produce an exponential model that crossed the corresponding median value. We considered this to be a reasonable approach in the absence of patient-level data from VIALE-A to undertake an analysis per the IVO+AZA arm of AGILE.

Section C: Textual clarification and additional points

C1. Please provide the footnotes for Document B table 27 as they are missing

See document B

C2. Please provide the table of abbreviations for Document B as it is missing

Abbreviation	Definition
2-HG	2-hydroxyglutarate
α-KG	Alpha- ketoglutarate
AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike's information criterion
AML	Acute myeloid leukaemia
AMLSG	Acute Myeloid Leukaemia Study Group
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASH	American Society of Haematology
AUC	Area-under-the-curve
AZA	Azacitadine

Abbreviation	Definition
BIC	Bayesian information criterion
BSC	Best supportive care
BNF	British National Formulary
BSA	Body surface area
BSH	British Society of Haematology
CEAC	Cost-effectiveness acceptability curve
CI	Confidence Interval
CR	Complete Remission
CRh	Complete remission with partial haematologic recovery
CRi	Complete Remission with incomplete count recovery
DCO	Data cut off
DIC	Deviance Information Criterion
DOCR	Duration of Complete remission
DOCRh	Duration of Complete remission with partial haematologic recovery
DOCRi	Duration of Complete Remission with incomplete count recovery
DOR	Duration of response
ECG	Electrocardiography
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
ED	Emergency Department
EHA	European Haematology Association
ELN	European LeukemiaNet
eMIT	electronic market information tool
EORTC QLC	European Organisation for research and treatment of cancer Quality of life questionnaire core
EPAR	European Public Assessment report
EQ5D	EuroQol-5 dimension 5-level health-related quality of life questionnaire
ESMO	European Society for Medical Oncology
EFS	Event Free survival
FAS	Full analysis set
FE	Fixed effects
HCRU	Healthcare Resource Use
HMA	Hypomethylating agent
HR	Hazard ratio
HRQOL	Health related quality of life
HSCT	Haematopoietic stem cell transplantation
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IDH1	Isocitrate dehydrogenase-1
INMB	Incremental net-monetary benefit
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
IVO	Ivosidenib
KM	Kaplan Meier
LDAC	Low-dose cytarabine
LTS	Long-term survival
LVEF	Left ventricular ejection fraction
LYG	Life years gained
MDS	Myelodysplastic syndrome
MIMs	Monthly Index of Medical Specialities
MLFS	Morphological leukaemia free state
MMRM	Mixed Model for Repeated Measures
mOS	Median overall survival
MUGA	Multi-gated acquisition
NCC	National Cost Collection

Abbreviation	Definition
NCCN	National Comprehensive Cancer Network
NE	Non estimable
NHB	Net-health benefit
NICE	National Institute for Health and Care Excellence
NMA	Network meta analysis
ONS	Office of National Statistics
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PartSA	Partitioned survival analysis
PAS	Patient access scheme
PD	Progressive disease
PICOS	Population, intervention, comparator, outcomes, study
PK	Pharmacokinetics
PLT	Platelet
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QD	Once daily
QOL	Quality of Life
RBC	Red blood cell
RCT	Randomised controlled trial
RDI	Relative dose intensity
RE	Random effects
RIC	Reduced-intensity conditioning
RL	Relapsed
RMST	Restricted mean survival time
RoB	Risk of Bias
RR	Relapsed refractory
SAS	Safety analysis set
SC	Subcutaneous
ScA	Scenario analysis
SD	Standard deviation
SLR	Systematic literature review
SmPc	Summary of product characteristics
SMR	Standardised mortality ratio
TA	Technology appraisal
TEAE	Treatment emergent adverse events
TF	Treatment failure
TLS	Tumour lysis syndrome
ToT	Time on treatment
TTCR	Time to complete remission
TTCRh	Time to Complete remission with partial haematologic recovery
TTCRi	Time to Complete Remission with incomplete count recovery
TTR	Time to response
VAS	Visual analogue scale
VEN	Venetoclax
WTP	Willingness to pay

Appendix: Revised base-case analysis

Based on the response to B1, the model has been updated to use ToT from the June 2022 data cut. This has impacted the base-case results of the cost-effectiveness model, and so the revised results are presented here for completeness. In the model shared alongside this response, we have re-run all the sensitivity analyses for consistency with this revised base-case analysis. Please refer to the 'Intro' tab of the model for a full description of edits made to the model following this response.

The remainder of this appendix presents all results as per Document B and Appendix J (Clinical outcomes and disaggregated results from the model). Of note, since only the ToT for IVO+AZA has changed, costs for the VEN+AZA arm, all QALYs, and all LYs remain unchanged compared to the submitted deterministic base-case results. However, probabilistic results have been re-run, so all components of the results may have changed slightly between runs.

B.3.9 Base-case results

Base case deterministic results are presented in Table 4, with net-health benefit (NHB) results provided in Table 5 (at willingness-to-pay [WTP] thresholds of £20,000 and £30,000 per QALY gained). These results demonstrate that IVO+AZA provides more QALYs (+[redacted]) with an incremental cost of -[redacted] giving a dominant result (i.e., more QALYs at a reduced cost).

Table 4: Base-case results (deterministic)

Technologies	Total			Incremental			
	Costs	LYG	QALYs	Costs	LYG	QALYs	ICER
VEN + AZA	£190,639	4.26	2.17				
IVO + AZA	[redacted]	5.97	[redacted]		1.71	[redacted]	Dominant

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 5: Net health benefit (deterministic)

Technologies	Total		Incremental			
	Costs	QALYs	Costs	QALYs	NHB at £20,000	NHB at £30,000
VEN + AZA	£190,639	2.17				
IVO + AZA	[redacted]					

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

The corresponding probabilistic results are presented in Table 6 (base-case) and Table 7 (NHB), respectively. These results are broadly aligned with the deterministic results.

Table 6: Base-case results (probabilistic)

Technologies	Total			Incremental			
	Costs	LYG	QALYs	Costs	LYG	QALYs	ICER
VEN + AZA	£193,085	4.33	2.18				
IVO + AZA	[redacted]	5.95	[redacted]		1.62	[redacted]	Dominant

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 7: Net health benefit (probabilistic)

Technologies	Total		Incremental			
	Costs	QALYs	Costs	QALYs	NHB at £20,000	NHB at £30,000
VEN + AZA	£193,085	2.18				
IVO + AZA	[redacted]					

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

B.3.10 Exploring uncertainty

Probabilistic sensitivity analysis

The PSA was run for 5,000 iterations, after which relatively small fluctuations in the mean incremental net monetary benefit (INMB) were noted, as shown in Figure 9 (please note PSA iterations are presented on a log scale).

Figure 9: PSA convergence

Key: INMB, incremental net monetary benefit; PSA, probabilistic sensitivity analysis.

The mean results of the PSA are presented earlier in Table 6, showing similar results to the deterministic base-case analysis (presented in Table 4). The corresponding PSA scatterplot is presented in Figure 10, and a cost-effectiveness acceptability

curve (CEAC) presented in Figure 11. At a WTP threshold of £30,000 per QALY gained, there is a(n) [redacted]% probability that IVO+AZA may be considered a cost-effective treatment option, compared to VEN+AZA.

Figure 10: PSA scatterplot

Key: k, thousand(s); PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Figure 11: Cost-effectiveness acceptability curve

Key: AZA, azacitidine; IVO, ivosidenib; k, thousand(s); VEN, venetoclax; WTP, willingness-to-pay.

Deterministic sensitivity analyses

One-way sensitivity analysis

The results of the OWSA are presented as a tornado diagram in Figure 12. The results of this analysis are presented with the outcome of INMB, at a WTP threshold of £30,000 per QALY gained.

Figure 12: Tornado diagram

Key: AZA, azacitidine; CR/CRi, complete remission or complete remission with incomplete count recovery; EF, event free; EFS, event-free survival; HR, hazard ratio; HCRU, healthcare resource use; INMB, incremental net monetary benefit; IV, intravenous; IVO, ivosidenib; k, thousand(s); LB, lower bound; PD/RL, progressed disease or relapse; UB, upper bound; VEN, venetoclax.

Scenario analysis

The results of the scenario analyses are provided in Table 8.

Table 8: Scenario analysis results

#	Label	ICER
-	*Base-case analysis*	Dominant
1	Time horizon, 15 years	[redacted]
2	Time horizon, 20 years	
3	Discount rates, 1.50%	
4	Discount rates, 6.00%	
5	Curve fit: IVO + AZA OS, Generalised gamma	
6	Curve fit: IVO + AZA OS, Log-logistic	
7	Curve fit: IVO + AZA OS, Weibull	
8	Curve fit: IVO + AZA EFS, Generalised gamma	
9	Curve fit: IVO + AZA EFS, Log-logistic	
10	Curve fit: IVO + AZA EFS, Weibull	
11	Curve fit: IVO + AZA ToT, Exponential	
12	Curve fit: IVO + AZA ToT, Log-logistic	
13	Curve fit: IVO + AZA ToT, Log-normal	
14	Long-term survival timepoint: 2 year(s)	
15	Long-term survival timepoint: 4 year(s)	
16	Long-term survival %: 80%	
17	Long-term survival %: 90%	
18	Long-term survival SMR: 1.1	
19	Long-term survival SMR: 1.2	
20	Long-term survival SMR: 2	
21	Non-LTS SMR: 1.1	
22	Non-LTS SMR: 1.2	
23	Apply LTS state for costs and utilities only	
24	Use HR against EFS for VEN+AZA ToT: 1.1	
25	Use HR against EFS for VEN+AZA ToT: 1.2	
26	Remove concomitant azole costs and dosing adjustments	
27	Remove subsequent treatment costs	
28	Utility source: Coyle (2020)	
29	Utility source: Pratz (2022)	
30	AE inclusion criteria: 5% cut off and consider DS	
31	VEN dosing every 28 days for all cycles	

Key: AZA, azacitidine; DS, differentiation syndrome; EFS, event-free survival; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IVO, ivosidenib; SMR, standardised mortality ratio; OS, overall survival; ToT, time on treatment; VEN, venetoclax.

J1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

Disaggregated results are presented for QALY gain by health state, costs by health state, and costs by item in Table 9, Table 10, and Table 11, respectively. Markov traces for IVO+AZA and VEN+AZA are presented in Figure 13 and Figure 14, respectively.

Table 9: Summary of QALY gain by health state

Health state	QALYs (IVO + AZA)	QALYs (VEN + AZA)	Δ	|Δ|	% |Δ|
EF					
PD/RL					
LTS					
Off tx*					
AEs†					
Total					

Key: Δ, incremental; |Δ|, absolute incremental; AEs, adverse events; AZA, azacitidine; EF, event-free; IVO, ivosidenib; LTS, long-term survivors; PD/RL, progressed disease or relapse; QALYs, quality-adjusted life years; tx, treatment; VEN, venetoclax.
Note: *Off treatment is applied as a decrement as it applies across the 'EF' and 'PD/RL' health states, hence shown here as negative QALYs; †AEs applied as a QALY loss in the first cycle only. **No change compared with originally submitted results.**
Source: Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 10: Summary of costs by health state

Health state	Costs (IVO + AZA)	Costs (VEN + AZA)	Δ	|Δ|	% |Δ|
EF					
PD/RL					
LTS					
EoL*					
Total					

Key: Δ, incremental; |Δ|, absolute incremental; AZA, azacitidine; EF, event-free; EoL, end-of-life; IVO, ivosidenib; LTS, long-term survivors; PD/RL, progressed disease or relapse; tx, treatment; VEN, venetoclax.
Note: *Not assigned to a particular health state as death can occur from any of the three health states described.
Source: Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 11: Summary of predicted resource use by category of cost

Item	Costs (IVO + AZA)	Costs (VEN + AZA)	Δ	|Δ|	% |Δ|
Drug					
Admin					
MRU					
AEs					
EoL					
Total					

Key: Δ, incremental; |Δ|, absolute incremental; admin, administration; AE, adverse event; AZA, azacitidine; EoL, end-of-life; IVO, ivosidenib; MRU, medical resource use; VEN, venetoclax.
Source: Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Figure 13: Markov trace: IVO+AZA

Key: AZA, azacitidine; EF, event-free; IVO, ivosidenib; LTS, long-term survivors; PD/RL, progressed disease or relapse.

Figure 14: Markov trace: VEN+AZA

Key: AZA, azacitidine; EF, event-free; LTS, long-term survivors; PD/RL, progressed disease or relapse; VEN, venetoclax.
Note: **No change compared with originally submitted results.**

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Leukaemia Care is the UK's leading leukaemia charity. For over 50 years, we have been dedicated to ensuring that everyone affected by leukaemia, MDS or MPNs receives the best possible diagnosis, information, advice, treatment and support. Approximately 80% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 20% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	Abbvie: £12,000 core funding and £450 honorarium Celgene: £65,000 patient activities of which £15,000 is for the Blood Cancer Alliance Jazz: £30,000 awareness and patient support Pfizer: £10,000 core funding

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information for this submission primarily gathered through Leukaemia Care patient experience survey – 'Living with Leukaemia'. The latest survey, run in 2017, had 2884 responses (including 443 AML patients). We also spoke to an AML patient in September 2023 for the purpose of the submission to understand their views on unmet needs and how the impact of an AML diagnosis. Additionally, we have gathered information through our online forums, helpline, support groups, and communication with our membership.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Acute myeloid leukaemia (AML) accounts for around a third of cases of leukaemia in adults in the UK. There are around 3,100 new acute myeloid leukaemia cases in the UK every year, that's more than 8 every day (2016-2018). Approximately two thirds of patients in the UK are diagnosed aged 65 and over; with the highest incidence rates in people aged 85-89 in the UK (2016-2018). Older age is associated with poorer prognosis; however, AML is an aggressive leukaemia and can affect people of any age. Due to the rapidly progressing nature of AML, 54% of patients in our Living with Leukaemia survey said they had experienced symptoms for less than a month before visiting their GP. The most common symptoms encountered by AML patients since their diagnosis are fatigue (73%), feeling weak or breathless (51%), memory loss or loss of concentration (38%), bleeding and bruising (37%), itchy skin (35%), nausea or vomiting (35%), sleeping problems (34%), infections (32%), bone or joint pain (31%), weight loss (28%) and muscle pain (23%). The National Cancer Intelligence Network 'Routes to Diagnosis' report shows that 53% of AML patients are diagnosed via emergency presentation, compared to a cancer average of 22%, and emergency diagnosis is correlated with poor prognosis. Patients with acute leukaemia often get ill suddenly and must start treatment quickly; 55% of AML patients surveyed started treatment within a week of diagnosis. AML also has a wider practical impact, with 52% of patients experiencing pain as a direct result of their condition (31% occasionally, 17% regularly and 4% constantly). Additionally, 51% of patients have difficulty moving around (sometimes 27%, often 15% and always 9%) and 69% of AML patients have difficulty performing some of their daily routines, such as cooking or cleaning. Another 38% reported that they have problems taking care of themselves. AML patients can also experience a considerable emotional impact as a result of their diagnosis, prompting them and their families to experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation and depression. Our survey reports 51% of AML patients have felt depressed or anxious more often since their diagnosis.

	77% of those in work or education experienced a negative impact on this post diagnosis (32% reduced hours, 45% no longer able to work or continue education). Consequently, 53% of AML patients reported a negative financial impact as a result of having cancer (increased costs or reduced income). This financial impact can have a ripple effect on family members and can also be particularly devastating when in those with a reduced income already, such for those who are retired. An AML patient we spoke to previously describes her experience of diagnosis on herself and those around her. She said *"the shock and upheaval was enormous and very disorientating. I have two young boys, my husband runs his own business and I am a singing teacher. We had to make immediate arrangements to cover childcare and work appointments and then look at how to sustain this for the coming months. The impact of a disease like this ripples through your immediate family and into your network of friends and colleagues."* The physical, financial and emotional impact of AML does not affect the patient in isolation and is often also felt by carers and family members. According to an international survey run by the Acute Leukaemia Advocates Network in 2019, 35% of patients reported their AML definitely had an emotional impact on their family, friends or carers. As such, improvements in a patient's treatment options and prognosis will have a wider impact on the lives of their family and friends. Another patient we spoke to for the purpose of this submission, said: *"The diagnosis of AML had a massive impact on me and my family - particularly as this occurred during the Covid pandemic. The illness and treatment alone had a significant effect on my physical health, going almost overnight from a 'normal' healthy active person - to struggling to get upstairs and needing to sleep during the day or after any small physical exertion due to extreme fatigue. However, I found the emotional impact of AML more significant and traumatic than the physical aspect - life was suddenly turned upside down - I didn't know if I would survive the illness; my kids were young so didn't understand the diagnosis and I was isolated from my family for long periods of time. It took a long time to process what had actually happened and how I could move on."*

	If patients are unable to care for themselves, these family and friends can then become carers. Many patients (41% of those surveyed) feel their AML has had an impact, to some extent, on the social activities of their family, friends or carers, this is likely due to increased responsibilities. This can be a huge change in dynamics in the relationship between the patients and their relative/friend, with emotional effects. Additionally, caring is physically exhausting and may be done in addition to paid work. Alternatively, family may have to give up work to care for the patients, leaving the family in even more financial difficulty.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Chemotherapy is an intensive treatment associated with severe side effects as reported by patients. One patient reports, "*I was given standard chemotherapy. I suffered various side effects from rashes, high fevers of 41.7, sepsis, erythema nodosum, lung fungal infections and the usual vomiting and diarrhoea. I also suffered an excruciating inflammation of the small intestine*". As such, there are AML patients who will be unsuitable for chemotherapy because they are unable to tolerate such an intensive treatment. This can often be (but is not limited to) older AML patients who are considered frailer. Venetoclax with azacitidine was approved for those unsuitable for chemotherapy in the last few years and is now the standard of care. Other treatment options in this setting are azacitidine (if patient has 20-30% blasts and multilineage dysplasia), low dose cytarabine and daunorubicin (LDAC) or best supportive care. However, these have limited efficacy, with low response rates and many patients experience relapse quickly, hence they are not often used in routine clinical commissioning.

8. Is there an unmet need for patients with this condition?	There is an unmet need for more treatment options for those who are unsuitable for chemotherapy, as both patients and clinicians strongly value having more options to personalize treatment plans. Patients prefer to have as few side effects from treatment as possible, as this often has a direct impact on their quality of life. There is therefore a need for more targeted treatment options, which could target specific mutations within AML, and have the potential of fewer or less severe side effects. Having treatments with different modes of action available, e.g., therapies that target certain mutations within AML such as IDH-1, is also important to clinicians so they can exercise some level of choice in the treatment plans they deliver. Personalised care and joint-decision making are also very important to leukaemia patients in their experience of treatment. What works for one patient, may not always work for another. A patient we spoke to for the purpose of this submission commented*: "Having a range of treatment options is vital for AML patients like me so we can make an informed choice about our care".* She went on to say: *"I think that existing treatments for AML focus mainly on chemotherapy and stem cell transplant (and rightly so as this is the most effective treatment) - however there needs to be more treatment options available for those for whom chemotherapy is not suitable in order to increase chance of survival."*

Advantages of the technology. What do patients or carers think are the advantages of the technology?	Ivosidenib with azacitidine is innovative as it targets the specific IDH1 mutation in AML. Patients with this mutation have worse prognosis, so a drug designed to inhibit the mutated cells could prove to be more effective than non-targeted therapies. In fact, the AGILE clinical trial demonstrated the effectiveness of the targeted treatment vs azacitidine. Results showed that at a median follow-up of 12.4 months, event-free survival was significantly longer in the ivosidenib with azacitidine group than in the azacitidine only group. Furthermore, the estimated probability that a patient would remain event-free at 12 months was 37% in the ivosidenib with azacitidine group and 12% in the azacitidine only group. Overall survival was also significantly better with ivosidenib with azacitidine than with azacitidine on its own, with median overall survival at 24.0 months vs 7.9 months. In addition, targeted therapies are likely to have fewer side effects than non-targeted therapies. The AGILE clinical trial showed that adverse side effects of grade 3 or more included febrile neutropenia (28% with ivosidenib with azacitidine and 34% with azacitidine only) and neutropenia (27% and 16%, respectively); the incidence of bleeding events of any grade was 41% and 29%, respectively. The incidence of infection of any grade was 28% with ivosidenib with azacitidine and 49% with azacitidine only. Ivosidenib and azacitidine showed significant clinical benefit as compared with placebo and azacitidine in this difficult-to-treat population. A patient we spoke to for the purpose of this submission stressed the importance of drugs with a reduced side effect profile in the treatment of AML, like ivosidenib with azacitidine. She said "*different treatments may have a range of differing side effects which will also impact on a patient's quality of life, so having options for treatment allows patients to choose the most suitable treatment for them (in conjunction with their healthcare team).*" Ivosidenib is an oral tablet treatment, which many leukaemia patients find to be the most convenient treatment delivery method. While the delivery of azacitidine will require patients to receive cycles in

	hospital, this is still beneficial compared with treatments requiring inpatient extended stays in hospital which can cause greater disruption to patients' lives. An alternative to this means patients can spend more time with family and friends and be in the comfort of their own homes.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As with any cancer treatment, patients are likely to experience side-effects including some grade 3 or higher adverse events. In the AGILE trial some grade 3 or higher adverse events that occurred in patients who took ivosidenib with azacitidine were febrile neutropenia, anaemia, neutropenia, thrombocytopenia, and pneumonia. However, the adverse events above were not as prevalent in those who took ivosidenib with azacitidine as they were in patients who took azacitidine alone. Another disadvantage is that bleeding events were more frequent with ivosidenib and azacitidine than with azacitidine alone (41% vs. 29%). However, many of these side effects, including differentiation syndrome, can be managed by clinicians, for example with the use of glucocorticoids, diuretics, and hydroxyurea. Furthermore, AML patients often rank survival and improved chances of remission as higher priorities for treatment than it having tolerable side effects. This trial demonstrated that ivosidenib with azacitidine is effective in extending event-free survival, increasing the likelihood of complete remission, and prolonging overall survival among IDH1 patients with AML who couldn't have chemotherapy.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	N/a

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	N/a

Other issues

13. Are there any other issues that you would like the committee to consider?	N/a

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• AML is a rapidly progressing life-threatening disease with high relapse rates. It also has a significant impact on the quality of life of the patient as well as on family, friends, and carers. • There is an unmet need for greater treatment options, such as targeted treatment options, for those with AML who are unsuitable for chemotherapy. • Ivosidenib with azacitidine shows improved event-free survival, overall survival and likelihood of complete remission in the target group than azacitidine alone. • Ivosidenib with azacitidine has an improved side effect profile than azacitidine alone and some of the side effects can be managed by clinicians. • Ivosidenib is an oral treatment which is convenient to patients.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Royal College of Pathologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	Non profit, professional body, self-funded
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To achieve remission, prolong overall survival and reduce the risk of relapse
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant response would be achievement of morphologic remission in the bone marrow (<5% blasts) accompanied by normalisation/or improvement of blood counts to plts ≥100 and neuts ≥1 (complete remission, CR) or CRi (complete remission with incomplete count recovery, plts<100, neuts <1) or CRh (CR with partial haematologic recovery, neuts ≥0.5, plts ≥50). These definitions are listed in the ELN 2022 guidelines on diagnosis and management of AML: https://ashpublications.org/blood/article/140/12/1345/485817/Diagnosis-and-management-of-AML-in-adults-2022
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Patients diagnosed with AML who are unsuitable for intensive chemotherapy have a poor prognosis and in most cases will ultimately die from their disease even with the current standard of care treatment (venetoclax and azacitidine). No targeted therapies for IDH-mutant AML are currently available in the UK despite approval in USA and Europe.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	The current standard of care would be to offer venetoclax and azacitidine combination chemotherapy for this patient population.
9a. Are any clinical guidelines used in the	Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN : https://ashpublications.org/blood/article/140/12/1345/485817/Diagnosis-and-management-of-AML-in-adults-2022

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The current pathway of care is well-defined in terms of understanding the appropriate patient population suitable for therapy with venetoclax and azacitidine (ven aza; older patients, medically unsuitable for intensive chemotherapy). In many cases, results of a myeloid gene panel (which would identify the presence of IDH1 mutations) is not available at the time of diagnosis of AML. Some patients with indolent, non-proliferative disease could wait for 3-4 weeks for this result to be available to guide targeted therapy (with an IDH1 inhibitor) if this were to be approved. Currently, due to the absence of access to a targeted therapy for IDH1 in the UK (and in those patients who are unwell due to their AML and needing to start therapy sooner e.g. due to proliferative disease) treatment with venetoclax and azacitidine would generally commence before the availability of results from the mutational screening. In general, the approach to managing patients deemed not fit for intensive chemotherapy is standardised across the UK in terms of choice of treatment (ven aza) although there are nuances to the management of patients on treatment, due to evolving data about management of the toxicity (side effects such as cytopenias) and the potential ability to de-escalate duration and dose of venetoclax therapy (not yet evaluated in a prospective randomised trial).
9c. What impact would the technology have on the current pathway of care?	If access to ivosidenib was introduced, then stable, non-proliferative patients who could await the results of mutational screening could be offered ivosidenib and azacitidine (ivo aza) instead of venetoclax and azacitidine. The availability of a targeted therapy may in turn drive the earlier turnaround of testing for IDH1 mutations potentially via a new separate test.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Ivosidenib is oral, therefore administration would be the equivalent of giving treatment with venetoclax in the outpatient setting. In the AGILE study, https://www.nejm.org/doi/pdf/10.1056/NEJMoa2117344?articleTools=true, tumour lysis syndrome (TLS) was not reported as a frequent AE; this has implications as currently intensive (often inpatient) monitoring is performed in new AML patients starting ven-aza therapy to monitor for biochemical TLS as a potentially serious (although infrequent) treatment complication. It is likely that ivo aza could be given exclusively in the outpatient setting although there would be a need for monitoring for differentiation syndrome, which occurred in 14% of patients on trial.
10a. How does healthcare resource use differ between the technology and current care?	As above, there may be fewer inpatient days accrued for patients receiving the combination of ivo aza at least in the first cycle.
10b. In what clinical setting should the technology be used? (For example,	Outpatient clinic, secondary care

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None – oral medication self-administered
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	There are currently no randomised comparative data analysing the effects of ivo aza versus ven aza. The comparator arm for the AGILE study (azacitidine monotherapy) would now no longer be considered the standard of care arm. Data analysing the outcomes for IDH1mut patients (who account for 6-10% of newly diagnosed AML patients) drawn from 2 studies evaluating the use of ven aza in these patients suggested high response rates for IDH1/2mut AML with this therapy https://aacrjournals.org/clincancerres/article/28/13/2753/705002/Impact-of-Venetoclax-and-Azacitidine-in-Treatment. Composite complete remission [CR+CRi] rates among patients for ven aza vs aza/PBO with IDH1/2mut were 79%/11% respectively, median duration of remission (mDoR) was 29.5/9.5 months respectively, and median overall survival (mOS) was 24.5/6.2 months respectively. In patients with IDH1mut AML, CRc rates (ven aza vs aza) were 66.7%/9.1% and mOS 15.2 months (95% CI, 7.0–NE) versus 2.2 months (95% CI, 1.1, 5.6), HR: 0.19 (0.08– 0.44) respectively. Patient numbers were small and accrued from the combination of 2 different studies (including one non-comparative early Phase study of ven aza alone); the number of IDH1mut patients included in total in this analysis was 44 (33 received ven aza, 11 received aza/PBO). There was a suggestion that IDH1mut patients responded less well than IDH2mut patients to ven aza however. CRc rates among patients with IDH1/2 wild-type (WT) were 63%/31%, mDoR 17.5/10.3 months, and mOS 12.3/10.1 months. For ivo aza, a selected IDH1mut population was treated (rather than subsequent subgroup stratification by molecular status), EFS rather than OS was the primary endpoint, therefore the study outcomes are not directly comparable and the studies were powered differently. Furthermore, the AGILE study terminated early due to benefit for ivo aza meaning that the full pre-planned analyses could not be completed. For IDH1mut patients randomised to ivo-aza vs aza/PBO with less mature data, the median OS was 24.0 months (95% CI, 11.3to 34.1) and 7.9 months (95% CI, 4.1 to 11.3) respectively (hazard ratio for death, 0.44; 95%CI, 0.27 to 0.73; P = 0.001). CRc rate was 54% for ivo aza versus 16% for aza/PBO. In summary it is therefore difficult to be certain that there will be definite clinical benefit for the small percentage (6-10%) of AML patients with IDH1mut disease receiving ivo aza. The small numbers of IDH1mut patients in the VIALE-A substudy (Pollyea study) suggest that ven aza is a valid therapy for IDH1mut patients (although their

	response rates may be inferior to IDH2mut patients); whether ivo aza presents an advantage over this is unclear. Furthermore, currently studies are evaluating novel combinations – ivo/ven vs ivo/ven/aza in early phase and likely a different ivo-containing combination might show additional benefit – the results of larger studies will need to be awaited.
11a. Do you expect the technology to increase length of life more than current care?	As above – this is unclear
11b. Do you expect the technology to increase health-related quality of life more than current care?	It is possible that HR QoL would be superior with ivo aza versus ven aza as the side effect profile may be less, however this has not been compared prospectively.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Only suitable for IDH1mut AML (6-10% of all AML cases)

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	No difference in administration. It is possible that fewer inpatient days in the first cycle of therapy will be required for treatment with ivo-aza due to lack of need for tumour lysis monitoring. However, monitoring for differentiation syndrome with blood tests and clinical review would be needed with ivo aza and less of an issue for ven-aza.

acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No data for stopping in remission patients i.e. continue until loss of response.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	I am not clear that there will be a substantial benefit over current standard of care.
16a. Is the technology a 'step-change' in the management of the condition?	Yes – the use of a targeted therapy providing one of the few options for a personalised medicine approach to treatment of AML.
16b. Does the use of the technology address any	Yes – the availability of personalised/targeted therapy for AML

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Ivo-aza is tolerable with a good safety profile and can be given in the outpatient setting therefore this would have a positive impact on patients' quality of life

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	No – standard of care arm is now obsolete
18a. If not, how could the results be extrapolated to the UK setting?	Only by considering the published data as outlined above relating to subgroup data arising from VIALE-A (ven aza vs aza/PBO) in comparison with AGILE (ivo aza vs aza/PBO). It is unlikely that a comparative trial will ever be performed as now venetoclax is being studied in combination with ivosidenib.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	OS and EFS as well as CR are the most important parameters and all were presented in the studies reviewed and described above.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were	Nil known

not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA765 and TA787?	The study by Pollyea https://aacrjournals.org/clincancerres/article/28/13/2753/705002/Impact-of-Venetoclax-and-Azacitidine-in-Treatment provided insight into the responses for IDH1/2mut AML patients that was not described in detail in VIALE-A
21. How do data on real-world experience compare with the trial data?	Real world data are lacking

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A

Topic-specific questions

23. The following treatments have been included as comparators in the scope for this evaluation (alongside ivosidenib with azacitidine): **- venetoclax with low dose cytarabine (if over 30% bone marrow blasts)** **- azacitidine (if not eligible for HSCT and have AML with 20% to 30% blasts and multilineage dysplasia)** **- low dose cytarabine.** **What proportion of people with untreated IDH1-positive acute myeloid leukaemia are likely to receive these treatments (if any)?**	At present all of IDH1mut patients suitable for treatment but unsuitable for intensive chemotherapy will receive most likely ven-aza (some will receive ven-cytarabine according to local physician preference).

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Ivosidenib combined with azacitidine significantly improves EFS and OS for older unfit patients with newly diagnosed IDH1mut AML • IDH1mut status is not available at diagnosis and can take up to 4-6 weeks to be available using current technologies meaning that only very stable, non-proliferative patients could wait to see the results of screening before starting therapy, were the targeted therapy to be approved • IDH1mut AML is infrequent at 6-10% of all cases • There are no comparative data for ivo-aza vs currently available standard of care options • Outcomes for patients with ven-aza and IDH1mut are reasonable and it is unclear if ivo aza would offer an advantage over that combination

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

A Single Technology Appraisal

Produced by

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Date completed 09/11/2023

Source of funding This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR136108.

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 report should be referenced as follows	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.

Author Contributions:

Maxwell S. Barnish	Project manager. Led the EAG's critique of the decision problem and clinical effectiveness evidence. Edited the report.
Brian O'Toole	Lead for the EAG's appraisal of the economic evidence, drafted economic sections of the report, writing and editorial input
Elham Nikram	Contributed to the EAG'S assessment of cost effectiveness. Conducted modelling for the EAG.
Justin Matthews	Wrote sections 3.4 (Critique of the indirect comparison) and 3.5.3, and contributed to 3.6 and 4.2.6 (Treatment effectiveness and extrapolation).
Sophie Robinson	Critical appraisal of the company's literature search strategies and conducted additional literature searches on behalf of the EAG.
Ahmed Abdelsabour	Contributed to the EAG's assessment of cost effectiveness.
Steven Knapper	Clinical advice to the EAG
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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, 1.5, and 1.6.

The EAG identified a decision problem key issue related to the exclusion of comparators. The EAG also identified another overarching key issue relating to the company's literature searches. This issue affected the identification of literature for both the clinical and cost-effectiveness reviews. The EAG did not identify any key issues that solely related to clinical effectiveness.

The key cost effectiveness issues related to the plausibility of the treatment effect of IVO+AZA vs VEN+AZA (derived from a Network Meta Analysis), the plausibility of modelled long term OS estimates (EFS and OS), the appropriateness of including a functionally cured health state in the model, the inclusion of a 3 year stopping rule for IVO+AZA and VEN+AZA, the proportion of patients estimated to have a complete response (CR/CRi) in the VEN+AZA treatment arm and the number of hospitalisation days estimated for VEN+AZA during treatment initiation.

