Medicinrådet

Bilag til Medicinrådets anbefaling vedr. ivosidenib til behandling af IDH1-muteret akut myeloid leukæmi

Nationalt dansk appendix til fælles nordisk rapport

Vers. 1.0

Bilagsoversigt

1. JNHB-rapport vedr. Tibsovo (ivosidenib) til IDH1-muteret akut myeloid leukæmi
2. Ansøgers notat til Rådet vedr. ivosidenib til IDH1-muteret akut myeloid leukæmi
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Joint Nordic HTA-Bodies

Joint Nordic HTA-Bodies
Health Technology assessment report

Tibsovo (ivosidenib)

Film-coated tablet

Assessed indication
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

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Case number DMC: EMS-2024-00028
Case number Fimea: FIMEA/2024/002022
Case number Landspitali: IS240403
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Case number TLV: 886/2024

Joint Nordic HTA-Bodies

Joint Nordic HTA-Bodies (JNHB) formerly known as FINOSE started as a bottom-up initiative by the HTA authorities in Finland, Norway and Sweden and was launched in Stockholm in 2018. The collaboration extended to comprise Denmark in 2023 and Iceland in 2024. In June 2024 FINOSE changed its name and became Joint Nordic HTA-Bodies (JNHB).

JNHB offers efficient and transparent joint health technology assessments of medicinal products in the five Nordic countries. The assessments include both relative effectiveness and health economics. Decisions on price and reimbursement as well as recommendations for use, are made at the national level in each country. By working together and sharing knowledge, JNHB aim to produce high-quality assessment reports that provide solid support for national decisions.

The basis for the collaboration is outlined in a Memorandum of Understanding, signed in April 2024 by the collaborating HTA bodies;

- Danish Medicines Council (DMC),
- Finnish Medicines Agency (Fimea),
- Landspitali - The National University Hospital of Iceland,
- Norwegian Medical Products Agency (NOMA) and
- Dental and Pharmaceutical Benefits Agency (TLV) in Sweden.

In this assessment of Tibsovo, DMC was assessor, TLV co-assessor and NOMA and Landspitali reviewers. Tibsovo is an out-patient drug in Finland, which means that the product is not within Fimea's remit. Therefore, Fimea were observers during the assessment.

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Clinical experts: Martin Höglund (associate professor, Uppsala University Hospital). The clinical experts have been consulted on current clinical praxis and in interpretation of the clinical material. The JNHB group is not bound to the statements of the experts, interpretations and opinions on which the cost-effectiveness analysis should be based on.

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Summary

- Acute myelogenous leukemia (AML) is a life-threatening type of blood cancer. AML most often affects individuals over the age of 50, with a median age at diagnosis of around 68 years.
- Ivosidenib in combination with azacitidine (Tibsovo + AZA) is indicated for the treatment of adult patients with newly diagnosed AML with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy.
- Ivosidenib is an oral isocitrate dehydrogenase-1 inhibitor that targets the mutant *IDH1* variants including R132H and R132C substitutions; in AML patients, susceptible *IDH1* mutations are those that lead to increased levels of the metabolite, 2-hydroxyglutarate (2-HG). IDH1 inhibition decreases levels of 2-HG, and causes increased myeloid differentiation, increased mature myeloid cell count, and reduced blast counts.
- For patients with AML who are ineligible for standard induction chemotherapy, treatment guidelines and practices are consistent across the Nordic countries, and a semi-intensive treatment regimen with venetoclax in combination with azacitidine (Venclyxto+AZA) is the preferred option and is therefore the only comparator in this assessment.
- Tibsovo+AZA has shown an increase in PFS and OS when compared to AZA monotherapy in the AGILE trial. Venclyxto+AZA has shown an increase in PFS and OS when compared to AZA monotherapy in the VIALE-A trial.
- In the absence of direct head-to-head studies of Tibsovo+AZA vs. Venclyxto+AZA, Servier has made an indirect treatment comparison using a network-meta-analysis (NMA).
- The NMA is supplemented by a Bucher analysis comparing only the studies AGILE (Tibsovo+AZA vs. AZA) and VIALE-A (Venclyxto+AZA vs. AZA).
- These analyses assume exchangeability between studies which may not apply since there are differences in the study populations, especially regarding *IDH1* mutation status. Whereas, AGILE included only patients with IDH1 mutations, this was not a criterion for inclusion in VIALE-A and only ~6 % harboured an IDH1 mutation. *IDH1* has not shown to be a prognostic factor for AML, but *post-hoc* subgroup analyses from the VIALE-A trial (Venclyxto+AZA. vs. AZA) indicate an increased relative effect of Venclyxto+AZA vs. AZA in the *IDH1* mutated subgroup. Interpretation of these analyses is hampered by the small numbers of enrolled IDH1 mutated patients in VIALE-A and the lack of baseline characteristics for these patients. The discrepancy in *IDH1* mutation status is an important limitation of the presented results.
- Point estimates of the hazard rates from the ITT-analysis suggest that treatment with Tibsovo+AZA may be more effective than Venclyxto+AZA in terms of event-free survival (EFS) and overall survival (OS). Concurrently, the effect size has wide credible intervals (CrIs) spanning 1, indicating a risk that Tibsovo+AZA could instead not be superior to Venclyxto+AZA. This is a crucial factor of uncertainty. The underlying assumption of proportional hazards is also uncertain.
- Safety data indicate that Tibsovo+AZA might have a better safety profile than Venclyxto+AZA with fewer and less severe adverse hematological events. QT prolongation and differentiation syndrome are important identified risks for Tibsovo+AZA.
- The drug cost of Tibsovo is in its recommended dose approximately 173,000 SEK per 30 days. Venclyxto in its recommended dose costs 50,000 SEK per 28 days. These

prices do not consider any commercial arrangements. The drug cost of azacitidine is very low in comparison but entails an administration cost.

- Servier has submitted a cost-effectiveness analysis using a partitioned survival model, in which patients who have been treated with Tibsovo+AZA are compared with patients who have received Venclyxto+AZA.
- Due to the high uncertainty in the indirect treatment comparison, and consequently in the effect size, JNHB presents two analyses: a cost-utility analysis assuming incremental effect and a cost-comparison analysis assuming equal effect between Tibsovo+AZA and Venclyxto+AZA.
- When assuming a treatment advantage (incremental effect) in line with the indirect treatment comparison the cost per QALY in the JNHB base case is approximately 6 million SEK. QALYs gained are 0.7.
- An analysis assuming equal treatment effect leaves only the incremental drug cost, which is considerable.
- Uncertainty of the analysis centers around the indirectly compared relative effect size and the extrapolated long-term relative effect.

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1 Scope

This JNHB report is the result of a joint Nordic assessment of ivosidenib (Tibsovo) in combination with azacitidine (AZA), for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy (SIC).

The assessment is primarily based on the documentation presented by Servier.

The aim of the JNHB report is to support national decisions on price and reimbursement as well as recommendations for use, in Denmark, Iceland, Norway and Sweden regarding ivosidenib. The primary focus of this report is the assessment of relative effectiveness, safety and cost effectiveness of Tibsovo. The JNHB report may be complemented with national appendices with additional local information and conclusions.

P (population)	Adult patients with newly diagnosed acute myeloid leukaemia with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy
I (intervention)	Ivosidenib in combination with azacitidine
C (comparison, comparators)	Venetoclax in combination with azacitidine
O (outcomes)	• Overall survival (OS) • Event-free survival (EFS) • Health-related quality of life • Safety
HE (health economy)	• QALYs • Costs • Incremental cost-effectiveness ratio (ICER)

2 Medical background

2.1 Acute myelogenous leukemia (AML)

Acute myelogenous leukemia (AML) is an acute and life-threatening type of blood cancer. AML most often affects individuals over the age of 50, with a median age at diagnosis of around 68 years. The disease is characterized by an overproduction of early myeloid precursor cells (blast cells), often with exclusion of other cell lines, resulting in anemia, thrombocytopenia, and neutropenia. Leukemic cells eventually move from the bone marrow into the bloodstream from where they can spread into other organs [1]. AML is a heterogeneous disease with various molecular genetic changes, including both chromosomal alterations and point mutations in specific genes, which in turn affect prognosis [2]. The disease has rapid progression and is associated with a low overall survival compared to other types of leukemia [3]. Symptoms of AML include fatigue, heart palpitations, headache, dizziness, difficulty breathing, severe life-threatening infections requiring hospitalization, and increased bleeding tendency [4], all of which affect patients' quality of life. Patients with AML have an increased risk of developing anxiety and depression in connection with the diagnosis of a fatal disease and its aggressive treatment [3].

The 5-year survival rate for the entire AML patient population has increased since the year 2000, but overall it is still below 30% [3,4].

The prevalence of AML in the Nordic countries is estimated to range from 12.2 to 16.8 per 100,000 [5,6]. In general, the incidence of AML increases with age, and slightly more males than females are diagnosed with AML. Approximately 8% of AML patients harbor IDH1 mutations [7].

Country	Number of new AML cases annually
Sweden	~350
Denmark	~275
Finland	~200
Norway	~175

Table above provide an overview of patients numbers in the Nordic countries [8] Approximately 25-30 % of newly diagnosed patients annually are not suitable for curative treatment with standard induction chemotherapy followed by consolidative treatment and/or stem cell transplantation, due to comorbidities or advanced age. These patients are candidates for first-line treatment with venetoclax in combination with an hypomethylating agent, such as azacitidine. The treatment goal for this group of patients is to extend the time to disease progression and death.

2.2 Tibsovo

2.2.1 Therapeutic indication

Tibsovo in combination with azacitidine is indicated 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.

Tibsovo monotherapy is also indicated for:

the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a mutation in the IDH1-gene (IDH1 R132) who were previously treated by at least one prior line of systemic therapy [9].

2.2.2 Mechanism of action

The active substance in Tibsovo, ivosidenib, is an inhibitor of the mutant IDH1 enzyme. Mutant IDH1 converts alpha- ketoglutarate (αKG) to 2-hydroxyglutarate (2-HG) which blocks cellular differentiation and promotes tumorigenesis in both hematologic and non-hematologic malignancies. The mechanism of action of ivosidenib beyond its ability to reduce 2-HG levels and restore cellular differentiation is not fully understood [9].

2.2.3 Posology and method of administration

The recommended dose is 500 mg ivosidenib (2 x 250 mg tablets) taken orally once daily. Ivosidenib should be started on Cycle 1 Day 1 in combination with azacitidine at 75 mg/m² of body surface area, intravenously or subcutaneously, once daily on Days 1-7 of each 28-day cycle.

The first treatment cycle of azacitidine should be given at 100% of the dose. It is recommended that patients be treated for a minimum of 6 cycles.
Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient.

2.3 Current treatment options

2.3.1 Current treatment options in Nordic countries

The goal in treating AML patients is to induce remission and prevent relapse.

Management of AML currently consists of four treatment principles:

- Standard induction chemotherapy with curative intent
- **Semi-intensive treatment with non-curative intent**
- Low-intensive treatment with non-curative intent
- Best supportive care (BSC) only.

In younger patients with newly diagnosed AML, treatment will primarily be standard induction chemotherapy which is an intensive chemotherapy regimen, if necessary followed by consolidation chemotherapy and/or stem cell transplantation (curative intent) – although certain AML subtypes require a different treatment or supplement to the standard treatment. Candidates for standard induction chemotherapy are assessed based on age, comorbidity and functional status. The goal for this patient group is to induce remission and prevent relapse.

Older patients with newly diagnosed AML (>75 years) and younger patients with newly diagnosed AML and comorbidity will not tolerate standard induction chemotherapy, i.e. they have an unacceptably high risk of treatment-related mortality. For these patients the alternative is a semi-intensive treatment combination with the Bcl-2-inhibitor venetoclax in combination with a hypomethylating drug, e.g.azacitidine (Venclyxto+AZA). The treatment goal for this group of patients is to extend the time to disease progression and death. Approx lately 30-40% are non-responders to Venclyxto. Technologies for screening for nonresponse before initiating treatment are under development.

Some patients are treated concurrently (both prophylactically and in case of infection) for fungal infections with CYP3A inhibitors (CYP3Ai). CYP3A inhibition requires a reduced dosage of venetoclax due to an increased absorption of venetoclax, as venetoclax is mainly eliminated through metabolism by CYP3A [10].

Patients that do not tolerate semi-intensive regimen or with bone marrow blasts > 30% can be treated with low-dose cytarabine (LDAC) or AZA monotherapy. AZA and LDAC are considered equally effective treatment alternatives. However, azacitidine is more effective for patients with AML with high-risk genetics [11].

For patients with newly diagnosed AML who are ineligible for standard induction chemotherapy, treatment guidelines and practices are consistent across the Nordic countries. In these cases, a semi-intensive treatment regimen with venetoclax in combination with azacitidine (Venclyxto+AZA) is the preferred option.

2.3.2 Comparator

Servier presents both Venclyxto+AZA and AZA monotherapy as relevant comparators to ivosidenib based on national AML treatment guidelines from the Nordic countries.

JNHB discussion of comparator
JNHB clinical experts state that the majority of newly diagnosed patients eligible for Tibsovo+AZA treatment will receive semi-intensive treatment with Venclyxto+AZA in current clinical practice. A few patients might not tolerate venetoclax and for those patients a low-intensity treatment regimen consisting of AZA monotherapy or low-dose cytarabine could be relevant.

JNHB conclusion: For patients with newly diagnosed AML who are ineligible for standard induction chemotherapy, treatment guidelines and practices are consistent across the Nordic countries. In these cases, a semi-intensive treatment regimen with venetoclax in combination with azacitidine (Venclyxto+AZA) is the preferred option for the vast majority of patients. Accordingly, a comparison of Tibsovo+AZA vs AZA monotherapy is not included in this assessment.

3 Clinical efficacy and safety

The assessment of clinical efficacy and safety is mainly based on the evidence included in the submission dossier prepared by Servier.

3.1 Clinical studies

3.1.1 Design and methods of the clinical studies

Table 1: Summary of relevant studies

Study NCT-number [primary reference]	**Study design**	**Treated study population**	**Intervention**	**Primary efficacy endpoints**
AGILE [NCT03173248] [12]	- Phase 3 - Randomised (1:1) - Double-blind - Placebo-controlled - Multicentre, international	Patients with newly diagnosed **IDH1-mutated** AML who are ineligible for intensive chemotherapy	Ivosidenib, 500 mg daily (oral) + 75 mg/m² azacitidine on days 1 to 7 of each treatment cycle (n = 72) Placebo + 75 mg/m² azacitidine on days 1 to 7 of each treatment cycle (n=74)	- Event-free survival (EFS)
VIALE-A [NCT02993523] [13]	- Phase 3 - Randomised (2:1) - Double-blind - Placebo-controlled - Multicentre, international	Patients with newly diagnosed AML who are ineligible for intensive chemotherapy	Venetoclax 400 mg daily (oral) + azacitidine 75 mg/m² on days 1 to 7 of each treatment cycle (n=286) Placebo + azacitidine 75 mg/m² on days 1 to 7 of each treatment cycle (n=145)	- Overall survival (OS)

AGILE
AGILE is an international, double-blind, randomized, placebo-controlled, phase 3 clinical study that investigates the efficacy and safety of ivosidenib in combination with azacitidine (Tibsovo+AZA) compared to placebo plus azacitidine (PBO+AZA) in patients with newly diagnosed IDH1-mutated acute myeloid leukemia (AML) who were not candidates for standard induction chemotherapy. AGILE is the pivotal study which the market authorisation in EU for the relevant indication is based on.

Patients were enrolled from March 2018 through May 2021. By March 18, 2021 (the data-cutoff date), out of 295 patients screened, 146 underwent randomization: 72 to the ivosidenib-and-azacitidine group (Tibsovo+AZA arm) and 74 to the placebo-and-azacitidine group (PBO+AZA arm). The majority of screening failures (78%) were due to negativity for *IDH1* mutation by central testing; the remaining screening failures (22%) were due to other eligibility criteria not being met.

Patients were randomized (1:1) to receive ivosidenib (500 mg oral) + azacitidine (75 mg/m^2, intravenous or subcutaneously) or placebo + azacitidine, and stratified according to geographic region (US and Canada; Western Europe, Israel, and Australia Japan; and rest of the world) – and disease status (primary vs secondary AML).

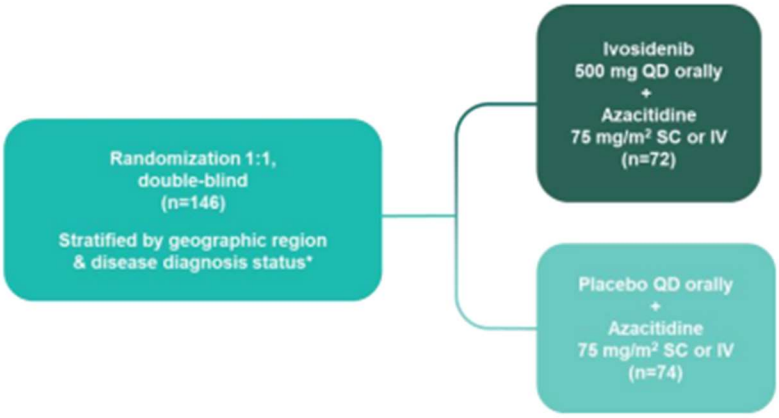


Figure 1 Study design AGILE

The primary end point was event-free survival (EFS), defined as 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.

Key secondary endpoints include overall survival (OS), complete remission (CR) rate, CR with partial hematologic recovery rate (CRi), and objective response rate (ORR).

Initially the study aimed to enroll 392 patients, but after the primary endpoint was changed to EFS the planned sample size was reduced to 200 patients. Based on recommendation of the Independent Data Monitoring Committee (IDMC), enrollment into the study was prematurely discontinued due to a clinically meaningful difference being observed between treatment arms [14] and therefore the final number of included patients only totalled 146.

Table 2 Baseline characteristics AGILE (n=146)

Baseline characteristics	Ivosidenib + 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 (%)			

Baseline characteristics	Ivosidenib + AZA (N = 72)	Placebo + AZA (N = 74)	Total (N = 146)
<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)
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)
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)

Baseline characteristics were similar in the two study groups (Table 2). The median age was 76 years in both the Tibsovo-AZA-arm (range 58 to 84) and the control-arm (range 45 to 94).

In the Tibsovo-AZA arm, 54 patients (75%) had primary AML and 18 (25%) had secondary AML; in the PBO+AZA arm, 53 (72%) had primary AML and 21 (28%) had secondary AML. A total of 16 patients (22%) in the Tibsovo-AZA-arm had poor-risk cytogenetic characteristics, as compared with 20 (27%) in the PBO+AZA arm. 39 patients were receiving treatment at the data-cutoff date (38% in the Tibsovo-AZA arm and 16% in the PBO+AZA arm).

Off study, 19.4% of patients in the Tibsovo+AZA arm and 21.6% in the PBO+AZA arm received another form of anticancer therapy, with the most common subsequent anticancer therapy being chemotherapy, more specifically antimetabolites.
4 patients (5.6%) in the Tibsovo+AZA arm and 7 patients (9.5%) in the PBO+AZA arm received venetoclax as subsequent treatment. 2 patients (2.7%) in the PBO+AZA arm received ivosidenib as subsequent anticancer therapy.

VIALE-A

VIALE-A is an international, double-blind, randomized, placebo-controlled, phase 3 clinical study that investigated the efficacy and safety of venetoclax in combination with azacitidine (Venclyxto+AZA) compared to placebo plus azacitidine (PBO+AZA) in patients with newly diagnosed AML who were not candidates for standard induction chemotherapy.

A total of 579 patients were screened from February 6, 2017, through May 31, 2019, 433 underwent randomization, and 431 were included in the intention-to-treat population from 134 sites across 27 countries.

Patients were randomized (2:1) to receive venetoclax (400 mg oral) + azacitidine (75 mg/m2, intravenous or subcutaneously) or placebo + azacitidine and stratified according to age and cytogenetic risk.

The primary endpoints were overall survival (OS) and composite complete remission rate (CR + CR with incomplete hematologic response (CRi)).

EFS was a secondary endpoint in VIALE-A and defined as the number of days from randomization to the date of progressive disease, relapse from CR or CRi, treatment failure or death from any cause.