Table 1: Summary of key issues

ID	Summary of issues	Report sections
#1	Exclusion of relevant comparators from the decision problem	2.4

ID	Summary of issues	Report sections
#2	Uncertainty surrounding the treatment effectiveness of IVO+AZA vs VEN+AZA	4.2.6
#3	Uncertainty surrounding OS and EFS extrapolation and the implementation of a functionally 'cured' health state	4.2.6 and 4.2.6.2 and 4.2.6.3 and 4.2.6.4
#4	Uncertainty surrounding the implementation of a 3-year stopping rule	4.2.8.1
#5	Uncertainty surrounding the proportion of patients with complete remission estimated in the model for VEN+AZA	4.2.6.6
#6	Uncertainty surrounding the number of hospitalisation days assumed for VEN+AZA during treatment initiation	4.2.8.2
#7	Concerns regarding the appropriateness of the company's clinical- and cost-effectiveness literature searches	3.1

In addition to the EAG corrections outlined in Section 6.1, the key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
OS and EFS extrapolation in the IVO+AZA arm	For IVO+AZA, the company modelled OS using an independent lognormal curve. EFS was also modelled using a lognormal curve.	For IVO+AZA, the EAG preferred to extrapolate OS and EFS using the Weibull distribution	4.2.6.2 and 4.2.6.3
Implementation of a functionally 'cured' health state	The company included a cured health state in the model termed 'long term survival' or LTS. At 3 years, 100% of patients in the EFS state moved into the LTS state.	The EAG preference was to remove the cure assumption at 3 years for patients in the EFS state i.e. patients do not move into the LTS state	4.2.6.4

	Company's preferred assumption	EAG preferred assumption	Report Sections
The implementation of a 3-year stopping rule	100% of patients stop treatment at 3 years (applies IVO+AZA and VEN+AZA)	No stopping rule applied to modelled treatments i.e. 100% of patients continue to receive treatment after year 3	4.2.8.1
The proportion of patients with complete remission estimated in the model for VEN+AZA	For VEN+AZA % of patients estimated to experience CR/CRi was estimated based on an equation by the company.	The EAG preferred to estimate % of patients with CR/CRi (in VEN+AZA arm) based on the odds ratio within the NMA.	4.2.6.6
Hospitalisation days assumed for VEN+AZA during treatment initiation	32 days for VEN+AZA based on published study by Raush et al[1].	14 days (based on clinical opinion)	4.2.8.2
Relative dose intensity (100% for all treatment arms)	IVO: [redacted] (from AGILE) VEN+AZA: Assumed to be the same as IVO	100% RDI for all treatments	4.2.8.1

Abbreviations:

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- From the company's base case analysis IVO+AZA increases both length of life and quality of life for patients when compared to VEN+AZA. Due to the increased effectiveness of IVO+AZA, a higher proportion of patients are estimated to be alive at key landmark time points when compared to VEN+AZA. The company estimates the incremental LY gain of IVO+AZA to be [redacted] compared to VEN+AZA.
- A higher proportion of patients on IVO+AZA remained event free over time compared to VEN+AZA. The EFS states (CR/Cri) and (No CR/Cri) are associated with higher utility and lower costs compared to the PD health state.

- All patients alive in the EFS health state at 3 years are assumed to be functionally cured and experience mortality based on general population estimates. This assumption applies to all treatment arms. At 3 years, a higher proportion of patients in the IVO+AZA arm enter the LTS state compared to patients on VEN+AZA. Approximately [redacted] QALYs or [redacted] of the total IVO+AZA QALY gain is derived from the modelled LTS health state. For Ven +AZA, approximately [redacted] QALYs or [redacted] of the total VEN+AZA QALY gain is derived from the modelled LTS health state.
- The model differentiates between remission (CR/CRi) and non remission (No CR/CRi) health states. The CR/CRi health state is associated with a higher utility value. A higher % of patients on IVO+AZA have CR/CRi compared to patients on VEN+AZA.

Overall, the technology is modelled to affect costs by:

- The company estimate that IVO+AZA is associated with considerably higher drug costs over the modelled time horizon compared to VEN+AZA ([redacted] vs [redacted] respectively). The EAG noted that results were sensitive to variation in modelled assumptions which impact on treatment cost i.e. stopping rule assumptions and dose assumptions.
- The company estimated that treatment with IVO+AZA would result in medical resource use savings compared to VEN+AZA ([redacted] vs [redacted] respectively). These savings were primarily driven by the company's assumption surrounding the number of hospitalization days required during treatment initiation for both treatment arms.
- Minor savings due to fewer adverse events were estimated for IVO+AZA. Adverse events were not considered a key driver of cost effectiveness results.

The modelling assumptions that have the greatest effect on the ICER are:

Based on the scenario analysis provided by the company, results were not particularly sensitive to a variation in key modelled parameters i.e. IVO+AZA remained dominant vs VEN+AZA for most scenarios. However, the EAG has conducted a range of scenario analyses to test additional uncertainty. The following assumptions had a moderate/large impact on the results.

- Use of alternative HR estimates for IVO+AZA
- Use of alternative OS and EFS parametric curves in the IVO+AZA arm
- Removal of LTS health state
- Use of alternative proportions receiving posaconazole

1.3. The decision problem: summary of the EAG's key issues

Key Issue 1: Exclusion of relevant comparators from the decision problem

Report sections	**2.4**
Description of issue and why the EAG has identified it as important	The company excluded three of the four comparators in the NICE scope from its decision problem. These were azacitadine monotherapy, low dose cytarabine and venetoclax with low dose cytarabine. Clinical expert advice to the EAG was that all scoped comparators are available for use in the UK. Venetoclax with azacitidine would be considered the standard of care. However, it can be quite a challenging regimen to tolerate and is better seen as a moderate intensity rather than low intensity treatment. Therefore, it is only suitable for the fitter among those people with AML who are not considered fit for high intensity chemotherapy. The other scoped comparators would be used for people with AML who are not sufficiently fit to tolerate venetoclax. Azacitidine monotherapy would be the least common option, although will occasionally be used for people with AML who are not fit to tolerate any of the other treatment options. The EAG considered that the exclusion of relevant comparators – that is to say comparators that may be used in clinical practice, regardless of how frequently they are used - may provide misleading estimates of cost-effectiveness. The EAG did not consider exclusion of three of the four scoped comparators to be appropriate.
What alternative approach has the EAG suggested?	The EAG suggested that all scoped comparators should be included in the company decision problem and presented consistently throughout the CS.
What is the expected effect on the cost-effectiveness estimates?	The EAG noted that NMA results for all the excluded comparators were presented in Appendix D ITC. The EAG noted that economic model results were not presented in the CS or appendices for any of the excluded comparators. However, the EAG also noted that model results for azacitadine monotherapy, but not the other

Report sections	2.4
	excluded comparators, were presented within the model file. Excluding relevant comparators from the decision problem can lead to misleading conclusions around cost-effectiveness.
What additional evidence or analyses might help to resolve this key issue?	The inclusion of all scoped comparators in the economic analysis, using the available NMA results, could help address uncertainty.

Abbreviations: EAG, Evidence Review Group

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified a decision problem key issue related to the exclusion of comparators (Key Issue 1). The EAG also identified another overarching key issue relating to the company's literature searches (Key Issue 8). This issue affected the identification of literature for both the clinical and cost-effectiveness reviews. The EAG did not identify any key issues that solely related to clinical effectiveness.

1.5. The cost effectiveness evidence: summary of the EAG's key issues

Key Issue 2: Uncertainty surrounding the treatment effectiveness of IVO+AZA vs VEN+AZA

Report sections	4.2.6 and 4.2.6.1
Description of issue and why the EAG has identified it as important	Due to the lack of direct head to head data, the company conducted an NMA to determine the effectiveness of IVO+AZA compared to VEN+AZA. There are several concerns surrounding the company's NMA and associated results including the following. • Credible intervals for EFS and OS HRs for IVO+AZA cross 1, indicating a non-significant difference in both outcomes vs VEN+AZA. • There is some heterogeneity across studies included within the NMA. The company selected FE over RE models, and therefore the credible intervals on treatment effects presented do not properly express heterogeneity. • There were some violations of the proportional hazards assumption • Inconsistency within the NMA could not be assessed because there were no closed loops

Report sections	4.2.6 and 4.2.6.1
	Whilst conducted to a reasonable standard, the EAG considered the results of the NMA to be uncertain, possibly more so than suggested by the CrIs.
What alternative approach has the EAG suggested?	In order to test uncertainty, the EAG conducted the following scenario analyses a) Vary IVO+AZA OS HR by +/- 25% b) Vary IVO+AZA EFS HR by +/- 25% c) Vary IVO+AZA EFS and OS HRs using upper and lower bound credible intervals
What is the expected effect on the cost-effectiveness estimates?	See Section 6.2 for results.
What additional evidence or analyses might help to resolve this key issue?	Direct head to head data comparing IVO+AZA to VEN+AZA would mitigate uncertainty surrounding comparative effectiveness. However, the EAG acknowledge that this would only be possible with a new RCT.

Abbreviations: EAG, Evidence Review Group

Key Issue 3: Uncertainty surrounding OS and EFS extrapolation for IVO+AZA and the implementation of a functionally 'cured' health state

Report sections	4.2.6.2 and 4.2.6.3 and 4.2.6.4
Description of issue and why the EAG has identified it as important	Due to the short-term nature of the AGILE study, the company estimated long term OS and EFS using parametric survival modelling. For IVO+AZA, the company extrapolated OS using a log normal curve. Using this curve, 10-year OS was estimated to be [redacted]. Based on clinical opinion to the EAG, this was considered to be implausibly high. Furthermore, the EAG noted that 2/3 clinician responses to the company suggested that either the Weibull or the Exponential provide more plausible OS estimates i.e. 10 year OS using the Weibull was estimated to be [redacted], and 10 year OS using the Exponential to be [redacted]. Additionally, the EAG noted that there was minimal difference between the Log normal and the Weibull curves based on AIC/BIC statistics. As part of the EAG preferred base case, the Weibull curve was used to extrapolate long term OS. Similarly, for EFS, the EAG considered the company's extrapolated results (using a lognormal curve), resulted in implausibly high EFS rates at key landmark time points. Based on clinical opinion to the EAG, the Weibull curve appeared to provide more plausible estimates. The EAG

Report sections	4.2.6.2 and 4.2.6.3 and 4.2.6.4
	therefore selected the Weibull curve for use in it's preferred base case. Furthermore, the model assumes that at 3 years, 100% patients remaining in the EFS health state can be considered functionally cured (this assumption applies to all modelled treatment arms). The company primarily justified the inclusion of a cured health state on the basis of precedence (TA765). The EAG consider that there is a lack of robust clinical evidence to support a cure assumption. It should be noted that when extrapolated OS is adjusted to reflect a cure point at 3 years, 10-year OS for IVO+AZA increases from [redacted] to [redacted]. Similarly, the OS rate at 10 years for VEN+AZA increases from approximately [redacted] to [redacted]. As noted previously, the EAG consider these estimates lack clinical plausibility. As part of the EAG preferred base case, the LTS health state was removed from the model.
What alternative approach has the EAG suggested?	To test uncertainty surrounding the long-term extrapolation of IVO+AZA OS and EFS, the EAG has conducted scenario analyses using an alternative plausible curve fit (exponential). To test uncertainty surrounding the modelled cure assumption, the EAG has conducted a scenario analysis that assumes only patients in the EFS health state with complete remission (CR/CRi) can be cured at 3 years.
What is the expected effect on the cost-effectiveness estimates?	These scenarios had a large impact on total costs and QALYs in the IVO+AZA arm and VEN+AZA arms.
What additional evidence or analyses might help to resolve this key issue?	Long term OS and EFS data would help to validate modelled extrapolated estimates and determine the appropriateness of a cure assumption. The EAG acknowledges that these data are currently not available.

Abbreviations: EAG, Evidence Review Group

Key Issue 4: Uncertainty surrounding the implementation of a 3-year stopping rule

Report sections	4.2.8.1
Description of issue and why the EAG has identified it as important	The company assumes that 100% of patients discontinue active treatment at 3 years. Based on clinical opinion to the EAG, it is plausible that clinicians may continue to use IVO+AZA if patients are responding to treatment. Furthermore, the SmPC for IVO does not state

Report sections	4.2.8.1
	that patients should discontinue treatment at 3 years. As part of the EAG preferred base case, the 3-year stopping rule for IVO+AZA and VEN+AZA has been removed
What alternative approach has the EAG suggested?	In order to test additional uncertainty, the EAG has conducted the following scenario analyses • Assume 50% of patients stop treatment at 3 years (applied to all treatments) • Apply stopping rule at 5 years i.e. assume 100% of patients discontinue treatment at 5 years (applied to all treatments)
What is the expected effect on the cost-effectiveness estimates?	These scenarios did not have an impact on results. See Section 6.2
What additional evidence or analyses might help to resolve this key issue?	Longer term time on treatment (ToT) data and RWE for all treatments would help to address uncertainty

Abbreviations: EAG, Evidence Review Group

Key Issue 5: 100% Relative dose intensity

Report sections	4.2.8.1
Description of issue and why the EAG has identified it as important	Drug costs in the model for IVO and AZA were based on the relative dose intensity (RDI) observed in AGILE ([redacted]). In the absence of data for VEN, the company assumed that the RDI for IVO would also apply to VEN. The EAG consider that modelled drug costs should be based on 100% RDI for all treatments, as the drugs are oral and given to the patient to consume at home, thus the cost of complete packages is incurred by the NHS.
What alternative approach has the EAG suggested?	As part of the EAG preferred base case, 100% RDI has been assumed for all treatments.
What is the expected effect on the cost-effectiveness estimates?	This scenario analysis resulted in a minor increase in total costs within the IVO+AZA and VEN+AZA treatment arms. See Section 6.2 for results.
What additional evidence or analyses might help to resolve this key issue?	Further research into the appropriateness of RDI within NICE health technology assessments should be conducted.

Abbreviations: EAG, Evidence Review Group

Key Issue 6: Uncertainty surrounding the proportion of patients with complete remission (VEN+AZA)

Report sections	4.2.6.6
Description of issue and why the EAG has identified it as important	Due to the lack of data availability, the company estimated the % of patients with CR/CRi in the VEN+AZA arm using an equation, which resulted in the proportion of patients with CR/CRi falling between the IVO+AZA and AZA arms of the AGILE study. The EAG noted that this approach introduces uncertainty into the analysis and furthermore does not utilise CR/CRi data estimated from the NMA.
What alternative approach has the EAG suggested?	As part of it's base case, the EAG preferred to estimate the % CR/CRi patients in the VEN+AZA arm based on the outcomes from the NMA. This is discussed further in Section 4.2.6.6 .
What is the expected effect on the cost-effectiveness estimates?	This analysis resulted in a minor decrease in VEN+AZA total costs.
What additional evidence or analyses might help to resolve this key issue?	Long term effectiveness data reporting complete response rates for all treatments would help to reduce uncertainty.

Abbreviations: EAG, Evidence Review Group

Key Issue 7: Uncertainty surrounding the number of hospitalisation days assumed for VEN+AZA during treatment initiation

Report sections	
Description of issue and why the EAG has identified it as important	For IVO+AZA the length of hospital stay during treatment initiation was [redacted] days. However, the company used a published study by Raush et al[1] to estimate the number of hospitalisation days associated with the comparator treatment VEN+AZA (32 days). Based on clinical opinion to the EAG, this was considered excessive and not representative of UK practice. The impact of assuming 32 day hospitalisation for VEN+AZA potentially overestimates costs in the comparator arm and biases the analysis in favour of IVO+AZA. The EAG assumed VEN+AZA would require 14 hospitalisation days for treatment initiation, as part of it's preferred base case.
What alternative approach has the EAG suggested?	A scenario analysis has been conducted which assumes VEN+AZA is associated with the same hospitalisation stay during treatment initiation as IVO+AZA ([redacted] days).
What is the expected effect on the cost-effectiveness estimates?	This scenario resulted in a moderate decrease in VEN+AZA total costs. See section 6.2 for results.

Report sections	
What additional evidence or analyses might help to resolve this key issue?	Robust UK data on VEN+AZA hospitalisation during treatment initiation would help to resolve uncertainty.

Abbreviations: EAG, Evidence Review Group

1.6. Other key issues: summary of the EAG's views

The EAG identified one additional key issue that is overarching across the clinical- and cost-effectiveness aspects of the appraisal. This relates to the appropriateness of the company's literature searches.

Key Issue 8: Concerns regarding the appropriateness of the company's clinical- and cost-effectiveness literature searches

Report sections	Appendix D
Description of issue and why the EAG has identified it as important	In each of the search strategies presented [Appendix D, pages 474 onwards] the population facet of the search has been narrowed to include only articles that specifically mention the phases first line/treatment naïve/untreated in the database record. Identifying first line treatment as a phrase search in a search strategy is difficult and there are no relevant indexing terms in the databases. It is highly possible that articles might not mention these phrases in the database record and that relevant papers might have been missed.
What alternative approach has the EAG suggested?	The searches should not have been narrowed in this risky way and the records thus excluded should have been screened to examine whether or not they are relevant to the review. It would be necessary to read the abstract in order to identify possible papers and in many cases it may also be necessary to look at the full text of the article.
What is the expected effect on the cost-effectiveness estimates?	Relevant evidence may not have been identified.
What additional evidence or analyses might help to resolve this key issue?	Papers excluded by the use of these terms in the search strategy should be identified and screened for relevance.

Abbreviations: EAG, Evidence Review Group

1.7. Summary of EAG's preferred assumptions and resulting ICER

The EAG's preferred base case results (based on a fully incremental analysis) are outlined in Table 3 and Table 4.

Table 3: EAG's preferred model assumptions (deterministic)

Preferred assumption	Comparator	Total Costs	Total QALYs	ICERs
Company base-case	AZA*	£110,384.07	0.88	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£190,639.07	2.17	[redacted]
EAG adjusted base case	AZA	£110,384.07	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£190,639.07	2.18	[redacted]
Weibull used to extrapolate OS (IVO+AZA)	AZA	£110,384.07	0.89	
	VEN+AZA	£170,130.13	2.05	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
Weibull used to extrapolate EFS (IVO+AZA)	AZA	£110,384.07	0.89	
	VEN+AZA	£211,629.03	2.02	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
No cure assumption + No stopping rule	AZA	£114,925.81	0.79	
	VEN+AZA	£217,639.77	1.82	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
100% Relative dose intensity	AZA	£110,864.33	0.89	
	VEN+AZA	£192,519.71	2.18	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
% of patients with CR/CRi based on NMA	AZA	£110,384.07	0.89	
	VEN+AZA	£185,309.44	2.19	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
14 day hospital stay for initiation with VEN+AZA	AZA	£110,384.07	0.89	
	VEN+AZA	£176,298.58	2.18	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
Cumulative	AZA	£115,408.11	0.79	
	VEN+AZA	£197,147.43	1.84	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year. *Extracted from company model: company did not report AZA comparisons in its submission

Table 4: EAG's preferred model assumptions (probabilistic)

Preferred assumption	Comparator	Total Costs	Total QALYs	ICERs
Company base-case	AZA*	£110,384.07	0.88	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£190,639.07	2.17	[redacted]
EAG adjusted base case	AZA	£110,384.07	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£194,565	2.20	[redacted]
Weibull used to extrapolate OS (IVO+AZA)	AZA	£95,493.77	0.77	
	VEN + AZA	£174,658.98	2.08	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Weibull used to extrapolate EFS (IVO+AZA)	AZA	£117,688.75	0.95	
	VEN + AZA	£168,164.29	1.63	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
No cure assumption + No stopping rule	AZA	£113,788.50	0.82	
	VEN + AZA	£206,901.25	1.68	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
100% Relative dose intensity	AZA	£123,558.09	0.99	
	VEN + AZA	£196,862.00	2.29	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
% of patients with CR/CRi based on NMA	AZA	£111,055.96	0.92	
	VEN + AZA	£163,491.62	2.17	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
14 day hospital stay for initiation with VEN+AZA	AZA	£103,668.79	0.88	
	VEN + AZA	£142,609.69	2.17	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Cumulative	AZA	£116,338.91	0.80	
	VEN + AZA	£197,923.37	1.86	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year. *Extracted from company model: company did not report AZA comparisons in its submission

Modelling errors identified and corrected by the EAG are described in 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see 6.2.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the Evidence Review Group (EAG) provides a review of the evidence submitted by Servier in support of ivosidenib with azacitidine for untreated IDH1-positive acute myeloid leukaemia.

2.2. Critique of the company's description of the underlying health problem

The company's description of the underlying health problem, untreated IDH1-positive acute myeloid leukaemia, is summarised in the CS Document B Section B.1.3. Leukaemia is a form of haematological cancer arising from dysfunctional proliferation of progenitor leukocytes. Based on growth rate, leukaemia is subdivided into two primary types: acute and chronic. Acute myeloid leukaemia (AML) is a sub-type of acute leukaemia and is an aggressive form of blood and bone marrow cancer, resulting in rapid disease progression.[2] As the most common form of leukaemia, it accounts for more than 80% of leukaemia cases diagnosed in adults.[3] AML is characterized by a population of cells developed from extensive and uncontrolled proliferation of myeloid progenitor cells.[3] Increasing age, male gender, genetic factors, environmental factors and lifestyle, drugs, chemical exposure, and antecedent blood disorders are associated with increased disease risk[4]. The EAG agrees with the company that evidence for an impact of IDH1 mutations on prognosis is mixed, but there may be evidence that people with IDH1 mutations fare worse.[5,6] It is acknowledged that establishing those patients not eligible for intensive therapy involves a degree of subjectivity, as criteria are not established. In this population, according to the company's definition, five-year survival rates fall from 41.6% in those aged under 65 years to 5.4% in those aged over 65.[7] The condition is considered to be both life threatening and chronically debilitating, due to the consequences of bone marrow dysfunction, including intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. As a result of fast progression, if left untreated, the condition may result in mortality within a few months.[8] The company estimates an eligible prevalent population for ivosidenib of approximately 100 patients in England.

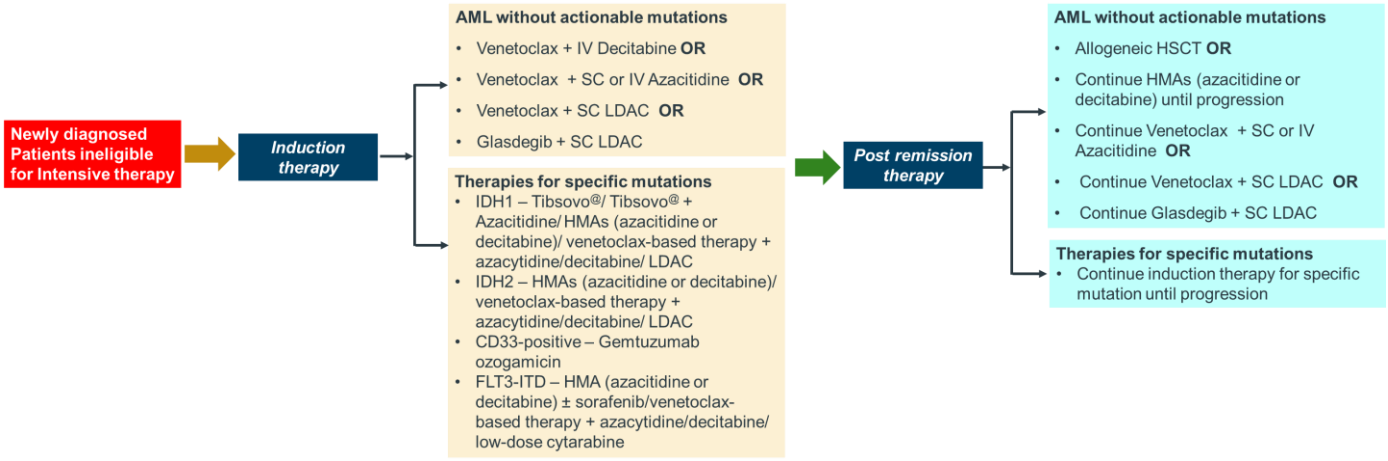
Clinical expert advice to the EAG was that ivosidenib would be relevant to those with IDH1 mutations, which is about 6% of the patient population. People with AML who are unable to tolerate intensive chemotherapy are typically older (estimated average age 75). The key

prognostic factors in AML were considered to be age (older age predicts poorer outcomes), genetics, white blood cell county and response to initial treatment. European LeukaemiaNet (ELN) 2022[9] risk classification criteria were considered relevant and commonly used in practice, with the caveat that they were developed for a younger patient population.

2.3. Critique of the company's overview of current service provision

The company's current care pathway is described in CS Document B Section 1.3. This is based on National Comprehensive Cancer Network (NCCN) guidelines[10] from the USA and depicted in a flowchart.

Figure 1. NCCN recommendations for the treatment of AML patients ineligible for standard intensive induction chemotherapy



Abbreviations: AML; acute myeloid leukemia; FLT3-ITD, FLT3 internal tandem duplication; G-CSF, granulocyte colony stimulating factor; HMAs, hypomethylating agents; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; IV, intravenous; LDAC, low-dose cytarabine; HSCT, hematopoietic stem cell transplantation; NCCN, national comprehensive cancer network; SC, subcutaneous

Source: CS Document B, Section B.1.3, p,17.

The company additionally cites the ELN guidelines for AML[9] and the European Society for Medical Oncology (ESMO)[11] guidelines for AML. Previous NICE guidance from TA218 (azacitidine)[12] and TA765 (venetoclax plus azacitidine)[13] is cited by the company.

There is no specific NICE guideline for leukaemia, however there is a broader NICE guideline (NG47)[14] which includes leukaemia treatment pathways. This was not cited by the company in its presentation of treatment pathways. The EAG considered that basing the company treatment pathways for this submission on American and European guidelines rather than NICE guidelines was not preferable, given the geographical remit of the present submission.

Clinical advice to the EAG was that the American NCCN guidelines as depicted in Figure 1 do not match well to UK practice. Decitabine and glasdegib are not available in the UK. In addition, the treatments outlined under 'Therapies for specific mutations' are not routinely available in the UK. Therefore, a combination of NG47 and NICE guidance on specific technologies would have been a more appropriate framing for treatment pathways.

Ivosidenib is an inhibitor of mutated IDH1 enzyme. Mutated IDH1 converts alpha- ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG) which blocks cellular differentiation and promotes tumourigenesis in both haematologic and non-haematologic malignancies. The mechanism of action of ivosidenib beyond its ability to suppress 2-HG and impair cellular differentiation is not fully understood across indications. The method of administration of ivosidenib is oral and the dosing is 500mg once daily, to be taken as 2*250mg tablets. A dose adjustment is required if concomitant azole antifungal therapy is used. Clinical advice to the EAG was that use of concomitant azole therapy is routine and reduces the necessary dose of ivosidenib without reducing efficacy. The list price of ivosidenib is £12,500 per patient per month. Clinical advice to the EAG was that ivosidenib has not been made available through compassionate use schemes. Therefore, as the EAG is not allowed to consult expert advisers who have worked on the company's AGILE trial, for reasons of conflict of interest, clinical advice to the EAG cannot be based on first-hand experience of using ivosidenib.

One implementation challenge for ivosidenib identified through clinical expert advice to the EAG is the need for rapid IDH1 testing. Currently in NHS practice IDH1 testing takes around three weeks to return results and is conducted as part of an array of 20 to 30 mutation tests. Therefore, the results of IDH1 testing are not routinely available to inform initial treatment decisions. The norm would be to standard treatment one to two weeks after diagnosis of AML. More rapid testing would be necessary to facilitate the introduction of ivosidenib, the prescription of which would be dependent on knowing the patient is IDH1 positive. These changes to testing procedures would have cost and resource implications.

2.4. Critique of company's definition of decision problem

The EAG considered the company's decision problem to be generally well aligned with the NICE scope, as described below in Table 5. There was, however, one major exception. The EAG did not consider the exclusion of three of the four scoped comparators to be appropriate. The EAG had significant concerns that this could lead to misleading cost-effectiveness conclusions.

Table 5: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with untreated IDH1-positive AML when intensive induction chemotherapy is unsuitable	In combination with azacitidine for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy	To align with licence	The licensed population is noted.
Intervention	Ivosidenib withazacitadine	Ivosidenib with azacitadine	N/A	N/A
Comparator(s)	• venetoclax with azacitidine • venetoclax with low dose cytarabine (if over 30% bone marrow blasts) • azacitidine (if not eligible for HSCT and have AML with 20% to 30% blasts and multilineage dysplasia) • low dose cytarabine	Venetoclax with azacitidine	Servier does not believe all these are relevant comparators. In TA218 (2011) azacitidine was recommended for AML only in those with 20-30% blasts. Therefore, low dose cytarabine was used in those with over 30% blasts. However, in TA765 (2022), the committee recommended venetoclax plus azacitidine as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable. This includes those in the 20% to 30% blast group and the over 30% blast group. Therefore, venetoclax	Clinical expert advice to the EAG was that all scoped comparators are available for use in the UK. Venetoclax with azacitidine would be considered the standard of care. However, it can be quite a challenging regimen to tolerate and is better seen as a moderate intensity rather than low intensity treatment. Therefore, it is only suitable for the fitter among those people with AML who are not considered fit for high intensity chemotherapy. The other scoped comparators would be used for people with AML who are not sufficiently fit to tolerate venetoclax.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			plus azacitidine now supersedes azacitidine as standard of care within the NHS. This is now considered standard of care via clinician feedback and endorsed by ELN 2022 guidelines and BSH 2022 good practice guideline, leaving azacitidine monotherapy as the treatment choice for MDS /AML patients with a blast level below 20%. In addition, low dose cytarabine monotherapy is also superseded by venetoclax plus azacitidine for any one with > 30% blasts. As a result of this low dose cytarabine is no longer used in clinical practice. Therefore, Servier believes the following comparators to not be suitable • low dose cytarabine- no longer used in clinical practice • azacitidine alone for adults who	Azacitidine monotherapy would be the least common option, although will occasionally be used for people with AML who are not fit to tolerate any of the other treatment options. The EAG considered that the exclusion of relevant comparators – that is to say comparators that may be used in clinical practice, regardless of how frequently they are used, may increase cost-effectiveness. The EAG noted that cost effectiveness results for ivosidenib with azacitadine compared to azacitadine monotherapy were presented in the model (though not discussed in the company submission), which was notable given this comparator was excluded from the company decision problem. The EAG also noted that NMA results (but not cost effectiveness results) were presented (Appendix D ITC) for all the excluded scoped

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			are not eligible for HSCT and have AML with 20% to 30% blasts and multilineage dysplasia Servier believes the population for venetoclax with low dose cytarabine if people have over 30% bone marrow blasts to be very small and therefore questions its suitability as a comparator. According to good practice BSH paper and clinical opinion this combination is reserved for very small group of patients who have >30% blast levels and + NPM1 mutation.	comparators. The EAG did not consider exclusion of three of the four scoped comparators to be appropriate.
Outcomes	The outcome measures to be considered include: • overall survival • event-free survival • disease-free survival • response rates, including remission • blood transfusion dependence	Per scope, excluding 'disease-free survival'	Disease-free survival is not an outcome relevant to the AGILE study, nor the population of patients for whom ivosidenib is indicated.	Clinical advice to the EAG was that event-free survival was a more common term than disease-free survival in this population, so the EAG was not concerned by this exclusion. However, it is important to note that event-free survival can be defined in different ways and the company used different

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• rate of complete remission and complete remission with partial haematologic recovery • adverse effects of treatment • health-related quality of life			definitions in the AGILE trial and in the model.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken	The company's reference case used QALYs to capture health benefit and results were presented using incremental cost per QALY. The time horizon used in the model was a lifetime horizon (25 years). Costs were considered from an NHS and Personal Social Services perspective. A PAS has been submitted for IVO. The company did not include the cost of associated with diagnostic testing for IDH1in people with AML. No sensitivity analysis was provided by the company which included this cost.	As per scope	The company's economic analysis was broadly aligned with the NICE scope and reference case. However, it should be noted that the company did not include the cost of associated with diagnostic testing for IDH1in people with AML. The EAG consider this to be an area of uncertainty.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	into account. The availability of any managed access arrangement for the intervention will be taken into account. The use of ivosidenib with azacitidine is conditional on the presence of the IDH1 mutation. The economic modelling should include the costs associated with diagnostic testing for IDH1 in people with AML who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual.			
Subgroups	None specified.	None specified.	N/A	N/A
Special considerations including issues related to equity or equality	None specified.	None specified.	N/A	Clinical advice to the EAG was that age was an important equality consideration as people with AML who are not eligible for intensive chemotherapy are on average much older (estimated average age 75) than those who can be treated with intensive chemotherapy regimens. Furthermore, higher age is an important

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				prognostic factor for worse outcomes in AML.

Abbreviations EAG, Evidence Review Group; NICE, National Institute for Health and Care Excellence

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify evidence on current and emergent treatments for newly diagnosed people with AML who are ineligible for intensive chemotherapy. The search sought to explore both efficacy and safety outcomes. Evidence for ivosidenib with azacitadine is presented in Section 3.2, while studies in the indirect treatment comparison are presented in Section 3.3. An overview of the methods used in the SLR is provided in Table 6 below.

Table 6: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Document B Section B.2.1; Appendix D Section 4.4, 8.2.	The search strategies were executed in a good range of sources. However, searches for acute myeloid leukaemia were narrowed to only include database records that had some version of the phrase first line/untreated/treatment naïve in them. It is highly possible that articles might not mention these phrases in the database record and that relevant papers might have been missed. Further information on this is at section 3.5.2. Several of the company searches were limited to exclude conference abstracts published between 2011-2015. In clarification the company stated that they wished to only search for conference abstracts from 2017 onwards, but this does not match what was done in the search strategies and the reasons for this discrepancy are unclear.
Inclusion criteria	Document B Section B.2.1; Appendix D Section 4.2.	The inclusion criteria for the clinical effectiveness review are considered to be broadly appropriate to the decision problem. The SLR was broader in scope in terms of eligible population than the NICE scope. The EAG did not consider this inappropriate but noted that a broader SLR increases the screening workload and the importance of screening to ensure no studies are missed. However, the EAG had significant concerns regarding the company searches as noted above and noted at least one relevant study had been missed.
Screening	Appendix D Section 4.7.	Screening was conducted independently by two reviewers for the SLR. Arbitration (a third reviewer) or reconciliation (discussion between the two reviewers) were used to resolve any disagreements. The EAG considered this to be appropriate and to minimise selection bias.