Table 3 Baseline characteristics VIALE-A

Baseline characteristics	Azacitidine–Venetoclax Group (N=286)	Azacitidine–Placebo Group (N=145)
Age		
Median (range) — yr	76 (49–91)	76 (60–90)
≥75 yr — no. (%)	174 (61)	87 (60)
Male sex — no. (%)	172 (60)	87 (60)
AML type — no (%)		
De novo	214 (75)	110 (76)
Secondary	72 (25)	35 (24)
Secondary AML — no./total no. (%)		
History of myelodysplastic syndrome or CMML	46/72 (64)	26/35 (74)
Therapy-related AML	26/72 (36)	9/35 (26)
ECOG performance-status score — no. (%)		
0–1	157 (55)	81 (56)
2–3	129 (45)	64 (44)
Bone marrow blast count — no. (%)		
<30%	85 (30)	41 (28)
≥30 to <50%	61 (21)	33 (23)

≥50%	140 (49)	71 (49)
AML with myelodysplasia-related changes — no. (%)	92 (32)	49 (34)
Cytogenetic risk category — no. (%)		
Intermediate	182 (64)	89 (61)
Normal karyotype — no.	128	62
Trisomy 8; +8 alone — no.	13	10
Poor	104 (36)	56 (39)
7 or 7q deletion — no.	20	11
5 or 5q deletion — no.	46	22
Complex, ≥3 clonal abnormalities — no.	75	36
Somatic mutations — no./total no. (%)		
IDH1 or *IDH2*	61/245 (25)	28/127 (22)
FLT3 ITD or TKD	29/206 (14)	22/108 (20)
NPM1	27/163 (17)	17/86 (20)
TP53	38/163 (23)	14/86 (16)
Baseline cytopenia grade ≥3		
Anemia — no. (%)	88 (31)	52 (36)
Neutropenia — no./total no. (%)	206/286 (72)	90/144 (62)
Thrombocytopenia — no. (%)	145 (51)	73(50)
Baseline transfusion dependence — no. (%)		
Red cells	144 (50)	76 (52)
Platelets	68 (24)	32 (22)
≥2 Reasons for ineligibility to receive intensive therapy — no. (%)	141 (49)	65 (45)

In both groups in VIALE-A, the median age was 76 years, and 60% of the patients were male. Secondary AML was reported in 25% of the patients in the Venclyxto+AZA-arm and in 24% of the patients in the PBO+AZA-arm, and poor cytogenetic risk was reported in 36% and 39%, respectively.

Nearly half the patients (49% in the Venclyxto+AZA-arm and 45% in the PBO+AZA-arm) had at least two reasons for ineligibility for standard induction chemotherapy.

3.1.2 JNHB discussion of design and methods of clinical studies for Tibsovo+AZA

The AGILE study was amended 9 times with amendment number 5 being a critical revision in which the primary endpoint was changed from OS to EFS along with an update of the statistical analysis plan and the reduction of required included patients from 392 til 200. The change from OS to EFS was not supported by EMA's CHMP since EFS is not a validated surrogate endpoint for OS in AML (EMEA/H/SA/3403/3/2018/PA/II).

In March 2020 OS results from VIALE-A showed a survival benefit of Venclyxto+AZA vs. PBO+AZA. In May 2020 the AGILE study changed the primary endpoint from OS to EFS and in May 2021 the AGILE study was discontinued due to imbalance of deaths.
The AGILE study was halted early due to an imbalance in the number of deaths (favoring the Tibsovo-AZA-arm) which prompted the independent data monitoring committee (IDMC) to recommend discontinuation of recruitment based on efficacy data. Early stopping leads to less precision in the estimation of the treatment effect as the size of the sample is reduced.

Of note the early stopping of AGILE after 74 OS events contradicts with the initial study plan which stated that the first interim analysis (futility analysis) would be performed when approximately 93 OS events had occurred [14] .

The event-free survival (EFS) definition that was applied in AGILE is different than in VIALE-A. This is exemplified in Table 4 below, comparing the EFS definitions in the AGILE study to the VIALE-A study. Servier has supplied post-hoc sensitivity analyses of EFS using a similar EFS definition as in VIALE-A.

Table 4 EFS definitions in AGILE

	AGILE	VIALE-A
Endpoint type	Primary	Secondary
Definition of EFS	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

JNHB conclusion:
The interpretation of AGILE is hampered by the change in primary endpoint and the early discontinuation of the study due to the inferiority of the comparator. Both the AGILE and VIALE-A study populations are representative for patient in Nordic clinical practice that are ineligible for standard induction chemotherapy. However, there are significant differences between the two populations (discussed in section 4).

3.2 Results for clinical efficacy (and quality of life) from the AGILE study

<u>EFS: prespecified analysis</u>
EFS was defined as the time from randomization until treatment failure (TF), relapse from remission, or death from any cause, whichever occurred first. 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 hazard ratio is estimated using a Cox's proportional hazards model stratified by the randomization stratification factors: AML status (primary vs. secondary AML) and geographic region).

At a median follow-up of 12.4 months and with 46 events (63.9%) in the Tibsovo+AZA-arm and 62 events (83.8 %) in the PBO+AZA-arm the hazard ratio for EFS (treatment failure, relapse from remission, or death) was HR: 0.33 (95% CI: 0.16; 0.69).

The EFS rate at 12 months was 37% in the Tibsovo+AZA-arm vs 12% in the PBO+AZA-arm.

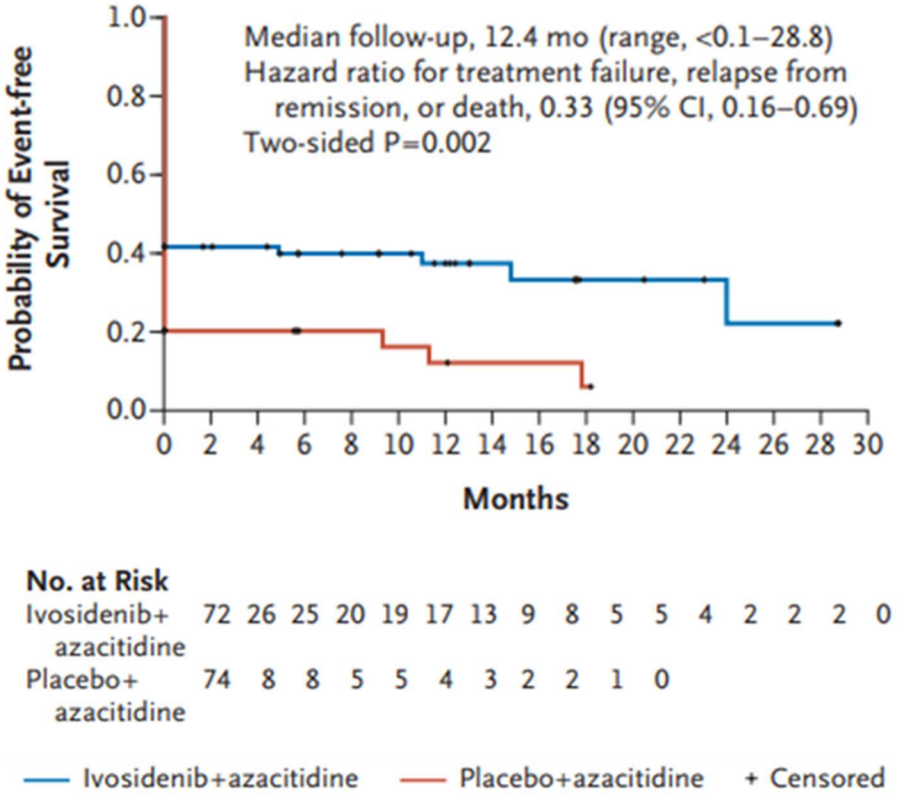


Figure 2 Kaplan-Meier plot of EFS, AGILE

EFS: post-hoc sensitivity analysis

In a sensitivity analysis EFS is defined as a lack of CR, CRi, or morphologic leukemia-free state (MLFS) after at least 24 weeks of study treatment.

The EFS definition in this sensitivity analysis is similar to the EFS definition used in VIALE-A and was applied in the health economic modelling.

The median EFS based in this sensitivity analysis was 22.9 months (95% CI: 7.5; NE) with Tibsovo+AZA and 4.1 months (95% CI: 2.7; 6.8) with PBO+AZA. HR: 0.39 (95% CI: 0.24; 0.64).

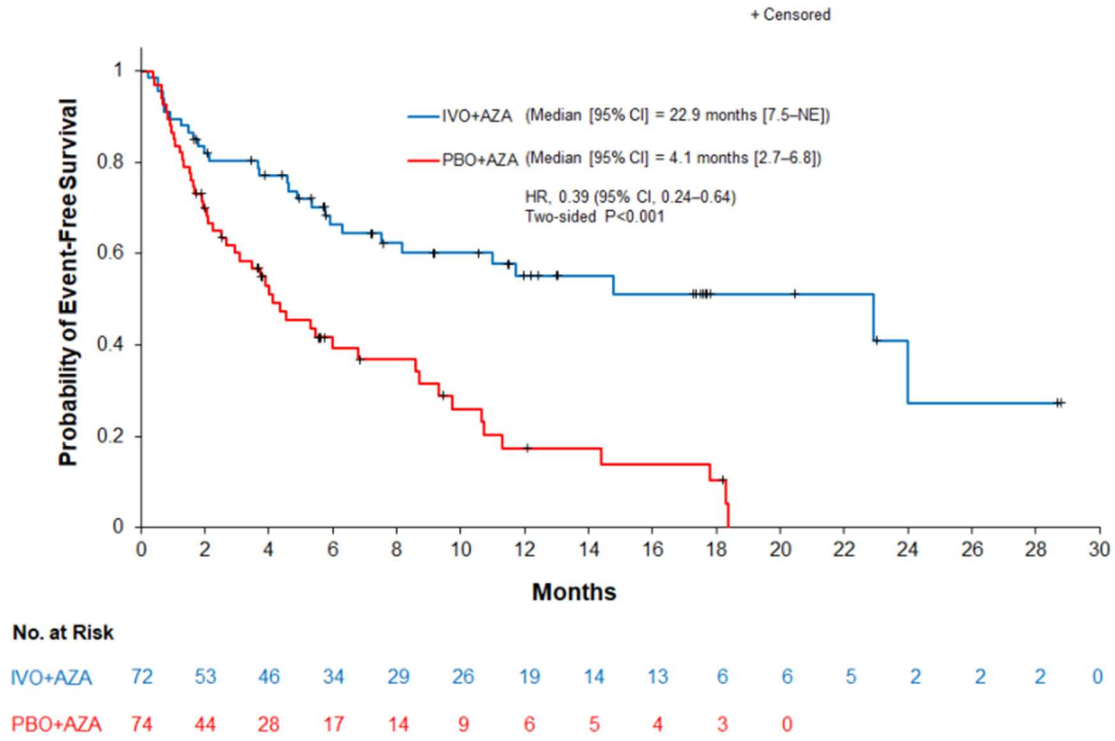


Figure 3 Kaplan-Meier plot of post-hoc EFS definition, AGILE

Overall survival

At a median follow-up of 28.6 months (DCO 30th June 2022) and with 37 events (50.7%) in the Tibsovo+AZA-arm and 58 events (77.3 %) in the PBO+AZA-arm the hazard ratio for death was 0.42 (95% CI: 0.27; 0.65).

OS rates were 62.9 % (50.4, 73.0) and 38.3 % (27.0, 49.5) at 12 months and 53.1 % (40.4, 64.2) and 17.4 % (8.9, 28.2) at 24 months, with Tibsovo+AZA and PBO+AZA, respectively.

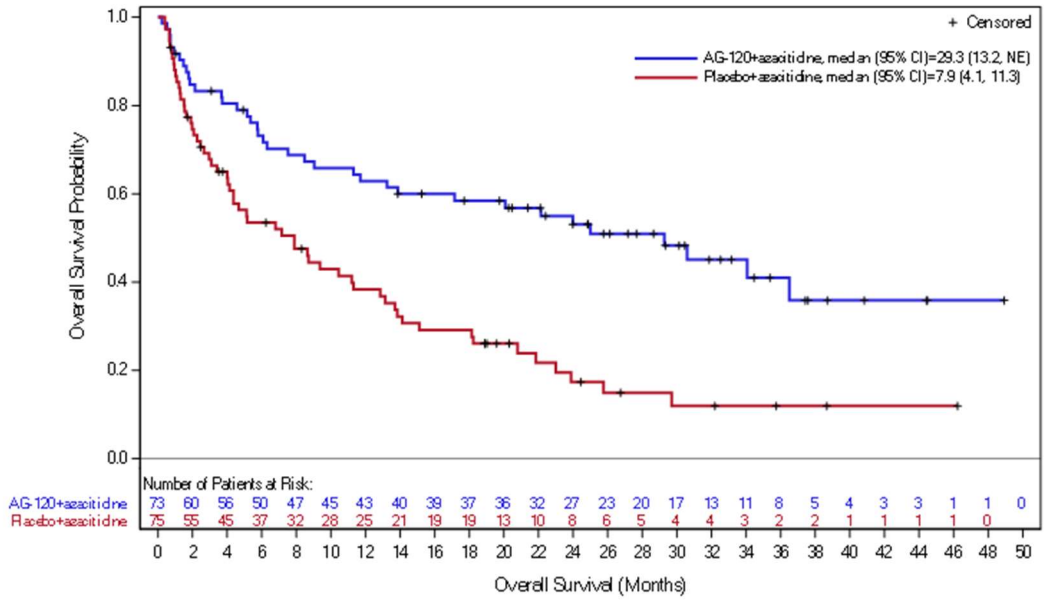


Figure 4 Kaplan-Meier plot of OS, AGILE

Response rate (ORR)
ORR, defined as the rate of CR, CRi (including CR with incomplete platelet recovery (CRp)), PR, and morphologic leukaemia-free state (MLFS), was achieved in 62.5% (95% CI, 50.3-73.6) of the patients in the Tibsovo+AZA arm and 18.9% (95% CI, 10.7-29.7) of the patients in the PBO+AZA arm. ORR was higher in the Tibsovo+AZA arm than in the PBO+AZA arm with odds ratio of 7.15 ([95% CI, 3.31-15.44]; p<0.001).

Table 5 ORR results, AGILE

	Tibsovo+AZA (N = 72)	Placebo + AZA (N = 74)
ORR 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	

Health-related quality of life: EORTC QLQ-C30
In AGILE patient-reported outcome were measured with European organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30).
The EORTC QLQ-C30 is developed to measure the quality of life in patients with cancer. The EORTC QLQ-C30 is a questionnaire with 30 questions and a total of 15 domains, including 5 function scales, 3 symptom scales, 6 single symptoms/circumstances and a global quality of life score (GHS) [15]. A scoring scale from 0 to 100 is used. A high score on the 5 function scales represents a high/positive level of function. A high score on global health status represents high quality of life, while a high score on the 3 symptom scales represents high prevalence of symptoms/problems.

A threshold of 10 points was used to define clinically meaningful group differences and 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.

At baseline, the mean scores for EORTC QLQ-C30 subscales were similar between the treatment arms, with no difference greater than 10 points.

After cycle 5 (C5D1) there are very few responders (<20) in the PBO+AZA arm. The same applies to the Tibsovo+AZA arm after cycle 11 (C11D1).
No statistically significant difference between the arms was seen in the Global Health score.

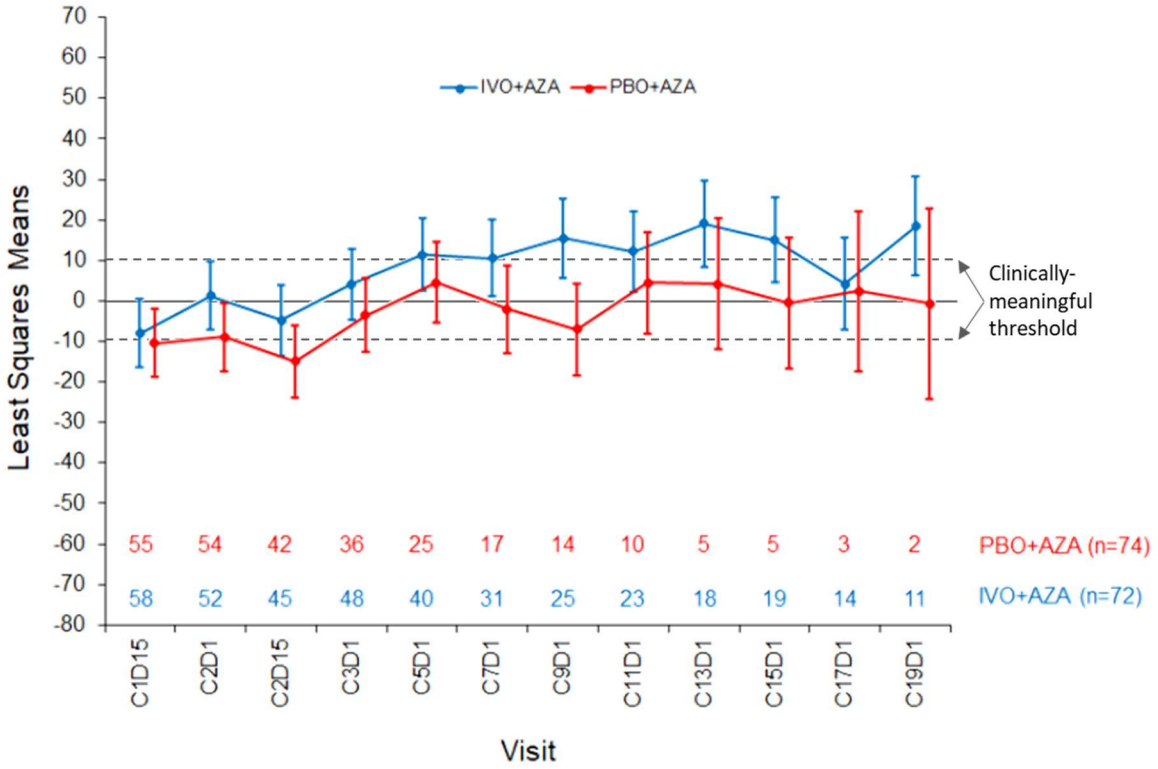


Figure 5 EORTC QLQ-C30 Global Health Status/QoL scorerom baseline (FAS), AGILE

Results for safety for Tibsovo+AZA

In AGILE the incidence of any grade AE reported was 70 patients (99%) treated with Tibsovo+AZA and 73 of 73 patients (100%) in the PBO+AZA arm.

The incidence of grade ≥3 AEs reported was 66 of 71 patients (93%) treated with Tibsovo+AZA and 69 of 73 patients (95%) in the PBO+AZA arm.

Grade ≥3 AEs that occurred in more than 15% of the patients in both the Tibsovo+AZA arm and the PBO+AZA 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%).

Table 6 Serious AEs, AGILE

N (%) of patients	Tibsovo+AZA (N = 71) n (%)	PBO+AZA (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)

N (%) of patients	Tibsovo+AZA (N = 71) n (%)	PBO+AZA (N = 73) n (%)
Differentiation syndrome	6 (8.5)	1 (1.4)
Pyrexia	4 (5.6)	3 (4.1)

AEs of special interest for Tibsovo+AZA

Differentiation syndrome

The percentage of patients with differentiation syndrome of any grade was 14.1% in the Tibsovo+AZA arm and 8.2% with PBO+AZA. In the Tibsovo+AZA arm 7 patients (9.9%-points) experienced a grade 2 event, with only 3 patients (4.2%-points) experiencing a grade 3 event.

Serious AEs of differentiation syndrome were reported in 6 patients (8.5%) in the Tibsovo+AZA arm and 1 patient (1.4%) in the PBO+AZA 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 Tibsovo+AZA arm was 19.5 days (range, 3.0 to 33.0). No deaths due to differentiation syndrome were noted in either group.

QT interval prolongation

Adverse events of QT interval prolonged on ECG of any grade were reported in 14 patients (19.7%) in the Tibsovo+AZA arm compared to 5 patients (6.8%) in the PBO+AZA arm.

The frequency of grade ≥3 QT prolongation was 9.9% (7 patients) with Tibsovo+AZA compared to 4.1% (3 patients) with PBO+AZA. All QT prolongation AEs were Grade 3 events.

Leukocytosis

Leukocytosis was reported in 8 patients (11.3%) in the Tibsovo+AZA arm and in 1 patient (1.4%) patient in the PBO+AZA arm. There were no serious nor grade ≥3 AEs of leukocytosis reported in either arm.

Table 7 AEs leading to treatment discontinuation, interruption and dose reduction

Adverse events leading to treatment discontinuation	Tibsovo+AZA (N = 71) n (%)	PBO+AZA (N = 73) n (%)
Adverse events leading to treatment discontinuation	19 (26.8)	19 (26.0)
Adverse events leading to treatment interruption	37 (52.1)	28 (38.4)
Adverse events leading to dose reduction	4 (5.6)	0

3.2.1 JNHB discussion of efficacy and safety results from AGILE

Results from AGILE indicate that Tibsovo+AZA is better than AZA monotherapy in terms of efficacy on EFS, ORR and OS in newly diagnosed AML patients with mutated *IDH1*. The results regarding health-related quality of life show no difference in effect.

Treatment with Tibsovo+AZA is associated with an increased risk of QT prolongation and differentiation syndrome. Point estimates suggest that there may be fewer serious AEs but more AEs leading to treatment interruptions or dose reductions with Tibsovo+AZA compared to PBO+AZA.

JNHB conclusion:
Results from AGILE show that patients in the Tibsovo+AZA arm have a better EFS and OS compared to patients in the PBO+AZA arm. Results regarding health-related quality of life show no difference between arms. Safety data indicate that the tolerability of Tibsovo+AZA and PBO+AZA are approximately comparable. QT-prolongation and differentiation syndrome are identified as important risks related to treatment with ivosidenib. Risk of QT prolongation requires continuous monitoring.

3.3 Indirect comparisons of Tibsovo+AZA vs. Venclyxto+AZA

There are no head-to-head trials for Tibsovo+AZA vs Venclyxto+AZA. Consequently, Servier conducted an indirect treatment comparison (ITC).

To inform the NMA, Servier conducted an SLR in October 2021 (updated in January 2023) to identify relevant clinical trials that investigated the efficacy and safety of therapies in adults with previously untreated AML who are ineligible for intensive chemotherapy.