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Data extraction	Appendix D Section 4.9.	Standardised data extraction forms were used. However, it is not stated whether data extraction was conducted independently by two reviewers, which may increase bias.
Tool for quality assessment of included study or studies	Appendix D Section 4.8.	Cochrane Risk of Bias tool (RoB 2.0) was used. The EAG considered this appropriate as the included studies were RCTs. However, it is not stated whether risk of bias assessment was conducted independently by two reviewers, which may increase bias.
Evidence synthesis	B2.9 Appendix D [ITC]	Standard methods were used to synthesise time-to-event (OS, EFS) and binary (CR, CRi, CRh, TI, conditional TI) outcomes within NMAs. The company were careful to present and discuss potential effect modifiers, concluding that there was 'low to moderate degree of heterogeneity'. The company adopt FE over RE models, so heterogeneity is not properly expressed in the presented credible intervals. The company indicate that RE credible intervals were implausibly wide, but no attempt was made to adopt informative priors e.g. from Turner et al.[15] The time-to-event analyses assume proportional hazards which was often supported, though not in every instance. Proportional hazards distributions were implied by the NMA methods, but the distributions selected by the company to model survival (B3.3) were not.

Abbreviations: CS, Company submission; EAG, Evidence Review Group

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The company presented evidence from two RCTs. AGILE compared ivosidenib plus azacitadine with azacitadine plus placebo. VEALE-A compared venetoclax plus azacitadine with azacitadine plus placebo. The venetoclax plus azacitadine arm of VEALE-A was used in an NMA to inform the company's base case model. However, although azacitadine monotherapy was excluded from the scope as a comparator in the company's decision problem, a model was provided using the trial results for ivosidenib plus azacitadine versus azacitadine plus placebo. However, no commentary is provided in the company submission on these trial-based model results.

Table 7: Clinical evidence included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Outcomes	Study type
AGILE[16] NCT03173248	RCT	Previously untreated patients with *IDH1* Mutation and ineligible for intensive induction chemotherapy (N=146)	Ivosidenib +azacitadine	Azacitidine + placebo	Primary outcomes: EFS Secondary outcomes: CR rate, OS, CR+CRh rate, ORR, HRQoL, Safety	Phase III Australia, Austria, Brazil, Canada, China, Czechia, France, Germany, Israel, Italy, Japan, Korea, Republic of Mexico, Netherlands, Poland, Russian, Federation, Spain, Taiwan, United Kingdom
VIALE-A[17] NCT02993523	RCT	Previously untreated, sAML, ineligible for intensive induction therapy (N=433)	Venetoclax + azacitidine	Azacitidine + placebo	Primary outcomes: OS Secondary outcomes: Composite complete remission (CRi), CRh, complete remission by the initiation of cycle 2, red-cell and platelet transfusion independence, composite complete remission, and OS in	Phase III Australia, Austria, Belgium, Brazil, Canada, China, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Japan, Norway, Poland, Portugal, Russia, South Africa, South Korea, Spain, Sweden, Taiwan, Turkey, United States

Study name and acronym	Study design	Population	Intervention	Comparator	Outcomes	Study type
					molecular and cytogenetic subgroups, EFS, measurable residual disease by flow cytometry, and quality of life according to patient-reported outcomes	

Abbreviations: RCT, randomized controlled trial

The company used the full VIALE-A trial population to inform its efficacy estimate for venetoclax plus azacitadine rather than results specific to people with the IDH1 mutation. These results are available from DiNardo et al[17] (VIALE-A sub-population with IDH1 mutation) and Pollyea et al[18] (pooled analysis from VIALE-A sub-population with IDH1 mutation and a single-arm phase Ib study in the same population). However, the company noted that these analyses were post-hoc and had small sample sizes. In VIALE-A, there were fewer than 20 people with the IDH1 mutation in the azacitadine plus placebo arm. The company say that this means it does not meet the inclusion criteria for the SLR. However, the EAG has reviewed table 1 of Appendix D, which outlines eligibility criteria for the clinical SLR, and notes that a minimum sample size is not stated in this table. The EAG considers it atypical to exclude studies in an SLR based on sample size and considered that a subgroup analysis of an already included study (VIALE-A) would not be considered a separate study, so this sample size requirement should not apply. However, the EAG also considered that larger studies are typically preferable. Clinical expert advice to the EAG was that IDH1 test results are currently not typically available before initial treatment decisions are made. Therefore, on balance, the EAG considered that the company's decision to prefer the full VIALE-A population was reasonable.

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

The write-up in this clinical section will focus on the AGILE[16] trial, as the VIALE-A[17] trial is solely used as a source of comparator data for venetoclax with azacitadine. Therefore, the VIALE-A trial was critiqued in the section on indirect treatment comparisons (Section 3.3).

AGILE was described by the company as a "Phase 3, multicenter, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of ivosidenib + azacitidine compared to placebo + azacitidine in newly diagnosed AML adult patients with an IDH1 mutation who are ineligible for intensive induction chemotherapy. Patients were randomized 1:1 to receive oral ivosidenib or matched placebo, both administered in combination with subcutaneous (SC) or intravenous (IV) azacitidine. Randomization was stratified by disease status (primary versus secondary AML) and geographic region (US and Canada; Western Europe, Israel, and Australia Japan; and rest of world)".

The trial compared ivosidenib plus azacitadine to azacitadine plus placebo. The active difference between arms was the addition of ivosidenib.

The company provided AGILE data from two different data cuts in its submission. The primary data cut was from 18 March 2021. In response to the clarification questions, the company clarified which data cut was used to inform the model for each key variable and also provided a new economic model with updated time on treatment data.

3.2.2.2. Population

Trial eligibility criteria

No table of trial eligibility criteria for AGILE in the CS could be identified by the EAG. The key trial publication[16] stated that the key inclusion criteria for AGILE were age of 18 years or older and a centrally confirmed diagnosis of previously untreated IDH1-mutated acute myeloid leukemia determined with the Food and Drug Administration–approved Abbott RealTime IDH1 in vitro polymerase-chain-reaction (PCR) assay. Additional eligibility criteria included no previous treatment with an IDH1 inhibitor or hypomethylating agent for myelodysplastic syndrome, an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 to 2 (on a 5-point scale in which higher scores indicate greater disability), and adequate hepatic and renal function. Ineligibility for intensive chemotherapy was defined by an age of 75 years or

older or at least one of the following medical conditions: an ECOG performance-status score of 2, a severe cardiac disorder (e.g., congestive heart failure resulting in treatment, a left ventricular ejection fraction of ≤50%, or chronic stable angina), a severe pulmonary disorder (e.g., a diffusing capacity of the lungs for carbon monoxide of ≤65% or a forced expiratory volume in 1 second of ≤65%), a creatinine clearance of less than 45 ml per minute, or a bilirubin level greater than 1.5 times the upper limit of the normal range.

The EAG noted that the trial population and the population in the company's decision problem were well matched, but that they were slightly narrower than the NICE scope. The EAG accepted the company's reasoning that this was to align with the licensed population and therefore had no concerns regarding the trial eligibility criteria for AGILE.

Baseline characteristics

Baseline characteristics for the AGILE full analysis set (FAS) for the main (March 2021) datacut were provided by the company in Section B.2.4 and are reproduced below as Table 8.

Table 8. AGILE – patient demographics and baseline characteristics (FAS) primary analysis March 18, 2021)

Endpoints	IVO + AZA (N = 72)	Placebo + AZA (N = 74)	Total (N = 146)
Age (years)			
Median (range)	76.0 (58.0, 84.0)	75.5 (45.0, 94.0)	76.0 (45.0, 94.0)
Age category (years), n (%)			
<75	33 (45.8)	31 (41.9)	64 (43.8)
≥75	39 (54.2)	43 (58.1)	82 (56.2)
Sex, n (%)			
Male	42 (58)	38 (51)	80 (55)
Female	30 (42)	36 (49)	66 (45)
Race or ethnic group, n (%) †			
Asian	15 (20.8)	19 (25.7)	34 (23.3)
White	12 (16.7)	12 (16.2)	24 (16.4)
Black	0	2 (2.7)	2 (1.4)
Other or not reported	45 (62.5)	41 (55.5)	86 (58.9)
ECOG PS, n (%) ‡			
0	14 (19.4)	10 (13.5)	24 (16.4)
1	32 (44.4)	40 (54.1)	72 (49.3)
2	26 (36.1)	24 (32.4)	50 (34.2)
Disease history according to investigator, n (%)			
Primary AML	54 (75.0)	53 (71.6)	107 (73.3)

Endpoints	IVO + AZA (N = 72)	Placebo + AZA (N = 74)	Total (N = 146)
Secondary AML§	18 (25.0)	21 (28.4)	39 (26.7)
History of myeloproliferative neoplasms	4 (5.6)	8 (10.8)	12 (8.2)
World Health Organization classification, n (%)			
AML with recurrent genetic abnormalities	16 (22.2)	24 (32.4)	40 (27.4)
AML with myelodysplasia-related changes	28 (38.9)	26 (35.1)	54 (37.0)
Therapy-related myeloid neoplasms	1 (1.4)	1 (1.4)	2 (1.4)
Cytogenetic risk status, n (%) **			
Favorable	3 (4.2)	7 (9.5)	10 (6.8)
Intermediate	48 (66.7)	44 (59.5)	92 (63.0)
Poor	16 (22.2)	20 (27.0)	36 (24.7)
Bone marrow blast level, median % (range)	54.0 (20.0-95.0)	48.0 (17.0-100)	52.5 (17, 100)

Abbreviations: AML, Acute myeloid leukemia; AZA, azacitidine; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; IVO, ivosidenib; n, number; PS, performance status.

Notes: The intention-to-treat population included all the patients who underwent randomization. Percentages may not total 100 because of rounding.

* IDH1 mutation for these patients was confirmed with local testing.
† Race or ethnic group was reported by the patient. “Other” includes American Indian or Alaska Native and Native Hawaiian or other Pacific Islander.

‡ Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with higher scores indicating greater disability.

§ Patients with secondary AML also included those with treatment-related AML (2 patients [3%] in the ivosidenib + azacitidine group and 1 [1%] in the placebo-and-azacitidine group), those with a history of myelodysplastic syndrome (10 patients [14%] and 12 [16%], respectively), and those with AML due to other causes (2 patients [3%] and none, respectively).

¶ IDH1 variants were determined with the use of the Abbott RealTime IDH1 in vitro polymerase chain reaction assay.

ǁ Variant allele frequency in bone marrow aspirates was quantified by next-generation sequencing.

** Cytogenetic risk status was reported as other or missing for 5 patients (7%) in the ivosidenib + azacitidine group and 3 patients (4%) in the placebo-and-azacitidine group.

Source: company submission Document B. Table 10, pp. 32-33.

The company considered in its submission that the AGILE trial is reflective of and generalisable to UK clinical practice. This was an international trial with sampling stratified by disease status and geographic region (US and Canada; Western Europe; Israel; Australia; Japan; Rest of the World). AGILE contains UK sites, although as it was an international trial, UK participants form a small minority of total participants. Clinical advice to the EAG was that substantial geographic differences in epidemiology of AML and IDH1 mutations are unlikely. However, differences in treatment pathways will occur between countries due to differences in prevailing clinical guidelines and drug approvals, as seen through how the American NCCN guidelines do not match well to UK practice, and these differences can be substantial. There are also differences in how outcomes such as event-free survival are measured between America and Europe. Therefore, the EAG considered that the company’s statement regarding generalisability to UK

practice is likely an overstatement, although there is likely to be moderate generalisability to the UK context.

3.2.2.3. Intervention

The intervention in the AGILE trial was ivosidenib 500mg QD orally days 1-28 plus azacitadine 75mg/m^2 SC or IV days 1-7 or days 1-5 and 8-9. This dosing regimen matched that in the SmPC. The total of 500mg is given as two tablets of 250mg. Dosing adjustments are made for concomitant azole antifungal use.

3.2.2.4. Comparator

The comparator in the AGILE trial was matched placebo orally days 1-28 plus azacitadine 75mg/m^2 SC or IV days 1-7 or days 1-5 and 8-9. The dosing regimen of azacitadine was identical to that in the intervention arm.

3.2.2.5. Outcomes

Event-free survival (primary endpoint)

The primary endpoint in the AGILE trial was event-free survival (EFS). This was defined as the time from randomisation until treatment failure (i.e., the patient did not have complete remission by week 24), relapse from remission, or death from any cause, whichever occurred first. The efficacy of ivosidenib was evaluated by investigator-assessed response to treatment on the basis of the modified International Working Group response criteria for acute myeloid leukemia[19] and European LeukemiaNet guidelines[20]. It should be noted that the definition of EFS used in AGILE differed from the definition used in the economic model. This is critiqued in the cost-effectiveness section.

Secondary endpoints

Secondary endpoints in AGILE included complete remission, overall survival (OS), complete remission or complete remission with partial hematologic recovery, objective response, safety, and health-related quality of life. Objective response was defined as complete remission, complete remission with incomplete hematologic recovery (including complete remission with incomplete platelet recovery), partial remission, and morphologic leukemia-free state. Responses were based on investigator assessment of bone marrow, peripheral blood, or both. The company decision problem covered all outcomes in the NICE scope except disease-free

survival and as described above, the EAG did not consider this exclusion to be particularly consequential.

3.2.2.6. Critical appraisal of the design of the studies

Critical appraisal for RCTs retained for data extraction in the company submission was conducted using the Cochrane Risk of Bias (RoB 2.0) tool.[21] This is an up-to-date and standard tool for the risk of bias assessment of RCTs and the EAG considered this to be appropriate.

The company conducted risk of bias assessment using RoB2.0 on 26 RCTs included from the clinical SLR. As stated in Section 3.3, these were not all included in the company NMA. The company assessed 11 of these trials as at low risk of bias, 13 studies as having some concerns about risk of bias, and two studies (LI-1[22] and LACEWING[23]) were considered at high risk of bias. The EAG verified the risk of bias assessment and had no concerns about its accuracy. The company's risk of bias table is reproduced below as Table 9.

Table 9. Risk of bias assessment table for studies in the clinical SLR

Study ID	Outcome	D1	D2	D3	D4	D5	Overall
VIALE-C Wei et al. 2020 [24]	Primary	+	+	+	+	+	+
VIALE-A DiNardo et al. 2020 [17]	Primary	+	+	+	+	+	+
BI 1230.4 Dohner et al. 2014 [25]	Primary	!	!	+	+	!	!
NCT00528333 Sekeres et al. 2013 [26]	Primary	+	+	+	+	+	+
BRIGHT AML 1003 Cortes et al. 2019 [27]	Primary	+	!	+	+	+	!
POLO-AML-2 Dohner et al. 2021 [28]	Primary	+	+	+	+	+	+
ISRCTN40571019 Burnett et al. 2015 [29]	Primary	!	+	+	+	+	!
NCT01358734 Medeiros et al. 2018 [30]	Primary	+	+	+	+	!	!
FIGHT-AML-301 Harousseau et al. 2009 [310]	Primary	+	+	+	+	+	+
FUSION-AML-001 Zeidan et al. 2019 [321]	Primary	+	+	+	+	+	+
AML-19 Amadori et al. 2016 [332]	Primary	+	+	+	+	+	+
Mohammed et al. 2021	Primary	!	!	+	+	+	!
AML-16 Burnett et al. 2013 [344]	Primary	!	+	+	+	+	!
PETHEMA-FLUGAZA Vives et al. 2021 [355]	Primary	!	!	+	+	+	!
SEAMLESS Kantarjian et al. 2021 [366]	Primary	+	!	+	+	+	!

+ Low risk

! Some concerns

- High risk

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

Study ID	Outcome	D1	D2	D3	D4	D5	Overall
AG221-AML-005 DiNardo et al. 2021 [377]	Primary	+	!	+	+	+	!
DECIDER Lubbert et al. 2020[38]	Primary	+	+	+	+	+	+
DACO-016 Kantarjian et al. 2012 [399]	Primary	+	+	+	+	+	+
ASTRAL-1 Roboz et al. 2019 [400]	Primary	!	!	+	+	+	!
AZA-AML-001 Dombert et al. 2015 [411]	Primary	+	+	+	+	+	+
NCT02472145 Montesinos et al. 2021 [422]	Primary	+	!	+	+	+	!
LI-1 Copland et al. 2021 [223]	Primary	!	-	+	-	!	-
LACEWING Wang et al. 2021 [234]	Primary	+	-	+	+	+	-
AGILE Montesinos et al. 2021 [165]	Primary	+	+	+	+	+	+
ENFORCE Thomas et al. 2022	Primary	+	!	+	+	+	!
SPARK-AML1 Kantarjian et al. 2020 [367]	Primary	!	!	+	+	+	!

Source: Company submission Appendix D, 5.1.9., Table 27.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Clinical effectiveness results

The company provided a table in its clarification response stating what data cut was used in the economic model. This is reproduced below as Table 10. Data are shown below for each of the three clinical outcomes used to inform the economic model, using the relevant data cut where available, plus health-related quality of life and adverse events.

Table 10: Data cuts used to inform the model for each time-to-event endpoint (original)

Endpoint	Data cut	Rationale
OS	June 2022	Final analysis – most up-to-date data for OS
EFS	March 2021	Primary data cut – no further EFS data collected beyond this time
ToT	October 2021	Safety update – provided additional data versus primary data cut

As described in Section 3.5, no minimally clinically important difference (MCID) values for EFS or OS in a relevant population could be identified by the EAG following a search. Therefore, the presentation of results for these outcomes focuses on the statistical results.

Event-free survival

Table 11: Summary of event-free survival data from AGILE (using full analysis set)

	Ivosidenib + azacitidine (N = 72)	Placebo + azacitidine (N = 74)
EFS (months), n (%) *		
Number (%) of events	46 (63.9)	62 (83.8)
Treatment failure	42 (58.3)	59 (79.7)
TF, on treatment >24 weeks without CR	16 (22.2)	11 (14.9)
TF, treatment discontinuation ≤24 weeks without CR	26 (36.1)	48 (64.9)
Relapse	3 (4.2)	2 (2.7)
Death	1 (1.4)	1 (1.4)
Percentiles (95% CI) **		
25th	0.03 (NE, NE)	0.03 (NE, NE)
50th (median)	0.03 (0.03, 11.01)	0.03 (NE, NE)
75th	23.98 (14.78, NE)	0.03 (0.03, 11.30)
Hazard ratio (95% CI) ***		0.33 (0.16, 0.69)
1-sided p-value****		0.0011
EFS rate (%) (95% CI) *****		
1 Day	41.7 (30.2, 52.7)	20.3 (12.0, 30.0)
3 Months	41.7 (30.2, 52.7)	20.3 (12.0, 30.0)
6 Months	39.9 (28.6, 51.0)	20.3 (12.0, 30.0)
9 Months	39.9 (28.6, 51.0)	20.3 (12.0, 30.0)
12 Months	37.4 (25.9, 48.9)	12.2 (4.3, 24.4)
18 Months	33.3 (20.9, 46.2)	6.1 (0.7, 20.9)
24 Months	22.2 (6.6, 43.4)	NE
36 Months	NE	NE

Source: CS, Document B, Table 11, p.35. Data cut: March 2021.

The primary efficacy endpoint was met with a significant improvement in EFS demonstrated for patients randomized to the ivosidenib + azacitidine arm relative to the placebo + azacitidine arm (HR = 0.33; 95% CI, 0.16-0.69; p = 0.002). However, median EFS did not differ between arms (0.03 in each arm), as more than half of participants in both arms did not have complete remission by 24 months. The probability of remaining event free at 6 months was 40% in the ivosidenib plus azacitadine group and 20% in the azacitadine plus placebo group. The probability of remaining event free at 12 months was 37% in the ivosidenib plus azacitadine group and 12% in the azacitadine plus placebo group.

Overall survival

	Ivosidenib + azacitidine (N = 73)	**Placebo + azacitidine (N = 75)**
Overall Survival (months)		
Number (%) of Events	37 (50.7)	58 (77.3)
Number (%) Censored	36 (49.3)	17 (22.7)
Alive	30 (41.1)	9 (12.0)
Lost to Follow-up	0	1 (1.3)
Withdraw by Subject	6 (8.2)	7 (9.3)
Percentiles		
25th Percentile (95% CI)	5.7 (1.8, 11.3)	2.0 (1.2, 3.4)
Median (95% CI)	29.3 (13.2, NE)	7.9 (4.1, 11.3)
75th Percentile (95% CI)	NE (36.5, NE)	20.8 (13.1, 29.7)
Hazard ratio (95% CI)		0.42 (95% CI: 0.27 – 0.65) p<0.0001
KM Survival Rate (%) (95% CI)		
3 Months	83.3 (72.4, 90.1)	67.8 (55.9, 77.1)
6 Months	73.1 (61.1, 82.0)	53.5 (41.3, 64.1)
9 Months	67.3 (55.0, 76.9)	44.5 (32.7, 55.6)
12 Months	62.9 (50.4, 73.0)	38.3 (27.0, 49.5)
18 Months	58.4 (45.9, 69.0)	29.1 (18.9, 40.1)
24 Months	53.1 (40.4, 64.2)	17.4 (8.9, 28.2)
36 Months	41.0 (26.7, 54.7)	11.9 (4.7, 22.9)
48 Months	35.8 (20.8, 51.2)	NE

Source: CS Document B, Table 14, p.44. Data cut: June 2022.

The updated OS data from June 2022 for the AGILE trial show a benefit for the ivosidenib + azacitidine arm relative to the placebo + azacitidine arm (HR for death = 0.42; 95% CI, 0.27-0.65; p = 0.0001). There was a median OS of 29.3 months (95% CI, 13.2-NE months) in the ivosidenib + azacitidine arm and 7.9 months (95% CI, 4.1-11.3 months) in the placebo + azacitidine arm.

Time on treatment

Figure 2. Kaplan Meier time on treatment estimates from the AGILE trial.

Source: CS, Document B, Figure 33, p.95. Data cut: October 2021.

Using observed data from the AGILE trial, longer time on treatment (i.e. lower discontinuation) was observed for ivosidenib plus azacitadine compared to azacitadine plus placebo. [redacted] of participants were still on ivosidenib plus azacitadine at three years, compared to [redacted] for azacitadine plus placebo. The data presented here for time on treatment are at an earlier data cut than used in the model, since no revised graph was presented for this variable at the clarification stage – rather the updated data were just implemented in the model.

The EAG identified separate plots for each arm within the model file that include ToT data. These use the updated data cut that informed ToT data in the model.

Figure 3. Data plots from the model including updated time on treatment data

Source: Economic model file.

Health-related quality of life

A benefit for ivosidenib plus azacitadine compared to azacitadine plus placebo was observed for EQ-5D-5L VAS and index scores. Results are shown in Table 12.

Table 12. AGILE – EQ-5D-5L VAS scores and change from baseline (Full Analysis Set)

Visit	Ivosidenib +azacitadine	Placebo +azacitadine
Baseline, mean (SD)	63.01 (20.947). n = 68	62.89 (20.011). n = 66
Change from baseline		
C5D1	**10.56 (22.589). n = 39**	-4.96 (21.143). n = 25
C7D1	**9.45 (16.906). n = 29**	1.63 (19.510). n = 16
C9D1	**10.63 (14.240). n = 24**	-6.64 (24.044). n = 14
C11D1	6.05 (18.248). n = 22	**7.50 (24.001). n = 10**
C13D1	**13.72 (16.153). n = 18**	4.00 (23.313). n = 5
C15D1	**8.53 (19.184). n = 19**	-6.40 (19.527). n = 5
C17D1	**9.36 (23.621). n = 14**	-7.67 (24.786). n = 3
C19D1	**10.27 (21.868). n = 11**	-5.50 (34.648). n = 2

Abbreviations: Cx, cycle x day y; EQ-5D-5L, 5-level EuroQol Five Dimensions Questionnaire; FAS, full analysis set; n, number; SD, standard deviation; VAS, visual analog scale.

Notes: Change from baseline is calculated only for the subjects having observed value at both baseline and post-baseline visits.

Baseline is defined as most recent measurement on or before the date of randomization. If there is no value available on or before the date of randomisation, the last measurement on or before the start of study treatment will be used as baseline. Unscheduled visits are excluded from the analysis.
Bold text indicates clinically meaningful difference from baseline (a difference from baseline of at least 7 points for EQ-5D-5L VAS scores was considered clinically meaningful).

Source: CS, Table 21, p.53.

Table 13. AGILE – EQ-5D-5L index values and score change from baseline (Full Analysis Set)

Visit	Ivosidenib +azacitadine	Placebo + azacitidine
Baseline, mean (SD)	0.7116 (0.27756). n = 68	0.6796 (0.28516). n = 66
Change from baseline		
C5D1	**0.1032 (0.29723). n = 39**	0.0082 (0.23908). n = 25
C7D1	**0.0796 (0.30054). n = 29**	0.0071 (0.25429). n = 16
C9D1	**0.0630 (0.26742). n = 24**	0.0049 (0.26003). n = 14
C11D1	0.0471 (0.27756). n = 22	**0.1046 (0.31273). n = 10**
C13D1	**0.1046 (0.29168). n = 18**	**0.0636 (0.12576). n = 5**
C15D1	0.0526 (0.29660). n = 19	0.0062 (0.15240). n = 5
C17D1	0.0328 (0.30635). n = 14	0.0363 (0.11585). n = 3
C19D1	**0.0626 (0.32590). n = 11**	**0.0995 (0.09405). n = 2**

Abbreviations: Cx, cycle x day y; EQ-5D-5L, 5-level EuroQol Five Dimensions Questionnaire; FAS, full analysis set; n, number; SD, standard deviation.

Notes: Change from baseline is calculated only for the subjects having observed value at both baseline and post-baseline visits.

Baseline is defined as most recent measurement on or before the date of randomization. If there is no value available on or before the date of randomization, the last measurement on or before the start of study treatment will be used as baseline. Unscheduled visits are excluded from the analysis.
Bold text indicates clinically meaningful difference from baseline (a difference from baseline of at least 0.06 points for US index values was considered clinically meaningful).

Source: CS, Table 22, p.54.

The company stated that a difference from baseline of at least seven points was considered clinically meaningful for EQ-5D-5L VAS scores, and a difference from baseline of at least 0.06 points was considered clinically meaningful for US index values (CS, p.53). However, no citation was provided to support these MCID values. Furthermore, the EAG considered that the use of US MCID values was unusual, although also noted that a UK valuation set was used to derive modelled utilities for the health economic model. Based on the available information, the EAG was satisfied that ivosidenib plus azacitadine offers benefit in terms of quality of life compared to placebo plus azacitadine.

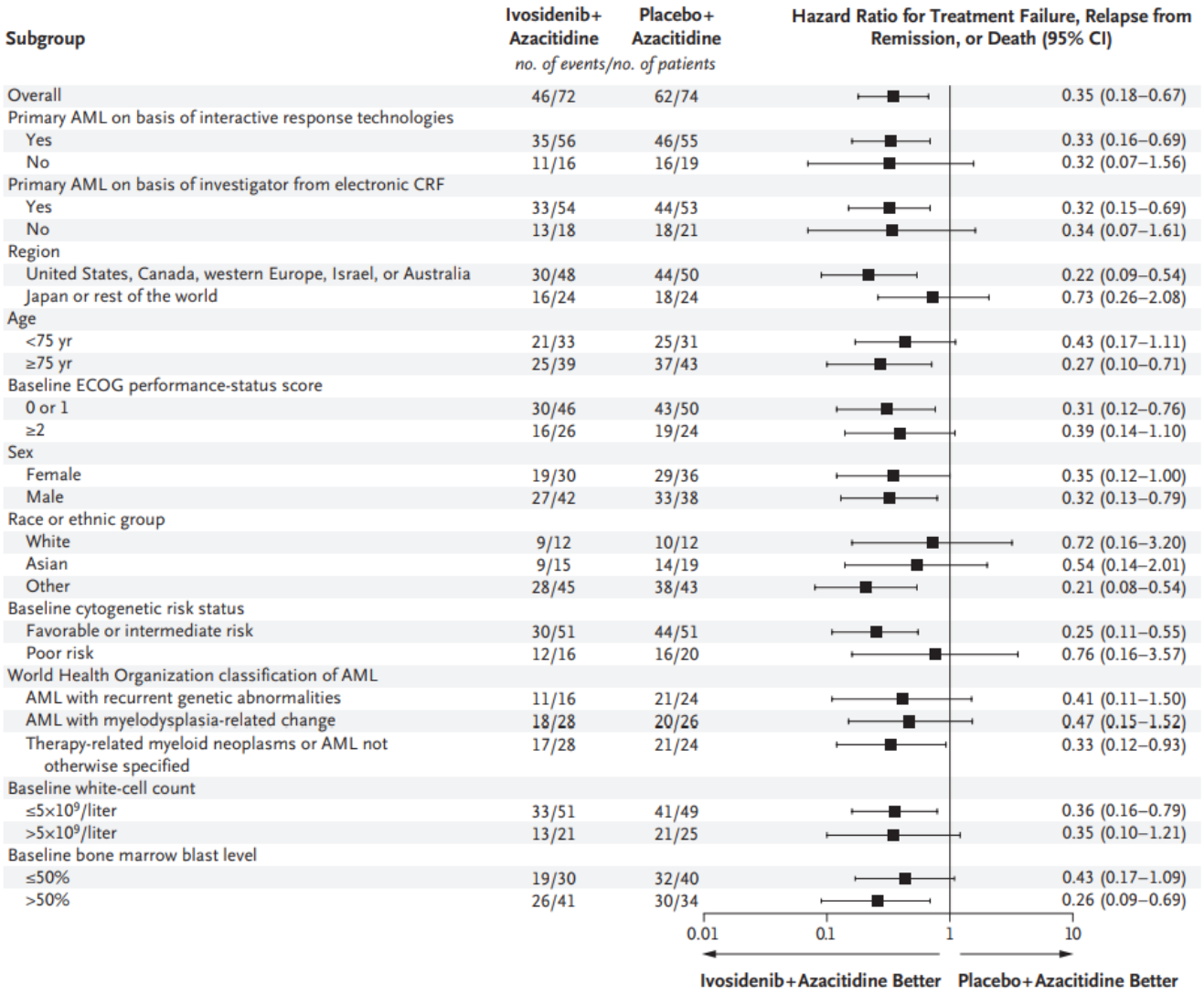
Subgroup analyses

The company did not include any subgroups in its decision problem, which is not problematic as no specific subgroups were included in the NICE final scope for this appraisal.

However, subgroup data for AGILE were presented in the CS. This was one of a number of inconsistencies in how results were presented across the CS, others including the presentation of NMA results for three excluded comparators and the presentation (in the model but not the report) of cost-effectiveness results for azacitadine monotherapy, which the company had excluded from its decision problem.

Subgroup results are presented for information, but not discussed, as they do not form part of the decision problem.

Figure 4: Subgroup analysis for the AGILE trial.



Source: CS, Document B, Figure 8, p.39.

Adverse effects

Adverse events were very common, being observed in 99% of patients treated with ivosidenib plus azacitadine (70/71) and 100% of patients in the placebo plus azacitadine arm (73/73). Grade 3+ adverse events were also very common, being observed in 93% (66/71) and 94.5% (69/73). Grade ≥3 AE's that occurred in more than 15% of the patients in both the ivosidenib + azacitidine arm and the placebo + azacitidine arm included febrile neutropenia (28% and 34%, respectively), anemia (25% and 26%), neutropenia (27% and 16%), thrombocytopenia (24% and 21%) and pneumonia (23% and 29%). Infection events were more common in the placebo plus azacitadine arm (49.3%) than the ivosidenib plus azacitadine arm (28.8%).

A summary of adverse events was provided in the CS Table 30 and is reproduced below as Table 14.

Table 14. AGILE – Summary of adverse events (Safety Analysis Set)

Event	Ivosidenib + azacitidine (N = 71) n (%)		Placebo + azacitidine (N = 73) n (%)	
	Any grade	**Grade 3+**	**Any grade**	**Grade 3+**
Any TEAE	70 (98.6)	66 (9.03)	73 (100.0)	69 (94.5)
Hematologic adverse events	55 (77.4)	50 (70.4)	48 (65.7)	47 (64.3)
Anemia	22 (31.0)	18 (25.4)	21 (28.8)	19 (26.0)
Febrile neutropenia	20 (28.2)	20 (28.2)	25 (34.2)	25 (34.2)
Neutropenia	20 (28.2)	19 (26.8)	12 (16.4)	12 (16.4)
Thrombocytopenia	20 (28.2)	17 (23.9)	15 (20.5)	15 (20.5)
Leukocytosis	8 (11.3)	0	1 (1.4)	0
Nonhematologic adverse events	-	-	-	-
Nausea	30 (42.3)	2 (2.8)	28 (38.4)	3 (4.1)
Vomiting	29 (40.8)	0	19 (26.0)	1 (1.4)
Diarrhea	25 (35.2)	1 (1)	26 (35.6)	5 (7)
Pyrexia	24 (33.8)	1 (1)	29 (39.7)	2 (3)
Constipation	19 (26.8)	0	38 (52.1)	1 (1)
Pneumonia	17 (23.9)	16 (23)	23 (31.5)	21 (29)
QT interval prolonged on ECG	14 (20)	7 (10)	5 (7)	2 (3)
Insomnia	9 (12.3)	1 (1)	9 (12.3)	0
Asthenia	24 (32.9)	0	24 (32.9)	5 (6.8)
Hypokalemia	11 (15.5)	2 (2.8)	21 (28.8)	6 (8.2)
Decreased appetite	19 (26.0)	1 (1.4)	19 (26.0)	6 (8.2)
Dyspnea	11 (15.5)	1 (1)	9 (12.3)	3 (4)
Differentiation syndrome	10 (14.1)	3 (4)	6 (8.2)	3 (4)
Pain in extremity	10 (14.1)	1 (1)	3 (4.1)	1 (1)
Fatigue	9 (12.7)	2 (3)	10 (13.7)	2 (3)
Hematoma	9 (12.7)	0	1 (1.4)	0
Edema peripheral	8 (11.3)	0	16 (21.9)	1 (1)
Platelet count decreased	8 (11.3)	6 (8.5)	6 (8.2)	6 (8.2)
Arthralgia	8 (11.3)	0	3 (4.1)	0
Headache	8 (11.3)	0	2 (2.7)	0
Bleeding	29 (41)	4 (6)	21 (29)	5 (7)
Infections	20 (28.8)	15 (21.1)	36 (49.3)	22 (30.1)

Abbreviations: ECG, electrocardiography; n, number; SAS, safety analysis set; TEAE, treatment emergent adverse events

Notes: The safety population included all the patients who received at least one dose of a trial agent. Events listed are those of any grade that occurred in at least 10% of the patients in the ivosidenib + azacitidine group.

Source: CS, Table 30, p. 69.

Clinical advice to the EAG is that the primary comparator venetoclax with azacitadine is associated with quite severe side effects related to myelosuppression that affect almost all patients. In contrast, based on available information (not first-hand practice), clinical advice to the EAG was that ivosidenib, being a lot more targeted, is likely to be a lot more tolerable, with cell differentiation syndrome affecting a small proportion of patients (approximately 5%). Available data support the notion that ivosidenib plus azacitadine has a comparable or favourable safety profile relative to azacitadine plus placebo.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company's clinical SLR sought to identify studies to inform a network meta-analysis (NMA) to compare ivosidenib plus azacitadine with venetoclax, due to the absence of directly comparative studies. The SLR itself has been critiqued in Section 3.1. A total of 26 studies met the criteria for inclusion in the systematic review. These were screened against further criteria to ascertain eligibility for inclusion in the feasibility assessment for potential inclusion in the NMA:

- Interventions: The respective study had to investigate one of the following agents: HMAs (decitabine or azacitidine), LDAC, venetoclax in combination with other agents, glasdegib in combination with other agents, and best supportive care (BSC) including blood transfusion, etoposide, mercaptopurine, or hydroxyurea. Investigational agents or any treatments not listed above were excluded from the feasibility assessment.
- Sample size: studies with < 20 patients per arm and phase II single-arm studies were excluded from the feasibility, because such studies are expected to yield considerably uncertain estimates and may risk the introduction of unnecessary bias due to quality of conduct issues.

The EAG on balance considered these criteria to be reasonable, although noted that the minimum of 20 patients per arm is arbitrary. The EAG agreed that larger studies are generally preferable and more likely to produce stable and informative estimates.

The issues noted by the EAG with the company's search (see Section 3.1) and the lack of clarity regarding the different stages of the feasibility assessment for inclusion in the NMA means the EAG could not be certain that all relevant studies were included in the NMA.

Out of the 26 studies included in the SLR, 10 were included in the feasibility assessment. Separate NMAs were conducted for EFS and OS. There was a lack of clarity in the CS regarding how the feasibility assessment and inclusion decisions were made. It appears that the feasibility assessment was shared between the two NMAs. It is unclear how the criteria differed for these two stages (feasibility assessment and final inclusion). For example, for EFS, the CS says that

the criteria listed in the bullets above were used to select studies to be included in the feasibility assessment (which reduced the number of studies from 26 to 10). It then references the same criteria as having guided the feasibility assessment itself (which reduced the number of studies from 10 to four). There was a lack of clarity as to what differentiated these two stages.

The network presented by the company for EFS contained four studies assessing five interventions. There are three studies besides AGILE, which has already been profiled in detail earlier in this chapter. Summary characteristics for these other three studies are tabulated below in Table 15. The in-text references for these studies in the CS did not populate the bibliography, however the EAG has managed to identify the studies.

Table 15. Summary characteristics of studies included in the company's EFS network meta-analysis

Study	Intervention 1	Intervention 2	Study design	Location	Sample size
DiNardo et al (2020)[17]	Venetoclax plus azacitadine	Azacitadine	RCT (double blind)	International (150 sites)	431
Dombret et al (2015)[41]	Azacitadine	LDAC	RCT (open label)	International (18 countries)	488
Wei et al (2021)[43]	Venetoclax plus LDAC	LDAC	RCT (double-blind)	International (101 sites)	211

Source: EAG extracted data from trial publications and where necessary trial registrations and protocols.

The network presented by the company for OS contained six studies assessing seven interventions. There are five studies besides AGILE. These are tabulated below.

Study	Intervention 1	Intervention 2	Study design	Location	Sample size
DiNardo et al (2020)[17]	Venetoclax plus azacitadine	Azacitadine	RCT (double blind)	International (150 sites)	431

Heuser et al (2021)[44]	Glasdeginib plus LDAC	Placebo plus LDAC	RCT (open label)	International (76 sites)	211
Kantarjian et al (2012)[39]	Decitabine	Patient choice with physician advice from supportive care or LDAC	RCT (open label)	International (65 sites)	485
Dombret et al (2015)[41]	Azacitadine	LDAC	RCT (open label)	International (18 countries)	488
Wei et al (2021)[43]	Venetoclax plus LDAC	LDAC	RCT (double-blind)	International (101 sites)	211

Source: EAG extracted data from trial publications and where necessary trial registrations and protocols.

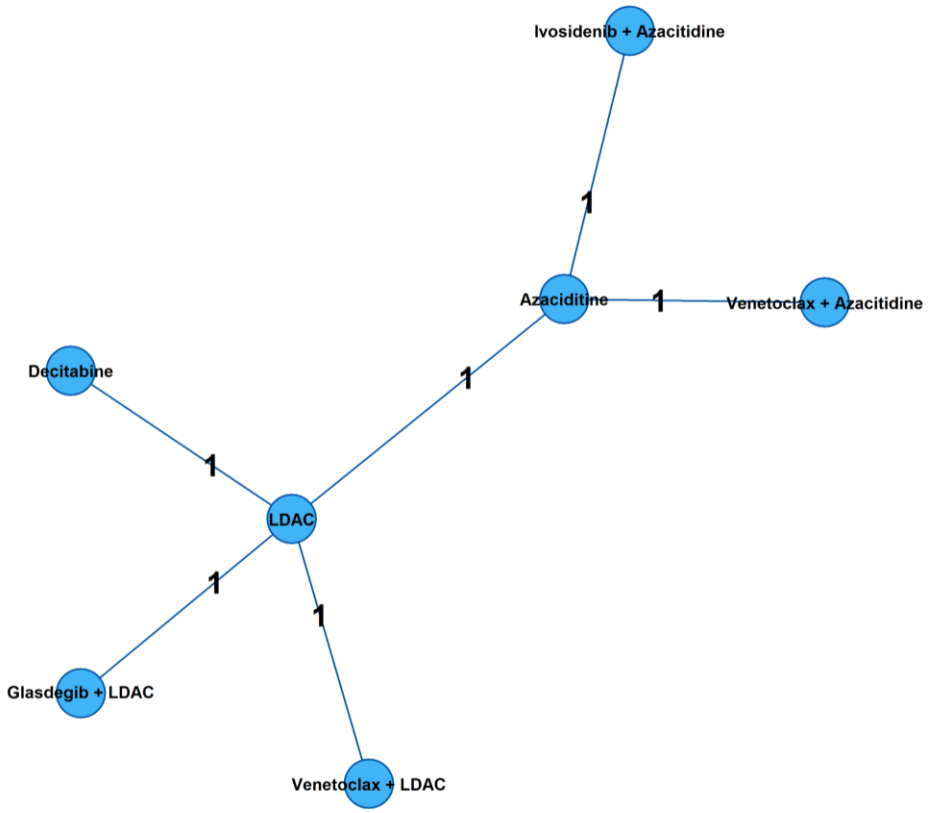
The EAG was satisfied that all studies included in the company's NMA are relevant to the decision problem. The EAG's concern is rather that, for reasons described above, there may be studies that would be eligible for inclusion in the NMA yet that the company has not included. The overall network was quite small. Furthermore, there were concerns expressed in Section 2.4 about the exclusion of additional comparators in the NICE Scope that could have provided a richer and potentially more informative network.

3.4. Critique of the indirect comparison and/or multiple treatment comparison

3.4.1. Overview

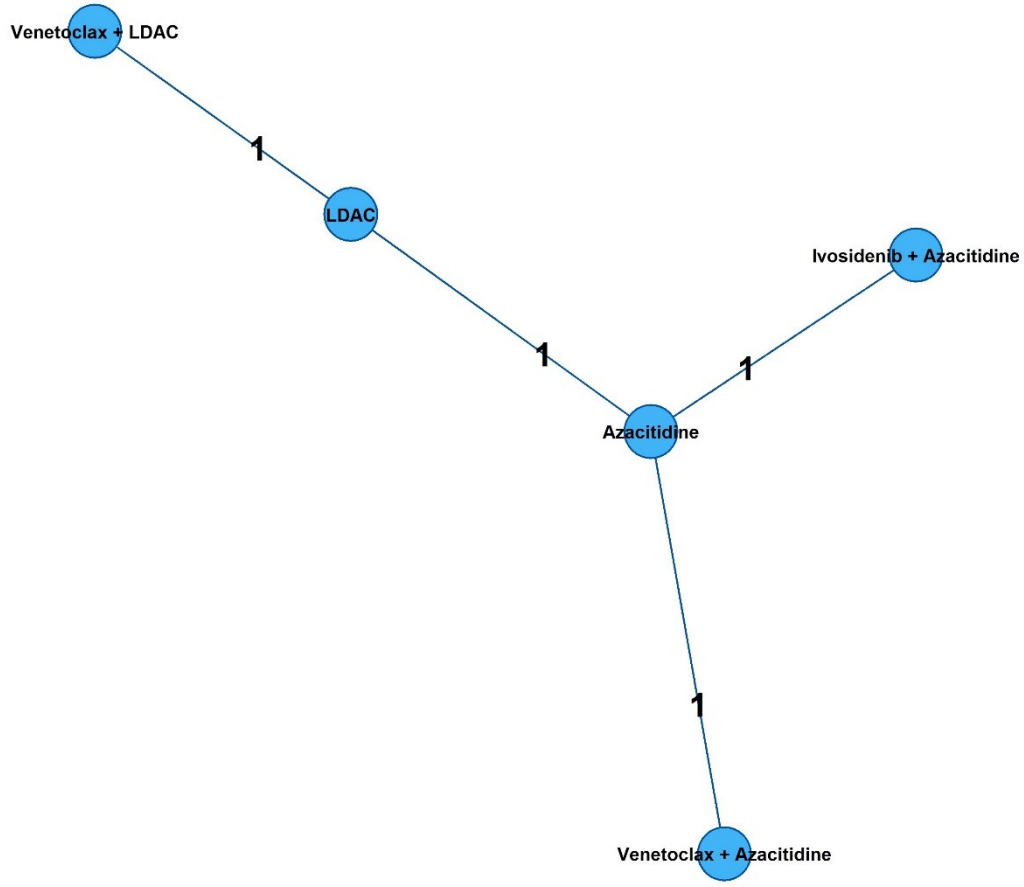
The full network and associated results are provided in Appendix D [ITC]. Figure 5 and Figure 6 show the networks for OS and EFS.

Figure 5: Network for OS



Source: CS doc B fig 18 / Appendix D [ITC] figure 2

Figure 6 : network for EFS



Source: CS doc B fig 17 / Appendix D [ITC] figure 3

The CS Doc B provides NMA results limited to EFS and OS for a three node network composed of IVO+AZA, AZA+Placebo and VEN+AZA. Results for all outcomes (OS, EFS, CR, CR/CRi, CR/CRh, conditional TI, and TI) in the full networks are available in Appendix D [ITC], and where results are included in the EAG report the full network results are used. No binary outcome NMAs were presented in the main CS/doc B nor used in the submitted economic model.

The NMA was carried out in a Bayesian framework, specifically using logit link for binary outcomes (CR, CR/CRi, CR/CRh, conditional TI, and TI) and identity link for continuous outcomes (EFS, OS). Code was provided for the former but not the latter, though the latter is understood to be standard Open/WinBUGS code (company response to CQ A8). The time-to-

event analyses used between-trial estimates of log HR as their data and implicitly therefore assume a time-independent HR / proportional hazards. Information towards this assumption is provided in the form of log cumulative hazard plots, Schoenfield residuals and PH tests (Appendix E of Appendix D [ITC]), but the company does not itself appear to comment on the plausibility of the assumption. This is covered further in section 3.4.3.

The company carried out a 'feasibility assessment' of the NMAs which examined study quality, risk of bias and heterogeneity in many characteristics including outcome definitions and study design. This is given in Appendix D [ITC] sections 4 and 6 and also Appendix C of the same document. The information provided was fairly detailed and the company concluded that NMAs were feasible for the 7 outcomes mentioned above (see AppD [ITC] Table 10).

No consistency assessments were made in the CS because there were no closed loops in the networks. The company stated they had fitted both random and fixed effects models, finding similar DIC values for each, and using FE as 'a more parsimonious model with fewer assumptions'. Because there was only one study per pairwise comparison, there is a reliance on prior information for the between-study variance. The CS indicates (AppD [ITC] p45) that RE models had very wide credible intervals, but these were not presented. The EAG understands the very wide intervals reflect the use of noninformative priors combined with a lack of data on between-study variation. No evidence was presented using RE with informative priors (e.g. those offered by Turner et al.).[15]

3.4.2. Results of NMAs

Only OS and EFS were presented within the main submission and used within the economic model. The estimated HRs for these outcomes are shown in Table 16 and Table 17 respectively. The EAG drew on the company CR/CRi NMA in its base case (section 4.2.6.6) and the estimated ORs are shown in Table 18. Note that the underlying model for these results is FE not RE, as selected by the company; the company indicates that these credible intervals were very wide under the RE model but did not provide these results.

In the following where Bayesian results we use the term 'significant' as shorthand for credible intervals not covering the null value.

Table 16: Hazard ratios for overall survival from company NMA

Comparison	LDAC	Azacitidine	Decitabine	Venetoclax + azacitidine	Venetoclax + LDAC	Glasdegib + LDAC	Ivosidenib + azacitidine
LDAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venetoclax + azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venetoclax + LDAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glasdegib + LDAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib + azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: App D [ITC] Table 13

Estimated treatment effects are shown for the three outcomes used in the economic model (OS, EFS and CR+CRi) in Table 16, Table 17 and Table 18. In all three cases, both IVO-AZA and VEN+AZA are favoured over AZA and the effects are statistically significant. For IVO-AZA vs AZA, HR=[redacted] for OS, and HR= [redacted] for EFS. For VEN+AZA vs AZA, HR=[redacted] for OS, and HR= [redacted] for EFS. Again for all three outcomes, IVO-AZA is favoured over VEN-AZA but the effect is not statistically significant. For IVO-AZA vs VEN+AZA, HR=[redacted] for OS and HR=[redacted] for EFS.

Table 17: Hazard ratios for event free survival from company NMA

Comparison	LDAC	Azacitidine	Venetoclax +azacitadine	Venetoclax + LDAC	Ivosidenib + azacitidine
LDAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venetoclax + azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venetoclax + LDAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib + azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Appendix D [ITC] Table 15

Table 18: Odds ratios for CR/CRi from company NMA

Comparison	LDAC	Azacitidine	Venetoclax + azacitidine	Venetoclax + LDAC	Glasdegib + LDAC	Ivosidenib + azacitidine
LDAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venetoclax + azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venetoclax + LDAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glasdegib + LDAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib + azacitidine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Appendix D [ITC] Table 19

The CS does not provide NMA results for the IDH1m subgroup. The company argue that there are several reasons that the network is not suitable for this, first and foremost that comparator trials were not carried out specifically in the IDH1m population, while AGILE was restricted to IDH1m.

The forest plot subgroup results shown for VIALE-A[17] (fig 3) show a *prima facie* stronger treatment effect for VEN+AZA among the IDH1 subgroup (HR=[redacted]) compared to the ITT ([redacted]). Using this, an exploratory NMA effect estimate in the IDH1 subgroup for OS was calculated by the EAG (section 3.5.33.5) as HR= [redacted]) for IVO-AZA vs VEN-AZA, which favours VEN+AZA in direction, but is not statistically significant (p=[redacted]). This result is heavily caveated and further discussed in section 3.4.4.2.

3.4.3. Proportional hazards assumption and transitivity

The NMAs for time-to-event data (EFS and OS) are premised on the notion of a time-independent hazard ratio (and so the HR can be represented as a scalar between any treatments): this is a proportional hazards (PH) setup. The EAG notes that the associated parametric survival distributions are exponential, Gompertz or Weibull.

The company covers the PH assumption with respect to outcome and trial in Appendix D of Appendix D [ITC], by supplying log-cumulative hazard plots, plots of Schoenfield residuals and results for statistical tests for PH. The CS itself does not seem to make an assessment of these results.

Of particular note are the AGILE and VIALE-A trial results. For EFS there is visual and statistical evidence for PH. For OS the results are less clear cut, with an initially steeper rise in cumulative hazard at a similar rate in both trials. For VIALE-A, there also appears to be another change in the rate of cumulative hazard towards the end of follow-up in the AZA arm. Related to these, for VIALE-A there is a highly significant rejection of the PH assumption (p=6e-4).

During survival modelling and extrapolation in the CS (doc B section 3.3), the company opt for lognormal survival distributions for IVO+AZA and AZA. The EAG notes here that there are network transitivity issues in doing so because the lognormal is not a PH distribution. Furthermore for VEN+AZA the CS modelling opts for a transformation in which $S_{ven+aza}(t)$ =

$S_{ivo+aza}(t)^{HR}$ where HR is a hazard ratio. The resulting distribution is not a standard parametric function and again not known to be PH. The EAG would have preferred the use of a Weibull distribution across the network, which is compatible with the NMA PH assumptions, and better aligned with clinical opinion when extrapolating survival. However, in the AZA arm the Weibull had a relatively poor fit, particularly for OS, and for extrapolation in that arm the EAG therefore adopted the company choice of lognormal (see section 4.2.6).

In conclusion, neither the EAG nor the CS adopted survival models that are fully compatible with the PH assumptions of the NMA. But as noted above, PH is violated to some extent within the trials. A more elaborate NMA might have led to more satisfactory NMA and survival modelling when viewed together.

3.4.4. Heterogeneity and Effect Modification

The company examined this issue in section 4.3 of Appendix D [ITC]. Heterogeneity across trials in factors that affect treatment effectiveness (effect modifiers) are of particular concern because they may bias NMA estimates.

3.4.4.1. Methodological heterogeneity (outcome definitions , study design)

The CS discusses outcomes over the network in Appendix D [ITC] sections 4.3.1 and 4.3.4 and provides definitions in their Table 6. Further comments by the EAG on particular items are made below.

EFS

The company used what they call the ‘sensitivity analysis definition’ of EFS for the NMA over the ‘prespecified definition’, to improve comparability with definitions used in other trials. The EAG supports this decision both on grounds of reduced heterogeneity, and because the prespecified definition results in ‘pathological’ survival curves with S(0)<1 (doc B fig 6). The latter is understood to be a result of a process described in CQ response A5: ‘Patients that experienced the event before week 24 were recorded as having the event on Day 1 which accounts for the immediate drop in the curve.’ The EAG statrongly prefers the company choice of ‘sensitivity analysis definition’ of EFS. Some differences remain, for example in the definition of treatment failure between AGILE and VIALE-A and, as noted by the company, the EFS definition in AZA-AML-001 does not include TF.

CR, CRh and CRi

The definitions between AGILE and VIALE-A are broadly similar (there are minor differences e.g. AGILE uses 'absence of blasts with Auer rods' among its CR criteria while VIALE-A does not).

Follow-up period

With respect to response outcomes (CR, Cri, CRh) the company provided details of the assessment schedules for AGILE and VIALE-A in response to CQ A9. There were some differences, for example in VIALE-A assessments continued 'until two consecutive samples confirmed a complete remission' but AGILE did not operate like this. No details were provided for other studies across the network. The scheduling differences across studies will likely affect the time to attainment of complete response outcomes and so times to relapse from them. Since relapse from complete response is also a component of EFS this heterogeneity propagates to EFS.

3.4.4.2. Clinical heterogeneity

Appendix D [ITC] Table 4 in the CS contains shows a summary of patient baseline characteristics across trials, which is reproduced here in Table 19. Note that Table 19 includes columns on a pooled study of an RCT and single arm trial (Pollyea et al 2022)[18] but this study is excluded from the network as no longer an RCT *sensu stricto*. The company also excluded the study by Mohammed 2021 'due to serious quality concerns' (AppD [ITC] p33). These excluded studies are not included in the discussion below.

The company states (ibid. p33) "Among the remaining studies, the patient populations are generally comparable, and a low-to-moderate degree of heterogeneity is identified" and the EAG broadly concurs. Further comments by the EAG on notable characteristics are made below, including those believed to be prominent potential effect modifiers (age, risk, IDH1m status) some that were not covered in Table 19.

Age and Gender

These were fairly consistent across trials. Median age was similar (between 73 and 77 years) across trials. There was a small gender difference with percentages mostly between 50 to 60% male, though the BRIGHT AML 1003 trial reported 76% and 61% in each arm.

Bone marrow blast percentage

The median bone marrow blast percentage was largely not reported. Where available the heterogeneity is high, with trials reporting around 70% (AZA-AML 001), and 40 to 55% (BRIGHT, AGILE).

Cytogenic risk

The percentage with poor cytogenic risk when reported was between 22 and 40%, though BRIGHT differed with 37% and 45 % in each arm. The percentage with intermediate cytogenic risk was around 60 – 65% risk across trials, though BRIGHT reported 37% in one arm.

Prior treatments

The company presented information on prior treatments across studies in Appendix D [ITC] Table 3. It was not clear to the EAG which of the items were inclusion and which were exclusion criteria. However there was clear heterogeneity in prior treatments and the durations of any embargos on prior treatments.

Further treatments

The treatments received after the trial period may vary across trials in the network and influence OS. The EAG did not find any information presented on this.

Table 19: Baseline characteristics of patients across the network

Study	AGILE		AZA-AML 001		VIALE-C		VIALE-A		Pooled VIALE-A+ Phase 1b		BRIGHT AML 1003		DACO-016		Mohammed, 2021	
Treatment Arm	IVO+AZA	PBO+AZA	AZA	CCR	VEN+LDAC	PBO+LDAC	VEN+AZA	PBO+AZA	VEN+AZA	PBO+AZA	Glasdegib + LDAC	LDAC	Decitabine	Supportive care or cytarabine	LDAC	BSC
Population for baseline characteristics (N)	72	74	240	245	143	68	286	145	81	28	78	38	242	243	30	30
Median age, years (range)	76.0 (58.0 - 84.0)	75.5 (45.0 -94.0)	75.0 (64.0 - 91.0)	75.0 (65.0 - 89.0)	76.0 (36.0 - 93.0)	76.0 (41.0 - 88.0)	76.0 (49.0 – 91.0)	76.0 (60.0 – 90.0)	76 (64.0-90.0)	77.5 (62.0-90.0)	77.0 (64.0 – 92.0)	76.0 (58.0 – 83.0)	73.0 (64.0 – 89.0)	73.0 (64.0 – 91.0)	64.0 (60.0 - 71.0)	64.5 (61.0 - 71.0)
Male, n/N (%)	42 (58.3)	38 (51.4)	139 (57.7)	149 (60.3)	78 (55.0)	39 (57.0)	172 (60.1)	87 (60.0)	47 (58.0)	17 (60.7)	59 (76.0)	23 (61.0)	137 (56.6)	151 (62.1)	15 (50.0)	17 (56.7)
ECOG 0-1, n (%)	46 (63.8)	50 (67.6)	NR (NR)	NR (NR)	74 (51.0)	34 (50.0)	157 (54.9)	81 (56.0)	46 (56.8)	19 (67.9)	36 (46.0)	20 (53.0)	184 (76.0)	183 (75.3)	12 (40.0)▪	12 (40.0)▪
ECOG 2, n (%)	26 (36.1)	24 (32.4)	55 (22.8)	58 (23.2)	63 (44.0)	25 (37.0)	129 (45.1) †	64 (44.0) †	35 (43.2)*	9 (32.1)*	41(53.0)	18 (47.0)	58 (24.0)	60 (24.7)	18 (60.0)	18 (60.0)
Primary/ de novo AML, n(%)	54 (75.0)	53 (71.6)	NR (NR)	NR (NR)	85 (59.0)	45 (66.0)	214 (75.0)	110 (76.0)	60 (74.1)	24 (85.7)	38 (49.0)	18 (47.0)	155 (64.0)	157 (64.6)	26 (86.7)	27 (90.0)
Cytogenetic risk: intermediate, n (%)	48 (66.7)	44 (59.5)	155 (64.3)	160 (64.5)	90 (63.0)	43 (63.0)	182 (64.0) ‡	89 (61.0) ‡	62 (76.5)	19 (67.9)	49 (63.0)	29 (37.0)	152 (63.1)	154 (63.6)	NR (NR)	NR (NR)
Cytogenetic risk: poor, n (%)	16 (22.2)	20 (27.0)	85 (35.3)	85 (34.4)	47 (33.0)	20 (29.0)	104 (36.0)	56 (39.0)	19 (23.5)	9 (32.1)	29 (37.0)	17 (45.0)	87 (36.1)	87 (36.1)	NR (NR)	NR (NR)
Median bone marrow blasts (95% CI)	54.0 (32.0 - 75.0)	48.0 (33.0 – 70.0)	70.0 (2.0 - 100.0)	72.0 (2.0 - 100.0)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	41.5 (16.0 – 99.0)	48.3 (13.0 – 95.0)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
IDH1, n (%)	70 (97.2)	73 (98.7)	NR (NR)	NR (NR)	21 (19.0)	12 (23.0)	61 (25.0)§	28 (22.0)•	33 (40.7) ¥	11 (39.3) ‖	19 (24.3)	6 (15.8)	NR (NR)	NR (NR)	NR (NR)	NR (NR)

Study	AGILE		AZA-AML 001		VIALE-C		VIALE-A		Pooled VIALE-A+ Phase 1b		BRIGHT AML 1003		DACO-016		Mohammed, 2021	
Treatment Arm	IVO+AZA	PBO+AZA	AZA	CCR	VEN+LDAC	PBO+LDAC	VEN+AZA	PBO+AZA	VEN+AZA	PBO+AZA	Glasdegib + LDAC	LDAC	Decitabine	Supportive care or cytarabine	LDAC	BSC
IDH2, n (%)	NR (NR)	NR (NR)	NR (NR)	NR (NR)					41 (50.61) ɣ	18 (64.3) ǁ			NR (NR)	NR (NR)	NR (NR)	NR (NR)

Abbreviations: Eastern Cooperative Oncology Group; NR, Not reported; IDH, isocitrate dehydrogenase; IVO, Ivosidenib; AZA, Azacitidine; PBO, Placebo; VEN, Venetoclax; LDAC, Low-dose cytarabine; CCR, Combined Conventional Care; BSC, Best Standard Care; AML; Acute Myeloid Leukaemia

† Defined as low/intermediate; ‡ Cytogenic risk intermediate is defined as intermediate I and II; ▪ Only includes patients with ECOG 0; * ECOG 2 -3; ɣ total of 81 IDH1/2 patients due to some patients having both IDH1/2 mutations. ǁ total of 28 IDH1/2 patients due to some patients having both IDH1/2 mutations. § Out of 245 patients. • Out of 127 patients.

Source: Appendix D [ITC] Table 4

Notes: Grey shading added to columns VIALE-A+ and Mohammed 2021. These trials were excluded by the company on study design or study quality criteria. See text for details.

IDH1m status

A prominent potential effect modifier that is a potentially dangerous source of bias to the NMA is IDH1 status. The company conclude (doc B p68) that 'One of the main limitations of the NMA analyses is heterogeneity in the analysis populations arising from a lack of published data for patients with IDH1m outside the AGILE study'. This can be seen in the data for IDH1 status shown in Table 19 where IDH1 status is almost 100% in AGILE but around 20% in other trials.

The company argue '…the fact that venetoclax is not specifically designed to target IDH1 mutated patients, efficacy between IDH1 mutant and IDH1 wild type patients is not expected to differ' (doc B p56). Clinical opinion to the EAG was that venetoclax is 'mutationally agnostic' and that the company's point is broadly correct.

Some evidence based on subgroup analysis is available that indicates a higher treatment effect for VEN+AZA OS within IDH1m (see section 3.4.2 for details). A further strand of evidence with respect to IDH1m is offered by the Pollyea 2022 study[18]. Among IDH1m patients for OS VEN+AZA vs AZA the authors report HR=0.19 (95% CI: 0.08 to 0.44) whilst for IDH1/2 wildtype HR= 0.74 (95% CI: 0.56 to 0.98), suggesting a difference in treatment effect across IDH1 subgroups. Because this study pools a single arm trial and an RCT, the EAG agree with the company that this cannot be treated as a randomized study (Appendix D [ITC] section 4.3.1).

The company argue against the apparent higher treatment effect in the IDH1m subgroup (App D [ITC] p28): 'Such inconsistencies are due to the IDH1-specific HRs being based on post-hoc subgroup analyses with small sample sizes where marked imbalances were observed in baseline characteristics'.

The EAG agrees that the subgroup analysis results are not prespecified/are exploratory, and the number of patients in this subgroup is very small (n=11 + 23). Also, with no randomization technique such as stratification implemented for the IDH1 subgroup during randomization, this could undermine the comparability of the arms in a subgroup. But the EAG has not found information *showing* the 'marked imbalances' mentioned by the company, indeed the company states Appendix D [ITC] p33 that 'baseline characteristics for the IDH1 subgroup are not available for venetoclox + azacitidine'. Though the Pollyea study[18] provides information on the IDH1m subgroup, the VIALE-A treatment arm has been pooled with data from a single arm trial, which breaks randomization and invalidates within-trial baseline comparisons. Nevertheless, a crude baseline comparison of IDH1 or 2 between the AZA arms of VIALE-A and AGILE is

shown in section 3.4.4.3. The EAG interprets the similarity as suggestive that there was not a marked imbalance within the VIALE-A IDH1 subgroup.

Another potential explanation for an anomalous result would be a trial implementation flaw such as inadequate allocation concealment, but the company assessed the VIALE-A study as being at low risk of bias for the randomization process (Appendix D [ITC] Table 8).

In conclusion, exploratory subgroup analysis indicated that within the IDH1 subgroup the point estimate indicates better treatment effectiveness of VEN+AZA over IVO+AZA. But this result does not have any strong statistical support, and would also contradict the argument, made by the company and supported by independent clinical advice to the EAG, of no anticipated difference in treatment effect across IDH1m vs wild-type under VEN+AZA biological mechanisms. A formal head-to-head comparison of VEN+AZA vs IVO+AZA restricted to IDH1m would help resolve uncertainty.

3.4.4.3. Azacitidine arm compared across the network

Though the wider network are not highly centralised (Figure 5 and Figure 6Figure 6 : network for EFS), the AZA arm is a common control arm for the focal network in the CS (AGILE and VIALE-A trials).

Median survival and CR info in the AZA arms of the network (control arm for AGILE and VIALE-A, intervention arm in AZA-AML-001) is summarised in Table 20, with IDH1m subgroup information where available. The information is largely extracted from Appendix D [ITC] Table 7.

The company highlight the differential prognosis (Appendix D [ITC], p28) between the AZA arms of AGILE (median OS 7.9 mo.) and the VIALE-A IDH1 subgroup (median OS 2.2 mo.). The EAG notes that the survival curve for the IDH1 subgroup for VIALE-A is shown in Pollyea et al 2022[18] fig 3B, in which all subjects have died by 12 mo.

Table 20: Summary of outcomes (median survival (OS or EFS and CR) for AZA arms in trials and IDH1m subgroups

	AGILE	VIALE A		AZA-AML-001
	IDH1m (n=74[a])	ITT (n=145[a])	IDH1m (n=11[b, c])	ITT (n=240[a])

Median OS (months)	7.9 (95% CI: 4.1 to 11.3)	9.6 (95% CI: 7.4 to 12.7)	2.2 (95% CI: 1.1 to 5.6)	10.4 (95% CI: 8.0 to 12.7)
Median EFS (months)	4.1 (95% CI: 2.7 to 6.8)	7.0 (95% CI: 5.6–9.5)	-	6.7 (95% CI: 5.0 to 8.8)
CR	14.9%	17.9%	0%	19.5%
CR + CRi	16.2%	28.3%	-	27.8%
CR + CRh	17.6%	22.8%	9.1%	-

Source: Statistical results from Appendix D [ITC] Table 7 and a: Appendix D [ITC] Table 4; b: Pollyea et al. 2022[18] fig 3B; c: DiNardo et al[17] fig 3

A crude comparison of the baseline characteristics between AZA arms of VIALE-A and AGILE can be made using information from the Pollyea study:[18] Table 21 shows this. Note that for the AZA arm IDH1 and IDH2 mutations are pooled. The baseline characteristics appear qualitatively quite similar, though VIALE-A has no favourable risk patients while AGILE does.

Table 21: comparison of baseline characteristics for IDH mutated subgroup

		AZA for IDH1/2 (VIALE-A, n=28)[a]	**AZA for IDH1 (AGILE, n=74)[b]**
Age		77.5	75.5
% female		39%	49%
ECOG 0-1		67.9%	67.6%
ECOG 2		32.1%	32.4%
Cytogenic risk	missing	-	4%
	favourable	-	9.5%
	intermediate risk	67.9%	59.5%
	poor risk	32.1%	27%

Median bone marrow blasts	-	48%

Sources: a: Pollyea 2022[18] Table 1; b: CS doc B Table 10

3.5. Additional work on clinical effectiveness undertaken by the EAG

3.5.1. Scoping search

The EAG conducted a scoping search to identify any relevant MCID values for the key clinical effectiveness EFS and OS in an AML population. Eight papers were identified, however there were no papers that considered these outcomes in an AML population. Available evidence generally focused on HRQoL rather than survival. The EAG identified one paper[45] proposing MCID values for OS and PFS, although this was in a population of people with chronic lymphocytic leukaemia (CML) rather than AML. In CML, as a chronic rather than acute leukaemia, progression is typically much slower.[46] Therefore, the EAG did not consider MCID values for OS based on a CML population to be useful for the purposes of this AML appraisal. This limits the ability of the EAG to consider the clinical significance of observed effects.