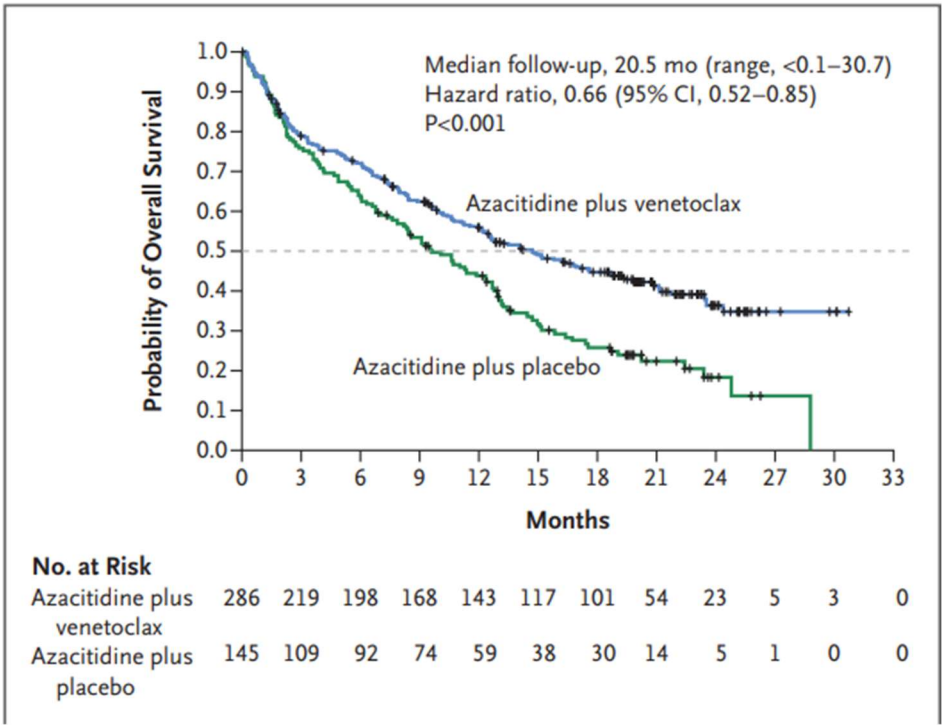
In total, 4,503 records were identified from the original literature search and a further 883 in the updated search. After removal of duplicate records and assessment for inclusion according to study eligibility criteria, 26 unique studies (reported in 69 publications) were prioritized for data extraction, based on a requirement for a randomized controlled trial (RCT) design and total study sample size (N) ≥20, as possibly relevant for ITC. Following screening of the 26 extracted studies, 10 studies were included in Serviers ITC feasibility assessment.

Servier has provided a network meta-analysis (NMA) in a Bayesian framework in order to estimate the efficacy of Tibsovo+AZA versus other existing therapies for newly diagnosed AML patients ineligible for standard induction chemotherapy. ITT analyses from a total of six studies contributed to the evidence networks for the outcomes of interest. Servier has deemed that an NMA considering all patients irrespective of *IDH1/2* mutation status was feasible. Only AGILE solely included newly diagnosed AML patients carrying *IDH1* mutations.
An NMA can produce estimates of the relative effects between any pair of interventions in the network, and it also allows estimation of the ranking and hierarchy of interventions. It relies on the overall assumption of exchangeability, consisting of assessment of similarity, homogeneity and consistency.

According to the JNHB clinical experts the Venclyxto+AZA combination is the most appropriate comparator for patients not eligible for standard induction chemotherapy This section will therefore only address the indirect treatment comparison of Tibsovo+AZA vs. Venclyxto+AZA and discuss the inclusion of the respective trials; VIALE-A and AGILE, while not discussing the other trials in the network.
JNHB has also requested a Bucher analysis including only data from the AGILE and VIALE-A studies.

Results for clinical efficacy and safety for the VIALE-A trial Venclyxto+AZA vs. AZA

The results of the VIALE-A trial showed an effect of adding Venclyxto. Median overall survival was higher in the Venclyxto+AZA arm compared to AZA alone (14,7 months vs 9,6 months; HR 0·66, 95% CI: 0·52 – 0·85). The Kaplan-Meier (KM) analysis of OS for the Venclyxto+AZA and AZA arms in VIALE-A is presented below.



Venetoclax also showed and effect on EFS (HR: 0.63; 95% CI, 0.50 to 0.80).

In VIALE-A all patients experienced an AE. 99 % and 97 % experienced a grade ≥3 AE and 79 % and 68 % experienced a grade 4 AE in the Venclyxto+AZA and PBO+AZA arm respectively. 83 % of patients in VIALE-A experienced a serious adverse event.
24 % experienced an AE leading to venetoclax discontinuation and 72 % experienced AE leading to dose reduction or interruption.

In VIALE-A 42 % and 19 % of patients experienced febrile neutropenia of grade ≥3 in the Venclyxto+AZA and PBO+AZA arm respectively. Serious adverse events related to neutropenia was 34 % and 12 % in the Venclyxto+AZA and PBO+AZA arm, respectively.

Results for clinical efficacy of Tibsovo+AZA vs. Venclyxto+AZA from the ITC

Eventfree survival

The NMA for EFS consists of four studies reporting estimates for five interventions. The following studies besides AGILE contributed to the network: VIALE-A with venetoclax plus azacitidine and azacitidine [16], AZA-AML-001 with azacitidine and LDAC [17] and VIALE-C with venetoclax plus LDAC and LDAC [18].

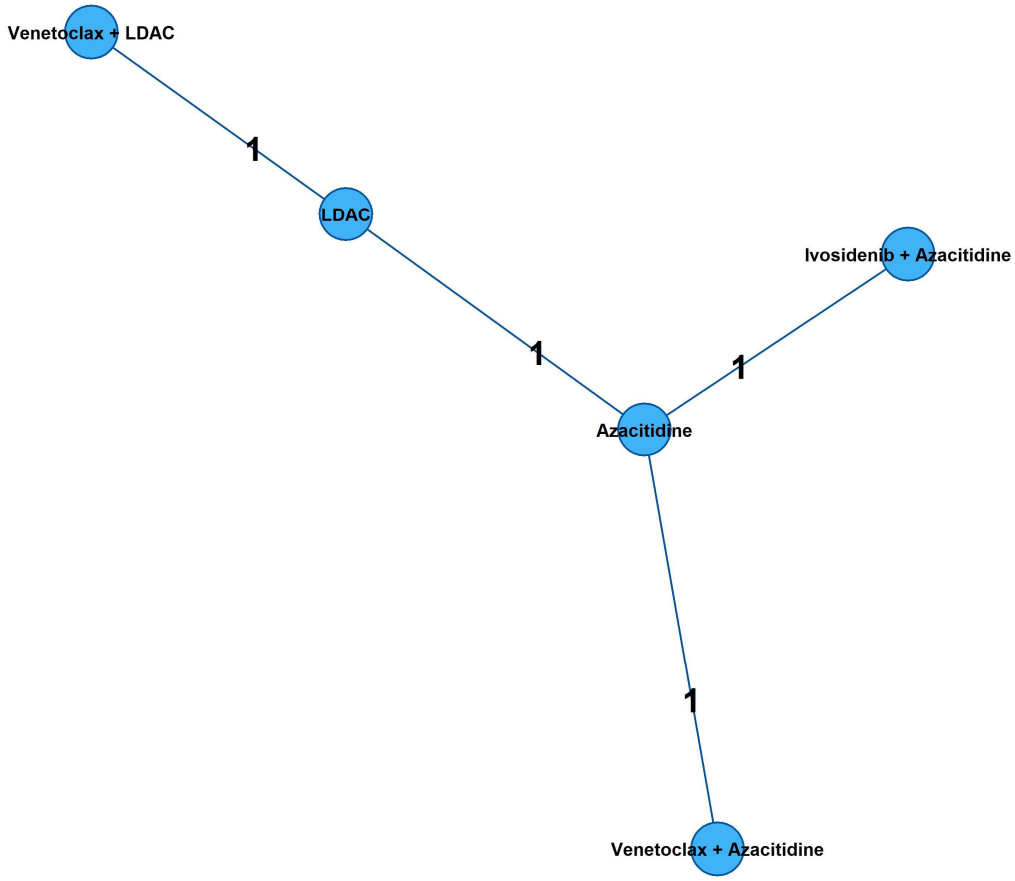


Figure 6 Evidence network for EFS

Table 8 Results matrix for EFS (based on the full evidence network)

Comparison	AZA	Venclyxto + AZA	Tibsovo + AZA
AZA	1	1.59 (1.25; 2.01)	2.57 (1.57; 4.20)
Venclyxto + AZA	0.63 (0.50; 0.80)	1	1.62 (0.94; 2.79)
Tibsovo + AZA	0.39 (0.24; 0.64)	0.62 (0.36; 1.07)	1

HRs for EFS with associated 95% credible intervals (CrI) for Tibsovo+AZA vs Venclyxto+AZA was 0.62 (95% CrI: 0.36; 1.07)

[redacted]

Overall survival

The evidence network consists of six studies besides AGILE reporting estimates for seven interventions. The following studies contributed to the network: VIALE-A with venetoclax plus azacitidine and azacitidine [16], BRIGHT-AML 1003 with glasdegib plus LDAC and LDAC [19], DACO-016 with decitabine and LDAC [20], AZA-AML-001 with azacitidine and LDAC [17] and VIALE-C with venetoclax plus LDAC and LDAC [18].

This NMA for OS including the most recent data from AGILE with DCO 30 June 2022; median follow-up 28.6 months and VIALE-A (DCO 01 December 2021; median follow-up 43.2 months).

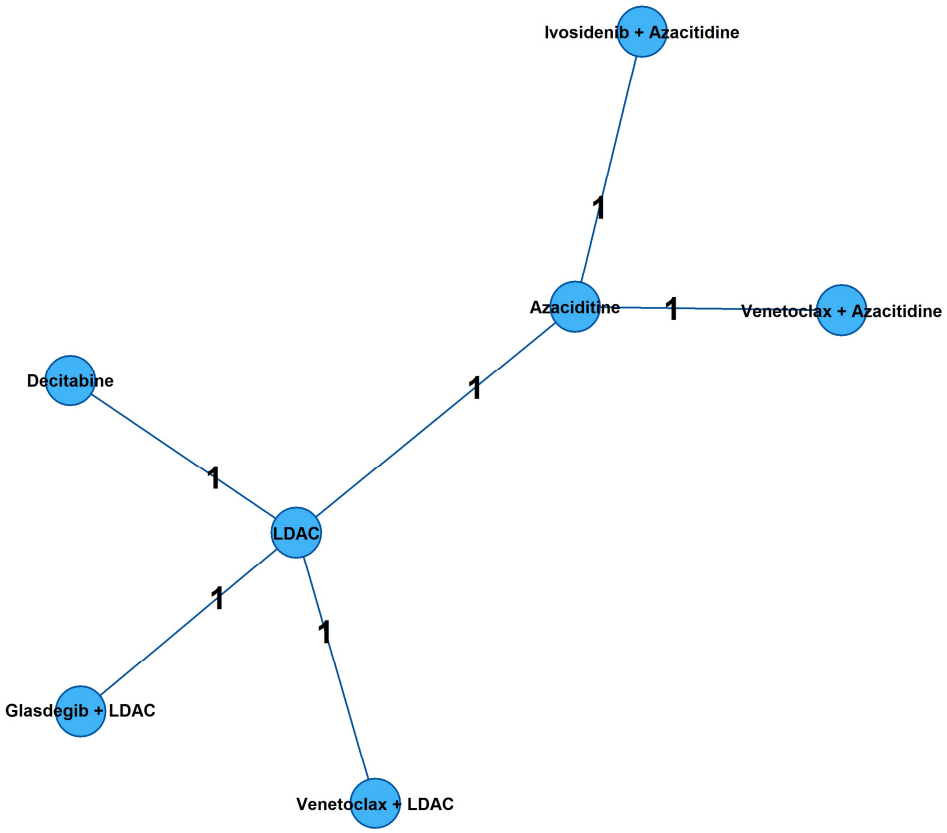


Figure 7 Evidence network for OS

Table 9 Results for OS (based on the full evidence network)

Comparison	AZA	Venclyxto + AZA	Tibsovo + AZA
Tibsovo + AZA	0.43 (0.28, 0.65)	0.74 (0.46, 1.18)	1

HRs for OS with associated 95% credible intervals (CrI) for Tibsovo+AZA vs Venclyxto+AZA was 0.74 (95% CrI: 0.46; 1.18).

[redacted]

3.3.1 JNHB discussion of the indirect treatment comparison

Discussion of effect

The results from the NMA comparing hazard ratios for OS and EFS from the ITT populations in AGILE and VIALE-A are overall highly uncertain and difficult to interpret, as it is questionable whether the underlying assumption of exchangeability across studies (*transivity*) is met. See table 11.

Table 10 Comparison of study design in AGILE and VIALE-A

	AGILE [14]	VIALE-A [16]	Importance and implications for the indirect treatment comparison
Mechanism of action	Ivosidenib is an inhibitor of the isocitrate dehydrogenase 1 (IDH1) enzyme which converts alpha-ketoglutarate (αKG) to 2-hydroxyglutarate (2-HG)	Venetoclax is an inhibitor of BCL-2 protein which is a negative regulator of apoptosis	Both are small molecule inhibitors but with different targets with different physiological functions
Study design	double-blind, randomized, placebo-controlled, phase 3 trial	double-blind, randomized, placebo-controlled, phase 3 trial	Comparable study design
Median follow up time Data cut(s)	30 June 2022; median follow-up: **28.6** months	01 December 2021; median follow-up: **43.2** months	Difference in follow-up time, maturity of data
Stratification	1) geographic region 2) disease status (primary vs. secondary acute myeloid leukemia	1) age 2) cytogenetic risk	Different stratification factors
Number of randomized patients, ITT population	ITT (n=146)	ITT (n=431)	Large variation in sample sizes
Key inclusion criteria	Have an isocitrate dehydrogenase 1 (IDH1) mutation. Have previously untreated AML, defined and ineligible for standard induction chemotherapy (SIC). Have an ECOG PS score of 0 to 2.	Have previously untreated AML, defined and ineligible for standard induction chemotherapy (SIC). Participant must be considered ineligible for induction therapy defined by the following: Participant must have an ECOG Performance status: 0 to 2 for Participants >= 75 years of age or 0 to 3 for Participants >= 18 to 74 years of age.	Only IDH1-mutated patients in AGILE, all mutation-patterns are included in VIALE-A Minor differences in criteria for eligibility for SIC ECOG PS 3 is allowed in VIALE-A
Key exclusion criteria		Favorable risk cytogenetics	Favorable risk cytogenetics is allowed in AGILE and is a validated positive prognostic marker Otherwise comparable

Definition of treatment failure	Treatment failure was defined as failure to achieve complete remission (CR) by Week 24. CR: Bone marrow blasts <5% and no Auer rods; absence of extramedullary disease; Absolute neutrophil count (ANC) ≥1.0 × 10^9 per litre (10^9/L) (1000 per microlitre [1000/µL]); platelet count ≥100 × 10^9/L (100,000/µL); independence of red blood cell transfusions. Participants who had an EFS event (relapse or death) after, 2 or more missing disease assessments were censored at the last adequate disease assessment documenting no relapse before the missing assessments.	Treatment failure, defined as failure to achieve CR, CRi, PR, or MLFS after at least 6 cycles of study treatment	Different definitions of treatment failure
Definition of primary endpoint	Initially overall survival (OS), changed to **event-free survival (EFS)** EFS is defined as the time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurred first. Treatment failure applies on day 1, even if this is determined at week 24.	**Overall survival (OS)** Overall survival is defined as the time from date of randomization to the date of death due to any cause	EFS definitions are different in AGILE and VIALE-A and impede indirect treatment comparison of EFS. In a post-hoc sensitivity analysis of EFS In AGILE, EFS was defined as: the time from randomization until progressive disease, relapse from CR or CRi, treatment failure, or death from any cause. This post-hoc definition of EFS aligns with the definition in VIALE-A
Definition of secondary endpoint	**Overall survival (OS)** Overall survival is defined as the time from date of randomization to the date of death due to any cause.	**Event-free survival (EFS)** Time from randomization to disease progression, treatment failure, confirmed relapse, or death. Treatment failure applies at the time of completing at least six cycles of treatment	OS definition is similar

The study populations in the Tibsovo+AZA-arm in AGILE and the Venclyxto+AZA-arm in VIALE-A are balanced in terms of: age (median 76) and share of patients with secondary AML (25 %).

In AGILE 14 % of patients were in ECOG performance status (PS) 0, 44 % in PS 1 and 36 % in PS 2. In VIALE-A 55 % were in ECOG PS 0-1 and 45 % were in ECOG PS 2-3 (In VIALE-A patients in PS 3 were included for age 18-74 years).

There were no patients in VIALE-A with a favorable cytogenetic risk status compared to 6,8 % in AGILE, and the share of patients with poor cytogenetic risk in VIALE-A was higher than in AGILE (36-39 % vs. 22-27 % respectively). This is deemed significant in a clinical context as

patients with poor cytogenetic risk may respond worse to treatment. There is also heterogeneity in patient demographics and disease characteristics between AGILE and VIALE-A regarding gender, type of AML diagnosis and median bone marrow blast.

A key difference between studies is the IDH1 mutation. In VIALE-A 6% of patients had mutated IDH1 – compared to a 100 % with mutated *IDH1* in the AGILE study population.
VIALE-A was not selected for IDH1-mutated AML patients, and the number of patients with IDH1 mutation was therefore very small (n=26). Although *IDH1* has not been shown to be a prognostic factor in newly diagnosed AML, the impact of *IDH1* mutations on survival after Venclyxto+AZA treatment is still not fully understood – possibly due to the influence of co-mutational patterns of IDH-mutated clones [21] and IDH1 mut cannot be ruled out as an effect modifier.

The somewhat similar outcomes of the PBO+AZA control arms in both trials may be considered reassuring for the use of the ITT population (7.9 months for AGILE and 9.6 months in VIALE-A). However there are notable differences in PBO+AZA arm efficacy estimates across AGILE and the *IDH1/2* and *IDH1* subgroup from VIALE-A as reported in EMA's orphan maintenance report (ref), which raises further concerns about the exchangeability of the underlying patient populations. See table 12. The median OS was 2.2 months for PBO+AZA arm in IDH1 subgroup in VIALE-A vs. 7.9 months for PBO+AZA arm AGILE.
This difference in survival in the PBO+AZA arms in AGILE and VIALE-A for IDH1 mutated patients also give rise to different estimates of relative efficacy for Tibsovo+AZA and Venclyxto+AZA. See table 12. Although a shorter median OS for *IDH1*-mutated patients in VIALE-A treated with Venclyxto+AZA compared to Tibsovo+AZA (10.2 vs. 29.3 months), the point estimate for the hazard ratio for OS is better for Venclyxto+AZA compared to Tibsovo+AZA (HR: 0.28 vs. HR: 0.42). See figure 10 for KM data for IDH1 subgroup in VIALE-A and table 12 for an overview of results.

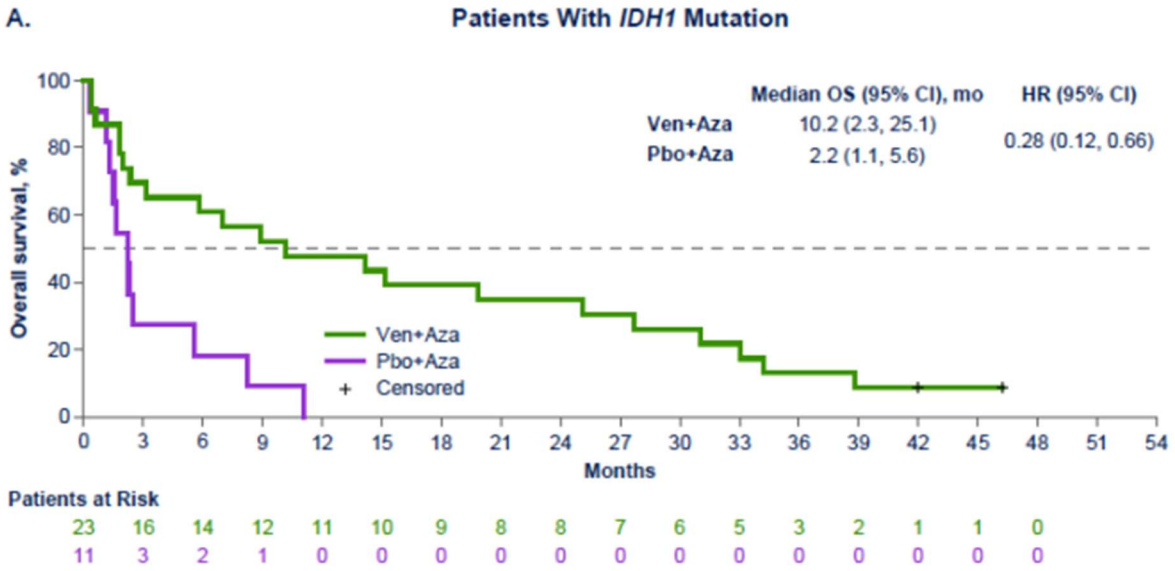


Figure 8 OS Kaplan-Meier from VIALE-A for *IDH1*-mutated patients (Pratz et al. 2022)

Table 11 OS results from AGILE and VIALE-A including IDH1 & IDH2 subpopulations

Study	VIALE-A	VIALE-A	VIALE-A	AGILE

study population	ITT		IDH1/2		IDH1		ITT (IDH1)	
sample size	n=431		n=49		n=26		n=146	
treatment arm	Venclyxto+AZA	PBO+AZA	Venclyxto+AZA	PBO+AZA	Venclyxto+AZA	PBO+AZA	Tibsovo+AZA	PBO+AZA
median OS	14,7 (12,2-18,7)	9,6 (7,4-12,7)	19,9 (12,2-27,7)	6,2 (2,3-12,7)	10,2 (2,3-NR)	2,2 (1,1-5,6)	29,3 (13,2-NR)	7,9 (4,1-11,3)
OS HR	0,58 (0,47-0,72)		0,31 (0,19-0,52		0,28 (0,12-0,52)		0,42 (0,27-0,65)	

Although the point estimates suggest higher relative efficacy of Venclyxto+AZA compared to AZA alone in IDH1-mutated patients, the analyses are not robust enough to support a conclusion. Interpreting the difference in efficacy estimates for the PBO+AZA and Venclyxto+AZA arms is hampered by the very small numbers of enrolled *IDH1* mutated patients in VIALE-A and the lack of baseline characteristics for these patients. The analyses of IDH1 subgroup were post-hoc analyses.

Servier reports that meta-regression to adjust for differences in study level effect modifiers was not carried out due to lack of data.

Finally, considering that the 95% CrIs for OS and EFS both spans 1 in the NMA, no certain conclusion can be drawn for these efficacy comparisons of Tibsovo+AZA vs. Venclyxto+AZA.

Discussion of safety

The differences in study populations confound a naive safety comparison of Tibsovo+AZA vs. Venclyxto+AZA. Nonetheless, based on point estimates of the frequence and severity of AEs, the present data indicate that Tibsovo+AZA have a better safety profile and is especially associated with less haematological toxicity and less infections. In the AGILE trial adding ivosidenib to AZA did not lead to more events of febrile neutropenia (28% vs 34 %), while adding venetoclax to AZA in the VIALE-A trial led to more events of febrile neutropenia (42% vs 19%).

In current clinical practice the vast majority of patients ineligible for standard induction chemotherapy would be offered Venclyxto+AZA. A few selected patients may be ineligible for Venclyxto+AZA therapy due to the high risk of haematological toxicity but could still be eligible for Tibsovo+AZA, as this combination appears to be less toxic than Venclyxto+AZA.

JNHB conclusion:
Tibsovo+AZA may be more effective than Venclyxto+AZA. The relative effect of Tibsovo+AZA vs. Venclyxto+AZA is, however, highly uncertain. The lack of a head-to-head study is a major limitation. Although the point estimate from ITT-analyses favour Tibsovo+AZA, the results are not statistically significant. The indirect treatment comparison is based on the AGILE and VIALE-A studies that differ in design, which question the assumption of exchangeability and may bias the results.
Safety data is sparse, but indicate that Tibsovo+AZA might have a better safety profile than Venclyxto+AZA with fewer and less severe adverse events.

4 Health economic analysis

Tibsovo+AZA may be more effective than Venclyxto+AZA in treating 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. More on this issue can be read in the previous section. Based on this assumption, JNHB has analyzed the modeled increase in effectiveness relative to the costs when these two treatment combinations are compared. However, as relative effectiveness is highly uncertain, an analysis assuming equal efficacy between the two treatments is also a relevant analysis.

Azacitidine monotherapy is included by Servier as a comparator. For patients not tolerating Venclyxto+AZA but tolerating Tibsovo+AZA it is relevant to compare Tibsovo+AZA against AZA. Those patients are probably counted in small numbers. ITT data from AGILE is of no use when analyzing this subgroup who will receive azacitidine monotherapy. No relevant data is at hand. Therefore, JNHB excludes this subgroup from the evaluation.

JNHB conclusion: Due to high uncertainty in the indirect treatment comparison JNHB analyses Tibsovo+AZA compared to Venclyxto+AZA under two basic assumptions. In a cost-effectiveness analysis JNHB assumes an incremental effect for Tibsovo+AZA versus Venclyxto+AZA (OS HR=1,35; EFS HR=1,62, favoring Tibsovo+AZA). In a cost comparison, JNHB assumes an equal treatment effect on both event-free survival (EFS) and overall survival (OS).

4.1 Cost effectiveness analysis

The following chapter is based on the dossier submitted by Servier. All assumptions described are based on the application if not otherwise stated. The conclusion boxes after each section give a short assessment of the choices related to key parameter inputs, methods used, simplifications and scientific judgements made by Servier. The results of the JNHB analyses are presented in section 5.2 and 5.3.

4.1.1 Company model description

To fulfil the purpose of cost-effectiveness analysis Servier has submitted a partitioned survival model consisting of three basic health states; event free survival (EFS), progressed disease/relapse (PD/Relapse), and death. Patients enter the model in the event-free health state. In each cycle, patients can either remain in the event-free state or transition to the progressed disease/Relapse or death health states. The event-free state is stratified into whether the patient has achieved CR/CRi or not. Patients arrive at the PD/Relapse state from EFS either due to progression (for those in No CR/CRi) or relapse (for those in CR/CRi). EFS and OS are modelled by the EFS and OS curve, respectively. The proportion of patients being in the PD/relapsed health state is the difference between the proportion alive based on the OS curve and the proportion being in the EFS state. Lastly, patients who have spent three years in the EFS state with CR/CRi are assumed to be cured from AML.

Being in different states means differences in costs and health related utility.

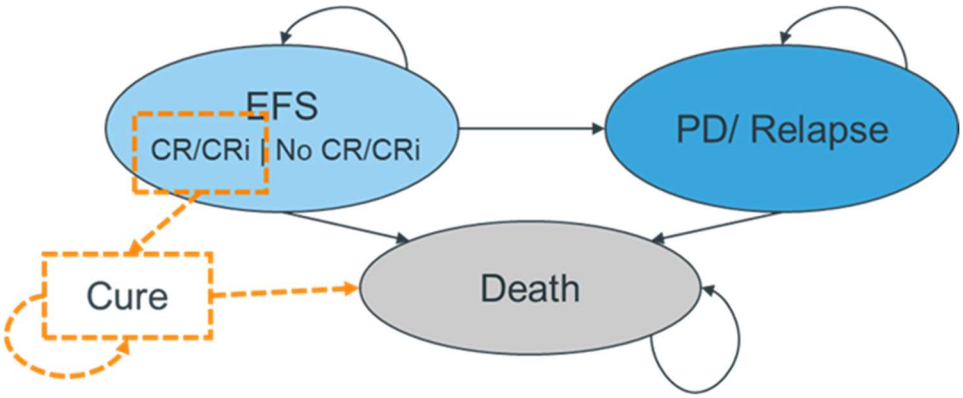


Figure 11 Servier's health economic model structure

Patient characteristics in Servier's model are based on mean values across the treatment arms of the AGILE study. Patients' starting age is assumed to be 74.8 years old, which by JNHB's clinical experts is considered to be valid. The model has a patient lifetime horizon (but maximum 100 years) and uses a cycle length of 28 days. All results are half cycle corrected.

JNHB conclusion: The basic setup of Servier's model with the three states is standard in anti-cancer drug evaluation. Patients with no CR/CRi would rather be relevant to include in a post event state together with progressed disease/relapse since costs and utilities of No CR/Cri are more aligned with PD/Relapse than with CR/Cri. That would, however, probably not have any influence on the outcome of the model and is therefore not changed by JNHB.

Cure in newly diagnosed AML for patients not eligible for induction chemotherapy is by JNHB considered unlikely except for a very few cases. Cure is therefore excluded in the JNHB base-case scenario except for a share of those patients going through hematopoietic stem cell transplantation. This exclusion of cure has a vast impact on the cost effectiveness results. Inclusion of cure is investigated in a sensitivity analysis.

4.1.2 Effectiveness outcomes

Clinical effectiveness

OS and EFS are the modelled clinical effectiveness measures. For the purpose of extrapolating EFS and OS in time beyond the point where clinical data is at hand, Servier explored the standard statistical distributions to determine which provided the best fit based on data from AGILE.

Overall survival

For the Tibsovo+AZA arm the extrapolations are based on Kaplan-Meier estimates from AGILE. Servier selected the log-normal distribution which had the lowest AIC/BIC scores, i.e. best statistical fit between Kaplan-Meier-estimates and extrapolation estimates. Servier claims that these distributions visually provide clinically plausible extrapolations. Up to month 36, Venclyxto+AZA is modelled with a constant hazard ratio in relation to Tibsovo+AZA (1,35; Tibsovo+AZA better effect), which is estimated in the indirect treatment comparison). After month 36, cure is assumed for every survivor in remission up to that point in time. Servier's reason for the cure assumption is the ending horizontal part of the Tibsovo+AZA Kaplan-Meier curve. Death of patients in the progressed/relapsed health state are from month 36 modelled independently.

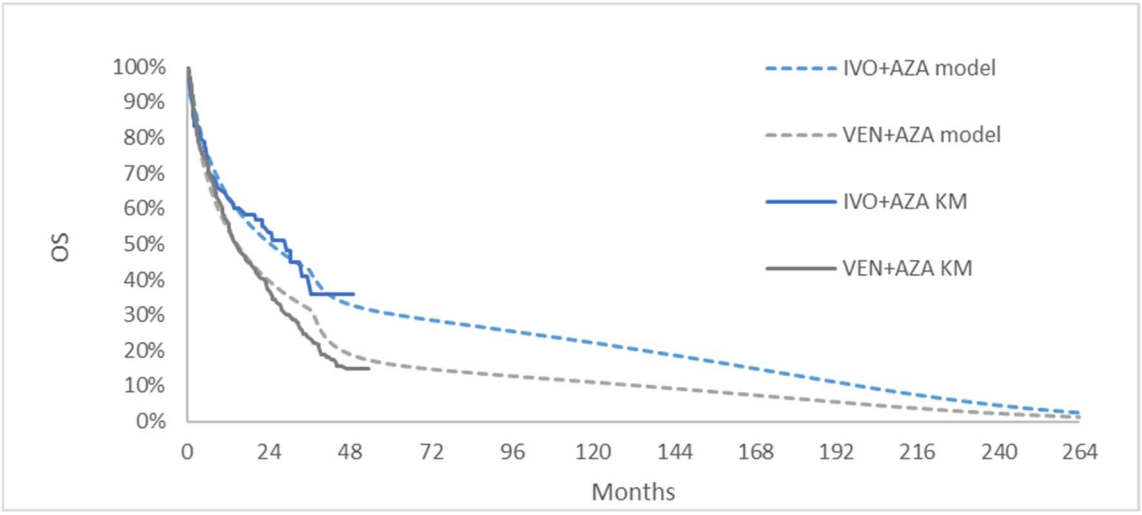


Figure 12 Servier's base case extrapolation of OS using log-normal distribution.

Event-free survival

A post-hoc definition of EFS was defined by Servier as the time from randomization until PD, relapse from CR or CRi, treatment failure (failure to achieve CR, CRi, or morphologic leukaemia-free state after at least 24 weeks of study treatment), or death from any cause.

In modelling EFS Servier basically followed the same principles as in modelling OS in that EFS extrapolations for Tibsovo+AZA, both for the ITT and for patients with CR/CRi and no CR/CRi separately, are based on AGILE results and that Venclyxto+AZA is modelled using a constant hazard ratio in relation to Tibsovo+AZA (1,62; Tibsovo+AZA better effect).

In the first 28-day period 54% (39 out of 72) of the patients in the EFS state of the Tibsovo+AZA arm had achieved CR/CRi. At the seventh 28-day cycle no patients without CR/CRi were left in the EFS state in either of the two arms. This was according to AGILE data. When it comes to patients on Venclyxto+AZA the same ratio as for Tibsovo+AZA was used but with an adjustment due to a hazard ratio for best overall response which stems from the indirect treatment comparison.

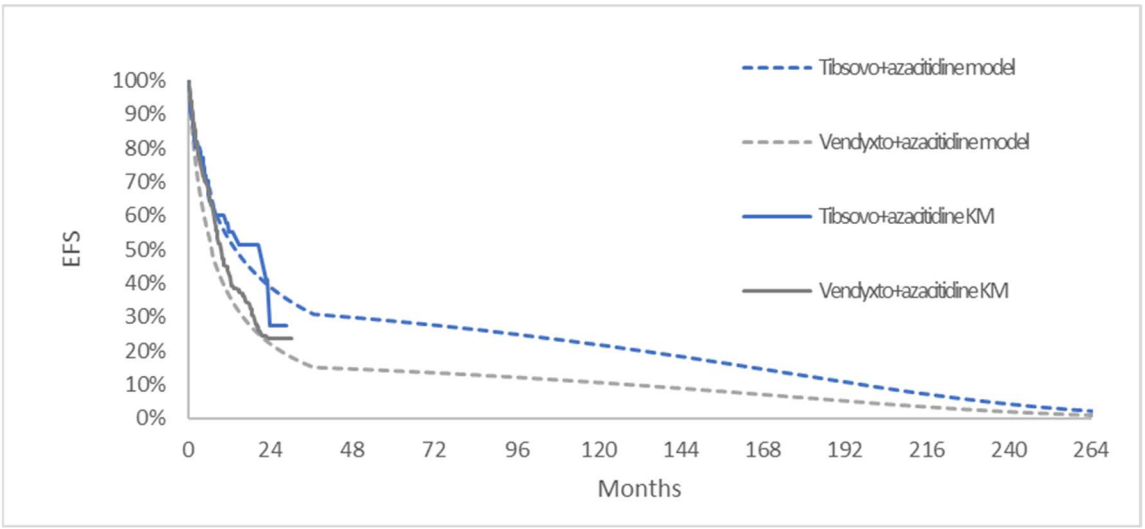


Figure 13 Servier's base case extrapolation of EFS

JNHB discussion of effectiveness outcomes

Since the indirect comparison is not statistically significant regarding either OS or EFS, and the underlying assumptions of the ITC may not be met, results should be interpreted cautiously.

Cure assumption

JNHB doubts the assumption of cure. JNHB bases this on non-existing signs of cure in the clinical data and opinions of nordic experts consulted by JNHB. According to clinical experts a few patients might be considered for stem cell transplantation (SCT) and subsequently assumed to be cured. Indeed, four patients received SCT as subsequent treatment in the Tibsovo+AZA study arm which could lead to cure for a share of these patients. However, this accounts for only 5.6 % of the patients in the Tibsovo+AZA arm and with no long-term follow-up data on these patients the assumption of cure is not substantiated.

Proportional hazard assumption

As the OS KM curve for Venclyxto+AZA is extrapolated through the application of a constant treatment effect relative to Tibsovo+AZA, the HR is assumed constant over time and independent on the follow-up time. Therefore, the validity of the HR relies on a proportional hazard (PH) assumption. From the graphs, it is evident that the slope of the KM curves of the two treatments are not proportionally constant during the entire time span neither when it comes to OS nor EFS. During most of the first year no difference can be seen. However, the difference in hazard between the treatments becomes larger thereafter and consequently the presented HR becomes more uncertain. This creates challenges for this model based on the assumption of proportional hazards.

OS extrapolation

As is evident from figure 14 below, exponential and Weibull are the only distributions that are possible to use when extrapolating OS of Tibsovo+AZA. Gamma distribution overestimates the OS observed in AGILE. The other distributions assume long-term OS, with implicit assumptions of cure, that is not clinically plausible. Moreover, survival with these distributions is catching up with the survival of the general population.

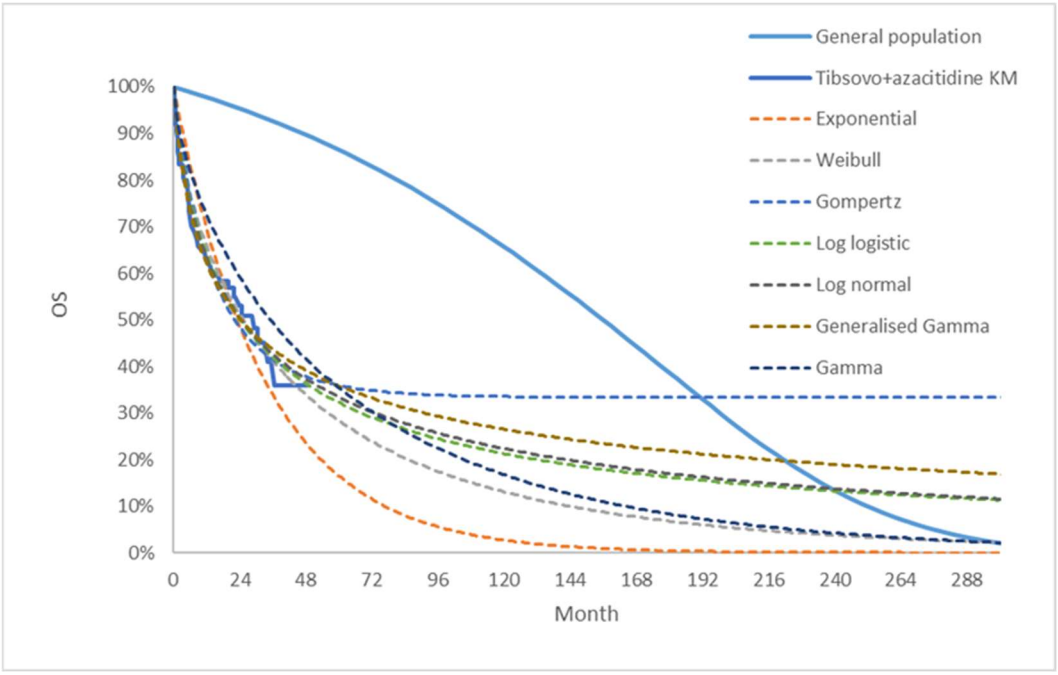


Figure 14 Extrapolated OS curves for Tibsovo+AZA in Servier's model when not assuming cure

Since only exponential or Weibull are of any validity for Tibsovo+AZA, they are the only ones that are explored further below when it comes to Venclyxto+AZA.

Extrapolation of OS with exponential distribution means that the hazard of death is constant. The Weibull distribution generates in this case a decreasing hazard, i.e as time passes probability of death within a certain period decreases. In the long-term a decreasing hazard can on one hand be reasonable since some patients, albeit very few, can benefit from stem cell transplantation. On the other hand, an increasing hazard of death is natural as patients reach very old age. At a late stage, about 14 years from randomization, hazard of death of the Weibull distribution is equal to the hazard of death of the general population (see appendix A). It is difficult to say if the latter speaks in favor of extrapolating with the Weibull distribution.

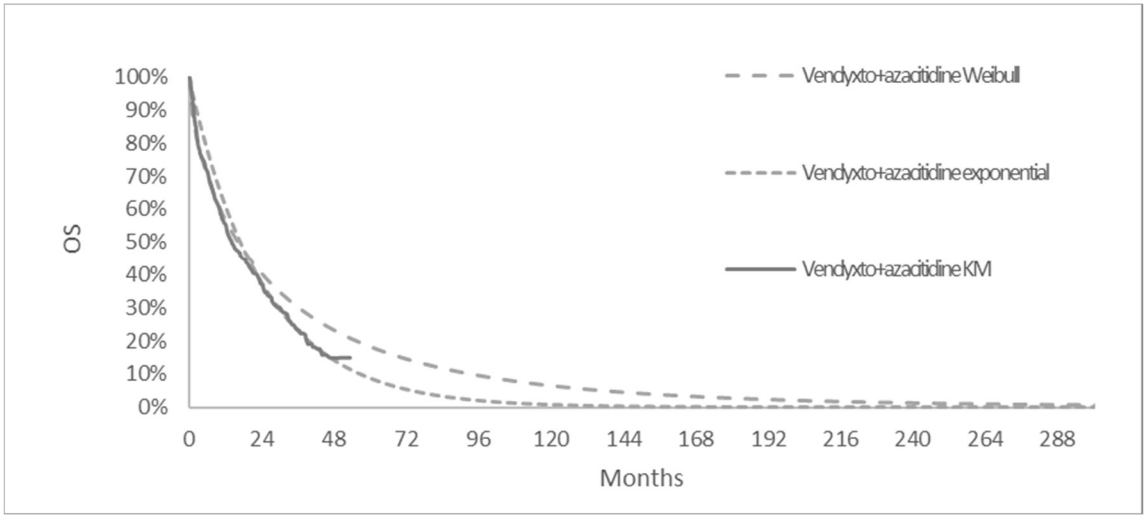


Figure 15 Extrapolated OS curves for Venclyxto+AZA in Servier's model when not assuming cure

Weibull extrapolation seemingly does not have an acceptable fit to the ITT population of the VIALE-A study. Since the modelling technique is proportional hazards the treatment arms have the same distribution. In this situation it matters which study is most aligned with the real clinical setting in the Nordic countries. If a curve is less aligned with the clinical setting in terms of patient characteristics, it does not cause a problem if the extrapolation curve is not perfectly aligned with the KM curve. The most obvious difference is that AGILE solely consists of patients with IDH1-mutation. However, IDH1-mutations are not clearly associated with a positive or negative OS outcome. Therefore, Weibull extrapolation is questionable since it is far above the VIALE-A KM curve without verified reasons such as detrimental patient characteristics in VIALE-A compared to the Nordic clinical setting.