3.5.2. Additional Medline search

The company searches for acute myeloid leukemia were narrowed to only include database records that had some version of the phrase first line/untreated/treatment naïve in them ["(first line or 1st line or 1LOT or first time or treatment naive or front line or naive or untreated or ((new$ or initial$) adj3 diagnos$) or ((initial$ or first or naive or primary or induction) adj3 (therapy or treatment))).mp."]. This is a risky strategy as identifying first line treatment as a phrase search in a search strategy is difficult and there are no relevant indexing terms in the databases. It is highly possible that articles might not mention these phrases in the database record and that relevant papers might have been missed. It would be safer to screen the records to examine whether or not they are relevant to the review.

In order to investigate whether relevant records could have been missed, the EAG conducted a revised version of the company searches. The company searches were reproduced but with the controversial first line treatment line omitted, in Medline only. When deduplicated against the CS results, a further 1336 papers were identified that had not been screened for this SLR, but should, in the EAG's view, have been screened. This number would potentially be doubled with

the addition of Embase and Cochrane records. It is very likely that some of these omitted records might have been relevant to this SLR and that articles may have been missed as a result of the narrow search strategy.

3.5.3. Exploratory analysis of OS HR between IVO+AZA and VEN+AZA in IDH1 subgroup

The EAG estimated a HR for IVO+AZA vs VAN+AZA in the IDH1 subgroup. Head-to-head RCT is available from AGILE (IVO+AZA vs AZA+PLACEBO HR=0.42 (95% CI: 0.27 to 0.73) ; 'updated analysis' doc B p42) while DiNardo et al[17] report the HR for the IDH1 subgroup in fig 3 (VEN+AZA vs IVO+AZA HR=0.28 (95% CI: 0.12 to 0.65)).

A frequentist analysis gives an OS estimate for IVO+AZA vs VEN+AZA in the IDH1 subgroup of HR =1.50 (95% CI: 0.67 to 3.35, p=0.32), which favours VEN+AZA in direction but is not statistically significant. This result should be treated as exploratory and is further caveated in 3.4.4.2.

3.6. Conclusions of the clinical effectiveness section

The CS presents results for one RCT (AGILE) comparing ivosidenib plus azacitadine with azacitadine plus placebo. The EAG was satisfied that this trial was well conducted and appropriate to the decision problem. The EAG agreed that the AGILE trial supported a clinical benefit for ivosidenib plus azacitadine compared to azacitadine plus placebo. The CS presented 26 studies as included in the SLR, four of which were considered eligible for the NMA, although it wasn't particularly clear how these were selected. The studies included in the network meta-analysis all appeared relevant. However, it was not clear that all relevant studies were included in the NMA. This is partly due to the lack of clarity regarding the two steps by which the 26 studies were narrowed down to 10 and then to four for EFS. However, it was also due to issues with the literature effectiveness searches, in which a population restriction to first line was applied in the search rather than at the screening stage. The EAG considered this to be a risky strategy that was likely to lead to the exclusion of relevant articles.

Time-to-event NMAs were presented in the CS and used in the economic model. These NMAs made assumptions of PH over the network which the EAG concluded were not always upheld by supporting information. The company assessed heterogeneity across the network in some detail and concluded that there was a 'low to moderate' level, and the EAG agrees with this. FE models were selected in the CS over RE, which could be justified but means reported credible

intervals are too narrow, not reflecting the heterogeneity. The most important potential effect modifier is likely IDH1 status. The EAG assessed the evidence and concluded that though there was a suggestion of a stronger treatment effect for azacitadine plus venetoclax in the IDH1 subgroup, the result did not have any strong statistical support, nor would this follow prior understanding of the biological mechanisms.

The NMA results as presented favour ivosidenib plus azacitadine over azacitadine plus venetoclax for EFS, OS and CR/CRi (the outcomes used in the economic model), but the differences are non-significant. These results should also be interpreted in light of concerns about the identification of all relevant evidence. NMA results were presented in Appendix D ITC for three comparators that the company had excluded from the decision problem compared to the NICE final scope. From these additional three comparators, cost-effectiveness results were only available (in the model file rather than in the CS) for azacitadine monotherapy. The EAG noted this lack of consistency to be a concern and could not identify a clear rationale for the approach taken.

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

Table 22. Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Document B Section B.2.1; Appendix D Section 4.4, 8.2. CS section 4.3 appendix D	The search strategies were executed in a good range of sources. However searches for acute myeloid leukaemia were narrowed to only include database records that had some version of the phrase first line/untreated/treatment naïve in them. It is highly possible that articles might not mention these phrases in the database record and that relevant papers might have been missed. Further information on this is at section 3.5.2. Several of the company searches were limited to exclude conference abstracts published between 2011-2015. In clarification the company stated that they wished to only search for conference abstracts from 2017 onwards, but this does not match what was done in the search strategies and the reasons for this discrepancy are unclear. The searches are well conducted, using a variety of sources and a good range of search techniques
Inclusion criteria	CS section 4.2.2 appendix D	The inclusion criteria adhered to good standards. They incorporated a population relevant to the decision problem, without constraining the interventions under consideration. The outcomes of interest encompassed costs, ICER, utilities, QALYs, disability-adjusted life years (DALYs), life years gained, hospitalisation rates, and healthcare resource utilisation. Furthermore, the inclusion criteria were designed to accommodate a wide array of complete and partial economic evaluation designs, as well as reports on resource utilisation
Screening	CS section 4.7 appendix D	Appropriate screening process
Data extraction	CS section 4.9 appendix D	Appropriate
QA of included studies	CS section 8.4 appendix D	Acceptable

Abbreviations: CS, Company Submission; EAG, Evidence Review Group; HRQoL, health-related quality of life; QA, quality assessment

Table 23. Summary of EAG's critique of the methods implemented by the company to identify health related quality of life

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Document B Section B.2.1; Appendix D Section 4.4, 8.2. 4.2.3 appendix D	The search strategies were executed in a good range of sources. However searches for acute myeloid leukemia were narrowed to only include database records that had some version of the phrase first line/untreated/treatment naïve in them. It is highly possible that articles might not mention these phrases in the database record and that relevant papers might have been missed. Further information on this is at section 3.5.2. Several of the company searches were limited to exclude conference abstracts published between 2011-2015. In clarification the company stated that they wished to only search for conference abstracts from 2017 onwards, but this does not match what was done in the search strategies and the reasons for this discrepancy are unclear. The EAG does not consider that search methods were appropriate.
Inclusion criteria	4.2.3 appendix D	encompassed a diverse array of study designs, along with both generic and disease-specific measures of patient-reported outcomes for health states and adverse events.
Screening	CS section 4.7 appendix D	The ERG considered the approach to screening appropriate, i.e., two reviewers screening independently and involvement of a third reviewer to resolve discrepancies.
Data extraction	CS section 4.9 appendix D	Appropriate
QA of included studies	NR	The ERG could not locate details of critical appraisal of included studies.

Abbreviations: CS, Company Submission; EAG, Evidence Review Group; HRQoL, health-related quality of life; QA, quality assessment

Table 24. Summary of EAG's critique of the methods implemented by the company to identify healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Document B Section B.2.1; Appendix D Section 4.4, 8.2. CS section 4.3 appendix D	The search strategies were executed in a good range of sources. However searches for acute myeloid leukemia were narrowed to only include database records that had some version of the phrase first

		line/untreated/treatment naïve in them. It is highly possible that articles might not mention these phrases in the database record and that relevant papers might have been missed. Further information on this is at section 3.5.2. Several of the company searches were limited to exclude conference abstracts published between 2011-2015. In clarification the company stated that they wished to only search for conference abstracts from 2017 onwards, but this does not match what was done in the search strategies and the reasons for this discrepancy are unclear. Appropriate
Inclusion criteria	CS section 4.3 appendix D	Appropriate
Screening	CS section 4.7 appendix D	Appropriate
Data extraction	CS section 4.9 appendix D	Appropriate
QA of included studies	NA	The ERG could not locate details of critical appraisal of included studies.

Abbreviations: CS, Company Submission; EAG, Evidence Review Group; HRQoL, health-related quality of life; QA, quality assessment

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklist

Table 25: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALYs were used as appropriate, which captured the health benefit to patients. The company did not include carer disutility.
Perspective on costs	NHS and PSS	NHS and PSS as appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company submitted a cost utility analysis and presented pairwise results (the company only included two comparators in its analysis).
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A lifetime horizon was used (assumed to be 25 years).

Synthesis of evidence on health effects	Based on systematic review	Clinical data (EFS and OS) used in the economic model for IVO+AZA was derived from the AGILE study, which compared IVO+AZA to AZA+placebo. For the primary comparator (VEN+AZA), clinical effectivenvess (EFS and OS) was derived from a NMA. The EAG noted that EFS and OS for VEN+AZA were estimated by applying the HR to the selected curve for the IVO+AZA arm,
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects were expressed as QALYs, as appropriate. QoL values were measured using the EQ-5D-5L.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Utility values were estimated using EQ-5D-5L data, which were collected directly from the AGILE study.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	EQ-5D-5L data from AGILE were mapped onto the 3L value set for the UK using an algorithm by Hernandez-Alva et al (2018).[47]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	There were no equity concerns.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource use and costs were primarily based on 2021/2022 NHS reference costs and the PSSRU, as appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and QALYs were discounted at 3.5% as appropriate. Life years were not discounted.

Key: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Pseronal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

Note(s):

Source(s):

4.2.2. Model structure

The company submitted a partitioned survival (PartSA) model, which included three broad health states including an event free state (also termed event free survival or EFS), progressed disease/relapse (PD/RL) and death (see diagram below). The EAG noted that modelled health states were informed by endpoints from the AGILE study. As per a PartSA approach, health state occupation over time (for EFS and OS) was informed by parametric curves. However, the EAG noted the company has referred to the model structure on p.82 of the CS as a cohort level hybrid PartSA and Markov model. During clarification (B.9), the company was asked to comment on what components within the model reflect a Markov structure, which are typically characteristed by the use transition probabilities. The company confirmed that the two Markov components were the estimation of % of patients with complete remission or complete remission without count recovery (CR/CRi), used to estimate modelled utility values and the % of patients moving to the long term survival or 'LTS' state.

The EAG has noted that model structure has varied in previous NICE TA's for AML i.e. in TA765[13], the company adopted a Markov approach to determine health state occupancy, whilst in TA642[48] for gilteritinib, the company used a partitioned survival model.The company provided justification for their PartSA approach on p.81 of the CS, and additionally note that a PartSA approach was selected given unavailable patient level data to inform transitions for VEN+AZA. During clarification (B8), the EAG asked the company to provide results based on a Markov modelling approach. The company confirmed that this was not possible given the lack of access to patient level data from VIALE-A or sufficient summary statistics to enable estimation of transition probabilities. Overall, the EAG considered the company's PartSA structure to be reasonable for the decision problem, however the hybrid Markov components do add additional uncertainty (see Sections 4.2.6.4 and 4.2.6.6 for further discussion).

To account for patient remission status and it's potential impact on HRQoL and rescource use, the company subdivided the EFS state into CR/CRi and No CR/CRi. The EAG noted that this appeared to reflect the approach in NICE TA765. Furthermore, based on clinical opinion to the EAG, seperating EFS into remission and non remission states was considered to be reasonable.

Additionally, the EAG noted that the definition the company used for EFS in the cost effectiveness model was different to the definition of EFS used in the AGILE study. On p.85 of the CS, the company states that this was *'to ensure alignment with the definition of EFS used in*

the VIALE-A study'. VIALE-A[17] was the primary study included within the NMA which formed the basis of the IVO+AZA vs VEN+AZA comparison. The company also noted that the definition also defined and aligned in accordance with FDA guidance due to improved association with overall survival. During clarification, the company was asked to clearly outline the difference in EFS definition between AGILE and the definition used in the economics. These differences are provided in the company's response to B2 of the EAG clarification questions (and Table 26 below).

To explore uncertainty surrounding the modelled definition of EFS, the EAG further asked the company to provide a scenario analysis using the definition of EFS as per AGILE, however the company stated that this was not possible. Based on the company's response to (B2 and B3) of the EAG clarification questions, using the AGILE definition would *'artificially assign some patients to the progressed disease or relapsed health state earlier than they should be defined as such'*. The company further stated that *'any survival models fitted to EFS according to the primary endpoint from AGILE would either be unrealistic (if including events on Day 1), or would need to be re-based from Day 1*. Overall, the EAG considered that there was uncertainty surrounding the modelled definition for EFS. Based on the company's response to EAG clarification questions, it may difficult/infeasible to characterise and explore the impact of using the AGILE definition of EFS.

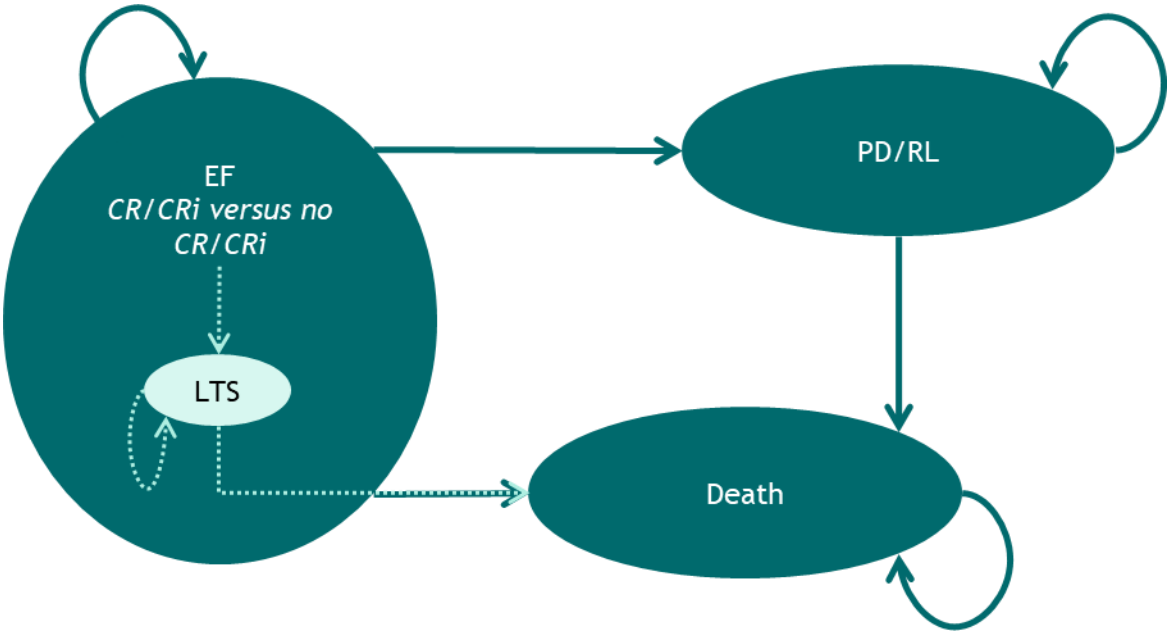
Table 26: Disparity in EFS definition

Definition of EFS in AGILE	Definition of EFS used in economic model (Aligned with VIALE-A)
The time from randomization until treatment failure (i.e., the patient did not have complete remission by week 24), relapse from remission, or death from any cause, whichever occurred first	Time from randomization to disease progression, treatment failure (failure to achieve complete remission or <5% bone marrow blasts after at least six cycles of treatment), confirmed relapse, or death.

Within the EFS state, the company included a further nested state termed the LTS state. The company assumed that patients who remain alive (in the EFS state) at 3 years are functionally cured and move into the LTS state (this assumption applies to all treatment arms). The EAG noted that these patients are considered long term survivors and no longer experience risk of disease progression or relapse. Patient survival is based on general population mortality/life tables. The EAG noted that the LTS state is associated with utility similar to the EFS (CR/CRi) and lowest health state costs. The company's rationale for including a cured health state was

based on NICE TA765[13] [veneteclax+azacitidine for the treatment of untreated acute myloid leukaemia when intensive chemotherapy is unsuitable]. See Section 4.2.6.4 for further discussion on the appropriateness of the company's cure assumption and LTS state.

Figure 7: Model structure



4.2.3. Population

The patient population in the company's economic analysis were those with untreated IDH1-positive acute myeloid leukaemia, as per the NICE scope. Modelled patient baseline characteristics were taken from the AGILE,[16] which was a phase III, randomised multicentred study which compared IVO+AZA to AZA+placebo. Based on clinical opinion to the EAG, the mean age and % female were considered generalisable to UK patients, though it was noted that mean body weight may be somewhat lower than the UK. The company provided one-way sensitivity analysis (OWSA) which varied baseline patient characteristics (including patient weight), however results were not sensitive to this. The EAG considered the baseline characteristics to be appropriate and acceptable for use in the model.

Table 27: Modelled patient baseline characteristics

Characteristic	Input value
Mean age (years)	74.84
Proportion female (%)	45.21

Mean body weight (kg)	71.17
Mean body surface area (m^2)	1.78

4.2.4. Interventions and comparators

In order to maximise the benefit to patients subject to the resources available, all possible treatment strategies for a particular patient should be compared simultaneously, with dominated and extended dominated options that do not lie on the efficient frontier excluded on the grounds of efficiency (a 'fully incremental' analysis). Excluding relevant comparators has the potential to generate highly misleading results relating to cost-effectiveness, and thus a failure to maximise the net health benefit to NHS patients subject to the resources available.

As discussed in Section 2.4 , the NICE scope highlighted several relevant comparator treatments including VEN+AZA, VEN+LDAC (if over 30% bone marrow blasts), LDAC and AZA (if not eligible for HSCT and have AML with 20% to 30% blasts and multilineage dysplasia). However, the primary comparator used by the company in the economic analysis was VEN+AZA. On p.85 of the CS the company state that VEN+AZA represents the current standard of care within this patient population. The EAG noted that the company included cost effectiveness results vs AZA within their economic model (which derived clinical effectiveness data from the phase III trial AGILE), however the company did not report these results in the CS, on the basis that VEN+AZA was the primary comparator of interest. For completeness, the EAG has presented the company's results comparing IVO+AZA to AZA alone and the company's fully incremental results which include AZA as a comparator (see Section 5.1.1 for results).

The EAG noted the following regarding the company's handling of comparator treatments

- VEN+AZA is not specifically licensed for use in the treatment of patients with untreated IDH1-positive acute myeloid leukaemia. The EAG note that whilst VEN+AZA is currently being used by clinicians in practice to treat these patients (as per clinical opinion to the EAG), VEN+AZA has been recommended by NICE within it's marketing authorisation, as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable.

- Based on clinical opinion to the EAG, VEN+AZA appears to represent current standard of care for patients under review, however treatments identified within the NICE scope (as noted above), may be used within the UK to treat a proportion of patients that are

unable to tolerate treatment with either IVO or VEN. The EAG understand that IVO+AZA could be considered a moderate intensity treatment suitable for fitter AML patients but who are not considered fit enough for high intensity chemotherapy. The EAG therefore consider that cost effectiveness comparisons versus AZA monotherapy, VEN+LDAC and LDAC remain relevant for consideration.

- The company did not provide cost effectiveness results comparing IVO+AZA to VEN+LDAC or LDAC. Due to the lack of robust data, the EAG were unable to conduct a cost effectiveness analysis versus these treatments. Although comparative clinical effectiveness results (derived from the NMA) and cost/dosing information (outlined in MIMs), suggest that IVO+AZA may result in improved clinical effectiveness and higher costs versus these comparators, the cost effectiveness of IVO+AZA compared to these treatments remains an area of uncertainty.

4.2.5. Perspective, time horizon and discounting

All costs and outcomes were estimated from an NHS and PSS perspective and costs and benefits were discounted at 3.5% as appropriate. The EAG noted that estimates of life years were not discounted. The company state these remained undiscounted for ease of interpretation. However, as per the NICE process manual (2022),[49] *'for the reference case, costs and health effects should be discounted at the same rate of 3.5% per year.'* As part of the EAG preferred base case life years have been discounted at 3.5%.

The time horizon used in the company's base case analysis was 25 years, which the EAG note to be shorter than the 40 year time horizon that had been previously used in TA 765 for veneteclax plus azacitidine. However, the EAG considered a 25 year time horizon appropriate, given the mean starting age of patients in the model was 74.84 years and the time horizon was sufficiently long to capture differences in costs and benefits between treatments; only a small proportion of patients remained alive at age 100 in both treatment arms.

The cycle length used in the model was 28 days (with half cycle correction). The company stated that 28 days is aligned with the duration of a treatment cycle for both IVO+AZA and VEN+AZA. The EAG considered the cycle length to be appropriate and in line with TA 765.

4.2.6. Treatment effectiveness and extrapolation

4.2.6.1. Clinical effectiveness of IVO+AZA, VEN+AZA and AZA

The clinical effectiveness data (OS and EFS) used in the economic analysis for IVO+AZA (and AZA) was derived directly from patient level data within the AGILE study.[16] The length of follow up in AGILE was relatively short (28.6 months, based on June 2022 data cut) and the study included small patient numbers (n=72 in each arm). Results have been reported and discussed in Section 3.2.3.1.

The EAG noted that key modelled clinical effectiveness outcomes included EFS, OS and the % of patients with complete remission or complete remission without count recovery (CR/CRi) and No CR/CRi. As discussed in Section 3.4, in order to estimate the relative treatment effect of IVO+AZA compared to a range of comparators (including VEN+AZA), the company conducted an NMA. The outputs from the NMA (EFS and OS used in the economic model to estimate the clinical effectivenss of IVO+AZA vs VEN+AZA are outlined in the following sections. The EAG note that the proportion of patients with CR/CRi used in the model for VEN+AZA was not taken from the NMA, but rather an equation estimated by the company. See Section 3.4 for further discussion.

Based on the NMA submitted by the company, IVO+AZA resulted in an EFS HR of [redacted] [95% CI [redacted]], compared to VEN+AZA. For OS, IVO+AZA resulted in a HR of [redacted] [95% CI [redacted]] compared to VEN+AZA. Due to uncertainty surrounding the NMA outputs (as outlined in Section 3.4), the EAG conducted a number of scenario analyses. For both EFS and OS, the HRs were increased by 25% (thereby reducing the relative effect of IVO+AZA), additionally, HRs were also varied between the 95% credible interval values (see Section 3.4 for further discussion and results).

4.2.6.2. Modelled EFS (IVO+AZA, VEN+AZA and AZA)

Based on the results from AGILE,[16] median patient EFS in the IVO+AZA arm was reported to be 22.9 months compared to median 4.1 months in the AZA arm (KM data are reported in Figure 8 below). In order to extrapolate long term EFS estimates in the IVO+AZA arm, the company used a parametric modelling approach. In the IVO+AZA arm, the company selected a lognormal distribution for extrapolation. On p.87 of the submission the company state that the lognormal was the best statistical fit (except for BIC) and produces plausible extrapolation estimates. Furthermore, the company states (doc B section B3.3) that "…the exponential and Gompertz

models produced extrapolations that were deemed too pessimistic and too optimistic, respectively by clinician feedback to the company (35)".[50] However, when the EAG examined the supplied record the IVO+AZA EFS extrapolations had not been covered by clinicians within the interview (response to question Q8).

Figure 9 below highlights the various parametric curve fits to the IVO+AZA EFS Kaplan Meier data from AGILE. Using the lognormal curve, the proportion of patients who were event free in the IVO+AZA arm at 5, 10 and 15 years was 23.3%, 13.8% and 7.4% respectively (see

Figure 10). Based on clinical opinion to the EAG, the EFS estimates produced for IVO+AZA appeared to lack clinical plausibility, and noted that estimates using a Weibull parametric curve appeared more reasonable. Using the Weibull curve, the proportion of patients who were event free in the IVO+AZA arm at 5, 10 and 15 years was 13.1%, 3.2% and 0.3% respectively.

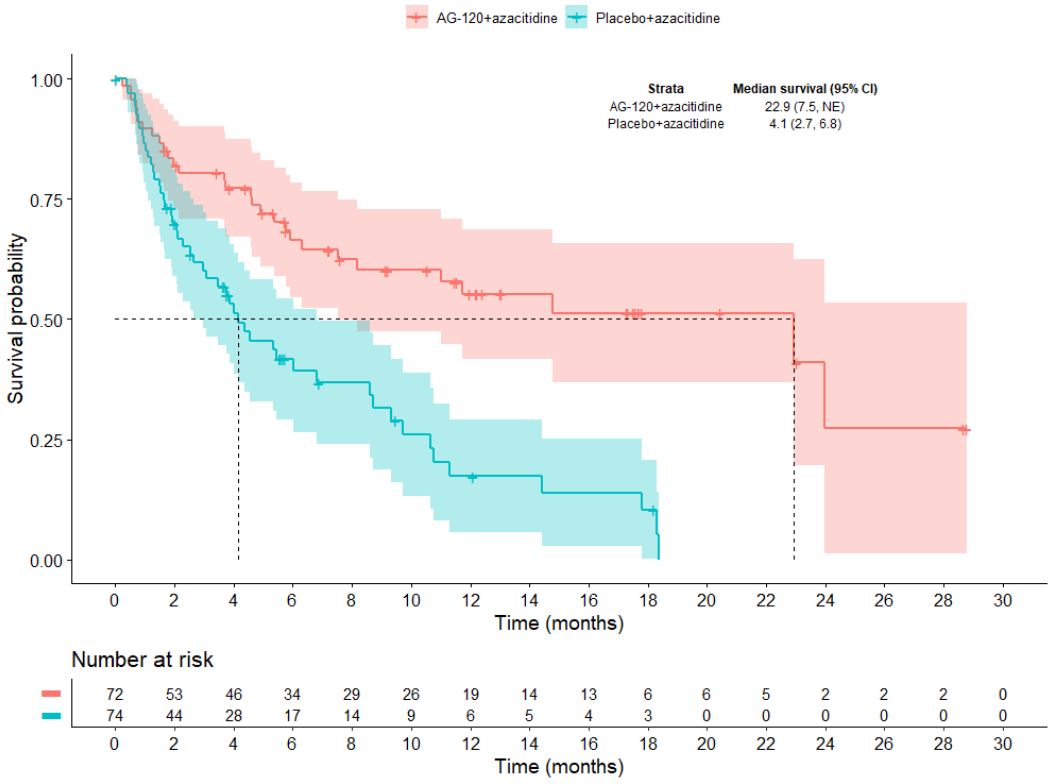
Based on clinician feedback to the EAG, reasonable statistical fit and the lack of long-term robust data underpinning the company's EFS estimates, the EAG selected the Weibull curve for use in it's base case, in the IVO+AZA arm. Note, that the application of the Weibull curve to the IVO+AZA arm, means that the modelled EFS for VEN+AZA is also changed to a Weibull, given that the relative effectiveness of IVO+AZA vs VEN+AZA was estimated using a proportional hazards approach and the Weibull is a proportional hazards distribution. Furthermore, the log-cumulative hazard plots for EFS in Appendix D of Appendix D [ITC] for VIALE-A and AGILE are more-or-less straight, which supports the use of a Weibull model. To explore EFS uncertainty, the EAG conducted a scenario analysis which uses the exponential curve to extrapolate EFS in the IVO+AZA arm. Results were sensitive to this analysis, as the exponential curve produced the most pessimistic EFS results (see Section 6.2.2 for results).

For AZA, EFS was extrapolated using the lognormal curve. Using the lognormal curve, the proportion of patients who were event free in the AZA arm at 5, 10 and 15 years was 1%, 0.2% and 0% respectively. Given that all curves produced reasonably low long term EFS estimates and the lognormal produced one of the lowest AIC/BIC statistics, the EAG considered the company's selection of lognormal in the base case to be reasonable. The EAG noted that the company has provided scenario analysis using alternative curve fits for IVO+AZA only. Results are outlined on p.127 of the CS.

Finally, the company provided plots of the estimated hazard function in response to clarification question A10 using two methods, basis splines and kernels, with the former producing smoother

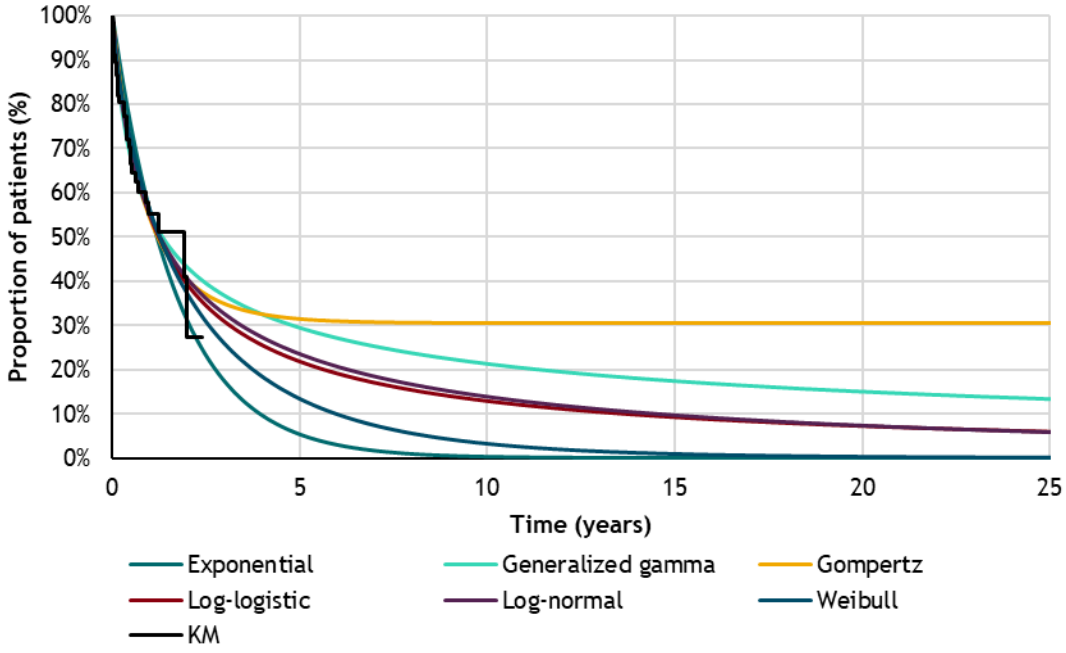
curves. For IVO+AZA, there is an increased hazard towards the end of follow-up with the kernel method (CQ response fig 7) and for AZA an increased hazard with both kernel and spline methods (CQ response fig 8). This may suggest a benefit to extending the range of models to include flexible models such as splines. However, the EAG did not ask for and the company did not supply a confidence region around the hazard estimate, but with few numbers at risk it is anticipated that precision is poor in this region of the curve. The EAG concludes there is no clear indication of a benefit to more flexible parametric modelling.

Figure 8: EFS KM data from AGILE (IVO+AZA vs AZA)



Source: company response to CQ, figure 2

Figure 9: Parametric models for EFS (IVO+AZA)



Note: Company selected the lognormal curve for base case extrapolation. The EAG preferred to extrapolate EFS using the Weibull curve.

Figure 10: Company base case EFS extrapolation (all arms)

Note: EFS for IVO+AZA extrapolated using a Lognormal curve. EFS for VEN+AZA estimated via a proportional hazards approach. EFS for AZA estimated using the Lognormal curve

4.2.6.3. Modelled OS

Based on the results from AGILE,[16] median patient OS in the IVO+AZA arm was reported to be 29.3 months compared to median 7.9 months in the AZA arm (KM data are reported in Figure 12 below). In order to extrapolate long term OS estimates in the IVO+AZA arm, the company used a parametric modelling approach. In the IVO+AZA arm, the company selected a lognormal distribution for extrapolation. The company justified the selection of the lognormal on the basis that it produced plausible extrapolated OS estimates, based on clinician feedback to the company,[50] and it reflected the model used to inform the majority of transitions to death in TA765.[13] However, based on a review of the clinician consultation document provided to the EAG, it was noted that 2/3 clinicians identified that the Weibull and Exponential curves (two of the lowest OS estimating curves), produced more plausible OS estimates (Table 28 below). **Note**: These OS estimates have not been adjusted to reflect the modelled cure assumption or background mortality. This is reported in Section 4.2.6.4.

For additional validation, the EAG sought further clinical input. Based on clinical opinion to the EAG, extrapolated OS estimated (using the lognormal curve) at key landmark timepoints lacked clinical plausibility and was considered highly optimistic. Due to the uncertainty surrounding the company's base case extrapolated OS estimates in the IVO+AZA arm, the EAG opted to select the Weibull as the appropriate OS curve for it's preferred base case. Furthermore, the Weibull was considered to produce OS estimates that are broadly in line with clinical expectation and produced reasonable AIC/BIC statistics. However it should be noted that the log-cumulative hazard plots in Appendix D of Appendix D [ITC] for IVO+AZA and VEN+AZA indicate a relatively steep initial cumulative hazard in the first 1-3 months of follow-up. This non-linearity is counter to a Weibull model, though perhaps mildly in this instance.

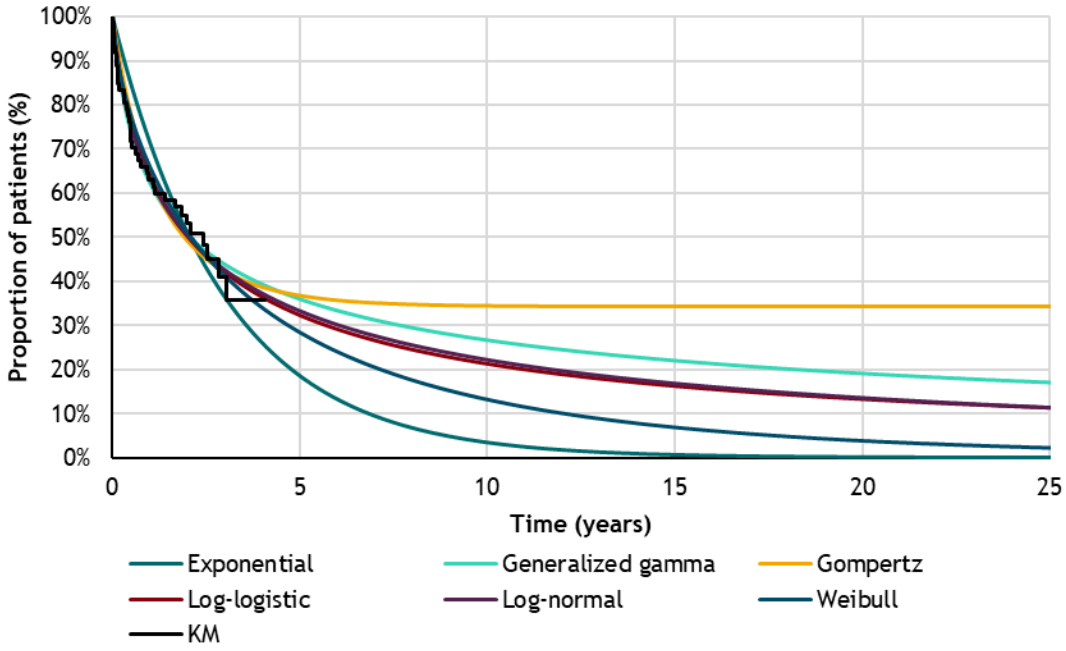
As a scenario analysis, the EAG have modelled OS for IVO+AZA using the exponential curve. The EAG considered this to be an exploratory analysis, given the poor statistical fit associated with the curve, however clinical opinion to the company has highlighted that OS estimates using the exponential could be plausible (See Section 6.2.2 for further discussion and results).