Exponential is, however, the distribution with the poorest fit measured in AIC and BIC in relation to the AGILE population. Since neither exponential nor Weibull distribution seems fully adequate, estimating OS by applying a mean of the two is a way to go forward. It provides an acceptable fit to Kaplan-Meier of both AGILE and VIALE-A (figure 16). It follows the KM-pattern of a slightly decreasing hazard. Moreover, in contrast to either exponential or Weibull extrapolation by themselves it results in quite similar time in subsequent treatment and progressed disease which could be clinically plausible.

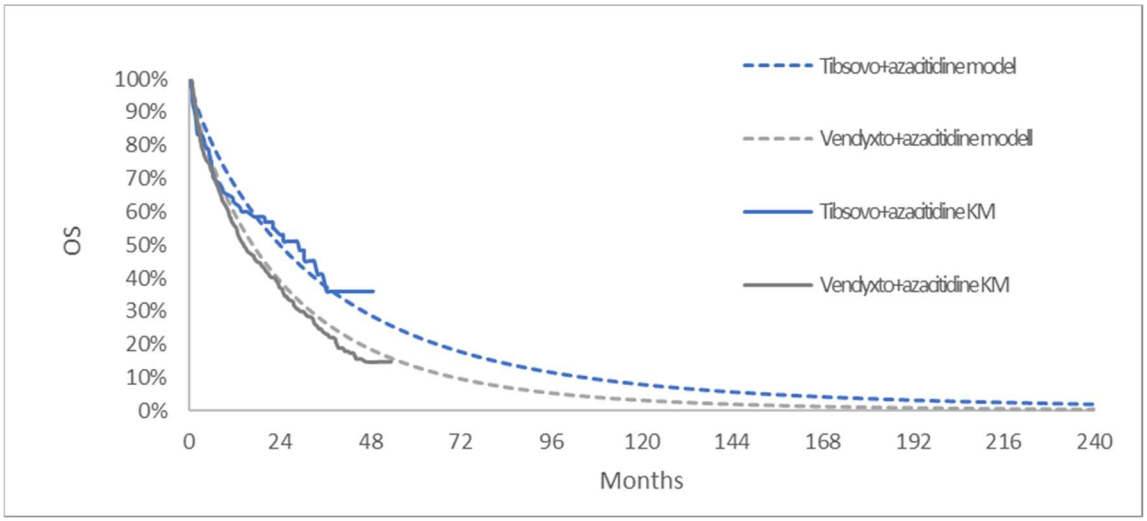


Figure 16 JNHB OS without cure. Weighted extrapolation of exponential and Weibull distribution

EFS extrapolation

When using an exponential or Weibull distribution to extrapolate OS, Weibull or gamma distribution makes most sense in extrapolating EFS. Exponential distribution does not fit the Kaplan Meier curve and the rest of the standard distributions reach the OS curve shortly after the period when there is Kaplan Meier estimates at hand. The Weibull distribution is the only suitable alternative for the time on treatment extrapolation and is therefore also used for EFS in the JNHB base case scenario.

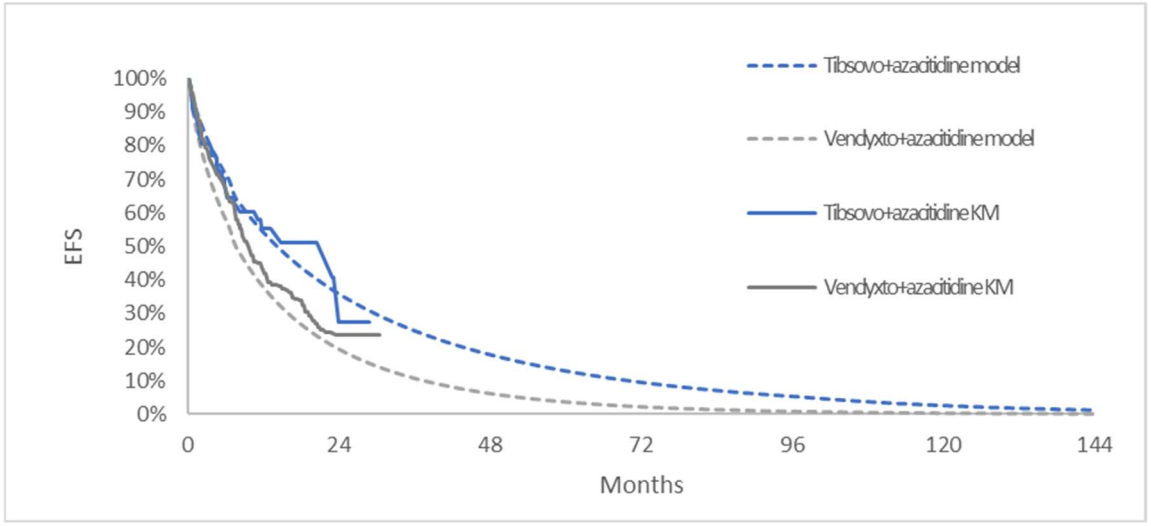


Figure 17 JNHB EFS with Weibull extrapolation

JNHB conclusion: JNHB does not assume that patients are cured after three years in remission. This is the main driver behind JNHB's less optimistic extrapolation of OS and EFS compared to Servier's choice. Exponential and Weibull distributions are by JNHB deemed to be the best possible choices for OS extrapolation. A weighted extrapolation of exponential and Weibull distribution, with equal weights on the two distributions, is chosen by JNHB. EFS is extrapolated with Weibull distribution. Due to very high uncertainty, a number of sensitivity analyses are made regarding relative efficacy.

4.1.3 Health-related quality of life

Data on health-related quality of life is based on EQ-5D-5L responses from AGILE, which are mapped to EQ-5D-3L using the algorithm by Hernandez-Alava and valued using UK tariffs [22]. Pooled utilities for both arms have been used in the model.

The EQ-5D-3L utility values were analysed by Servier using a Mixed Model for Repeated Measures (MMRM). The final model resulting from the variable selection process is presented in table 13 below.

Table 13 EQ-5D index scores (utility values) regarding the final MMRM model with implementation of the UK tariffs (base case)

		β	SE	95% CI	t	p-value
Intercept		0.769	0.03	(0.711, 0.827)	25.974	<0.001
EFS Status	*Progressive disease / Relapse*	-0.035	0.024	(-0.082, 0.012)	-1.477	0.14
	EFS	0				
Best response CR/CRi	*No*	-0.140	0.038	(-0.214, -0.065)	-3.69	<0.001
	Yes	0				
Treatment status	*Treatment discontinuation*	-0.073	0.029	(-0.131, -0.015)	-2.776	0.013
	Still on treatment	0				

Three states were analysed in AGILE: EFS with CR/CRi, EFS without CR/CRi and PD/Relapse. On a scale between 0 and 1 the results were: 0.733, 0.593 and 0.606, respectively. In all three cases the results were calculated as a mean of the utility of still being on treatment or having discontinued treatment, e.g. EFS with CR/CRi=(0.769+(0.769-0.073))/2=0.733. This mean calculation is due to the cure assumption with a treatment stop at a fixed date meaning that a large part of time in EFS is spent without treatment. Servier assumes that cured patients have the same health related quality of life as those in the state EFS with CR/CRi state.
Same data are assumed to be valid for the Venclyxto+AZA arm. Disutilities for adverse events are included. These have a marginal impact on the cost-effectiveness results.

JNHB discussion of HRQoL

Without assuming cure there is no case for calculating health-related quality of life data of the EFS states as means of time spent on treatment and off treatment. Treatment until progression is more congruent with modelled health-related quality of life data regarding time spent on treatment for the EFS states and time spent off treatment for the PD/relapse state. The utilities therefore end up at 0,769 in the EFS state with CR/CRi, 0,629 in the EFS state with no CR/CRi[1], and 0,570 in the PD/relapse state[2].

JNHB conclusion: It is a strength that health-related quality of life is measured in AGILE and is thus estimated from a relevant patient population. JNHB alters the modelled estimates to be congruent with not assuming cure resulting in 0.769 in EFS with CR/CRi, 0.629 in EFS without CR/CRi, and 0,570 in PD/relapse. Sensitivity analyses around the utility values are included.

[1] 0,629=0,769-0,14. See table 13.
[2] 0,570=0,769-0,0350-0,140*(1-0,349)-0,073. See table 13. (1-0,349) is the percentage who never responded.

4.1.4 Costs and resource utilisation

Dosage and medicine costs

Dosage in the model is overall[3] according to recommended start doses and relative dose intensity, table 12. The relative dose intensity of AGILE was, however, also assumed to be valid for patients treated with Venclyxto+AZA, although the relative dose intensity of Venclyxto+AZA in VIALE-A was much lower[4]. Commercial arrangements are not considered in table 14. Wastage is considered for the tablets. Vial sharing is allowed.

Table 14 Drug cost in Servier´s health economic model

	Cost per package	Dose per administration	Relative dose intensity	Cost per 28 day cycle
Tibsovo+azacitidine				**147 304 SEK**
Tibsovo	173 459 SEK per 60 tablets of 250 mg	500 mg once daily	89,2%	144 427 SEK
Azacitidine	358 SEK per 100 mg	134 mg (75 mg/m^2 once daily first seven days of 28-day cycle)	85,9%	2 878 SEK
Venclyxto+azacitidine				**47 468 SEK**
Venclyxto	49 983,18 SEK per 112 tablets of 100 mg	400 mg once daily	89,2%	44 590 SEK
Azacitidine	358 SEK per 100 mg	134 mg (75 mg/m^2 once daily first seven days of 28-day cycle)	85,9%	2 878 SEK

A central assumption of Servier is that treatment in both arms stops after three years with the logic that patients at that time are cured. Up to year three time on treatment (ToT) is extrapolated from AGILE data for Tibsovo+AZA (figure 18) with log-normal distribution. Venclyxto+AZA ToT is modelled according to EFS adjusted for published percentage discontinuation.

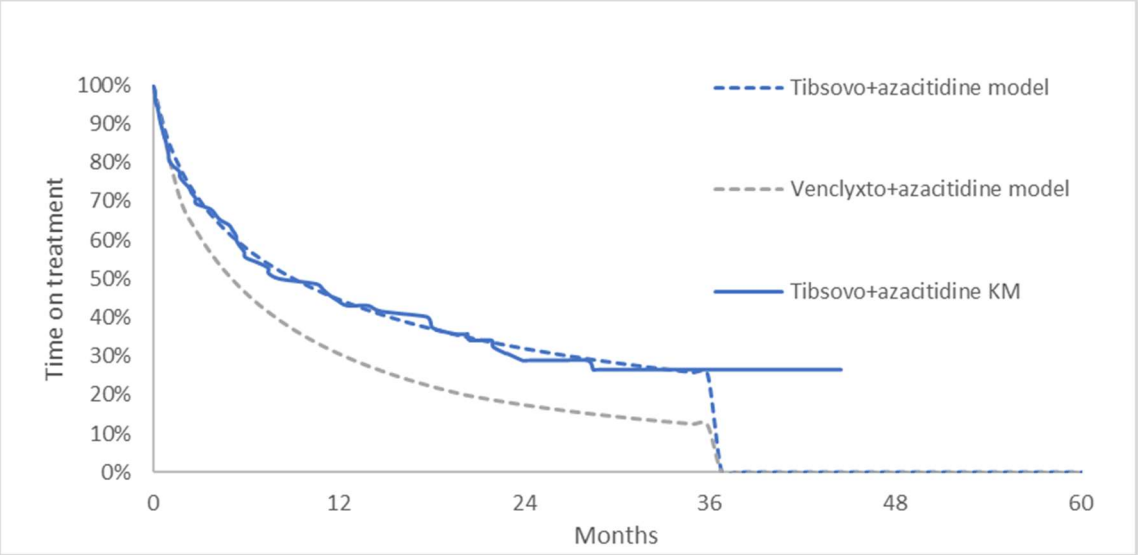


Figure 18 Servier´s modelled time on treatment

[3] First two administrations of venetoclax are 100 mg and 200 mg respectively.
[4] Relative dose intensity in VIALE-A was 60% and 71% for venetoclax and azacitidine,respectively.

JNHB discussion
It is problematic to assume that the relative dose intensity is equal between the two treatments. AGILE and VIALE-A had different relative dose intensity, with Tibsovo+AZA as in table 14 and venetoclax (60%) + azacitidine (71%) considerably lower. In contrast, the placebo arms in the studies showed more consistent relative dose intensities, at 89% in AGILE and 93% in VIALE-A.

According to JNHB's consulted clinical experts, long-term treatment could be gradually reduced over time. They give, however, no support for a stopping rule at month 36. Neither do the dosage instructions of the EPAR.

When not assuming a stopping rule after 36 months of treatment, the Weibull distribution seems to be the most suitable option for extrapolating time on treatment. Exponential distribution has a poor fit and the other distributions assume eventually that all remaining patients continue treatment until death.

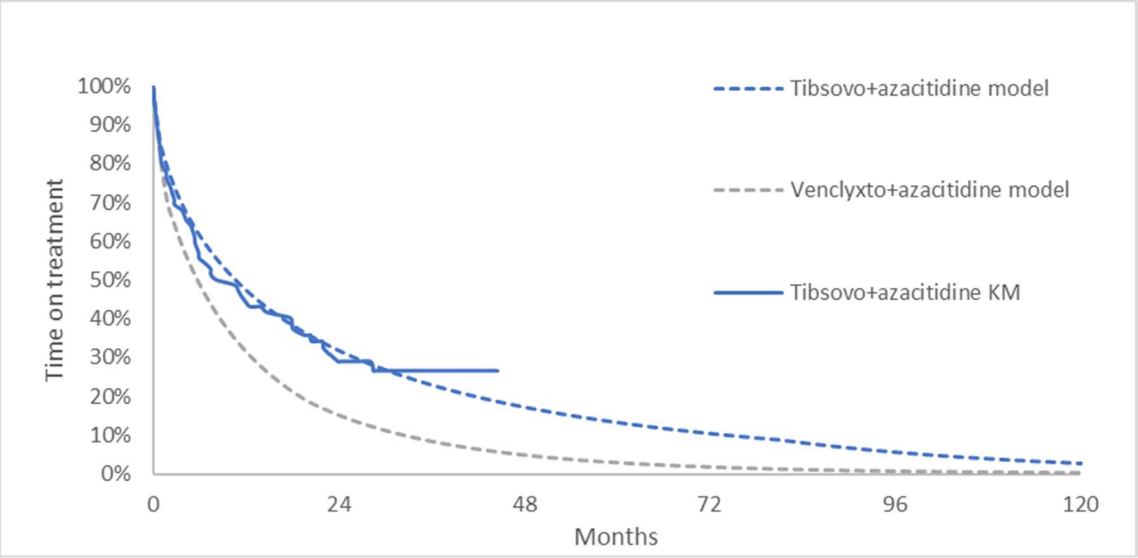


Figure 19 JNHB´s extrapolated time on treatment

JNHB conclusion: JNHB prefers to use the relative dose intensity from the clinical studies for coherence in the model between clinical effect and relative dose intensity. Accordingly, JNHB adjust relative dose intensity to 60 % for Venclyxto and 71% for AZA.

JNHB does not find it reasonable to assume that patients who have not experienced an event or unacceptable toxicity would discontinue treatment at month 36. Time on treatment is extrapolated according to figure 19. JNHB includes sensitivity analyses exploring stopping of treatment at different years.

Costs for health care and use of resources and other directs costs
Drug administration costs were sourced from "Regionala priser och ersättningar för södra sjukvårdsregionen 2023" [23] and amounted per administration to 6 448 SEK for intravenous injection and 3 285 SEK for subcutaneous injections. These costs are applied at each administration event in each treatment cycle and are used for both first- and second-line therapies. Servier assumes that half of the administrations of azacitidine are intravenous and half are subcutaneous. Azacitidine is assumed to be administered the first seven days of each admin-

istration cycle, which is in accordance with the European posology. Added to this are administration costs that are due to patients being hospitalized during the first 28-day period. The assumption is that patients during the first 28-day period are hospitalized 11,8 days (Tibsovo+azacitidine) or 23 days (Venclyxto+azacitidine). A day of hospitalization is assumed to cost 10 343 SEK and is sourced from "Regionala priser och ersättningar för södra sjukvårdsregionen 2023" [23].

Only a small percentage are assumed to receive subsequent treatment. Data that are used by Servier in the health economic analysis stem from AGILE according to the table below. Assumptions regarding subsequent treatment are the same for all patients, regardless of whether they have previously been treated with Tibsovo+AZA or Venclyxto+AZA.

Table 15 Servier´s modelled subsequent treatments

	Azacitidine	Venclyxto	Cytarabin	Allogenic stem cell transplant
Tibsovo+azacitidine	8,3%	6,9%	5,6%	6,8%
Venclyxto+azacitidine	8,3%	6,9%	5,6%	6,8%

The model also includes monthly health state costs accounting for the cost of monitoring in both EFS and PD/Relapse according to table 16. Servier uses the same unit costs for the treatment arms and in the same amounts according to the table below.

Table 16 Servier´s modelled monthly health use in different health states

	EFS, CR/CRi	**EFS, no CR/CRi**	**PD/Relapse**
Haematologist visits	1,00	2,63	2,79
Nurse visits	0,00	2,77	3,05
General practitioner visits	0,00	1,00	1,67
ED visits	0,00	0,27	0,58
Hospitalisation days	0,00	1,03	2,13
Imaging procedures	0,00	0,71	0,57
Bone marrow biopsy	0,00	1,07	0,32
Lumbar puncture	0,00	0,18	0,16
Red blood cell transfusion	0,00	1,73	2,41
Platelet transfusion	0,00	1,50	1,82
Plasma transfusion	0,00	0,56	0,90
ICU stay	0,00	0,00	0,22

JNHB discussion

In Denmark and Sweden it is clinical practice to administer azacitidine subcutaneously for five days during the 28-day treatment cycle. In Norway seven days, as in the posology, and subcutaneously is the most common clinical practice. JNHB uses seven days per cycle subcutaneously in the base-case and five days in sensitivity analysis.

Hospitalization costs associated with the first cycle administration are likely overestimated. Why patients using Venclyxto+AZA would need about double the number of days in hospital is not motivated. Furthermore, some amount of double counting can be present when both including cost for patients being hospitalized as a part of the administration and as a state cost. JNHB concludes, based on opinions from its experts, that the number of days of hospitalization due to treatment is significantly lower than the estimates provided by Servier.

JNHB clinical experts suggest resource use to be somewhat higher in the state of EFS no CR/CRi each month (table 17).

Table 17 JNHB clinical experts´ preferred monthly health use in EFS no CR/CRi

	EFS, no CR/CRi
Haematologist visits	3,50
Nurse visits	3,50
General practitioner visits	0,50
ED visits	0,27
Hospitalisation days	2,00
Imaging procedures	0,71
Bone marrow biopsy	1,07
Lumbar puncture	0,00
Red blood cell transfusion	2,00
Platelet transfusion	2,00
Plasma transfusion	0,00
ICU stay	0,00

JNHB conclusion: In this analysis, health care resource use has a limited effect on the cost-effectiveness results. JNHB do, however, make some adjustments from Servier's base-case scenario. JNHB has adjusted modelled healthcare use according to JNHB clinical experts preferred assumptions. In JNHB base-case hospitalization costs associated with the first cycle is adjusted to 5 days for patients treated with Tibsovo and 7 days for patients treated with Venclyxto.

All costs used in the model from "Regionala priser och ersättningar för södra sjukvårdsregionen 2023" are updated to costs for 2024. Almost all costs have increased, especially administration of subcutaneous injections, which almost have doubled in unit cost to 7 044 SEK. Lastly, in clinical practice azacitidine is administered subcutaneously. The model is altered to take account of that.

5 Results of the cost-effectiveness analysis

5.1 Servier's base case

5.1.1 Key assumptions in Servier base case scenario

- OS and EFS extrapolations for Tibsovo+azacitidine (log-normal distribution) are based on ITT patients in AGILE.
- Proportion of patients who achieve CR/CRi for Tibsovo+azacitidine are from AGILE.
- Hazard ratios for EFS and OS of Venclyxto+azacitidine compared to Tibsovo+azacitidine are derived from the indirect treatment comparison.
- Odds ratio for the proportion of patients who achieve CR/CRi for Venclyxto+azacitidnine compared to Tibsovo+azacitidine are derived from the indirect treatment comparison.
- Patients cured if CR/CRi three years from randomization or after stem cell transplantation. Cure entails no progression, mortality as the general population and end of treatment.
- 3-Level Euroqol Five Dimensions Questionnaire (EQ-5D-3L) based health state utilities for EFS patients with CR/CRi (0.733), EFS patients with no CR/CRi (0.593), and

PD/Relapse patients (0.606). These inputs were derived from a utility analysis using AGILE data.

- Relative dose intensity of 89% for both Tibsovo and Venclyxto.

5.1.2 Results in Servier base case scenario

Table 18 Company base case results for Tibsovo, SEK

	Tibsovo+ azacitidine	Venclyxto+ azacitidine	Difference vs Venclyxto+ azacitidine
Drug acquisition costs	2,491,202	567,927	1,923,275
Administration costs	698,161	645,466	52,696
Monitoring costs	642,666	753,008	-110,342
Subsequent treatment costs	96,762	155,515	-58,752
Other direct costs	188,404	191,979	-3 575
Total costs	4,117,196	2,313,894	1, 803,302
Life years (undiscounted)	5.30	3.35	1.95
Quality-adjusted life years (QALYs)	3.06	1.95	1.11
Cost per QALY gained			**1,626,349**

5.2 JNHB base case modelling better efficacy for Tibsovo-azacitidine versus Venclyxto+azacitidine based on indirect comparison

5.2.1 Changes in assumptions in the JNHB base case scenario

- No cure for patients in remission three years from randomization.
- Extrapolation of OS data according to weighted exponential and Weibull distribution.
- Extrapolation of EFS and time on treatment data according to Weibull distribution.
- Health-related quality of life estimates are 0.769 in EFS with CR/CRi, 0.629 in EFS without CR/CRi, and 0,57 in PD/relapse.
- No treatment stopping rule after 3 years.
- No vial sharing.
- Relative dose intensity of 60 % for venetoclax.
- Hospitalization first month of treatment five days for patients on Tibsovo and seven days for patients on Venclyxto.
- Updated cost of subcutaneous administration and monitoring.
- Updated monitoring resource use.

5.2.2 Results in JNHB base-case scenario

Table 19 JNHB base case results for Tibsovo, SEK

	Tibsovo+ azacitidine	Venclyxto+ azacitidine	Difference vs Venclyxto+ azacitidine
Drug acquisition costs	3,900,933	452,987	3,447,946
Subcutaneous administration costs	1,344,996	738,204	606,793
Monitoring	1,419,792	1,389,170	30,621
Subsequent treatment costs	205,464	213,601	-8,137
Other health care costs	244,657	248,030	-3,373
Total costs	7,115,842	3,041,993	4,073,850
Life years (undiscounted)	3.57	2.45	1.12
Quality-adjusted life years (QALYs)	2.16	1.47	0.69
Cost per QALY gained			**5,881,491**

The monthly drug cost of Tibsovo is much higher than Venclyxto's. The longer modelled treatment of Tibsovo increases the incremental drug cost of Tibsovo versus Venclyxto. Since treatment with azacitidine takes place seven days per 28-day cycle until progression or toxicity, and treatment with Tibsovo+azacitidine is longer than Venclyxto+azacitidine treatment, administration is also an important cost driver.

The modelled incremental QALYs of 0.69 in Tibsovo's favor in JNHB base case is by no means a conservative estimate considering the high uncertainty in the data at hand. Cost per QALY gained is, however, estimated to be very large because of the high incremental cost.

5.2.3 JNHB sensitivity analyses

Table 20 JNHB sensitivity analyses based on better efficacy for Tibsovo-azacitidine versus Venclyxto+azacitidine according to the indirect comparison, SEK

Variable (JNHB base case within parenthesis)	Sensitivity analyses	+/- Δ Costs	+/- Δ Lys (undiscounted)	+/- Δ QALYs	Cost/ QALY
JNHB base case		4,073,850	1.12	0.69	5,881,491
OS distribution (mean exponential/Weibull)	Exponential (appendix figure B1)	3,664,659	0.72	0.54	6,848,176
	Weibull (appendix figure B2)	4,345,586	1.43	0.81	5,380,973
EFS distribution (Weibull)	Gamma (appendix figure B3)	3,834,170	1.12	0.66	5,769,704
OS relative effect HR (0.74)	0,47 lower CI (appendix figure B4)	5,279,233	2.21	1.23	4,296,749
	1,18 upper CI (appendix figure B5)	2,143,158	-0.79	-0.15	Tibsovo worse effect and higher cost

EFS relative effect HR (0.62)	0.36 lower CI (appendix figure B6)	3,881,308	1.12	0.80	4,822,655
	1.06 upper CI (appendix figure B7)	4,346,797	1.12	0.50	8,669,243
Utility in EFS, CR/CRi health state (0.769)	0.711 lower CI	4,073,850	1.12	0.62	6,376,570
	0.827 upper CI	4,073,850	1.12	0.75	5,457,750
Utility in EFS, no CR/CRi (0.629)	0.679 (+0.05)	4,073,850	1.12	0.69	5,885,473
	0.579 (-0.05)	4,073,850	1.12	0.69	5,877,515
Utility in PD/relapse (0.570)	0.620 (+0.05)	4,073,850	1.12	0.69	5,906,018
	0.520 (-0.05)	4,073,850	1.12	0.70	5,857,263
Treatment stopping rule (no; treatment stop according to extrapolated TTD curve)	3 years	2,446,552	1.12	0.69	3,532,146
	4 years	2,850,587	1.12	0.69	4,115,444
	5 years	3,159,881	1.12	0.69	4,561,978
Cure for every patient in remission after three years (no)	Yes (appendix figure B8-B9)	2,265,813	1.73	1.05	2,159,222
Number of administrations of azacitidine per cycle (7)	5	3,876,080	1.12	0.69	5,595,938

5.3 JNHB analysis assuming no difference in effect between Tibsovo+azacitidine and Venclyxto+azacitidine

This scenario compares the monthly cost of the two treatment alternatives when assuming no difference ineffect. As a consequence, time on treatment is also assumed to be the same. The drugs differ in cost per package, dosing, and relative dose intensity. The relative dose intensity stems from their pivotal studies, AGILE and VIALE-A.

Table 21 JNHB drug cost comparison between Tibsovo+azacitidine and Venclyxto+azacitidine

	Cost per package	Dose per administration	Relative dose intensity	Cost per 28 day cycle
Tibsovo+azacitidine				**147 304 SEK**
Tibsovo	173 459 SEK per 60 tablets of 250 mg	500 mg once daily	89,2%	144 427 SEK
Azacitidine	358 SEK per 100 mg	134 mg (75 mg/m^2 once daily first seven days of 28-day cycle)	85,9%	2 878 SEK
Venclyxto+azacitidine				**32 370 SEK**
Venclyxto	49 983,18 SEK per 112 tablets of 100 mg	400 mg once daily	60%	29 990 SEK
Azacitidine	358 SEK per 100 mg	134 mg (75 mg/m^2 once daily first seven days of 28-day cycle)	71,2%	2 380 SEK

Costs and health effects related to safety are minor compared to the drug costs shown in table 21. In both JNHB's (5.2.2) and the Servier's (5.1.2) base-cases QALY increase due to adverse events were only 0.006 in an entire lifetime horizon when using Tibsovo instead of Venclyxto. Modelled costs due to adverse events management decreased with less than 4 000 SEK in the entire lifetime horizon. Compared to the difference in drug cost these effects are neglectable.

Other costs are considered equal between the treatment arms due to no difference in effect.

JNHB conclusion: Tibsovo is by far more expensive than Venclyxto.

6 Patient numbers

According to Servier the estimated numbers of eligible patients are according to the table below.

Table 22 Eligible patients for treatment with Tibsovo+azacitidine

Denmark	Finland	Norway	Sweden
13	9	9	18

7 Referencer

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Appendix A Hazard of the different OS extrapolation distributions

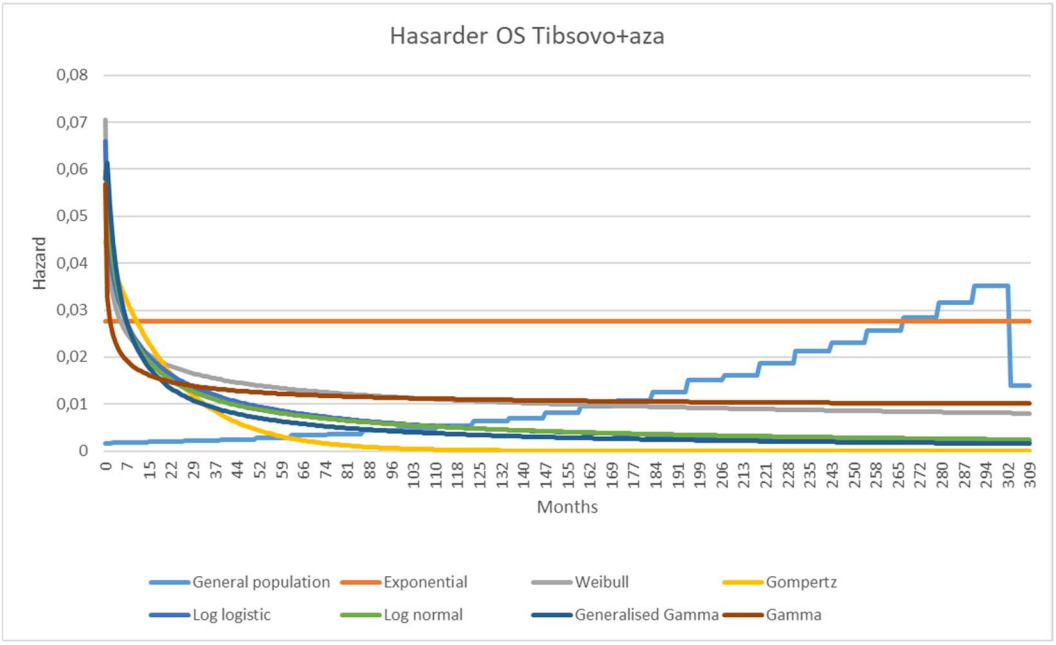

Figure A1 Hazard in different OS curves in Servier's model

Appendix B EFS and OS in sensitivity analyses

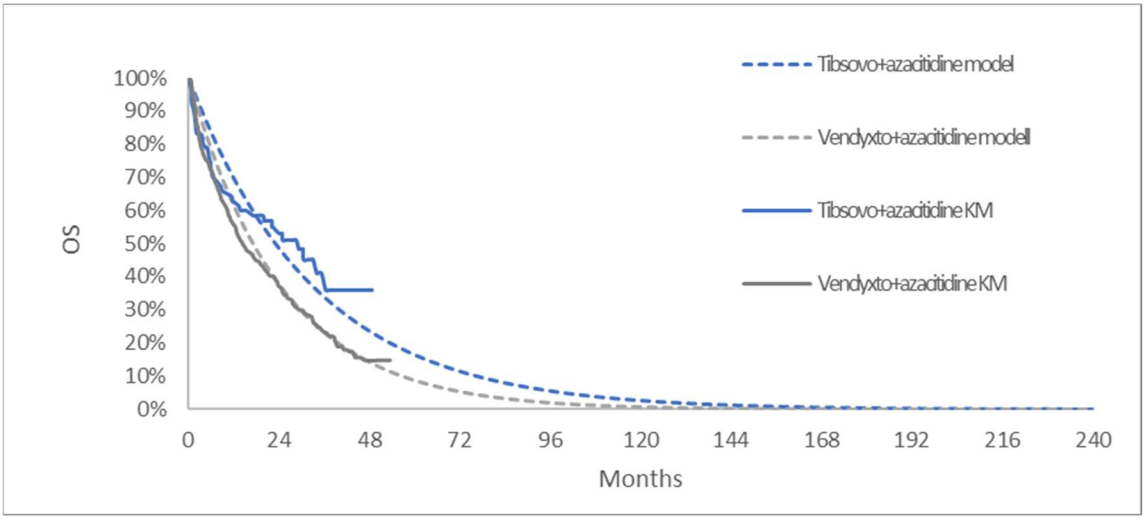

Figure B1 JNHB sensitivity analysis OS exponential distribution.

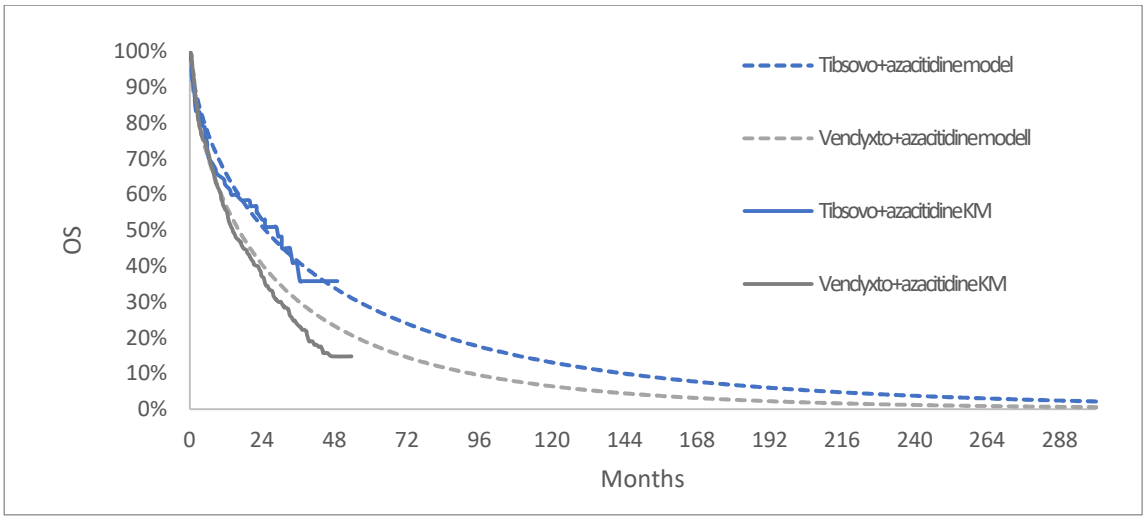

Figure B2 JNHB sensitivity analysis OS Weibull distribution.

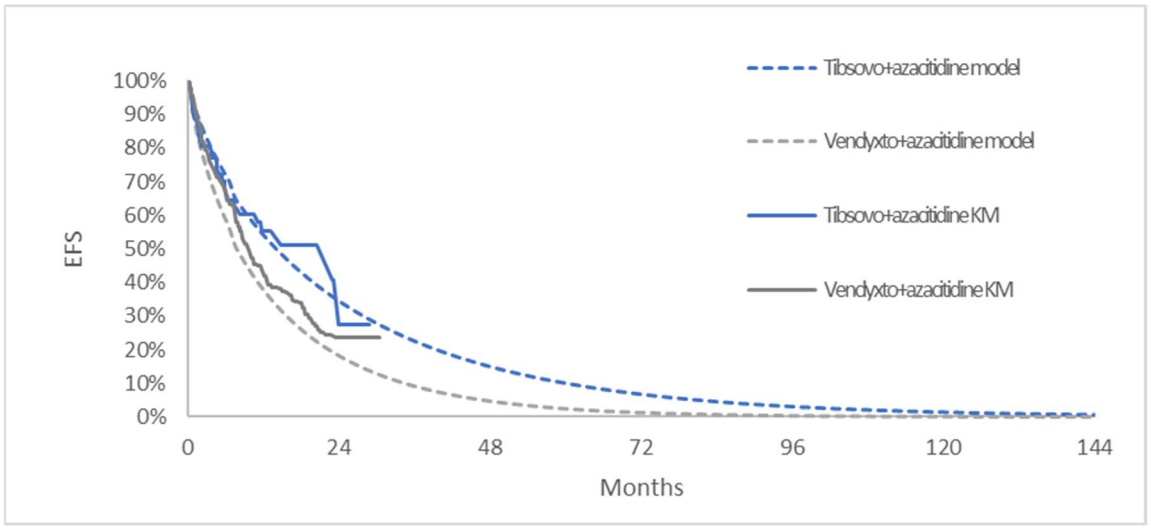

Figure B3 JNHB sensitivity analysis EFS Gamma distribution.

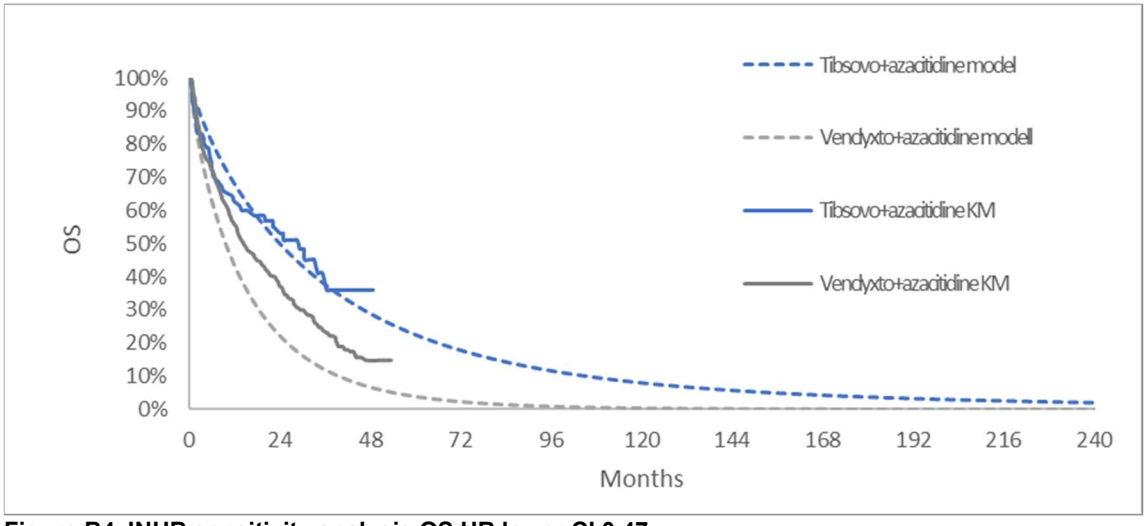

Figure B4 JNHB sensitivity analysis OS HR lower CI 0,47.

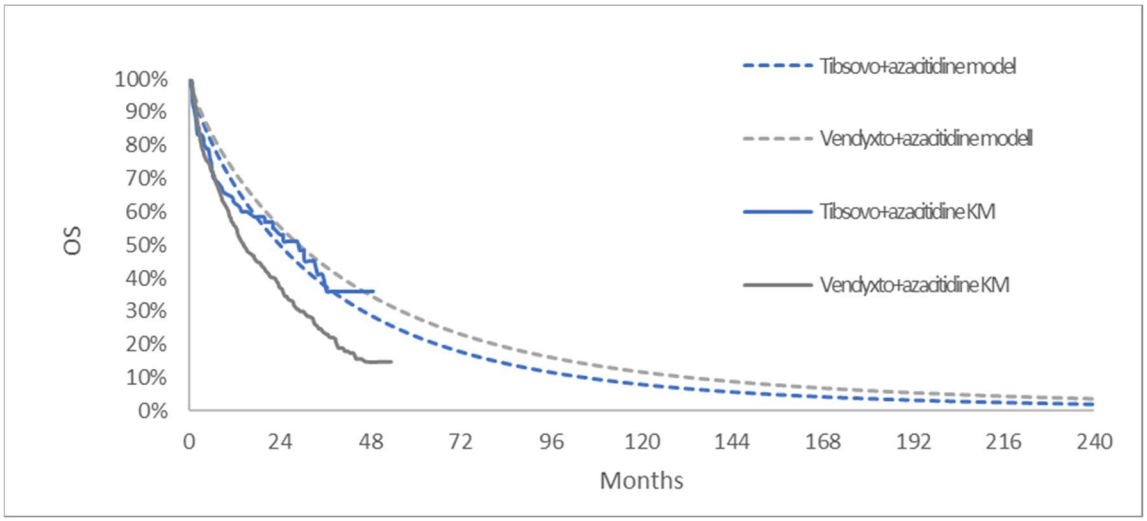

Figure B5 JNHB sensitivity analysis OS HR upper CI 1,18.

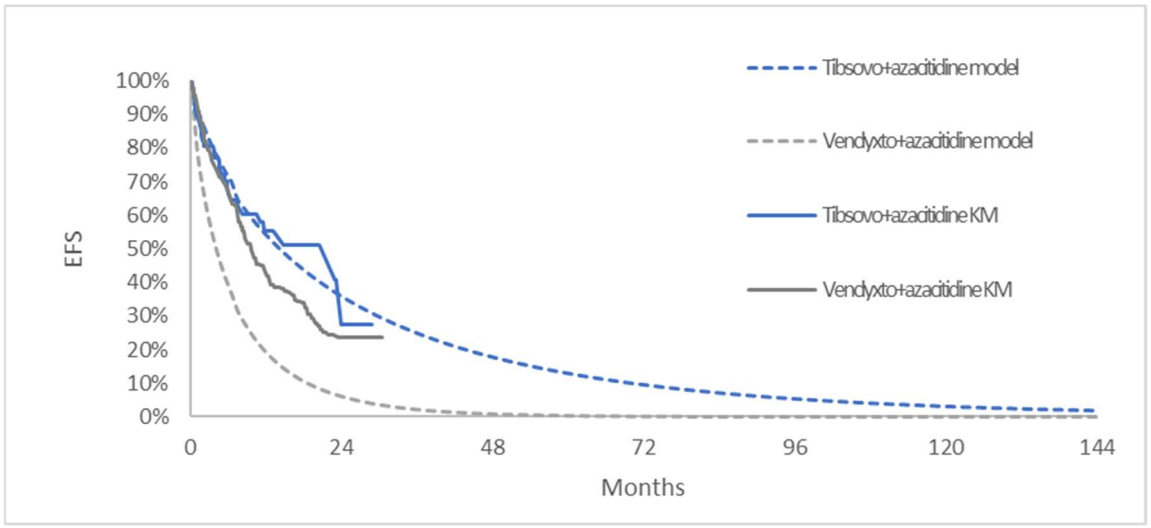

Figure B6 JNHB sensitivity analysis OS HR upper CI 0,26.