Table 28: IVO+AZA OS at landmark time points

Model	Modelled OS at 3 years	Modelled OS at 5 years	Modelled OS at 10 years	Modelled OS at 20 years
Exponential	35.5%	18.1%	3.4%	0.1%

Generalized Gamma	43.5%	35.8%	26.6%	19.1%
Gompertz	42%	36.8%	34.5%	34.4%
Log-logistic	41.6%	32.1%	21.3%	13.3%
Log-normal	42.3%	33.2%	22.3%	13.7%
Weibull	40.7%	28.1%	13.1%	3.8%

Figure 11: Company modelled OS for IVO+AZA



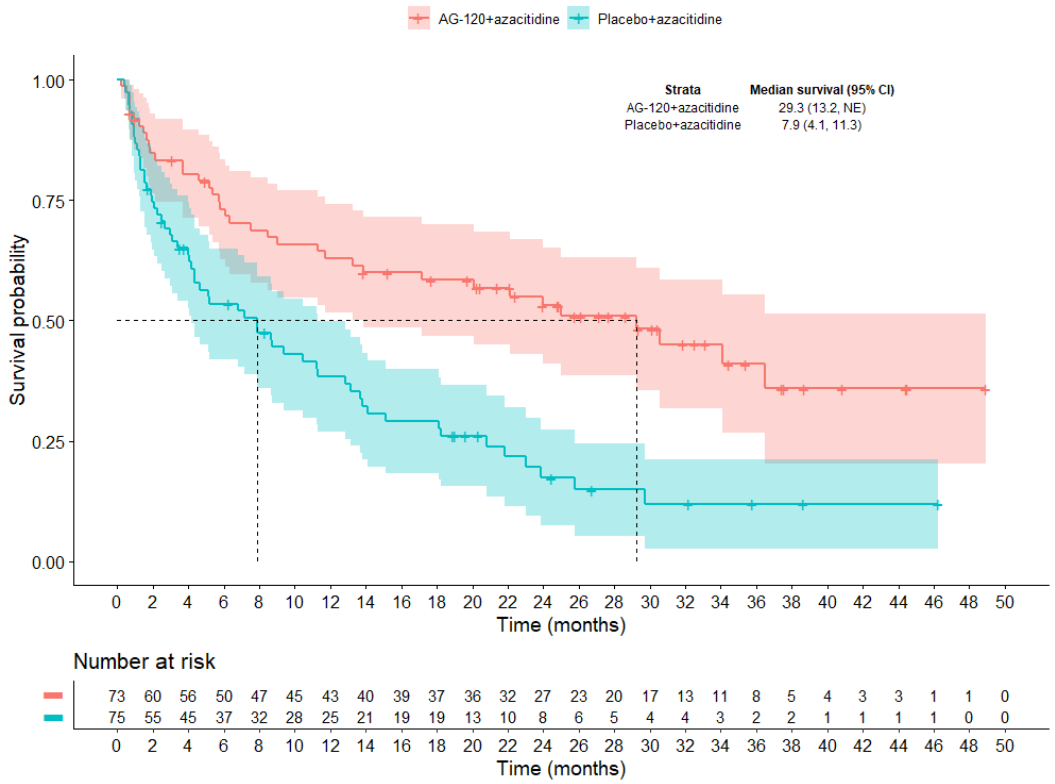
Note: For IVO+AZA the company extrapolated OS using a Lognormal curve. The EAG preferred base case uses the Weibull to extrapolate OS.

For VEN+AZA, OS was estimated by applying the relevant HR from the NMA to OS in the IVO+AZA arm. For AZA, OS was modelled using the lognormal curve. Using the lognormal curve, OS in the AZA arm was estimated at 5, 10 and 15 years to [redacted], [redacted] and [redacted] respectively. The EAG noted that the lognormal was the best fitting curve based on AIC/BIC statistics. Based on clinical opinion to the EAG, extrapolated OS estimates at key landmark timepoints appeared to be reasonable. Overall, the EAG considered the use of the lognormal curve to extrapolate OS in the AZA arm to be reasonable (see Section 3.4.3).

Note: The company provided plots of the estimated hazard function in response to CQ A10 using two methods, basis spline and kernel-based estimates, with the former producing

smoother curves. For OS (CQ response figures 5 and 6), all models used (barring the exponential) can in principle fit to a declining hazard curve as observed, though visually the Weibull fit is poor for the AZA arm.

Figure 12: OS KM data from AGILE (IVO+AZA vs AZA)



Source: company response to CQ, figure 4

4.2.6.4. Cure assumption and long-term treatment effect

The company assumed that all patients in the EFS state at 3 years are considered functionally cured. These patients were assumed to experience mortality similar to the UK general population and no longer received primary treatment. As can be seen in Figure 14 and Figure 15, a higher proportion of patients in the IVO+AZA arms move into the LTS state at 3 years, compared to the VEN+AZA arm. Table 2 (p.31) of the company response to EAG clarification questions), highlights that the LTS health state produces the majority of the incremental QALY gain associated with IVO+AZA.

The company's rationale for including a cured 'LTS' state in the model was primarily based on prior NICE guidance for VEN+AZA [TA765][13]. In NICE appraisal [TA765], the committee appeared to agree that it was plausible that a proportion of patients could be considered cured, although the evidence for including a cured state in the model was uncertain. The EAG noted that the company's approach to modelling cure was broadly aligned with the committee's preferences [for TA765] i.e. cure assumed to apply from 3 years to patient in all treatment arms. However, a key difference between the appraisals is that in TA765 only CR/CRi patients were capable of moving into the cured health state. Within the current appraisal, both CR/CRi and No CR/CRi patients in the EFS state at 3 years were considered functionally cured. Based on clinical opinion to the EAG the company's assumption was noted to be unreasonable and did not represent clinical practice. In order to explore uncertainty, the EAG has conducted a scenario analysis which assumes that only CR/CRi patients can be considered functionally cured at 3 years (see Section 6.2.3 for results).

Additionally, the CS argues that the most recent AGILE datacut 'demonstrated a plateau in the IVO+AZA OS, which implies potential to 'cure' the target AML patients' (doc B p93). However, the associated KM plot (doc B fig 9) did not show a confidence band. The EAG notes the comment by Altman p386[51] "It is common for survival curves to flatten out after a while, as events become less frequent. It is unwise to interpret this flattening as meaningful unless there are many subjects still at risk". The EAG requested CLs be provided in CQ A4 and these are shown in this report in Figure 8 and Figure 12; the EAG interprets the graphs received as showing considerable uncertainty about a terminal plateau in the survival curve.

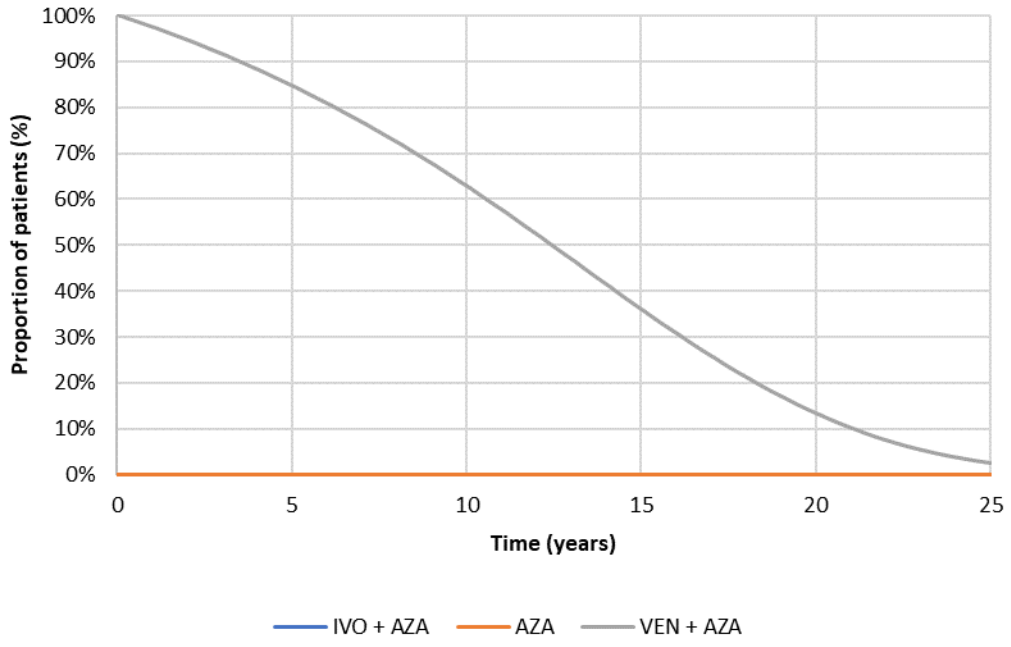
The EAG also requested plots of the estimated hazard in CQ A10. If the remaining patients at the end of the trial are 'functionally cured', the EAG believes the EFS hazard should tend to zero (though it will rise again in the longer term as age-related mortality takes effect). In both arms of AGILE, the (smoother) basis spline estimates of the hazard do not approach zero in the OS plot, but the kernel based estimates do (figs 5 and 6 of CQ response to A10). It is notable that the pattern is the same in the IVO-AZA arm (where a cure fraction is posited) and the AZA arm (where it is not). The EAG did not ask for, and the company did not supply, a confidence region around the hazard estimate, but it is anticipated that precision is poor in this region of the hazard curve.

In order to further validate the appropriateness of including a functionally cured health state, the EAG sought clinician opinion. Based on clinical opinion to the EAG, the potential curative effect

of IVO+AZA remains an area of uncertainty. It was highlighted that until recently there have been no meaningful treatments for this patient population and that the introduction of VEN+AZA has resulted in superior response rates when compared to AZA monotherapy. Furthermore, patients receiving VEN+AZA are more likely to enter 'deep remission'. Overall, the EAG noted there is considerable uncertainty surrouding the long term clinical effectiveness of IVO+AZA and the company's approach to modelling cure.

The company provided scenario analysis which varied assumptions surrounding the LTS state (see p.33/34 of the company's response to EAG clarification document). Scenarios included the use of alternative time points at which cure is applied (2 and 4 years), using alternative cure proportions (80% and 90%), using alternative standardised mortality ratios for the LTS state and removal of OS implications in the LTS state i.e. only LTS costs and utilities are considered. The EAG noted that IVO+AZA remained the dominant treatment compared to VEN+AZA for all these scenarios. Due to the lack of long-term robust data underpinning the modelled cure assumption, the EAG removed the cure assumption from the model as part of its preferred base case.

Figure 13 Modelled OS by treatment (adjusted for cure)



Note: For IVO+AZA the company extrapolated OS using a Lognormal curve. OS for VEN+AZA estimated via a proportional hazards approach. OS for AZA estimated using the Lognormal curve. OS was adjusted in the IVO+AZA and VEN+AZA treatment arms to account for a cure assumption at year 3.

Figure 14: Markov trace (IVO+AZA)

Figure 15: Markov trace (VEN+AZA)

4.2.6.5. Mortality

The EAG noted that mortality was captured via the following approaches in the company's model

- On treatment mortality. As outlined in 4.2.6.3, OS for all treatment arms was estimated via the use of parametric survival modelling.
- Background mortality adjustment: The company compared mortality as estimated via the parametric extrapolation approach, to general population mortality estimates (UK life tables). If the extrapolated hazard was lower than that of the age and sex adjusted general population, then the hazard from the life table estimates was used. The EAG considered this to approach to be reasonable.
- Mortality within the LTS state: Patients in the LTS state were assumed to experience mortality/OS as per general population estimates (UK lifetables). From 3 years onwards an SMR of 1 was applied. The EAG sought clinical opinion to determine whether this was reasonable. Based on the clinician's response, it seems reasonable to assume that mortality will drop back to UK population levels if the patient is considered 'functionally cured' after treatment. As noted previously, the company provided scenario analyses which used alternative standardised mortality ratios for the LTS state and a further analysis that did not adjust OS estimates in the LTS state i.e. only LTS costs and utilities are considered. Results were not sensitive to these analyses.

4.2.6.6. Modelling time dependent CR/CRi

As noted in Section 4.2.2, the company separated the EFS health state into CR/CRi and no CR/CRi, to account for differences in patient QoI and costs between those in remission (CR/CRi) and those who are in non-remission (No CR/CRi). The approach follows TA765, which considers patients in remission to be those with CR or CRi and non-remission patients to be those who did not achieve CR or CRi. For each modelled treatment arm, the company estimated the % of patients with CR/CRi (see approach below). The EAG noted that the proportion of patients estimated to have a CR/CRi impacts the model up to year 3, after which patients no longer remain in the EFS state i.e. they either enter the LTS state or continue to progressed disease state or death state (Figure 14 and Figure 15).

IVO+AZA and AZA

As outlined in the company's response to EAG clarification questions (B5), the proportion of patients in CR/CRi between baseline and week 72 were estimated in 4-weekly intervals using patient-level data from AGILE. The company stated that a simple count approach was used (i.e., denominator = number of patients in EFS, numerator = number of patients in EFS and in CR/CRi). Although not explicitly reported by the company in the CS, a similar approach appears to have been adopted to estimate the proportion of patients with CR/CRi in the AZA treatment arm.

The EAG noted that the company used several important assumptions to account for changing CR/CRi status over time

- No patients are in CR/CRi for the first two modelled cycles. The company justified this on the basis that the first recorded CR/CRi occurred between 4 and 8 weeks.
- Patients could achieve CR/CRi from cycle two onwards. On p.102 of the CS, the company notes that the change in CR/CRi status was captured in the model via a simple second order polynomial, which was fitted to the data between cycles 2 and 12. By cycle 12 the company state that the proportion of patients was relatively stable.
- From cycle 13 onwards, te proportion of patients was assumed to remain static i.e. a last observation carried forward approach was used.

The EAG noted that the company's assumptions introduced uncertainty into the model. The EAG sought additional clinical opinion for validation purposes. Based on clinical opinion to the EAG, the assumption that a patients CR/CRi status no longer changes from cycle 13 onwards, appeared reasonable, however it was noted that the modelled estimates at cycle 12 (44 weeks) appeared high for all treatment arms. The proportions however, could be considered plausible if they reflect the % of patients who remain on treatment at week 44 (as non responding patients are likely to have discontinue treatment earlier).

VEN+AZA

In B5 of the company's response to EAG clarification questions, the company noted that patient level data were not available from VIALE-A and further noted that a higher proportion of patients in the VIALE-A study (AZA arm) achieved CR/CRi compared to the AZA arm of the AGILE study (see company quotation below). As outlined on p.103 of the CS, the company therefore used a two-step approach to derive the % of patients with CR/CRi in the VEN+AZA arm. The first step

involved producing an estimate for VEN+AZA that aligned with the AGILE study, using the equation below.

$$Rate_{AZA\ in\ AGILE} \times \frac{Rate_{VEN+AZA\ in\ VIALE-A}}{Rate_{AZA\ in\ VIALE-A}} = 16.2\% \times \frac{66.4\%}{28.3\%} = 38.0\%$$

The EAG interprets this equation as making an estimate of risk in the VEN+AZA group in the AGILE population by multiplying the risk in the AZA group of the AGILE study by the raw rate ratio from the VIALE-A study. (The EAG believes these binary outcomes are more properly described as risks not rates).

The second step involved in the company's approach used the VEN+AZA CR/CRi estimate of 38% as a weighted average of the AGILE estimates for IVO+AZA and AZA. The argument in this second step is not clear to the EAG. The result of the company's approach produced modelled VEN+AZA CR/CRi estimates that fell broadly between the modelled IVO+AZA and AZA CR/CRi estimates (see Figure 16).

Excerpt from company response to EAG clarification question (B5): *'This analysis was performed to obtain an estimate for VEN+AZA that falls between the IVO+AZA and AZA arms of the AGILE study, since the relative proportions of CR/CRi from the AGILE and VIALE-A studies suggest that while more patients on VEN+AZA achieved CR/CRi in VIALE-A compared with IVO+AZA patients in AGILE, the CR/CRi rate for AZA was notably higher in VIALE-A compared with AGILE (16.2% in AGILE versus 28.3% in VIALE-A). This expectation of the VEN+AZA estimate falling between IVO+AZA and AZA is consistent with the other outcomes explored via the ITC (such as OS and EFS).'*

The EAG acknowledged the company's attempt to estimate VEN+AZA CR/CRi estimates that reflect a midway between IVO+AZA and AZA, however it was not clear why the NMA was not used (given that CR/CRi was assessed). Overall, the EAG preferred to use CR/CRi results from the NMA to estimate the % of patients with CR/CRi in the VEN+AZA arm because the NMA utilizes the full network information including treatment effects, baseline values and their uncertainty, while the company equation above relies on the point estimate of the risk ratio from the VIALE-A trial alone. This was considered as part of the EAG preferred base case.

The EAG utilised the CR/CRi NMA estimate as follows:

odds(VEN+AZA) = odds(AZA) x odds ratio (VEN+AZA:AZA)

The odds ratio is obtained from the company NMA estimate for this outcome ([redacted]) obtained from Appendix D [ITC] Table 19. Here the odds for AZA are time-dependent baseline values from the AGILE study which are available from the company's IPD which were modelled by the company with a polynomial (yellow line in Figure 16). The risks are obtained from the estimated odds using the inverse logit function. Note that the NMA gives an OR for IVO+AZA vs AZA of [redacted]), so the VEN+AZA treatment effect lies between IVO+AZA and AZA, as anticipated by the company's text above.

Figure 16: Proportion of patients in EFS with CR/CRI (by treatment arm)

4.2.7. Health-related quality of life

4.2.7.1. Health state utility values

The company collected EQ-5D-5L data from the pivotal study AGILE, which was used to inform modelled utilities. In order to estimate utilities according to the modelled health states the company defined time periods i.e. EQ-5D responses collected within the AGILE study were considered to fall into one of the defined time periods (see company definitions in Table 29

below. These data were then mapped to EQ-5D-3L, using the Hernandez Alva et al (2018)[47] crosswalk algorithm. The EAG consider the use of QoL data from the pivotal study to be appropriate. The EAG noted that baseline EQ-5D appears to have been captured in AGILE i.e. in the IVO+AZA arm baseline EQ-5D data were collected in 68 patients, whilst in the AZA arm baseline EQ-5D data were collected from 66 patients. The model however, did not incorporate a baseline utility estimate, which the EAG considered counterintuitive.

Table 29: Time period definitions for EQ-5D responses

Definition for model	Definition in AGILE
Baseline	Cycle 1 Day 1 before the start of study treatment. If no value was available on or before the date of randomisation, the last measurement on or before the start of study treatment was considered as the baseline.
EFS (with CR/CRi as the best response)	Time from randomisation until progressive disease, relapse from CR or CRi, treatment failure defined as failure to achieve CR, CRi, or MLFS after at least 24 weeks of study treatment or death from any cause, with the state of CR/CRi as the best response as assessed by investigators using the IWG Response Criteria for AML.
EFS (without CR/CRi as the best response)	Time from randomisation until progressive disease, relapse from CR or CRi, treatment failure defined as failure to achieve CR, CRi, or MLFS after at least 24 weeks of study treatment or death from any cause without the state of CR/CRi as the best response as per the IWG Response Criteria for AML.
PD/RL	The phase following relapse from remission or disease progression

Key: AML, acute myeloid leukaemia; CR/CRi; complete remission or complete remission with incomplete count recovery; EFS, event-free survival; IWG, International Working Group; MLFS, morphologic leukaemia-free state; PD/RL, progressed disease or relapse.

Given that patients may have provided multiple QoL assessments (repeated measures) during the study period, the company used a Mixed Methods for Repeated Measures (MMRM) model. The MMRM included individual variables, deemed relevant by the company including EFS, CR/CRi as best response and treatment arm. Interactions between these variables were also assessed. On p.101 of the CS the company stated that if coefficients were not statistically significant, interactions were excluded from the model. A step-wise approach was used to select

the best fitting model (based on AIC statistics). The coefficients from the model used to estimate health state utility values are outlined in Table 45 in the CS. The EAG noted that the intercept value of 0.769 was used to represent the health state utility of patients in the EFS (CR/CRi) health state. Health state utilities and utility decrements used in the economic model are outlined in Table 31.

The company made several assumptions surrounding the modelled utility values. It was assumed that patients in the PD/RL health state had no CR/CRi as their best response to treatment and it was also assumed that patients in the LTS health state had the same utility as patients in the EFS (CR/CRi) health state. The EAG note that the company did not provide rationale for these assumptions.

The company tested uncertainty surrounding modelled utilities via one-way sensitivity analysis and scenario analyses, which uses alternative literature sources to estimate health state utility. Alternative literature sources included publications by Coyle et al (2020)[52] and Pratz et al (2022)[53]. Colye et al (2020) was an economic evaluation of azacitidine in elderly patients with AML, with high blasts counts. The EAG noted that the study was conducted from a Canadian healthcare payer perspective. The study estimated utility for two health states AML in remission and relapsed AML (Table 30). Baseline utility was derived directly from a pivotal trial comparing AZA to conventional care regimens (AZA-AML-001).[41] Change in utility was captured via a disease specific questionnaire (EORTC QLQ-C30), which was administered at cycles 3, 5, 7 and 9. These estimates were then converted to utility scores using a mapping algorithm outlined in a published study by McKenzie and van der Pol.[54]

Pratz et al[53] was a US study which assessed the cost effectiveness of veneteclax in combination with azacitidine compared to azacitidine monotherapy in patients with AML who were ineligible for intensive chemotherapy. Qol data within the study were taken from the VIALE-A trial. Health state utility was then assessed by pooling EQ-5D-5L data from both treatment arms in the study and applying US preference weights. Values were then adjusted using a linear mixed effects model to account for correlation within patients' repeated assessments. The EAG noted that utility values estimated from Pratz et al were considerably lower for the No CR/CRi and progressed disease health states, than the AGILE esimates (see Table 30 and Table 31). This appears to be due differences in patients' characteristics between studies as well as the use of US/UK preference weights.

Overall, the EAG considered that both studies appeared to lack generalisability to the UK. Based on the company's sensitivity analysis, results were not particularly sensitive to variation in health state utilities or use of alternative literature sources (see p.30 and p.31 of the company response to EAG clarification questions).

Table 30: Utility values from alternative literature sources

Health state	Coyle et al (2020)[52]	Pratz et al (2022)[53]
AML in remission	0.751	-
Relapsed AML	0.675	-
EFS (CR/CRi)	-	0.796
EFS (No CR/CRi)	-	0.787
PD	-	0.723

During clarification with the company (B7), the EAG sought additional clarity on how the 'off treatment' utility decrement of [redacted] was applied in the model. Based on the company's response, the EAG understand that it is possible for patients to be off treatment in the EFS states. The disutility is therefore applied to any patient in the EFS health states who are no longer on active treatment and to those patients who reside in the PD/RL health state. For patients in the LTS health state, no utility decrement is applied as it is assumed that these patients experience utility as per those in the EFS (CR/CRi) health state.

Table 31: Modelled health state utility values

Health state	Mean	Source
EFS (CR/CRi)	[redacted]	AGILE (analysis of patient level data)
EFS (No CR/CRi)	[redacted]	AGILE (analysis of patient level data)
PD/RL	[redacted]	AGILE (analysis of patient level data)
LTS	[redacted]	Assumption
Off treatment decrement	[redacted]	AGILE (analysis of patient level data)

4.2.8. Resources and costs

4.2.8.1. Drug acquisition costs and Time on Treatment (ToT)

Drug acquisition costs were included for all modelled treatments including IVO, VEN and AZA (see Table 32). Drug acquisition costs (list prices) used in the model forVEN and AZA were derived from eMIT and BNF (2023). The EAG noted that the cost of a 100mg pack of azacitidine in eMIT (2023) was stated to be £31.66, which deviates from the £45.16 value used in the submission. However, this variance is unlikely to have a material impact on results, given that all arms in the economic model involve the use of azacitidine. The company submitted a patient access scheme (PAS) for IVO resulting in a [redacted] discount on the list price of the treatment. The EAG noted that a PAS is in place for VEN (see cPAS appendix for results incorporating cPAS).

Table 32: Unit drug costs considered in the model

Treatment	Units (mg)	Pack size	Pack cost	Source
Ivosidenib	250	60	List: £12,500.00 With PAS: £[redacted]	Servier
Azacitidine	100	1	£45.16	eMIT (2023)
Venetoclax	100	7	£299.34	BNF (2023)

Key: BNF, British National Formulary; eMIT, electronic market information tool; PAS, patient access scheme.

Time on treatment

Modelled drug costs were estimated using Time on Treatment (ToT). For IVO+AZA, ToT data from AGILE were used. To model ToT over the longer-term, the company fitted an independent parametric to the available data. It should be noted that during clarification with the company (B1), a later ToT data-cut was identified (up to June 2022). The company subsequently updated the cost effectiveness results and model using the updated ToT data for IVO+AZA. The ToT information outlined on p.94-96 of the CS is therefore not accurate. The EAG noted that in the company's original ToT analysis, as outlined in the CS, a Weibull curve was selected as the preferred model for extrapolation in the IVO+AZA arm, on the basis that the AIC/BIC statistics were similar across the various model types (despite the Lognormal curve providing the lowest

AIC/BIC results). The company did not provide justification for their decision to ignore the Log normal a plausible option.

Based on the most recent ToT data-cut, it appears that the company used the Lognormal to extrapolate ToT in the IVO+AZA arm i.e. whilst the company provided updated results using the updated data-cut, additional explanation was not provided on whether an alternative parametric fit was selected. Based on a review of the company's model, it appeared that the company selected the Lognormal on the basis that it produced the lowest AIC/BIC results. The EAG noted that at 5 years, the estimated proportion of patients to remain on treatment was [redacted], using the Lognormal curve. The EAG consider that there is some uncertainty surrounding the appropriate curve selection to extrapolate ToT in the IVO+AZA arm, however on balance the Lognormal appeared reasonable, based on AIC/BIC results. Furthermore, selecting a curve which produces lower ToT estimates (such as the Weibull) would lead to a reduction in IVO treatment costs and reduce the ICER. The Lognormal curve therefore does not bias the analysis in favour of the company.

As outlined previously, the company did not adequately discuss the comparison against AZA in the CS, though the EAG has noted that the company presented the ToT AIC/BIC results for each parametric model (Table 41 in the CS). Additionally, no discussion was provided in the company's response to the EAG clarification questions, outlining whether the extrapolation approach for AZA had changed as a result of using the latest data-cut. Within the company's latest version of the model (submitted in response to EAG clarification questions), the company appear to have extrapolated AZA ToT using the exponential function. Based on this function, the estimated % of patients on AZA at 5 years was 0%. The EAG noted that most parametric curves used to extrapolate ToT in the AZA arm produced low proportions remaining on treatment at 5, 10 and 15 year time points. Overall, the company's decision to use the exponential curve does not appear to have biased the analysis.

To estimate ToT for VEN+AZA, the company's base case approach remains unchanged as per company detail on p.96/97 of the CS. In the company's base case, data on mean number of cycles from VIALE-A was used. Specifically, the company converted the mean number of cycles to estimate median duration of treatment. This resulted in a median duration of treatment of 29.83 weeks. An exponential curve was then fitted to model long term ToT.

Finally, it should be noted that the company's model incorporated a stopping rule at 3 years for both IVO+AZA and VEN+AZA i.e. 100% of patients are assumed to discontinue treatment with

IVO and VEN at 3 years (see Figure 17). The cost associated with IVO and VEN use therefore only extends to 3 years in the model. Based on clinical expert opinion to the EAG, it was considered likely that patients responding to treatment with either IVO or VEN, would continue to receive treatment. Furthermore, the EAG noted that a stopping rule at 3 years is not specified in the SmPC for IVO or VEN. As part of the EAG preferred base, the 3-year stopping rule has been removed (see Section 6.3 for results). The EAG has conducted additional scenario analysis testing alternative stopping rule assumptions (see Section 6.2). Overall, the EAG considered that uncertainty surrounding ToT and stopping rule assumptions were not adequately explored or characterised by the company.

Figure 17: Modelled ToT

Concomitant use of posaconazole

The EAG noted that within the economic analysis the company made several alterations to the dosing in both the IVO+AZA and VEN+AZA treatment arms. A key alteration was to the dose of IVO and VEN due to assumed concomitant posaconazole use. In the economic analysis the dose for IVO was reduced to 250mg (from the licensed dose of 500mg) and the dose for VEN was reduced to 100mg (from the licensed dose of 400mg), to accommodate for patients requiring a strong to moderate CYP3A4 inhibitor/antifungal treatment, specifically posaconazole. The EAG noted that in the committee papers of TA765,[13] clinical opinion to the EAG reported

that the usual dose for VEN in practice was 100mg (as the use of posaconazole alongside VEN increases bioavailability). In their base case, the company assumed that 100% of patients in both the IVO+AZA and VEN+AZA treatment arms would receive concomitant treatment with posaconazole, based on TA765.

The EAG noted the following regarding posaconazole use in the model.

- The assumption that 100% of patients receiving either IVO would require posaconazole did not reflect posaconazole use in the AGILE study. The EAG noted that 53.5% of patients in the pooled arms of the AGILE study received concomitant posaconazole.
- The modelled dose does not reflect the licensed dose outlined in the SmPC for IVO (500mg). However, the EAG acknowledges that the SmPC states that the recommended dose of ivosidenib should be reduced to 250 mg once daily if use of moderate or strong CYP3A4 inhibitors cannot be avoided.

Based on clinical opinion to the EAG, the company's assumption that 100% of patients on IVO+AZA or VEN+AZA would receive posaconazole, may be reasonable, however it was noted that when patients enter long term remission (and are not neutropenic), it is likely that patients would stop posaconazole and then receive the full dose of either IVO or VEN. This could be applicable for up to two thirds of patients who enter full remission. The company provided a scenario analysis which removed concomitant posaconazole costs and dosing adjustments. Results were sensitive to this analysis (see Section 5.2.3). The EAG noted that assumptions surrounding the proportion of patients receiving posaconazole in the model is considered a key driver of results, given the implications it has for modelled drug costs. To explore additional uncertainty, the EAG has conducted a number of scenario analyses surrounding the proportion of patients modelled to receive posaconazole, including a scenario which uses the full licensed dose (as per the SPC for both IVO and VEN). See Section 6.2.4 for discussion and results.

Additionally, the EAG noted that the company altered the dosing regimen for VEN+AZA within the model. Based on the SmPC for VEN+AZA, VEN is provided on days 1-28 of each cycle, however the company opted to use 1-28 days dosing for cycle 1 and 1-14 day dosing for cycle 2 onwards. The EAG noted that the company's altered dosing for VEN reflected clinical expert opinion to NICE (as outlined in TA765), and therefore is considered reasonable for use in the base case. Furthermore, the company provided sensitivity analysis results using the SmPC dose for VEN (1-28 days), however results were not sensitive to this analysis.

Relative dose intensity

The company estimated relative dose intensity (RDI) for IVO using data from the AGILE study ([redacted]. In the absence of available data for VEN, RDI was assumed to be the same as IVO. The EAG considered this to be a conservative assumption, as assuming 100% RDI for VEN would have resulted in increased drug costs in the comparator arm, biasing the analysis in favour of IVO+AZA. For AZA, RDI appeared to have also been derived from the AZA arm of the AGILE study ([redacted]). The company applied this to the AZA component of the IVO+AZA and VEN+AZA treatment arms. Overall, the EAG considered that there was some uncertainty surrounding the appropriate RDI to use within the model. Whilst the use of trial data reflects missed doses and dosing holidays within a structured trial environment, RDI is likely to differ in clinical practice. Furthermore, from an NHS payer perspective, it could be argued that the full cost (100% RDI) associated with drug acquisition should be considered, as refunds are not generally issued by the company for missed doses where an entire package is dispensed to the patient. The exception is where drugs are dispensed individually as required, e.g. on an inpatient or outpatient basis. As a conservative approach, the EAG has opted to use 100% RDI for both IVO and VEN, as part of it's preferred base case (see Section 6.3 for results).

4.2.8.2. Administration and monitoring costs

Administration and monitoring costs were included in the analysis. As IVO and VEN are oral treatments, the company did not include administration costs. The EAG considered this to be reasonable. AZA is administered either via IV or subcutaneously (for 7 days in 28 day cycles). The cost of either IV or SC AZA outlined in the CS was reported to be £381.97, based on NHS National Cost Collection (2020/21) data, code SB12Z (Daycase, Deliver Simple Parenteral Chemotherapy at First Attendance). However, the EAG noted that the cost used in the company's model was derived from a more recent date (2021/2022). This was estimated to be £207.59. The EAG considered the modelled cost to be appropriate.

Hospitalisation associated with treatment initiation

The EAG understand that treatment initiation occurs within a hospital setting. In the company's base case analysis, hospitalisation/initiation costs for the first cycle were considered for all treatment arms. For IVO+AZA, patients were estimated to be hospitalised for [redacted] days during

initiation, based on an equation which estimated the % of patients in the AGILE study who were alive between days 0-28 to be [redacted] (see p.109 of the CS for further detail). This resulted in a modelled first cycle initiation cost of £[redacted]. Similarly, for AZA, bed days were estimated based on an equation which estimated the % of patients in the AGILE study who were alive between days 0-28 ([redacted]). This resulted in a modelled first cycle initiation cost of £[redacted]. For VEN+AZA, the number of hospitalisation days was based on a published study by Rausch et al (2021),[1] which examined the duration of cytopenias with concomitant venetoclax and azole antifungals in patients with acute myeloid leukaemia. The EAG noted that the study was a US based, retrospective analysis of patients with newly diagnosed AML and therefore lacks generalisability to the UK. Based on this study, VEN+AZA resulted in a median hospitalisation stay of 32 days and a modelled cost of £[redacted].

Based on clinical opinion to the EAG, 32 days was not considered to be representative of UK practice, and that 2 weeks would be reflect a more reasonable treatment initiation period for VEN+AZA. As part of the EAG preferred base case, the EAG assumed treatment initiation for VEN+AZA patients to require 14 days of hospitalisation. This is in line with the published UK study by Othman et al (2021).[55]

4.2.8.3. Subsequent treatment costs

The company assumed that a small proportion of patients who progress or relapse will have both IDH1 and FLT-3, and therefore be eligible for treatment with gilteritinib. For patients without this co-mutation, it was assumed they go on to receive hydroxycarbamide/hydroxyurea. The EAG noted that in TA765, the committee's preference was to assume that 5% of patients in the VEN+AZA arm receive subsequent treatment with gilteritinib and 3% of patients in the AZA arm. In the current appraisal, the company assumed that the proportion of patients with both mutations (eligible to receive gilteritinib) was 2.5%, on the basis that this would be 50% of the value used in NICE TA765[13] for VEN+AZA (5%). The company provided further justification on p.111, stating that the co-mutation rate is approximately half the mutation rate for an all comers AML population. Based on clinical opinion to the EAG, the company's base case estimation appeared reasonable. However, for completeness, the EAG conducted scenario analyses which varied the % of patients assumed to receive gilteritinib. See Section 6.2 for results.

Table 55 on p.111 of the CS outlines the company's approach to estimating the cost per treatment course associated with either gilteritinib or hydroxycarbamide/hydroxyurea. Drug

acquisition costs for gilteritinib and hydroxycarbamide/hydroxyurea were derived from the BNF 2023, as appropriate. Note: there is a PAS in place for gilterinib. See the accompanying cPAS appendix for results including the PAS for gilteritiib.

4.2.8.4. Health state costs

The model included health state costs (see Table 33). The EAG noted that health state costs were based on a combination of two factors. These include the expenses related to pre cycle screening: the imaging and investigations conducted before initiating the treatment cycle, visits to the haematologist, GP, hospital stay, and visits to the ED. Additionally, the cost of blood transfusions is informed by the prices specified in the NHS Blood & Transplant: Blood and Components Price List (2021/22), taking into account the frequency of blood transfusions observed during the trial for each health state. The EAG noted that the Blood and Components Price List (2023/2024) is likely to provide a more current reflection of the costs associated with blood components for the NHS. However, any variations in these costs are not expected to impact the overall analysis, as the difference is small and these costs are applicable to all comparators.

Table 33 Modelled health states costs

Health state	Cost
EF - CR/CRi	£655
EF - No CR/CRi	£5,491
PD/RL	£5,653
LTS	£185

4.2.8.5. Adverse event costs:

Grade 3 or 4 adverse events, those occurring in more than 5% of patients in the AGILE and VIALE-A trials, have been incorporated into the model with appropriate reference to the resources of managing those adverse events. The EAG notes there may be double-counting of costs related to specific adverse events. This occurs when both the name of the condition and the corresponding laboratory findings are used in the model. Specifically, the costs related to managing adverse events such as neutropenia and thrombocytopenia have the corresponding laboratory findings (Neutrophil count decreased and Platelet count decreased) are considered, leading to potential inaccuracies in the cost estimation for these events. The AGILE trial protocol further confirms the interchangeability of the terminologies.

The EAG also noted that the company used a cost reference from 2020/21 for the routine ECG investigation required to monitor the adverse event QT interval prolongation associated with ivosidenib, with a cost of £162.46. However, the EAG considered that it may be more appropriate to derive costs from 2021/22 for the same ECG investigation, which is reported to be £222.62.

Modelled adverse events were not considered to be a key driver of cost effectiveness results.

4.2.8.6. End of life costs

The company incorporated End of Life (EoL) care costs into the economic model, representing a one-time expense applied during the cycle in which the patient dies. In the absence of AML-specific cost data, the company relied on a study conducted by Round et al. (2015),[56] which estimated EoL care costs to be £6,774 (inflated to 2020/21 costs). The EAG noted that was the mean cost per patient death, based on 4 cancer types (breast, colorectal, lung and prostate). Furthermore, the definition of end-of-life care in the Round et al. (2015)[56] study differed from the NICE definition i.e. NICE defines end of life care as applicable to patients meeting one of these criteria: Advanced, progressive, incurable conditions, increased risk of dying within 12 months, existing conditions with sudden acute crisis risk, and life-threatening acute conditions caused by catastrophic events, whilst Round et al. (2015)[56] defined the end-of-life care period as commencing when patients begin using strong opiates.

The difference in definitions could potentially lead to differences in end-of-life costs, particularly given recent changes in NHS policy aimed at reducing unnecessary opiate prescriptions. These changes have resulted in an 8% decrease in opiate prescriptions, which might impact the interpretation of EoL costs in the model. However, overall the EAG did not consider EoL costs to be a key driver of results. The company conducted one-way sensitivity analysis which varied EoL costs. Results were not sensitive to this analysis.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1. Base case results

As noted in Section 4.2.4, the primary comparator selected by the company was VEN+AZA (results reported in the CS). The CS did not contain results versus AZA, however, the company's model did contain cost effectiveness results versus this treatment. Given the potential relevance of AZA as a treatment for this patient population, the EAG have presented the company's base case results for both comparator treatments VEN+AZA and AZA. Note: The company did not present cost effectiveness results comparing IVO+AZA to LDAC and VEN+LDAC.

Results reported below include the PAS for IVO. The EAG note that PAS discounts are in place for both VEN and gilteritinib (which has been included within the model as a subsequent treatment). Company base case results including these discounts have been included in the supporting Appendix.

For the comparison versus VEN+AZA, IVO+AZA was considered dominant i.e. it was estimated to be both cheaper and more effective than VEN+AZA, resulting in incremental savings of [redacted] and incremental QALY gain of [redacted]. The EAG noted that the incremental savings were primary driven by lower costs in the progressed disease health state ([redacted] for IVO+AZA and £90,600 for VEN+AZA) and the incremental QALY gain was driven by the LTS health state i.e. a higher proportion of patients on VEN+AZA entered the LTS state (were cured at 3 years) compared to VEN+AZA. For the comparison versus AZA, IVO+AZA resulted in an ICER of [redacted] based on an incremental cost of [redacted] and incremental QALY gain of [redacted]. The EAG noted the key driver of incremental costs to be the high drug costs associated with IVO (total drug costs in the IVO+AZA arm were reported to be [redacted], compared to £5,809 in the AZA arm). IVO+AZA also resulted in higher administration costs and resource use costs.

The EAG noted that the company also presented IVO+AZA vs VEN+AZA results in the format of Net Health Benefit (NHB). This can be found on p.120 and 121 of the CS.

Table 34: Discounted company base case results (IVO+AZA vs VEN+AZA)

	Total costs	Total LYs gained	Total QALYs	Incremental costs	Incremental Lys	Incremental QALYs	Cost per QALY gained
	Company deterministic base case						
IVO+AZA	[redacted]	5.97	[redacted]	[redacted]	1.71	[redacted]	[redacted]
VEN+AZA	£190,639	4.26	2.17	-	-	-	-
	Company probabilistic base case						
IVO+AZA	[redacted]	5.95	[redacted]	[redacted]	1.62	[redacted]	[redacted]
VEN+AZA	£193,085	4.33	2.18	-	-	-	-

Abbreviations: QALYs, quality adjusted life years; LYs, life years

Table 35: Discounted company base case results (IVO+AZA vs AZA)*

	Total costs	Total LYs gained	Total QALYs	Incremental costs	Incremental Lys	Incremental QALYs	Cost per QALY gained
		Company deterministic base case					
IVO+AZA	[redacted]	5.97	[redacted]	[redacted]	4.26	[redacted]	[redacted]
AZA	£110,384	1.71	0.88	-	-	-	-
		Company probabilistic base case					
IVO+AZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZA	£110,768.24	1.76	0.91				

Abbreviations: QALYs, quality adjusted life years; LYs, life years *Extracted from company model: company did not report AZA comparisons in its submission

Table 36: Discounted company base case results (VEN+AZA vs AZA)*

	Total costs	Total LYs gained	Total QALYs	Incremental costs	Incremental Lys	Incremental QALYs	Cost per QALY gained
		Company deterministic base case					
VEN+AZA	£190,639.07	4.26	2.17	£80,255	2.55	1.29	[redacted]
AZA	£110,384.07	1.71	0.88	-	-	-	-
		Company probabilistic base case					
VEN+AZA	£193,437.75	4.32	2.18	£82,670	2.56	1.27	[redacted]
AZA	£110,768.24	1.76	0.91	-	-	-	-

*Extracted from company model: company did not report AZA comparisons in its submission

5.2. Company's sensitivity analyses

5.2.1. One-way sensitivity analysis (OWSA)

For the comparison versus VEN+AZA, the company provided OWSA whereby parameters were varied by their upper and lower bounds. The results of the company's OWSA were presented in the format of incremental net monetary benefit (INMB) and outlined on p.125 of the CS. Note these results were updated based on revised ToT data and presented on p.30 of the company's response to EAG clarification questions (see Figure 18).

Based on the company's results, parameters which had the largest impact on results were the OS HR for IVO+AZA vs VEN+AZA, EFS HR IVO+AZA vs VEN+AZA and the number of bed days required for the intiation of VEN+AZA. Although OWSA is useful in identifying parameters which are likely to have a large impact on base case results when varied, the EAG are of the opinion that the analysis is not useful to inform decision making (as parameters are varied individually and without context). In the CS, the company did not report OWSA results for the comparison versus AZA alone. However, OWSA results (costs, LYs and QALYs) were reported in the company's model provided to the EAG.

Figure 18: Company OWSA results (vs VEN+AZA)

5.2.2. Probabilistic sensitivity analysis

To explore joint parameter uncertainty, the company conducted probabilistic sensitivity analysis (PSA). The PSA was run for 5000 iterations. Based on the results of the PSA, IVO+AZA was considered to have [redacted] probability of being cost effective comparaed to VEN+AZA (see Figure 19). PSA results versus AZA were not included in the CS, however the EAG noted that the model contained probabilistic results and a cost-effectivenss plane versus AZA (see Figure 20). The EAG note that the company did not provide the CEAC versus AZA and did not explicitly state the probability of being cost effective at a WTP of £30,000, however based on the mean PSA and deterministic results (as per the cost-effectivenss plane below), IVO+AZA appears to have a [redacted] probability of being cost effective at a willingness to pay of £30,000.

Figure 19: Company's PSA scatterplot (vs VEN+AZA)

Figure 20: Company's PSA scatterplot (vs AZA)*

*Extracted from company model: company did not report AZA comparisons in its submission

5.2.3. Scenario analyses

The company reported results for 31 scenarios whereby key modelled parameters were varied using alternative inputs. For the comparison versus VEN+AZA, key scenarios included the use of alternative time horizons (15, 20 years), alternative cost and benefit discount rates (1.5% and 6%), alternative OS and EFS curve fits in the IVO+AZA arm, alternative time points for cure application (2 years, 4 years), long-term survival SMR (1.1, 1.2 amd 2), removal of concomitant azole costs and dosing adjustments, removal of subsequent treatment costs and alternative source for utility values (see p.31 of the the company's response to EAG clarification questions for full list). The EAG noted that IVO+AZA remained dominant in all scenarios apart from seven. The highest ICER ([redacted]) was produced when the Weibull curve was used to extrapolate EFS in the IVO+AZA arm. This was due to fewer patients in the IVO+AZA arm entering the LTS state, which ultimately reduced OS.

As noted previously, the company did not present sensitivity analysis results versus AZA within the CS, however the EAG noted that these were provided in the company's model. The scenario which had the largest impact on the ICER, was the removal of concomitant azole costs and dose adjustments. This increased the ICER to [redacted]. Results were also reasonably sensitive to the use of a Weibull curve for the extrapolation of EFS in the IVO+AZA arm and the application of LTS for costs and utilities only, resulting in ICERs of [redacted] and [redacted] respectively.

Whilst the list of scenarios conducted by the company is reasonably comprehensive, the EAG considered that the analyses did not appropriately capture uncertainty. Two or three-way scenario analysis, varying multiple paramters simultaneously, would have been helpful to explore combined uncertainty.

5.3. Model validation and face validity check

On p.127 of the CS, the company stated that the model was reviewed for coding errors, inconsistencies and input plausibility by an external economist. Additionally, the company used clinical opinion to validate model assumptions including choice of comparator, treatment dosing, healthcare resource use and long term survivor assumptions. Overall, the EAG considered the model to be well constructed and did not identify an major coding errors. However, the EAG

considered there to be substantial uncertainty surrounding several model assumptions (see Section 6.2).

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The EAG identified a number of limitations within the company's base case and has explored the impact of parameter values, and assumptions, which the EAG believes are more plausible.

This section is organised as follows: Section 6.1 details the impact of errors identified in the EAG's validation of the executable model. Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the EAG. These analyses were conducted within the company corrected base-case analysis.

The scenario analyses presented in Section 6.2 focus on exploring the following issues and uncertainties:

- Uncertainty surrounding the treatment effect associated with IVO+AZA
- Uncertainty surrounding long term OS and EFS extrapolation assumption in the IVO+AZA and VEN+AZA treatment arms
- Uncertainty surrounding the modelled long-term survival (LTS) health state
- Uncertainty surrounding the % of patients receiving posaconazole
- Uncertainty surrounding the % of patients achieving CR/CRi in the VEN+AZA treatment arm
- Uncertainty surrounding the application of a stopping rule for VEN+AZA and IVO+AZA
- Uncertainty surrounding the % of patients receiving subsequent treatment with gilteritinib
- Length of hospital stay during treatment initiation for VEN+AZA

In Section 6.3, the EAG base-case is presented based on a combination of the exploratory analyses presented in Section 6.2.

6.1. EAG corrections and adjustments to the company's base case model

Overall, the EAG considered the model to be well constructed, However, two minor adjustments were made:

- General population utility was estimated using the Hernandez-Alva algorithm (Hernandez-Alva et al 2022)[47]

- Life-years were discounted at 3.5%

6.1.1. Fully incremental analysis results

Table 37: EAG-adjusted company base case results

	Total costs	Total LYs gained	Total QALYs	Incremental costs	Incremental Lys	Incremental QALYs	Cost per QALY gained
	Company deterministic base case						
AZA	£110,384	1.71	0.89				
IVO+AZA	[redacted]	5.97	[redacted]	[redacted]	4.26	[redacted]	[redacted]
VEN+AZA	£190,639	4.26	2.18	£1,307	-1.71	-1.05	[redacted]
	Company probabilistic base case						
AZA	£111,540	1.77	0.92				
IVO+AZA	[redacted]	5.95	[redacted]	[redacted]	4.18	[redacted]	[redacted]
VEN+AZA	£194,565	4.33	2.20	£1,345	-1.62	-1.01	[redacted]

Abbreviations: QALYs, quality adjusted life years; LYs, life years.

6.1.2. Pair wise analysis results

Table 38: EAG-adjusted company base case results (IVO+AZA vs VEN+AZA)

	Total costs	Total LYs gained	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Cost per QALY gained
	Company deterministic base case						
IVO+AZA	[redacted]	5.97	[redacted]	[redacted]	1.71	[redacted]	[redacted]
VEN+AZA	£190,639.07	4.26	2.18				
	Company probabilistic base case						
IVO+AZA	[redacted]	5.95	[redacted]	[redacted]	1.62	[redacted]	[redacted]
VEN+AZA	£194,565.16	4.33	2.20				

Abbreviations: QALYs, quality adjusted life years; LYs, life years

Table 39: EAG-adjusted company base case results (IVO+AZA vs AZA)

	Total costs	Total LYs gained	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Cost per QALY gained
		Company deterministic base case					
IVO+AZA	[redacted]	5.97	[redacted]	[redacted]	4.26	[redacted]	[redacted]
AZA	£110,384.07	1.71	0.89				
		Company probabilistic base case					
IVO+AZA	[redacted]	5.95	[redacted]	[redacted]	4.18	[redacted]	[redacted]
AZA	£111,539.68	1.77	0.92	-	-	-	-

Abbreviations: QALYs, quality adjusted life years; LYs, life years

Table 40: EAG-adjusted company base case results (VEN+AZA vs AZA)

	Total costs	Total LYs gained	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	Cost per QALY gained
		Company deterministic base case					
VEN+AZA	£190,639.07	4.26	2.18	£80,255	2.55	1.30	[redacted]
AZA	£110,384.07	1.71	0.89				
		Company probabilistic base case					
VEN+AZA	£194,565.16	4.33	2.20	£83,025	2.56	1.28	[redacted]
AZA	£111,539.68	1.77	0.92	-	-	-	-

Abbreviations: QALYs, quality adjusted life years; LYs, life years

6.2. Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted a number of scenario analyses to test uncertainty surrounding key modelled parameters/assumptions. These are outlined below.

6.2.1. The treatment effect estimated for IVO+AZA vs VEN+AZA

As noted in Section 4.2.6.1, there is uncertainty surrounding the comparative treatment effect estimated for IVO+AZA from the NMA i.e. confidence intervals for both the OS and EFS HRs crossed 1 indicating a non-significant difference in treatment effect. The NMA was also subject to heterogeneity (section 3.4.4) and this was not properly expressed in the credible intervals

because FE models were selected over RE models (Section 3.4.1). Due to these limitations the EAG considered that the results from the NMA were subject to uncertainty and warranted further testing. To explore the impact of using alternative IVO+AZA OS and EFS HRs on the ICER, the EAG conducted the following scenarios

OS

a) Increase the IVO+AZA OS HR by 25% (from [redacted] to [redacted]): This scenario has a moderate/large upward impact on VEN+AZA total costs and moderate upward impact on VEN+AZA total QALYs. Note that 25% has been arbitrarily selected by the EAG and therefore this scenario is considered exploratory. See Section 6.2.9 for results.

b) Decrease the IVO+AZA OS HR by 25%: This scenario has a moderate/large downward impact on VEN+AZA total costs and moderate downward impact on VEN+AZA total QALYs. Note that 25% has been arbitrarily selected by the EAG and therefore this scenario is considered exploratory. See Section 6.2.9 for results.

c) Vary OS using the lowerbound credible interval: For this analysis the OS HR was changed to [redacted] (95% CI lower bound). This scenario has a large downward impact on VEN+AZA total costs and large downward impact on VEN+AZA total QALYs. The EAG considered this to be an exploratory analysis. See Section 6.2.9 for results.

d) Vary OS using the upperbound credible interval: For this analysis the OS HR was changed to [redacted] (95% CI upper bound). This scenario has a large upward impact on VEN+AZA total costs and large upward impact on VEN+AZA total QALYs. The EAG considered this to be an exploratory analysis. See Section 6.2.9 for results.

EFS

a) Increase the IVO+AZA EFS HR by 25% (from [redacted] to [redacted]: This scenario analysis has a moderate downward impact on VEN+AZA total costs and total QALYs. Note that 25% has been arbitrarily selected by the EAG and therefore this scenario is considered highly exploratory. See Section 6.2.9 for results.

b) Decrease the IVO+AZA EFS HR by 25%: This scenario analysis has a moderate upward impact on VEN+AZA total costs and minor downward impact on VEN+AZA total QALYs Note that 25% has been arbitrarily selected by the EAG and therefore this scenario is considered exploratory. See Section 6.2.9 for results.

c) Vary EFS using the lowerbound credible interval. For this analysis the EFS HR was changed to [redacted] (95% CI lower bound). This scenario had a large upward impact on VEN+AZA costs and resulted in a reduction in VEN+AZA total QALYs. The EAG considered this to be an exploratory analysis. See Section 6.2.9 for results.

d) Vary EFS using the upperbound credible interval: For this analysis the EFS HR was changed to [redacted] (95% CI upper bound). This scenario had a large downward impact on VEN+AZA costs and resulted in a reduction in VEN+AZA total QALYs. The EAG considered this to be an exploratory analysis. See Section 6.2.9 for results.

6.2.2. Long term OS and EFS extrapolation (IVO+AZA)

The EAG considered there to be uncertainty surrounding the base case parametric curve used by the company to extrapolate OS in the IVO+AZA treatment arm. Based on clinical opinion to the EAG, modelled OS at key landmark time points (5, 10 and 15 years) lacked clinical plausibility i.e. the use of the Lognormal curve appeared to overestimate OS. The EAG also noted that when the company asked clinical experts to validate modelled OS in the IVO+AZA arm, it was noted that alternative curve fits, including the Weibull and the Exponential, produced plausible survival estimates. As noted in Section 4.2.6.3, the EAG opted to use the Weibull in its preferred base case. Similarly, in Section 4.2.6.2, the EAG noted several limitations surrounding the company's curve selection for EFS extrapolation in the IVO+AZA arm and therefore opted to use the Weibull within it's preferred base case. When the Weibull curve is used to extrapolate OS, this resulted in a moderate reduction in total costs in both the IVO+AZA and VEN+AZA treatment arms, and a moderate reduction in total QALY gain in both arms. For EFS, the Weibull curve resulted in a large increase in total costs in both treatment arms and moderate decrease in total QALYs in both arms. See Section 6.2.9 for results.

As part of this scenario analysis, the EAG tested the impact of selecting the exponential curve to extrapolate OS and EFS in the IVO+AZA treatment arm. When the exponential curve is used to extrapolate EFS, this resulted in a moderate to large increase in total costs in both the IVO+AZA and VEN+AZA treatment arms, as well as a moderate to large decrease in total QALYs in both arms. For OS, the exponential curve resulted in a moderate decrease in total costs in both treatment arms and a moderate reduction in total QALYs. See Section 6.2.9 for results.

6.2.3. Only CR/CRi patients considered functionally cured

In the company's base case analysis, all patients in the EFS state i.e. those with CR/CRi (remission) and those with No CR/CRi (non remission) were capable of experiencing cure at 3 years. This assumption was applied to the IVO+AZA and VEN+AZA arms only in the model, as cure was not applied to patients modelled to receive AZA. As noted in Section 4.2.6.4, the EAG had concerns surrounding the application of a cure assumption to patients in the EFS state who were not in remission i.e. No CR/CRi. In this scenario analysis the EAG assumed that only patients in remission i.e. CR/CRi are allowed to move into the LTS health. This scenario resulted in a minor upward increase in total costs in both treatment arms and decrease in total QALYs. See Section 6.2.9 for results.

It should be noted that due to the lack of long term robust clinical data, the EAG did not consider the inclusion of a cured health state to be appropriate. As noted in Section 4.2.6.4, there is considerable uncertainty surrounding the assumption that 100% of patients in the EFS state at 3 years are considered functionally cured. As part of its preferred base case, the EAG removed the LTS state from the model.

6.2.4. Proportion of patients receiving Posaconazole

Whilst the EAG considered the company's decision to assume 100% of patients (in all treatment arms) receive posaconazole to be appropriate (see section 4.2.8.1), drug costs remain a key driver of incremental results and therefore it was considered appropriate to vary the proportion of patients assumed to receive concomitant treatment with posaconazole in the VEN+AZA treatment arms. The EAG note that varying the % of patients who receive concomitant treatment with posaconazole acts as a proxy for varying drug costs, given that concomitant use of posaconazole requires a reduction in the dosing of IVO and VEN.

A) Assume that 0% of patients receive posaconazole. This scenario excludes posaconazole treatment costs and assumes that the full dose for each treatment (IVO, VEN and AZA) is administered as per the SPC. Drug costs are therefore based on 500mg for IVO and 400mg for VEN. The EAG noted that concomitant use of posaconazole does not affect the dose of AZA, therefore for this scenario AZA the dose for AZA remained 75mg/m^2, as per the base case (the analysis only removed posaconazole drug costs from this treatment arm). This scenario had a moderate to large upward impact on total costs in both the IVO+AZA and VEN+AZA treatment arms.

IVO+AZA no longer results in incremental savings versus VEN+AZA. See Section 6.2.9 for results.

B) Assume that 90% of patients receive posaconazole. This scenario assumes that the majority of patients receiving IVO and VEN will have reduced dosing i.e. 250mg for IVO and 100mg for VEN, however a small proportion (10%) will not receive posaconazole, and therefore the full dose for these treatments will be given. As above, for AZA the dose remained 75mg/m^2. The analysis only removed posaconazole drug costs from the AZA treatment arm for the 10% of patients who were not assumed to receive treatment). This scenario had a minor upward impact on total costs in both the IVO+AZA and VEN+AZA treatment arms. See Section 6.2.9 for results.

6.2.5. Proportion of patients achieving CR/CRi in the VEN+AZA treatment arm

For this scenario analysis, the EAG estimated the proportion of patients with CR/CRi in the VEN+AZA arm based on NMA results (see 4.2.6.6). This scenario resulted in reduced total costs in the VEN+AZA arm, by approximately £3,000. VEN+AZA resulted in lower total costs compared to IVO+AZA. See section 6.2.9 for results.

6.2.6. Removal of a 3-year stopping rule for VEN+AZA and IVO+AZA

As noted in Section 4.2.8.1. The company applied a stopping rule to the IVO+AZA and VEN+AZA treatment arms at 3 years. The EAG did not consider this to be appropriate and therefore as part of its preferred base case, removed the 3-year stopping rule. For this scenario analysis, the impact of using alternative stopping rule assumptions were varied.

A) Assume 50% of patients in both treatment arms discontinue at 3 years + removal of modelled cure assumption. This scenario assumes that 50% of patients will continue to receive treatment after 3 years in the model. Additionally, the EAG removed the company's modelled cure assumption given that 100% of patients in the EFS state at 3 years were assumed to be functionally cured and discontinued treatment i.e. the modelled cure assumption acted as a proxy stopping rule. See Section 6.2.9 for results.

B) Apply stopping rule at 5 years: In this scenario it was assumed that 100% of patients in both the IVO+AZA and VEN+AZA treatment arms continue to receive treatment until year 5, at which point all patients discontinue. As above, the EAG removed the company's modelled cure assumption. See Section 6.2.9 for results.

6.2.7. Proportion of patients receiving subsequent treatment with gilteritinib

Although clinical opinion to the EAG noted that it is reasonable to consider that 2.5% of patients who progress whilst on IVO+AZA and VEN+AZA will receive gilteritinib (see Section 4.2.8.3), the EAG considered that there is still some uncertainty surrounding the % of patients likely to receive this treatment in practice.

A) Subsequent treatment as per NICE preference in TA765: For this scenario, the EAG adopted the gilteritinib subsequent treatment % which NICE preferred in TA765, that is 5% of patients in the VEN+AZA arm and 3% of patients in the AZA arm were assumed to receive subsequent treatment with gilteritinib. As a simplifying assumption and to align with VEN+AZA, the EAG assumed that 5% of patients in the IVO+AZA arm would also receive gilteritinib. Note that the model only accounts for treatment costs and not treatment benefits. This scenario had a minor upward impact on the total costs for all treatment arms. See Section 6.2.9 for results.

B) No subsequent treatment. This scenario assesses the impact of assuming no subsequent treatment with gilteritinib. This scenario had a minor downward impact on the total costs for all treatment arms. See Section 6.2.9 for results.

6.2.8. Length of hospital stay during treatment initiation for VEN+AZA

In the company's base case analysis, it was assumed that patients in the VEN+AZA arm would require 32 hospitalisation days during treatment initiation (based on a published study by Rausch et al 2021).[1] As noted in Section 4.2.8.2, clinical opinion to the EAG did not consider this to be appropriate. The EAG preferred to assume 14 days hospitalization for VEN+AZA. For this scenario analysis, the EAG assumed that there is no difference in hospitalisation days between IVO+AZA and VEN+AZA during treatment initiation i.e. it was assumed that both treatments would require [redacted] hospitalisation days (as per IVO+AZA, based on trial data from AGILE). Based on this analysis, VEN+AZA resulted in lower total costs, compared to IVO+AZA. See Section 6.2.9 for results.

6.2.9. Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG made the changes described in Section 6.2. Each change has been made individually. The results of the EAG's exploratory analyses are outlined in Table 41 and Table 42.

Table 41: Fully incremental analysis on EAG's exploratory analyses (deterministic)

Preferred assumption	Comparator	Cost	QALYs	ICERs
Company base-case	AZA*	£110,384.07	0.88	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£190,639.07	2.17	[redacted]
EAG adjusted base case	AZA	£110,384.07	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£190,639.07	2.18	[redacted]
EAG's exploratory analyses (including EAG corrections)				
Treatment effect (OS HR for VEN+AZA vs IVO+AZA)				
a) Increase OS HR by 25% to [redacted]	AZA	£110,384.07	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£245,852.78	2.56	[redacted]
b) Decrease the OS HR by 25% to [redacted]	AZA	£110,384.07	0.89	
	VEN+AZA	£127,167.16	1.75	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
c) OS HR at [redacted] (95% CI lower bound)	VEN+AZA	£100,297.04	1.52	
	AZA	£110,384.07	0.89	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
d) OS HR at [redacted] (95% CI upper bound)	AZA	£110,384.07	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£312,944.38	3.01	[redacted]
Treatment effect (EFS HR for VEN+AZA vs IVO+AZA)				
a) Increase EFS HR by 25% to [redacted])	AZA	£110,384.07	0.89	
	VEN+AZA	£155,326.60	2.41	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
b) Decrease the EFS HR by 25% to [redacted]	AZA	£110,384.07	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£229,550.75	1.93	[redacted]
c) EFS HR at [redacted] (95% CI lower bound)	AZA	£110,384.07	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£250,411.76	1.79	[redacted]

d) EFS HR at [redacted] (95% CI upper bound)	AZA	£110,384.07	0.89	
	VEN+AZA	£113,373.94	2.68	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
OS extrapolation				
Weibull curve used to extrapolate OS (IVO+AZA)	AZA	£110,384.07	0.89	
	VEN+AZA	£170,130.13	2.05	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
Exponential curve used to extrapolate OS (IVO+AZA)	AZA	£110,384.07	0.89	
	VEN+AZA	£153,262.75	1.93	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
EFS extrapolation				
Weibull curve used to extrapolate EFS (IVO+AZA)	AZA	£110,384.07	0.89	
	VEN+AZA	£211,629.03	2.02	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
Exponential curve used to extrapolate EFS (IVO+AZA)	AZA	110,384.07	0.89	
	VEN+AZA	234,910.56	1.86	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
Cure assumption				
a) No cure assumptions	AZA	£114,863.44	0.79	
	VEN+AZA	£216,995.87	1.82	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
b) No cure assumption + No stopping rule	AZA	£114,925.81	0.79	
	VEN+AZA	£217,639.77	1.82	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
Only CR/CRi patients are functionally cured	AZA	£110,806.77	0.84	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£192,433.32	2.10	[redacted]
% of patients receiving posaconazole				
a) 0% of patients	AZA	£109,314.08	0.89	
	VEN+AZA	£212,297.93	2.18	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
b) 90% of patients	AZA	£110,277.07	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£192,804.95	2.18	[redacted]
CR/CRi VEN+AZA				
% of patients with CR/CRi based on NMA	AZA	£110,384.07	0.89	
	VEN+AZA	£185,309.44	2.19	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
Stopping rule				
	AZA	£114,894.62	0.79	

a) 50% of patients discontinue at year 3 (includes no cure assumption)	VEN + AZA	£217,317.82	1.82	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
b) Discontinue at year 5 (includes no cure assumption)	AZA	£114,923.43	0.79	
	VEN + AZA	£217,586.11	1.82	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
c) No stopping rule	AZA	£110,384.07	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£190,639.07	2.18	[redacted]
Relative dose intensity (RDI)				
100% Relative dose intensity (RDI)	AZA	£110,864.33	0.89	
	VEN+AZA	£192,519.71	2.18	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
Subsequent therapy use				
a) 5% of patients receive gilteritinib, while 3% of patients on AZA receive gilteritinib	AZA	£111,298.16	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£191,948.39	2.18	[redacted]
b) no subsequent therapy	AZA	£109,469.97	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£189,329.74	2.18	[redacted]
Length of hospital stay during treatment initiation				
a) [redacted] days for all treatment arms	AZA	£112,495.97	0.89	
	VEN+AZA	£174,434.32	2.18	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
b) 14 days for VEN+AZA	AZA	£110,384.07	0.89	
	VEN+AZA	£176,298.58	2.18	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year. Note that for the stopping rule scenarios (a and b), the EAG has also removed the modelled cure assumption). *Extracted from company model: company did not report AZA comparisons in its submission

Table 42: Fully incremental analysis on EAG's exploratory analyses (probabilistic)

Preferred assumption	Comparator	Total Costs	Total QALYs	ICERs
Company base-case	AZA*	£111,337.90	0.91	
	IVO + AZA	£193,113.03	3.19	[redacted]
	VEN + AZA	[redacted]	[redacted]	[redacted]
EAG adjusted base case	AZA	£110,384.07	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£194,565	2.20	[redacted]
EAG's exploratory analyses (including EAG corrections)				

Treatment effect (OS HR for VEN+AZA vs IVO+AZA)				
a) Increase OS HR by 25% to [redacted]	AZA	£110,899.29	0.87	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£214,535.60	2.67	[redacted]
b) Decrease the OS HR by 25% to [redacted]	AZA	£116,160.25	0.85	
	VEN+AZA	£146,626.20	1.64	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
c) OS HR at [redacted] (95% CI lower bound)	AZA	£112,186.93	0.92	
	VEN + AZA	£122,297.25	1.46	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
d) OS HR at [redacted] (95% CI upper bound)	AZA	£117,973.46	0.97	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£312,765.76	3.16	[redacted]
Treatment effect (EFS HR for VEN+AZA vs IVO+AZA)				
a) Increase EFS HR by 25% to [redacted])	AZA	£103,229.76	0.85	
	VEN + AZA	£151,624.74	1.96	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
b) Decrease the EFS HR by 25% to [redacted]	AZA	£97,172.25	0.83	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£214,951.75	1.69	[redacted]
c) EFS HR at [redacted] (95% CI lower bound)	AZA	£126,653.69	1.07	
	VEN + AZA	£188,442.94	3.30	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
d) EFS HR at [redacted] (95% CI upper bound)	AZA	£103,736.30	0.89	
	VEN+AZA	£119,479.86	2.48	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
OS extrapolation				
Weibull curve used to extrapolate OS (IVO+AZA)	AZA	£95,493.77	0.77	
	VEN + AZA	£174,658.98	2.08	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Exponential curve used to extrapolate OS (IVO+AZA)	AZA	£112,126.42	0.92	
	VEN + AZA	£142,897.34	1.78	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
EFS extrapolation				
Weibull curve used to extrapolate EFS (IVO+AZA)	AZA	£117,688.75	0.95	
	VEN + AZA	£168,164.29	1.63	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Exponential curve used to extrapolate EFS (IVO+AZA)	AZA	£101,944.63	0.88	
	VEN + AZA	£203,969.13	1.77	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]

Cure assumption				
a) No cure assumptions	AZA	£126,372.10	0.80	
	VEN + AZA	£219,881.95	1.66	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
b) No cure assumption + No stopping rule	AZA	£113,788.50	0.82	
	VEN + AZA	£206,901.25	1.68	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Only CR/CRi patients are functionally cured	AZA	£99,464.25	0.84	
	VEN + AZA	£170,929.26	1.74	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
% of patients receiving Posaconazole				
a) 0% of patients	AZA	£102,008.06	0.91	
	VEN + AZA	£222,962.22	1.90	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
b) 90% of patients	AZA	£104,922.31	0.88	
	VEN + AZA	£209,638.09	2.19	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
CR/CRi VEN+AZA				
% of patients with CR/CRi based on NMA	AZA	£111,055.96	0.92	
	VEN + AZA	£163,491.62	2.17	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Stopping rule				
a) 50% of patients discontinue at year 3 (includes no cure assumption)	AZA	£115,797.20	0.85	
	VEN + AZA	£217,488.94	1.85	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
b) Discontinue at year 5 (includes no cure assumption)	AZA	£115,955.72	0.80	
	VEN + AZA	£217,041.71	1.84	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
c) No stopping rule	AZA	£117,427.43	0.90	
	VEN + AZA	£164,381.08	1.85	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Relative dose intensity (RDI)				
100% Relative dose intensity (RDI)	AZA	£123,558.09	0.99	
	VEN + AZA	£196,862.00	2.29	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Subsequent therapy use				
a) 5% of patients receive gilteritinib, while 3% of patients on AZA receive gilteritinib	AZA	£110,157.46	0.86	
	VEN + AZA	£167,961.38	1.97	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]

b) no subsequent therapy	AZA	£112,647.27	0.91	
	VEN + AZA	£183,635.53	1.87	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Length of hospital stay during treatment initiation				
a) [redacted] days for all treatment arms	AZA	£120,405.23	0.94	
	VEN + AZA	£164,218.53	1.97	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
b) 14 days for VEN+AZA	AZA	£103,668.79	0.88	
	VEN + AZA	£142,609.69	2.17	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year. Note that for the stopping rule scenarios (a and b), the EAG has also removed the modelled cure assumption). *Extracted from company model: company did not report AZA comparisons in its submission

6.2.10. Contents of associated cPAS appendix

A cPAS appendix is provided alongside this EAG report in order to provide model results using confidential prices for comparator treatments.