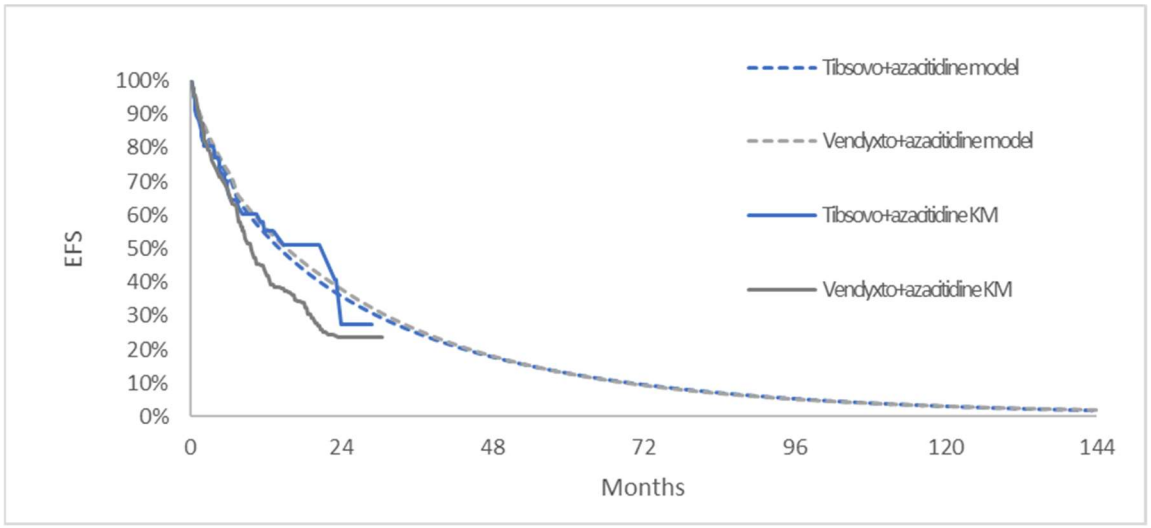

Figure B7 JNHB sensitivity analysis EFS HR upper CI 1,06.

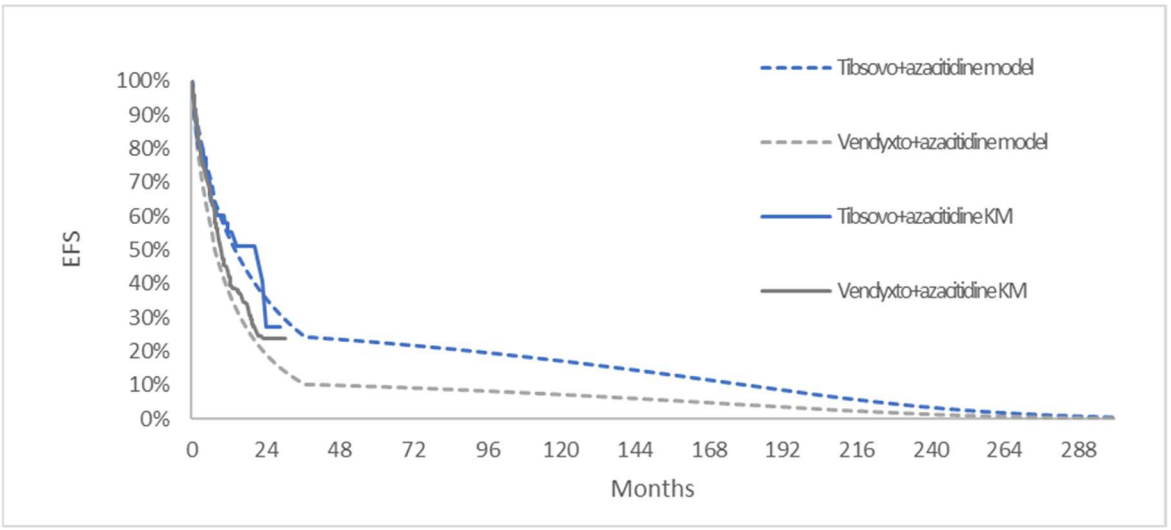

Figure B8 JNHB sensitivity analysis assuming cure after 3 years remission, EFS.

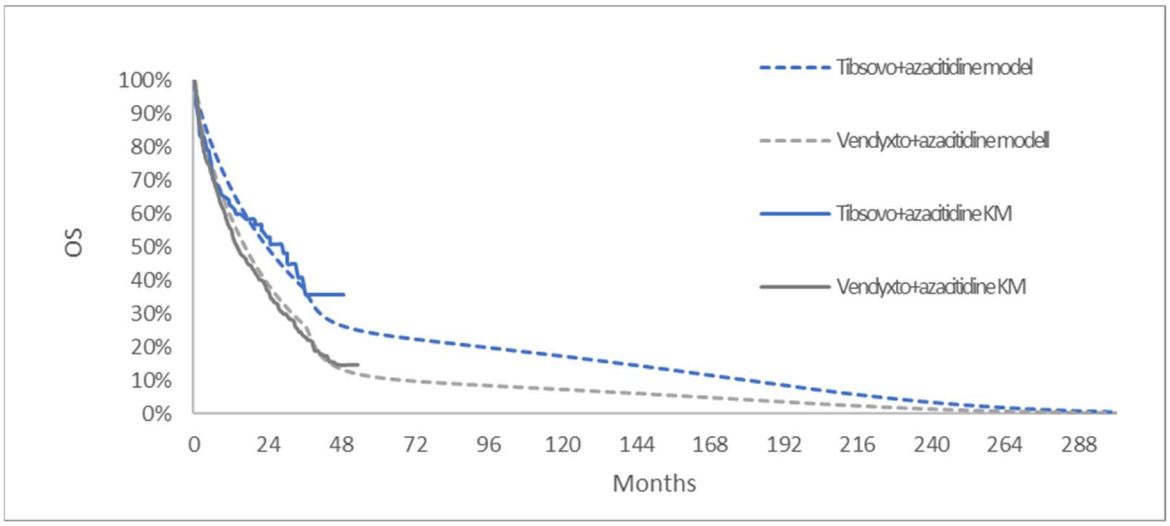

Figure B9 JNHB sensitivity analysis after 3 years remission, OS.

JNHB report AML Tibsovo assessment, reply from Servier - November 28, 2024

Firstly, we thank JNHB for the opportunity to leave our remarks on the preliminary draft assessment report. We have left a review comment with the numbering directly in the assessment report, and the comments corresponding to each number can be found below. In addition, Servier wishes to particularly point out that JNHB's exclusion of the cure assumption in the base case is in contrary to what has been accepted by both NICE and other HTA agencies, and what TLV accepted in the assessment of Venclyxto+AZA (see comment #8).

1- We kindly remind JNHB group that we would like to highlight that these analyses have been performed specifically for JNHB, and having not been published should be deemed confidential and thus not included in any assessment report published.

2- We would like the following sentence to be added in the Summary: "Ranking metrics from the ITC strongly suggest Tibsovo+AZA to be superior to Venclyxto+AZA in terms of EFS and OS (probability between 90% and 98%)."

3- We oppose the wording of inferiority of Tibsovo+Aza and would rather suggest that the adequate wording should be "...Tibsovo+AZA is not superior to Venclyxto+AZA", supported with the rationale provided in comment #6 below.

4- We suggest the following reworded sentence: "The EFS definition in this sensitivity analysis is similar to the EFS definition used in VIALE-A and was applied in the health economic modelling".

5- As previously discussed, we would also like the median OS in the ITT overall population of VIALE-A to be reported, and the to include the following sentence: "The similar outcomes of the PBO+AZA control arms in both trials may however be considered reassuring for the use of the ITT population (7.9 months for AGILE and 9.6 months in VIALE-A)." The JNHB group should also consider that the rarity of the population to be reviewed limits the number of clinical studies completed with potential comparators and adds to the practical challenges when indirectly comparing treatment options, namely Venclyxto+AZA. Overall, the life-threatening nature of AML, the rarity of the indication reviewed, and the significant need to improve morbidity and mortality, should be taken into consideration when assessing the validity and interpretability of the submitted evidence. Furthermore, as IDH1 mutation was not a stratification factor in VIALE-A, there is a potential imbalance between arms in terms of patient profile and prognostic factors. Any comparison between the arms is then subject to bias as no detail on this potential imbalance has been shared.

6- We respectfully ask JNHB group to modify the sentence: "[…] comparisons of Tibsovo+AZA vs. Venclyxto+AZA, despite the ITC ranking metrics strongly suggesting a favorable effect of Tibsovo+AZA."- as well as to include details about ranking of treatments for further transparency of the ITC results: "Based on a posterior sample drawn from the outputs of the Bayesian NMA there is a(n) 90% and a(n) 96% probability that the HR for OS and EFS is less than 1 (i.e., favouring IVO+AZA). As an alternative metric, the surface under the cumulative ranking curve (SUCRA) placed IVO+AZA as the best treatment option with a very high probability (94% probability for OS and 98% probability for EFS)."

7- Typo, it should read EFS.

8- We would as well like to point out to the JNHB group that the cure/long-term survival assumption for Tibsovo+AZA was broadly accepted by other HTA bodies such as NICE, SMC, and CDA (ex-CADTH), as well as to mention in the report that it was accepted by TLV in their assessment of Venclyxto+AZA and Xospata.

9- We would like to highlight that there seems to be no sensitivity analysis performed by JNHB with the cure assumption included in Table 20 and would like to ask JNHB to add the results of such analysis, highlighting the chosen timepoint of the cure, for which we could not comment on since it was not in the present JNHB assessment report.

10- We wish for it to be clarified in the JNHB report that there is additional rationale for this modelling choice and suggest JNHB to add the following in the report: "The cure assumption for Tibsovo+AZA has precedence

from assessments from other HTA agencies, e.g. NICE, SMC and CDA (ex-CADTH). From a Nordic perspective, TLV accepted to include cure (at 36 months) in the agency's base case in the case of Venclyxto+AZA" (see comment #8).

11- We kindly ask the JNHB group to consider the updated model (attached to this response) in which after 100 months the OS now relies on the hazards from the general population for both Tibsovo (ENGINE_IVO$125:P799) and Venclyxto (ENGINE_VEN$125:P799). We hope that this change will convince JNHB to use the lognormal distribution for OS (and EFS) which has the best fit in terms of AIC/BIC (lowest statistics) and visual inspection, instead of relying on the exponential distribution which as highlighted in the JNHB report had the highest AIC/BIC for OS.

12- We oppose the conclusion that the uncertainty surrounding the assumptions in the cost-effectiveness model and the indirect treatment comparison mentioned by the JNHB group in their assessment should imply that Venclyxto+AZA and Tibsovo+AZA have similar efficacy (see also our comment #6 on the ITC results). Consequently, we believe that a naïve cost-comparison is not a suitable methodology for this case. It is our firm conviction that this comparison should not be presented in the JNHB report.

We would also like to refer to previous examples of decisions by NICE where NICE supported their conclusion via a cost-effectiveness or cost-utility analysis despite the 95%CrI (or 95% CI) of the indirect treatment comparison results overlapped with 1:

A) In TA741 (apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer), the final guidance states: "The committee noted that although the hazard ratio was below 1, which indicates a benefit, the confidence interval included the possibility of no benefit." […] "The committee concluded that the company's indirect treatment comparison suggests that apalutamide plus ADT has an advantage over docetaxel plus ADT for efficacy and is well tolerated."

B) In TA666 (atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma): "increased progression-free survival compared with lenvatinib (HR 0.91, 95% credible interval [CrI] 0.23 to 3.65) increased overall survival compared with lenvatinib (HR 0.63, 95% CrI 0.32 to 1.25)." […] "agreed that the NMA results suggested atezolizumab plus bevacizumab was more effective than lenvatinib."

C) In TA587 (lenalidomide plus dexamethasone for previously untreated multiple myeloma): "Based on the results of the indirect comparison, lenalidomide plus dexamethasone improved overall survival compared with VMP (hazard ratio [HR] 0.70, 95% credible interval [CrI] 0.50 to 0.98). For progression-free survival, the hazard ratio for lenalidomide plus dexamethasone compared with VMP was 0.74 (95% CrI 0.52 to 1.05)." […] "concluded that lenalidomide plus dexamethasone was more clinically effective than VMP, although by how much was uncertain."

Also, we would like to highlight that AGILE trial had to be discontinued earlier study due to the inferiority of the comparator (PBO+AZA); more patients included in AGILE would have led to more power in the statistical comparison of the treatment effect between Tibsovo+AZA and PBO+AZA for both EFS and OS, which would then likely have led to more narrow 95% CrI that would not overlap with 1 in the ITC.

Lastly, recent evidence from a real-world study (Smith et al. 2023) further reduces the uncertainty around the significant benefit of the Tibsovo+AZA versus Venetoclax+AZA.

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19.12.2024
CAF/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.01.2025
Leverandør	Servier Sverige AB
Lægemiddel	Tibsovo (ivosidenib)
Ansøgt indikation	Behandling af IDH1 muteret akut myeloid leukæmi (AML)
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel vurderet som en del af fælles nordisk proces i JNHB. To indikationer for Tibsovo behandles på samme Medicinrådsmøde.

Prisinformation

To indikationer cholangiocarcinom (CCA) og akut myeloid leukæmi (AML) for Tibsovo behandles på samme møde i Medicinrådet. Leverandøren har derfor givet tilsagn om forskellige tilbudspriser afhængigt af hvilke indikationer, som anbefales af Medicinrådet.

- Scenarie A: Hvis både CCA og AML anbefales af Medicinrådet eller udelukkende AML anbefales af Medicinrådet
- Scenarie B: Udelukkende CCA anbefales af Medicinrådet
- Scenarie C: Ingen af de to indikationer anbefales af Medicinrådet

Amgros har forhandlet følgende priser på Tibsovo (ivosidenib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Scenarie A - SAIP (DKK) (rabat ift. AIP)	Scenarie B - SAIP (DKK) (rabat ift. AIP)	Scenarie C - SAIP (DKK) (rabat ift. AIP)
Tibsovo	250 mg (60 stk. tabletter)	113.400	[redacted]	[redacted]	[redacted]

Priserne i scenarie A og B er betinget af Medicinrådets anbefaling, mens prisen i scenarie C ikke er betinget af Medicinrådets anbefaling.

Aftaleforhold

[redacted] Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

Tabel 2 viser lægemiddeludgifter på Tibsovo sammenlignet med Venclyxto (venetoclax).

*Tabel 2: Sammenligning af lægemiddeludgifter pr. patient**

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Scenarie A - Pris pr. pakning (SAIP, DKK)	Scenarie A - Lægemiddeludgift pr år (SAIP, DKK)
Tibsovo	250 mg (60 stk.)	500 mg 1 gang dagligt, oral	[redacted]	[redacted]
Venclyxto	100 mg (112 stk.)	Dag 1: 100 mg 1 gang dagligt, oral Dag 2: 200 mg 1 gang dagligt, oral Dag 3 og derefter: 400 mg 1 gang dagligt, oral	[redacted]	[redacted]

* Både Tibsovo og Venclyxto gives i kombination med azacitidin. Dosis for azacitidin er identisk i de to kombinationer og indgår derfor ikke i denne sammenligning af lægemiddeludgifter pr. patient.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering	En del af den fælles nordiske JNHB-proces. Afventer beslutning.	
England	Anbefalet		Link til anbefaling
Sverige	Under vurdering	En del af den fælles nordiske JNHB-proces. Afventer beslutning.	

Opsummering

[redacted]

QUANTIFY

Tibsovo® (ivosidenib) for the treatment of acute myeloid leukaemia (AML) patients with an isocitrate dehydrogenase 1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy

Medical dossier – Sweden (TLV)/FINOSE

Final version 1.0

Prepared for:

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Date submitted:

2024-03-25

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About Quantify

Quantify is an experienced partner in health economics, outcomes research, real-world evidence, and market access. Our goal is to continuously deliver high quality services, combining our scientific and quantitative skills with a solution-oriented mindset and business focus.

We have our roots in academia with a broad technical competence in value strategy, modelling, evidence generation, biostatistics, study design and analysis.

Through extensive experience within both the governmental and private sectors, we have acquired a dynamic and efficient work model, putting emphasis on communication and finding tailored solutions to fit our clients' needs.

Table of Contents

Tables and figures

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List of abbreviations

Abbreviation	Definition
2-HG	2-hydroxyglutarate
AE	Adverse events
AESI	AEs of special interest
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ASCT	Allogeneic stem cell transplantation
AZA	Azacitidine
BSC	Best supportive care
CAG	Cytarabine, aclarubicin, granulocyte colony-stimulating factor combination regimen
CCA	Cholangiocarcinoma
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRh	Complete remission with partial hematologic recovery
Cri	Complete remission with incomplete hematologic recovery
CRp	Complete remission with incomplete platelet recovery
CSR	Clinical study report
DCO	Data cut-off
DIC	Deviance Information Criterion
DOCR	Duration of complete remission
DOCRh	Duration of complete remission with partial hematologic recovery
DOCRi	Duration of complete remission with incomplete hematologic recovery
DOR	Duration of response
DSU	Decision Support Unit
ECG	Electrocardiography
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ED	Emergency department
EFS	Event-free survival
ELN	European LeukaemiaNet
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ	European Organization for the Research and Treatment of Cancer core Quality of Life Questionnaire
EQ-5D-3L	EuroQol 5-dimensions 3-levels
EQ-5D-5L	EuroQol 5-dimensions 5-levels
ESMO	European Society of Medical Oncology
EU	European Union
FAS	Full analysis set
FDA	United States (US) Food and Drug Administration
FE	Fixed effects

Abbreviation	Definition
GHS	General health score
GP	General practitioner
HCT-CI	Hematopoietic cell transplantation-specific comorbidity index
HMA	Hypomethylating agent
HR	Hazard ratio
HRQoL	Health-related quality of life
HRU	Healthcare resource utilisation
HSC	Hematopoietic stem cell
ICER	Incremental cost-effectiveness ratio
IDH	Isocitrate dehydrogenase
IDH1m	Isocitrate dehydrogenase 1 mutation
IDMC	Independent Data Monitoring Committee
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intra-venous
IVO	Ivosidenib
IWG	International Working Group
KM	Kaplan-Meier
KPS	Karnofsky performance status
LDAC	Low dose cytarabine
LS	Least squares
LVEF	Left ventricular ejection fraction
MDS	Myelodysplastic syndrome
MLFS	Morphologic leukaemia-free state
MPN	Myeloproliferative neoplasms
MRD	Measurable residual disease
MUGA	Multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NGS	Next-generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ORR	Objective response rate
OS	Overall survival
PBO	Placebo
PLT	Platelet
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
QD	Once daily
QoL	Quality of life
RBC	Red blood cell
RCT	Randomized controlled trial
RMST	Restricted mean survival time
SAE	Serious adverse event

Abbreviation	Definition
SAS	Safety analysis set
SC	Subcutaneous injection
SD	Standard deviation
SIC	Standard induction chemotherapy
SLR	Systematic literature review
SPPB	Short physical performance battery
SUCRA	Surface under the cumulative ranking curve
TEAE	Treatment-emergent adverse event
TF	Treatment failure
TI	Transfusion Independence
TLS	Tumour lysis syndrome
TTCR	Time to complete response
TTCRh	Time to complete remission with partial hematologic recovery
TTCRi	Time to complete remission with incomplete hematologic recovery
TTR	Time to response
US	United States
VAS	Visual Analogue Scale
VEN	Venetoclax
WHO	World Health Organization

1 Regulatory status and general information

1.1 Approved indications

On 4 May 2023, Tibsovo® (ivosidenib) received a marketing authorization by the European Medicines Agency's (EMA) valid throughout the European Union (EU) for the following indications (1):

1. In combination with azacitidine (AZA), for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy (SIC)
2. As monotherapy, for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma (CCA) with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy.

This dossier aims to facilitate the FINOSE Joint Assessment, only discussing the AML indication. A separate dossier for the CCA indication is submitted in parallel to FINOSE. Simultaneously, dossiers adjusted to the national requirements are submitted to the corresponding national authorities for the pricing and reimbursement negotiation. The requested reimbursement for Tibsovo® (tablets) in AML is identical to the indication approved by EMA.

The intended price for Tibsovo® in the FINOSE countries is presented in Table 1.

Table 1: Applied wholesale/pharmacy purchase prices of Tibsovo® in each country

Product	Vnr number	Package	Finland	Sweden	Norway	Denmark
Tibsovo	135124	60 tablets of 250 mg	[redacted]	[redacted]	[redacted]	[redacted]

1.2 General administrative information

Approval of marketing authorisation, approval of Nordic article number (135124) and the summary of product characteristics (SmPC) are appended to this submission. Additionally, a summary of the clinical assessment report is provided in section 4.3.

2 Description of the disease

2.1 Aetiology / pathophysiology

AML is an aggressive form of blood and bone marrow cancer, resulting in fast disease progression. It is the most common form of leukaemia and accounts for approximately 80% of leukemia cases diagnosed in adults (2, 3). AML constitutes a diverse range of hematopoietic stem cell disorders arising from aberrant and immature blood cells (4). This results in hematologic 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) (4).

The clinical characterisation of AML is mutations in the genes involved in haematopoiesis. The mutation causes clonal expansion of undifferentiated myeloid precursors (blasts) in the bone marrow and peripheral blood leading to ineffective erythropoiesis and bone marrow failure. In most cases AML are caused by somatic variations that occur de novo in previously healthy patients. Up to 97% of studied AML cases are caused by genetic mutations, other causes are chromosomal translocations and changes in molecular levels (5).

2.1.1 IDH1 mutations in AML

AML pathogenesis is described by a multi-hit model that explains the importance of dysregulating mutations in genes for proliferation (FLT_3, KRAS, KIT, $IDH_{1/2}$), differentiation, and epigenetic factors (6). Accumulation of these genetic alterations throughout an individual's lifetime increases the risk of AML in elderly patients (3).