The cPAS appendix provides the following analyses:

- Company base case applying confidential prices for comparator treatments
- EAG base case applying confidential prices for comparator treatments
- EAG scenario analyses applying confidential prices for comparator treatments

Source of confidential prices:

- Patient Access Scheme for gilterinib and venetoclax as supplied by NICE

6.3. EAG's preferred assumptions

The EAG preferred base case ICER is based on the following changes

- Overall survival: OS is extrapolated using the Weibull parametric function for IVO+AZA. As OS for VEN+AZA is estimated via proportional hazards approach, VEN+AZA uses the Weibull parametric function, which has been applied to the IVO+AZA treatment arm. For AZA, no change was made i.e. the log normal curve was used to extrapolate OS as per company's base case.

- Event free survival: EFS is extrapolated using the Weibull parametric function for IVO+AZA. For AZA, no change was made i.e. the log normal curve was used to extrapolate EFS as per company's base case.
- Cure assumption: The cure assumption has been removed from the model. Patients in the EFS state do not enter the LTS state at year 3.
- Stopping rule: No stopping rule considered for IVO+AZA or VEN+AZA
- Relative dose intensity: Assumes 100% RDI for all treatments (IVO, AZA and VEN)
- % of patients with CR/CRi in the VEN+AZA arm: Based on NMA estimate
- Length of hospitalisation stay during treatment initiation with VEN+AZA: Assumed to be 14 days

Note: The EAG adjusted the company's base case to discount LYs by 3.5% and estimate general population utility based on the latest DSU algorithm.

Table 43: EAG's preferred model assumptions (deterministic)

Preferred assumption	Comparator	Total Costs	Total QALYs	ICERs
Company base-case	AZA*	£110,384.07	0.88	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£190,639.07	2.17	[redacted]
EAG adjusted base case	AZA	£110,384.07	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£190,639.07	2.18	[redacted]
Weibull used to extrapolate OS (IVO+AZA)	AZA	£110,384.07	0.89	
	VEN+AZA	£170,130.13	2.05	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
Weibull used to extrapolate EFS (IVO+AZA)	AZA	£110,384.07	0.89	
	VEN+AZA	£211,629.03	2.02	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
No cure assumption + No	AZA	£114,925.81	0.79	
	VEN+AZA	£217,639.77	1.82	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]

stopping rule				
100% Relative dose intensity	AZA	£110,864.33	0.89	
	VEN+AZA	£192,519.71	2.18	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
% of patients with CR/CRi based on NMA	AZA	£110,384.07	0.89	
	VEN+AZA	£185,309.44	2.19	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
14 day hospital stay for initiation with VEN+AZA	AZA	£110,384.07	0.89	
	VEN+AZA	£176,298.58	2.18	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]
Cumulative	AZA	£115,408.11	0.79	
	VEN+AZA	£197,147.43	1.84	[redacted]
	IVO+AZA	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year. *Extracted from company model: company did not report AZA comparisons in its submission

Table 44: EAG's preferred model assumptions (probabilistic)

Preferred assumption	Comparator	Total Costs	Total QALYs	ICERs
Company base-case	AZA*	£110,384.07	0.88	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£190,639.07	2.17	[redacted]
EAG adjusted base case	AZA	£110,384.07	0.89	
	IVO+AZA	[redacted]	[redacted]	[redacted]
	VEN+AZA	£194,565	2.20	[redacted]
Weibull used to extrapolate OS (IVO+AZA)	AZA	£95,493.77	0.77	
	VEN + AZA	£174,658.98	2.08	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Weibull used to extrapolate EFS (IVO+AZA)	AZA	£117,688.75	0.95	
	VEN + AZA	£168,164.29	1.63	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
No cure assumption	AZA	£113,788.50	0.82	
	VEN + AZA	£206,901.25	1.68	[redacted]

+ No stopping rule	IVO + AZA	[redacted]	[redacted]	[redacted]
100% Relative dose intensity	AZA	£123,558.09	0.99	
	VEN + AZA	£196,862.00	2.29	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
% of patients with CR/CRi based on NMA	AZA	£111,055.96	0.92	
	VEN + AZA	£163,491.62	2.17	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
14 day hospital stay for initiation with VEN+AZA	AZA	£103,668.79	0.88	
	VEN + AZA	£142,609.69	2.17	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Cumulative	AZA	£116,338.91	0.80	
	VEN + AZA	£197,923.37	1.86	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year. *Extracted from company model: company did not report AZA comparisons in its submission

6.4. Conclusions of the cost-effectiveness section

Based on the EAG's preferred fully incremental analysis, IVO+AZA (with PAS) is ranked as the most expensive treatment option, and results in the largest QALY gain. When compared to AZA, IVO+AZA results in an ICER of £[redacted]. VEN+AZA (the second most expensive treatment option) results in higher total costs and QALYs compared to the cheapest treatment (AZA). When compared to AZA, VEN+AZA results in an ICER of £[redacted]. Based on a willingness to pay threshold of £30,000, VEN+AZA and IVO+AZA are not cost-effective vs AZA alone.

Please see the accompanying cPAS appendix for results including comparator PAS discounts.

7. QALY MODIFIER

The company state that this technology does not meet the criteria for a severity weight

Table 45: Summary of QALY shortfall analysis

Expected total QALYs for the general population	**Total QALYs that people living with a condition would be expected to have with current treatment**	**QALY shortfall**
7.29 (based on the QALY shortfall calculator by Schneider *et al.*, 2021; assuming 45% female aged 75 years at baseline)	VEN+AZA: 2.17 (obtained from the cost-effectiveness model base-case analysis)	Absolute: 5.12 Proportional: 70.22% QALY weight: x 1

Key: AZA, azacitidine; QALY, quality-adjusted life year; VEN, venetoclax.

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

Summary of results including the company's revised patient access scheme

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Date completed	13/11/2023.
Source of funding	This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR136108.
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 report should be referenced as follows	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.

All CIC (Commercial in Confidence) data has been highlighted in blue and underlined

1. INTRODUCTION

The purpose of this appendix is to update the company's base case economic results and present the preferred EAG base case results and EAG scenario analyses results, using the revised patient access scheme (PAS) discount for ivosidenib (December 2023) stated in Table 1. List prices are used for all other drugs.

Table 1: Application of PAS discounts for each treatment

Treatment	Application of PAS
Ivosidenib	[redacted]

Abbreviations: PAS, patient access scheme

2. COMPANY'S BASE CASE RESULTS (PAIRWISE)

The following tables present the company's pairwise base case results including the intervention PAS discount and the list prices for the comparators. See Table 4 and Table 5 for analysis including all relevant comparators with fully incremental analyses using the company's base case assumptions.

Table 2: Discounted company base case results (IVO+AZA vs VEN+AZA)

	Total costs	Total LYs gained	Total QALYs	Incremental costs	Incremental Lys	Incremental QALYs	Cost per QALY gained
Company deterministic base case							
VEN+AZA	£190,639	4.26	2.17				
IVO+AZA	[redacted]	5.97	[redacted]	[redacted]	1.71	[redacted]	[redacted]
Company probabilistic base case							
VEN+AZA	£193,866	4.34	2.19				
IVO+AZA	[redacted]	5.96	[redacted]	[redacted]	1.62	[redacted]	[redacted]

Abbreviations: QALYs, quality adjusted life years; LYs, life years

Table 3: Discounted company base case results (IVO+AZA vs AZA)

	Total costs	Total LYs gained	Total QALYs	Incremental costs	Incremental Lys	Incremental QALYs	Cost per QALY gained
Company deterministic base case							
AZA	£110,384	1.71	0.88				
IVO+AZA	[redacted]	5.97	[redacted]	[redacted]	4.26	[redacted]	[redacted]
Company probabilistic base case							
AZA	£111,352	1.77	0.91				
IVO+AZA	[redacted]	5.96	[redacted]	[redacted]	4.19	[redacted]	[redacted]

Abbreviations: QALYs, quality adjusted life years; LYs, life years

3. EAG PREFERRED BASE CASE RESULTS (FULLY INCREMENTAL)

The following tables present the EAG's preferred fully incremental base case results using the relevant PAS discounts.

Table 4: EAG's preferred model assumptions (deterministic)

Preferred assumption	Comparator	Total Costs	Total QALYs	ICERs
Company base-case*	AZA	£110,384	0.88	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£190,639	2.17	[redacted]
EAG corrected base case	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£190,639	2.18	[redacted]
Weibull used to extrapolate OS (IVO+AZA)	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£170,130	2.05	[redacted]
Weibull used to extrapolate EFS (IVO+AZA)	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£211,629	2.02	[redacted]
No cure assumption + No stopping rule	AZA	£114,926	0.79	
	VEN + AZA	£217,640	1.82	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
100% Relative dose intensity	AZA	£110,864	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]

	VEN + AZA	£192,520	2.18	[redacted]
% of patients with CR/Cri based on NMA	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£185,309	2.19	[redacted]
14 day hospital stay for initiation with VEN+AZA	AZA	£110,384	0.89	
	VEN + AZA	£176,299	2.18	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Cumulative	AZA	£115,408	0.79	
	VEN + AZA	£197,147	1.84	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year. * Fully incremental results including all relevant comparators, using company's base case assumptions.

Table 5: EAG's preferred model assumptions (probabilistic)

Preferred assumption	Comparator	Total Costs	Total QALYs	ICERs
Company base-case*	AZA	£110,804	0.90	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£192,900	2.17	[redacted]
EAG corrected base case	AZA	£110,386	0.91	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£193,692	2.19	[redacted]
Weibull used to extrapolate OS (IVO+AZA)	AZA	£110,875	0.92	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£175,736	2.08	[redacted]
Weibull used to extrapolate EFS (IVO+AZA)	AZA	£111,737	0.92	
	VEN + AZA	£212,943	2.08	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
No cure assumption + No stopping rule	AZA	£114,715	0.80	
	VEN + AZA	£217,884	1.84	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
100% Relative dose intensity	AZA	£111,362	0.91	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£193,903	2.19	[redacted]
% of patients with CR/CRi based on NMA	AZA	£111,430	0.92	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£185,398	2.22	[redacted]
	AZA	£110,829	0.91	
	VEN + AZA	£178,302	2.22	[redacted]

14 day hospital stay for initiation with VEN+AZA	IVO + AZA	[redacted]	[redacted]	[redacted]
Cumulative	AZA	£115,897	0.80	
	VEN + AZA	£196,927	1.87	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year * Fully incremental results including all relevant comparators, using company's base case assumptions.

4. EAG SCENARIO ANALYSES RESULTS (FULLY INCREMENTAL)

The following tables present the fully incremental results for the EAG's scenario analyses, using the relevant PAS discounts.

Table 6: Fully incremental analysis on EAG's exploratory analyses (deterministic)

Preferred assumption	Comparator	Cost	QALYs	ICERs
Company base-case*	AZA	£110,384	0.88	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£190,639	2.17	[redacted]
EAG corrected base case	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£190,639	2.18	[redacted]
EAG's exploratory analyses (including EAG corrections)				
Treatment effect (OS HR for VEN+AZA vs IVO+AZA)				
a) Increase OS HR by 25% to [redacted]	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£ 245,853	2.56	[redacted]
b) Decrease the OS HR by 25% to [redacted]	AZA	£110,384	0.89	
	VEN + AZA	£127,167	1.75	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
c) OS HR at [redacted] (95% CI lower bound)	VEN + AZA	£100,297	1.52	
	AZA	£110,384	0.89	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
d) OS HR at [redacted] (95% CI upper bound)	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£312,944	3.01	[redacted]

Treatment effect (EFS HR for VEN+AZA vs IVO+AZA)				
a) Increase EFS HR by 25% to [redacted])	AZA	£110,384	0.89	
	VEN + AZA	£155,327	2.41	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
b) Decrease the EFS HR by 25% to [redacted]	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£ 229,551	1.93	[redacted]
c) EFS HR at [redacted] (95% CI lower bound)	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£ 250,412	1.79	[redacted]
d) EFS HR at [redacted] (95% CI upper bound)	AZA	£110,384	0.89	
	VEN + AZA	£113,374	2.68	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
OS extrapolation				
Weibull curve used to extrapolate OS (IVO+AZA)	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£170,130	2.05	[redacted]
Exponential curve used to extrapolate OS (IVO+AZA)	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£153,263	1.93	[redacted]
EFS extrapolation				
Weibull curve used to extrapolate EFS (IVO+AZA)	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£211,629	2.02	[redacted]
	AZA	£110,384	0.89	

Exponential curve used to extrapolate EFS (IVO+AZA)	VEN + AZA	£ 234,911	1.86	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Cure assumption				
a) No cure assumptions	AZA	£114,863	0.79	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£216,996	1.82	[redacted]
b) No cure assumption + No stopping rule	AZA	£114,926	0.79	
	VEN + AZA	£217,640	1.82	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Only CR/CRi patients are functionally cured	AZA	£110,807	0.84	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£192,433	2.10	[redacted]
% of patients receiving posaconazole				
a) 0% of patients	AZA	£109,314	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£ 212,298	2.18	[redacted]
b) 90% of patients	AZA	£110,277	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£192,805	2.18	[redacted]
CR/CRi VEN+AZA				
% of patients with CR/CRi based on NMA	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£185,309	2.19	[redacted]
Stopping rule				
a) 50% of patients discontinue at year 3	AZA	£114,895	0.79	
	VEN + AZA	£217,318	1.82	[redacted]

(includes no cure assumption)	IVO + AZA	[redacted]	[redacted]	[redacted]
b) Discontinue at year 5 (includes no cure assumption)	AZA	£114,923	0.79	
	VEN + AZA	£217,586	1.82	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
c) No stopping rule**	AZA	£110,384	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£190,639	2.18	[redacted]
Relative dose intensity (RDI)				
100% Relative dose intensity (RDI)	AZA	£110,864	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£192,520	2.18	[redacted]
Subsequent therapy use				
a) 5% of patients receive gilteritinib, while 3% of patients on AZA receive gilteritinib	AZA	£111,298	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£191,948	2.18	[redacted]
b) no subsequent therapy	AZA	£109,470	0.89	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£189,330	2.18	[redacted]
Length of hospital stay during treatment initiation				
a) [redacted] days for all treatment arms	AZA	£112,496	0.89	
	VEN + AZA	£174,434	2.18	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
b) 14 days for VEN+AZA	AZA	£110,384	0.89	
	VEN + AZA	£176,299	2.18	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year. Note that for the stopping rule scenarios (a and b), the EAG has also removed the modelled cure assumption). *Fully incremental results including all relevant comparators, using company's base case assumptions. **Note no stopping rule is same as EAG corrected base case due to survival assumption at 3 years remaining in place.

Table 7: Fully incremental analysis on EAG's exploratory analyses (probabilistic)

Preferred assumption	Comparator	Total Costs	Total QALYs	ICERs
Company base-case*	AZA	£110,804	0.90	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£192,900	2.17	[redacted]
EAG corrected base case	AZA	£110,386	0.91	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£193,692	2.19	[redacted]
EAG's exploratory analyses (including EAG corrections)				
Treatment effect (OS HR for VEN+AZA vs IVO+AZA)				
a) Increase OS HR by 25% to [redacted]	AZA	£110,817	0.91	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£240,361	2.59	[redacted]
b) Decrease the OS HR by 25% to [redacted]	AZA	£110,511	0.92	
	VEN + AZA	£134,930	1.69	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
c) OS HR at [redacted] (95% CI lower bound)	AZA	£111,460	0.92	
	VEN + AZA	£113,326	1.40	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
	AZA	£112,827	0.92	
	IVO + AZA	[redacted]	[redacted]	[redacted]

d) OS HR at [redacted] (95% CI upper bound)	VEN + AZA	£306,921	3.05	[redacted]
Treatment effect (EFS HR for VEN+AZA vs IVO+AZA)				
a) Increase EFS HR by 25% to [redacted])	AZA	£110,983	0.91	
	VEN + AZA	£167,234	2.39	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
b) Decrease the EFS HR by 25% to [redacted]	AZA	£111,708	0.92	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£232,078	1.98	[redacted]
c) EFS HR at [redacted] (95% CI lower bound)	AZA	£111,956	0.92	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£250,128	1.81	[redacted]
d) EFS HR at [redacted] (95% CI upper bound)	AZA	£110,349	0.91	
	VEN + AZA	£132,780	2.60	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
OS extrapolation				
Weibull curve used to extrapolate OS (IVO+AZA)	AZA	£110,875	0.92	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£175,736	2.08	[redacted]
Exponential curve used to extrapolate OS (IVO+AZA)	AZA	£111,090	0.91	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£155,569	1.91	[redacted]
EFS extrapolation				
Weibull curve used to extrapolate EFS (IVO+AZA)	AZA	£111,737	0.92	
	VEN + AZA	£212,943	2.08	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]

Exponential curve used to extrapolate EFS (IVO+AZA)	AZA	£111,211	0.92	
	VEN + AZA	£233,305	1.92	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Cure assumption				
a) No cure assumptions	AZA	£115,892	0.81	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£214,562	1.84	[redacted]
b) No cure assumption + No stopping rule	AZA	£114,715	0.80	
	VEN + AZA	£217,884	1.84	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
Only CR/CRi patients are functionally cured	AZA	£110,956	0.86	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£196,509	2.14	[redacted]
% of patients receiving Posaconazole				
a) 0% of patients	AZA	£109,536	0.92	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£213,430	2.21	[redacted]
b) 90% of patients	AZA	£110,554	0.91	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£196,045	2.21	[redacted]
CR/CRi VEN+AZA				
% of patients with CR/CRi based on NMA	AZA	£111,430	0.92	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£185,398	2.22	[redacted]
Stopping rule				
	AZA	£117,925	0.80	

a) 50% of patients discontinue at year 3 (includes no cure assumption)	VEN + AZA	£200,345	1.86	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
b) Discontinue at year 5 (includes no cure assumption)	AZA	£118,359	0.81	
	VEN + AZA	£201,522	1.86	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
c) No stopping rule**	AZA	£110,386	0.91	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£193,692	2.19	[redacted]
Relative dose intensity (RDI)				
100% Relative dose intensity (RDI)	AZA	£111,362	0.91	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£193,903	2.19	[redacted]
Subsequent therapy use				
a) 5% of patients receive gilteritinib, while 3% of patients on AZA receive gilteritinib	AZA	£112,750	0.92	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£195,983	2.23	[redacted]
b) no subsequent therapy	AZA	£110,495	0.92	
	IVO + AZA	[redacted]	[redacted]	[redacted]
	VEN + AZA	£192,575	2.22	[redacted]
Length of hospital stay during treatment initiation				
a) [redacted] days for all treatment arms	AZA	£112,854	0.91	
	VEN + AZA	£176,102	2.20	[redacted]
	IVO + AZA	[redacted]	[redacted]	[redacted]
b) 14 days for VEN+AZA	AZA	£110,829	0.91	
	VEN + AZA	£178,302	2.22	[redacted]

	IVO + AZA	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year. Note that for the stopping rule scenarios (a and b), the EAG has also removed the modelled cure assumption). *Fully incremental results including all relevant comparators, using company's base case assumptions. **Note no stopping rule is same as EAG corrected base case due to survival assumption at 3 years remaining in place.

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 20 November 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Production of images in the EAR

Description of problem	Description of proposed amendment	Justification for amendment
The EAR includes some plots extracted from the submitted economic model, but these have been pasted into the EAR as plots rather than images. Consequently, when the link between the model and report is broken, these plots have not rendered correctly.	Please can the EAG check and replace the following images with non-linked plots: - Figure 13 - Figure 17 - Figure 20	By addressing this, the images will be corrected and avoids any risk of embedded confidential data being inadvertently included within the EAR.

Issue 2 Description of the AGILE definition of EFS

Description of problem	Description of proposed amendment	Justification for amendment
On p.65 of the EAR, it states: *"The EAG believes is a highly erroneous imputation and strongly prefers the company choice of 'sensitivity analysis definition' of EFS"*. While the company acknowledges the EAG's view, this statement describes the definition of EFS used in AGILE (as the primary endpoint) as a 'highly erroneous imputation'.	The company requests that the description of the primary endpoint in AGILE as being 'highly erroneous imputation' be removed: *"The EAG strongly prefers the company choice of 'sensitivity analysis definition' of EFS, over the primary endpoint definition used in AGILE"*. Alternatively, the company would propose that the endpoint definition could be described as *'inappropriate for informing a cost-effectiveness model'* or a similar description.	The choice of terminology to describe the primary endpoint of AGILE focuses on its applicability to the appraisal. There are other instances where the primary endpoint definition may be used outside the context of this appraisal (for example, by the FDA). This proposed amendment maintains the EAG's view, but without dismissing the endpoint for other situations where it was preferred.

Issue 3 Marketing authorisation for venetoclax

Description of problem	Description of proposed amendment	Justification for amendment
On p.83 of the EAR, it states: *"VEN+AZA is currently not licensed for use in the treatment patients with untreated IDH1-positive acute myeloid leukaemia."* This is factually inaccurate. While the marketing authorisation does not explicitly recommend use in patients with IDH1-positive AML, this group of patients can be considered a subgroup of the overall population covered by the marketing authorisation for venetoclax.	The company requests that this text be revised as follows: *"VEN+AZA is not specifically licensed for use in the treatment of patients with untreated IDH1-positive acute myeloid leukaemia."*	This amendment avoids any risk of misinterpretation that use of VEN+AZA in an IDH1-positive AML population is not in keeping with its marketing authorisation.

Issue 4 Base-case comparison to AZA

Description of problem	Description of proposed amendment	Justification for amendment
Throughout the EAR, the EAG refers to the company's base-case results against AZA. This is factually inaccurate as although the model submitted allowed for a comparison to AZA to be produced, this did not form part of the company's submission.	The company requests that all references to a company base-case ICER for IVO+AZA versus AZA not be referred to as a company base case. If the EAG wishes to present results based on the default settings contained within the submitted economic model file, these can be referred to as 'results using the pre-loaded settings in the submitted model'. In particular, the company highlights the following: - Section 5.1.1.1 (including Table 35 and Table 36)	The company does not consider AZA as a relative comparator, and therefore did not present a base-case analysis against AZA within its submission. Referring to these results as a company base-case is contradictory to this, and so the company requests that these results be described using correct terminology.

	- Section 5.2.2. (including Figure 20) - Section 6.1.1. (Table 37) - Section 6.1.2. (Table 39 and Table 40) - Section 6.2.9. (Table 39 and Table 40) - Section 6.3. (Table 41 and Table 42)	

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EAG appendix with updated PAS – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG appendix to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of the day on **Friday 19 January 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Base-case comparison to AZA

Description of problem	Description of proposed amendment	Justification for amendment
Throughout the EAR, the EAG refers to the company's base-case results against AZA. This is factually inaccurate as although the model submitted allowed for a comparison to AZA to be produced, this did not form part of the company's submission	The company requests that all references to a company base-case ICER for IVO+AZA versus AZA not be referred to as a company base case. If the EAG wishes to present results based on the default settings contained within the submitted economic model file, these can be referred to as 'results using the pre-loaded settings in the submitted model'.	The company does not consider AZA as a relative comparator, and therefore did not present a base-case analysis against AZA within its submission. Referring to these results as a company base-case is contradictory to this, and so the company requests that these results be described using correct terminology.

Issue 2 EAG comparison to AZA

Description of problem	Description of proposed amendment	Justification for amendment
Throughout the results, the company believes the EAG comparison to AZA monotherapy has been calculated without applying a 1.2 severity modifier	The company notes that if AZA is selected as the comparator by the EAG, a disease severity modifier should be set at x1.2 in line with the EAG's preferred estimate of 0.79 QALYs for AZA. Based on the QALY shortfall calculator (https://shiny.york.ac.uk/shortfall/), unless the total QALYs for AZA exceed 1.09, a x1.2 modifier should be applied."	This error will need correcting to give fair pairwise analysis ICERS, taking the severity modifier in to account

Issue 3

Description of problem	**Description of proposed amendment**	**Justification for amendment**
Give full details of inaccuracy found including page number in EAG report	Give details of any corrections that should be made	Justify why the error needs correcting and the impact it will have

(please cut and paste further tables as necessary)

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.

(Please add further lines to the table as necessary)

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with IDH1-positive acute myeloid leukaemia or caring for a patient with IDH1-positive acute myeloid leukaemia. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5:00pm** on **Monday 15 January 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, 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 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.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with IDH1-positive acute myeloid leukaemia

Table 1 About you, IDH1-positive acute myeloid leukaemia, current treatments and equality

1. Your name	Esther Beswick
2. Are you (please tick all that apply)	☐ A patient with IDH1-positive acute myeloid leukaemia? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with IDH1-positive acute myeloid leukaemia? ☐ A patient organisation employee or volunteer? ☒ Other (please specify): A patient with a diagnosis of AML which was not IDH1 positive
3. Name of your nominating organisation	Leukaemia Care
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing this statement
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Aswell as personal experience of AML I am also a qualified

	nurse currently working in clinical haematology and caring for patients with AML and other blood cancers. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with IDH1-positive acute myeloid leukaemia? **If you are a carer (for someone with IDH1-positive acute myeloid leukaemia) please share your experience of caring for them**	Living with AML was an entirely traumatic experience for myself and my family both physically and mentally. I was diagnosed and admitted as an emergency presentation during the initial stages of the Covid pandemic which brought its own additional challenges. Although the treatment I received was physically gruelling and had unpleasant and unwanted side effects, the emotional effects of the disease were equally if not more distressing and took longer to recover from than the physical aspects. Due to having low risk mutations after genetic analysis, I received the traditional 7+3 chemotherapy – 7 days of Cytarabine and 3 days of Danorubicin plus an additional targeted therapy called Mylotarg – these medications were all administered intravenously over a prolonged period of time (eg 1st cycle of cytarabine 24 hours per day for 7 days) which meant that I had to stay in hospital for an extended time. Each treatment resulted in an infection requiring additional stays in hospital, and I also spent several days per week on the hospital day unit having supportive treatment in the form of blood and platelet transfusions. Thankfully my treatment was successful and I have been in remission for over 3 years and was very fortunate that I did not need to have a stem cell transplant. I have returned to full health and strength and have not been left with any unwanted side effects for which I am very grateful. As a result I was able to return to my job as a nurse, and I am now working on the same haematology ward where I received my chemotherapy treatment and am able

	to help others who are currently going through similar treatments as myself for AML and other blood cancers.
7a. What do you think of the current treatments and care available for IDH1-positive acute myeloid leukaemia on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**a) Although there are some other treatments available for 1DH1 positive leukaemia, these are very limited and may be less effective than standard treatments which may still result in relapse, or not be effective in achieving remission in the first place.** **b) having been through treatment for AML and having experienced the inevitable side effects that come with the treatment, this gives me a unique insight into treatment available for AML. Speaking personally, the more treatment options available for patients, the better, particularly if these treatments come with reduced side effects and increased efficacy compared with others as this allows patients to have some control over the choice of their treatment.**
8. If there are disadvantages for patients of current NHS treatments for IDH1-positive acute myeloid leukaemia (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Some current treatments may require longer inpatient hospital admissions which can have a negative impact on patients as it takes them away from their families/friends for longer periods of time. This can result in a negative effect on their mental health during an already difficult and traumatic experience. Current treatments also have a higher relapse rate and a an increased risk of unwanted side effects compared to the treatment regime currently being appraised.
9a. If there are advantages of Ivosidenib with azacitidine over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	**a)Advantages of Ivosidenib with azacitidine include longer event free survival/overall survival rates compared to current treatments. The rate of unwanted side effects was also lower with this combination of medication which would contribute to less of a negative effect on quality of life/mental health etc.** **b)In my opinion, overall survival would be the most important advantage to me, as the goal of treatment for AML is to achieve remission, then once this is achieved, to then be able to remain in remission. Others may have different opinions and priorities for treatment – but in my case, as a 41 year old wife**

9c. Does Ivosidenib with azacitidine help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	**and mother of 2 children – my only goal from treatment was to survive AML regardless of the side effects I may have to endure during the treatment process** **c) Ivosidenib with azacitidine shows an increased overall survival rate compared to other current treatments for IDH1- positive AML. If I was given the choice then I would choose a treatment that would give me the best chance of survival.**
10. If there are disadvantages of Ivosidenib with azacitidine over current treatments on the NHS please describe these. For example, are there any risks with Ivosidenib with azacitidine? If you are concerned about any potential side effects you have heard about, please describe them and explain why	All treatments come with risks and benefits, advantages and disadvantages. As long as these are clearly communicated to a patient then this allows them to make an informed decision about their treatment. Many of the side effects listed for Ivosidenib and azacitidine are very similar to other treatments for AML such as neutropenia, bleeding etc so this would not prevent me from considering this treatment as long as the risks and benefits had been explained to me in advance.
11. Are there any groups of patients who might benefit more from Ivosidenib with azacitidine or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I think any patient with IDH1 positive AML would benefit from the addition of Ivosidenib with azacitidine as a potential treatment as it is a targeted therapy specific to this particular mutation. This makes the treatment likely to be more effective in this group of patients. Some patients may respond well to this treatment whereas others may not, but given its increased rates of overall survival and reduced rates of side effects if would make sense to offer this treatment for consideration to all eligible patients.
12. Are there any potential equality issues that should be taken into account when considering IDH1-positive acute myeloid leukaemia and Ivosidenib with azacitidine? Please explain if you think any groups of people with this condition are particularly disadvantage	All patients should have the right to make an informed choice about their treatment – and should be offered information about all the options available for their specific condition. Patients have the right to choose what is the right treatment path for them – taking into account the possibility of side effects/rate of relapse and overall survival. For some patients, the choice of best supportive care may be the right choice for them, regardless of age. Treatment for AML is gruelling for anyone – even those who are young and fit (as I was) –so it is understandable that some patients may choose not to go ahead with such treatments.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	If the patient is able to understand the risks and benefits of a treatment; its advantages and disadvantages, then their informed choice should be respected – even if it is not the decision that the health care professional might necessarily advise. A particular treatment can work well for one person, but not as well for another so patients should be offered all options in order to allow them to decide the best course of action for themselves.
13. Are there any other issues that you would like the committee to consider?	No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- AML is a physically and emotionally traumatic illness, not just for patients but also for their families due to the prolonged nature of its treatment and its associated side effects.
- AML is a complex disease which requires intensive treatment – some treatments cannot be tolerated by certain patients so more options need to be made available in order to increase chances of survival.
- Ivosidenib with azacitidine offers an additional treatment option to patients who are unable to tolerate standard chemotherapy regimes.
- All treatment for AML carries risk of relapse/side effects but Ivosidenib with azacitidine has a reduced risk of side effects and an increased rate of overall survival compared with other similar treatments for IHD1 positive AML
- All AML patients should be able to make informed decisions about their treatment and should be offered all available treatments specific to their disease/mutation for consideration.

Thank you for your time.

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