The isocitrate dehydrogenase (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 (7). IDH proteins play a role in several types of tumors, and exist as three isoforms: IDH_1, IDH_2, and IDH_3 (8). Approximately 8% of AML patients harbor IDH_1 mutations (9). IDH proteins catalyze the oxidative decarboxylation of isocitrate to produce carbon dioxide (CO_2) and alpha ketoglutarate (α KG) (8).

Mutations in IDH proteins leads to production of high levels of 2-hydroxyglutarate (2-HG), which inhibits α-KG dependent dioxygenases that play a key role in regulating the epigenetic state of cells (10-12). Other studies have demonstrated that IDH mutations are associated with extensive, coordinated hypermethylation; and that overexpression of mutated IDH_1 can induce histone and DNA hypermethylation, and impair normal cellular differentiation (13-15). Thus, the cancer-associated IDH mutations block normal cellular differentiation and promote tumorigenesis via the abnormal overproduction of 2-HG (8). Inhibition of mutant IDH_1 is expected to reduce 2-HG levels and restore cellular differentiation, thereby act as relevant therapeutic targets in AML (16-21).

The prognostic impact of $mIDH_1$ on patients with AML has been assessed in several studies and there is no clear evidence for an important difference in prognosis. A large meta-analysis investigating the prognosis of IDH_1 mutations, Xu et al. 2017 (22), 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 $mIDH_1$

AML were found to have a slightly poorer overall survival (OS) (hazard ratio (HR) 1.17; p = 0.0047) and event-free survival (EFS; HR 1.29, p = 0.011) compared to those patients without mIDH1 AML. Complete remission (CR) rates were also worse in patients with mIDH1 AML (RR 1.21, p = 0.029).

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. Observational and controlled studies have suggested that mIDH1 is an unfavourable prognostic factor in AML (23, 24), although the difference in clinical response and OS between patients with mutant and wild-type IDH1 in some studies lacked statistical significance (25, 26). For example, a retrospective database analysis (N=826; January 2010 to December 2014) in the US which sought to define the natural history and prognosis of patients with AML and IDH1 and IDH2 mutations found no statistically significant differences in either treatment response or OS in the presence of mIDH1 (25).

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 (22, 27, 28) 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. This is also reflected in the current European LeukaemiaNet (ELN) guidelines, which state that current evidence does not yet warrant the assignment of IDH-1 mutation status to a distinct prognostic group (29).

2.2 Clinical presentation

Commonly reported symptoms are due to abnormalities observed in blood cell count which leads to fatigue, pale skin, dyspnea, infection, dizziness, headache, and coldness in hands and feet (3, 30, 31). It has been shown to worsen during induction chemotherapy and is managed primarily with blood transfusions (3, 30, 31). There is no role for the use of erythropoietic stimulating agents during induction therapy of AML (31). Leukopenia and neutropenia increase the risk of infections and fever, while thrombocytopenia increases the likelihood of bruising, bleeding, frequent or severe nosebleeds, bleeding gums, and heavy menstrual bleeding in women. Other symptoms include weight loss, night sweats, and loss of appetite (2, 32).

2.3 Disease diagnosis and testing

AML patients are diagnosed and treated in accordance with the national guidelines of each FINOSE country. 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, or sometimes lumbar puncture (when there is a suspected spread to spinal cord and brain based on neurologic symptoms) (33). Other procedures include immunophenotyping and cytogenetic and molecular testing (34-37).

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 SIC usually involve evaluation of physical performance, comorbidities, and cognitive functions (38). Physical performance is quantitatively evaluated using Eastern Cooperative Oncology

Group performance status (ECOG PS), the Karnofsky performance status (KPS), and the short physical performance battery (SPPB). Comorbid conditions are quantitatively measured using either the CCI or the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) (38). 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 (39). The European LeukaemiaNet (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) (29). In general, the ESMO and the ELN guidelines provide a list of possible the tests that could be used to identify mutations (40, 41). But the guidelines give room for selecting the appropriate tests based on the locally available expertise, laboratory equipment and clinician preference (40-42).

The ELN guidelines, ECOG, and HCT-CI are utilized according to the national treatment guidelines, whilst the type of tests or the purpose of certain test differs between countries (43-45). In general, the ELN guidelines are used to map the patients' genetic risk factors, whilst ECOG is used to determine the patients' comorbidities. The outputs are used in combination to inform the risk stratification of patients, leading to a more appropriate treatment selection. In addition, HCT-CI is used for comorbidity assessment to decide on providing allogenic stem cell transplantation (ASCT) to AML patients (43, 44, 46). The utilized genetic tests however may differ between the countries due to the available expertise and equipment.

In Sweden, next generation sequencing (NGS) is used to screen for AML mutations (43), whilst in Norway and Denmark it is one possible test to identify minimal residual disease (MRD) after a treatment course (43, 44, 46, 47) The Finnish national treatment guideline on the other hand does not mention the use of NGS to identify mutations or MRD (47).

2.4 Epidemiology of AML

Despite being the most common leukemia among the adult population AML remains rare especially when considering specific mutations. Additionally, the 5-year survival rate of AML patients is relatively low, with the highest mortality rates in older people. The prevalence of AML in the Scandinavian countries is estimated to range from 12.2 to 16.8 per 100,000 (48, 49). In general, the incidence of AML increases with age, and slightly more males are diagnosed with AML than females (48, 50, 51). Approximately 8% of AML patients harbor IDH1 mutations (9). Published studies have reported the age-adjusted incidence rate of mIDH1 AML to be even lower, less than 1 per 100,000 individuals per year (52-54). The 5-year survival rate of patients with AML is only 24%, with the highest mortality rates in older people (49, 55).

The incidence of AML is the highest in Sweden and the lowest in Norway based on the available data as summarized in Table 2. Nearly 350 patients are diagnosed with AML in Sweden each year (43). This corresponds to an incidence rate of 3-4 cases per 100,000 inhabitants per year. Next, Denmark has the second-highest prevalence with 1099 cases

diagnosed between 2019 and 2022, giving an estimate of 274 new adult AML patients every year (46). In Finland, 2,086 cases of AML were diagnosed between 2011 and 2020 (48). That is approximately 200 new adult AML patients every year (48). Lastly, an average of 175 new AML cases were diagnosed in Norway, annually in the past 5 years (56).

Table 2 - The number of new AML cases annually in each country

Country	Number of new AML cases annually
Sweden (43)	~350
Denmark (46)	~274
Finland (48)	~200
Norway (56)	~175

IDH1 mutation is prevalent in about 6-10% of AML patients (25). More detailed patient numbers are presented in section 0.

The average age at diagnosis slightly differ country to country, but usually more males are diagnosed with AML than females among the elderly. The average age at diagnosis in Norway is slightly below 70 years (44). In Sweden the average age is 68.9 years and the median is 72 years at diagnosis (50, 57). According to the available data, the average age at diagnosis is approximately 70 years in Finland (48, 58). Lastly, the median age at diagnosis in Denmark was approximately 70 years (59).

Mortality due to AML has decreased in each country since the 1970s. Between 2015-2019 the 5-year survival was the highest in Sweden and the lowest in Finland (60). The 5-year survival was approximately 34% in Sweden, 28% in Denmark and Norway, and 24% in Finland (60).

2.5 Burden of disease

A significant clinical, humanistic, and economic burden is imposed on patients with AML. This is partially attributable to the heterogenous characteristics at diagnosis, such as varied age distributions and cytogenetic or molecular abnormalities, combined with prolonged hospitalizations and high rates of infectious complications (61). AML is a rare, aggressive, and fast progressing disease, for which patients with newly diagnosed AML who are ineligible for SIC have access to limited treatment options associated with toxicities and no durable remission (2). The lack of effective and tolerable treatment options contributes further to the burden of illness in this patient population (61).

2.5.1 Clinical burden

Clinical events

AML presents a significant clinical burden on patients, owing primarily to associated disease symptoms, morbidity, and hospitalizations (62-64). Blood abnormalities, one of the clinical signs of AML, can cause aggravating symptoms including anemia, leukopenia, neutropenia, and thrombocytopenia (64, 65). Anemia leads to fatigue, pale skin, dyspnea, infection, dizziness, headache, and coldness in hands and feet. Leukopenia and neutropenia increase

the risk of infections and fever, whereas thrombocytopenia increases the likelihood of bruising, bleeding, and frequent or severe nosebleeds (64, 65).

Healthcare resources

Treating AML is also associated with a considerable clinical burden, with patients requiring frequent hospitalizations and extensive use of hospital resources. In general, elderly AML patients (≥60 years) required more inpatient care and a longer length of hospital stay, and this incurred greater outpatient resource utilization than younger patients (<60 years) (66-68).Healthcare resource utilization also depends on the type of therapy that the patients receive.

Among European patients on first-line treatment, those eligible for SIC generally required fewer healthcare resources than ineligible patients. Ineligible patients had more general practitioner (GP) (3.3 vs. 2.1), nurse/physiotherapist (3.8 vs. 3.0), and emergency department (ED) (1.2 vs. 0.8) visits and greater use of healthcare-related transport (5.7 vs. 3.1) (66). In patients who were ineligible or unfit for intensive chemotherapy, hospitalization rates and length of hospital stay varied across treatment regimens.

In a publication based on real world data in a UK setting, examining the toxicity and patient outcomes of VEN in combination with low-dose cytarabine (LDAC) or azacitidine, in SIC ineligible AML patients, patients spent a median of 14 days in the hospital, in the first cycle of treatment (69).

Transfusions

Among AML patient's ineligible for intensive chemotherapy, a higher transfusion burden to manage abnormalities observed in blood cell count was observed in those receiving first-line low-intensity treatment or BSC (70-81). Red blood cell (RBC) transfusions were more commonly required than platelet (PLT) transfusions, regardless of the treatment modality received. Furthermore, patients who were ineligible for SIC required slightly fewer transfusions than eligible patients (79, 81).

2.5.2 Humanistic burden

Reduced quality of life (QoL) and psychological well-being often appear to be associated with the disease process and treatment. Symptom burden, hospitalization, and frequency of blood transfusions can have a substantial detrimental impact on the physical and psychosocial well-being of patients ineligible for intensive chemotherapy (61). These aspects of AML also contribute towards the economic burden, as discussed in section 2.5.3.

A few studies have evaluated health-related quality of life (HRQoL) outcomes in patients with AML who are not eligible for intensive chemotherapy. However, with their advanced age, associated comorbidities, and poorer prognosis, HRQoL outcomes are likely to be similar or worse compared with the wider AML population (82).

A systematic review by Forsythe et al. 2019 found that low baseline HRQoL scores, especially physical function and fatigue, were significant and independent predictors of poor survival in patients with AML who were not eligible for intensive chemotherapy. Treatment of AML patients with less intensive chemotherapy agents have been associated with general improvements in HRQoL, including the domains of fatigue, physical function, and general health score (GHS). Although treatment for AML may improve OS, it may also cause significant toxicity and a reduction in HRQoL (82).

The use of targeted therapies has generally shown a greater improvement in HRQoL in comparison to both LDAC and HMA in previously untreated AML patients unfit for SIC. Patients treated with venetoclax (VEN) plus LDAC showed a greater improvement in both fatigue and global health status and a trend for longer time to deterioration across each sub-scale of the European Organization for the Research and Treatment of Cancer core Quality of Life Questionnaire (EORTC-QLQ-C30[1]) compared to patients treated with LDAC plus placebo (84). However, among secondary AML (sAML) patients ineligible for SIC who received HMA plus VEN or HMA plus placebo, statistically significant improvements were only found in physical functioning on the EORTC-QLQ-C30 scale (84).

In AML patients with an IDH2 mutation unfit for intensive chemotherapy, a minor difference in HRQoL was found between patients who received enasidenib plus AZA compared to AZA monotherapy. Mean HRQoL scores were worse in all domains, except dyspnea in the enasidenib plus AZA arm, and fatigue and global health status in the AZA monotherapy arm (85).

2.5.3 Economic burden

Despite the relatively low incidence rate of AML compared with other cancers, the economic burden of AML is substantial. Economic burden data in AML are limited and frequently underreported, particularly in patients ineligible for intensive chemotherapy; however, available evidence suggests that AML management is associated with high healthcare resource utilization (HRU) and costs, especially from hospitalization, transfusions, stem cell transplantation for eligible patients, and medication costs (86, 87).

Data regarding the economic burden of AML is also scarce in the Nordic countries. In Norway, one study in 2015 estimated the expected 5-year costs per patient to be NOK 1,401,521 among AML patients (88). In Sweden, the expected 5-year costs per patient varied depending on treatment (€115,830 for high-dose chemotherapy, €80,010 for HMA and €23,291 for palliative care) and costs were driven by hospitalizations (including for ASCT), mainly due to the administration of high-dose chemotherapy treatments, as well as treating complications due to drug toxicity (89). The authors suggested that newer therapies that can be given in outpatient setting are likely to reduce costs, as long as they induce and maintain AML remission with less toxicity (89).

The duration of hospitalization differs based on the type of treatment the patients receive. According to real-world data in the UK, VEN + AZA patients required 14 days of hospitalization on average in the first treatment cycle (69). The National Health Services (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). Hospital stays during

[1] The EORTC QLQ-30 is Quality of Life questionnaire for developed to assess the QoL of cancer patients. The EORTC QLQ-C30 comprises 30 items (i.e. single questions), 24 of which are aggregated into nine multi-item scales, that is, five functioning scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting) and one global health status scale. The remaining six single-item (dyspnoea, appetite loss, sleep disturbance, constipation, diarrhoea and the financial impact) scales assess symptoms 83. EORTC. Quality of Life 2022 [Available from: https://qol.eortc.org/.

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 SIC treated in current NHS practice. A study by Rausch et al. (2021) reported that patients treated with VEN + AZA required a median of 32 days of hospitalization during the first cycle of treatment (90). The population in this study has greater alignment to the population in consideration for this submission, albeit in a US context.

Patients in the AGILE study required 11.80 days and 9.10 days of hospitalization in the first treatment cycle of Tibsovo® + AZA and placebo + AZA, respectively (91). Considering the contribution of hospitalizations to the economic burden, the CEM presented in this submission also accounts for the hospitalization during the first cycles, utilizing the previously reported for VEN + AZA, Tibsovo® + AZA, and AZA. The implementation of hospitalization is further discussed under Section 5.3 – Disease management in the technical report.

3 Disease management and national guidelines for AML

Treatment for patients with newly diagnosed AML who are eligible for SIC consists of three phases (92, 93): induction, post-remission, and consolidation. The aim of the induction phase is to induce remission by eradicating as many leukemic cells as possible (92, 93). In newly diagnosed AML, the preferred primary induction treatment is intensive chemotherapy. (92, 93).The second phase of treatment is post-remission, when patients who achieved, CR are treated to prevent a relapse. The post-remission phase typically consists of consolidation therapy using similar chemotherapy as in the induction phase, with the aim of destroying any remaining leukemic cells. Eligible patients with an available donor can undergo hematopoietic stem cell transplantation (HSCT) (93). Following consolidation or HSCT, the surveillance phase is initiated, where patients are monitored for disease relapse.(92).

Figure 1 depicts the treatment scheme for SIC ineligible patients from the current ESMO guidelines (39).

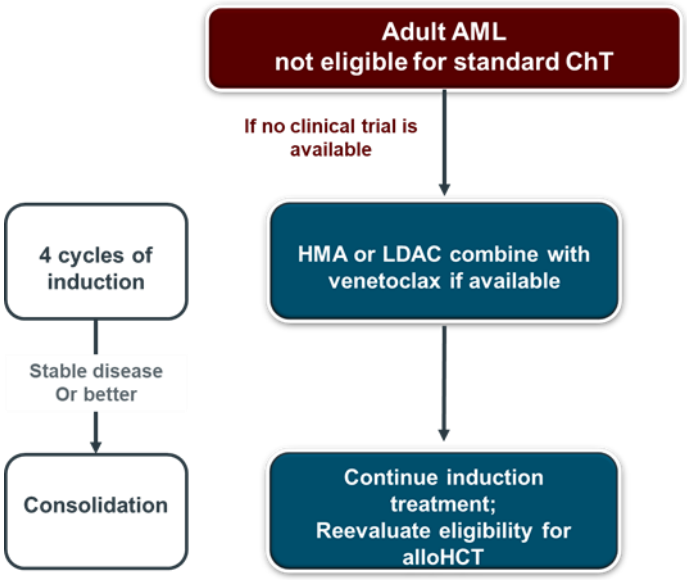


Figure 1. ESMO recommendations for the treatment of AML patients ineligible for standard intensive induction chemotherapy

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 (39)

However, some patients with newly diagnosed AML are ineligible for SIC due to factors such as advanced age, pre-existing comorbidities, or a high incidence of unfavorable genomic features (94, 95). These patients are typically treated with low-intensity therapies, best supportive care, or are enrolled in clinical trials (34). The primary treatment goal for previously untreated AML patients who are ineligible for intensive induction chemotherapy is event free survival (EFS) with one of the following outcomes (34, 39, 96):

- CR, defined as: bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 x 109/L (1000/µL); platelet count ≥100 x 109/L (100,000/µL)
- CR with incomplete hematological recovery (CRi), defined as: all CR criteria except for residual neutropenia (<1.0 x 109/L [1000/µL]) or thrombocytopenia (<100 x 109/L [100,000/µL])
- Partial remission (PR) defined as: hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pre-treatment bone marrow blast percentage by at least 50%
- Morphologic leukemia-free state (MLFS), defined as: bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required.

3.1 Current treatment guidelines for patients ineligible for SIC

3.1.1 Sweden

Swedish guidelines for the treatment of AML are published by the Regional Cancer Centres in Sweden (43). The guidelines recommend SIC for most patients up to the age of 75 years, and for patients that are ineligible for SIC, a HMA such as AZA is recommended, alone or in combination with VEN. This treatment (especially the combination) is described to be a more intensive treatment than the conventional low dose chemotherapies and can provide a better disease management and in some cases prolonged survival. Following the assessment and decision by the Dental and Pharmaceutical Benefits Agency (TLV), VEN in combination with a HMA is reimbursed in Sweden (97).

However, VEN treatment is also associated with toxicity and myelosuppression. Additionally, the Risk Management plan of Venclyxto published by the EMA also highlight serious infections as an important identified risk of VEN treatment (98).

3.1.2 Finland

Treatment recommendations for AML in Finland have been published by the Finnish Society of Hematology (*Suomen Hematologiyhdistys*), with a latest update in November 2023 (47). The guidelines are divided into recommendations for an induction and a consolidation treatment phase, and the treatment regimens vary depending on the patient's risk level. The treatment guidelines state that a mutation panel (NGS) should be done for patients for whom intensive chemotherapy is planned (47).

Patients who are deemed unfit for SIC according to the Ferrara criteria (typically patients over the age of 75 years, or younger patients with other risk factors such as comorbidities or an ECOG score ≥3) can be treated with hypomethylating agents (HMA) alone or in combination with VEN. The HMAs available in Finland are AZA and decitabine, however the guidelines only mention the former (47). Neither AZA nor decitabine are reimbursed in Finland (99). In October 2022 HILA approved the conditional reimbursement of VEN for AML in Finland (100). VEN in combination with HMA or LDAC has demonstrated improvements in clinical response and OS in AML patients ineligible for SIC (101).

If there is no possibility of anti-leukemic treatment, the treatment should focus on controlling the symptoms of leukemia (palliative treatment) (47).

3.1.3 Denmark

Danish treatment guidelines recommend the combination of AZA and VEN as first line treatment for SIC ineligible patients (mentioned as semi-intensive treatment) (45), following the assessment and recommendation by the Danish Medicines Council (102).

- VEN and AZA combination is given in 28-days cycles, as long as patient responds.
- AZA can be given 100 mg/m2 for 5 days or 75 mg/m2 for 7 days, and VEN p.o. 400 mg daily for 14-21 (with a ramp-up for the first 3 days of the first cycle (100-200-400 mg).

Additionally, the guidelines also provide recommendations for low-intensive treatment:

- Low dose cytarabine 20 mg subcutaneous (SC) two times daily for 7-10 days, possibly administered for another 7 days, if necessary, in the first course to control leukocyte counts. Then every 4 to 6 weeks.
- AZA 75-100 mg/m2 SC daily for 5-7 days, repeated every four weeks.
- Decitabine 10-20 mg/m2 daily for 5-10 days, every 4 weeks

3.1.4 Norway

In Norway, treatment guidelines for hematological malignancies, including AML, are published by the Norwegian Directorate of Health, with a recent update in December 2023 (44, 45, 103). First choice for patients ineligible for SIC, is the combination of VEN and AZA, which is also approved for use by Nye Metoder (104). Treatment response should be evaluated already in day 14-21 of the first treatment cycle and continued treatment and dosing depends on the outcome. Treatment should be assessed for discontinuation at a CR/CRi duration of 12 months.

Additional treatment alternatives mentioned for the SIC ineligible patients are decitabine (20 mg/m2 per day, day 1-10 in a 28 day cycle) and low-dose cytarabine (20 mg SC two times daily for 10 days, repeat after 4-6 weeks) (44, 45).

3.2 Real-world treatment patterns

A non-interventional, retrospective chart review was undertaken across multiple centers in 22 countries, including Europe, in 2015-2018. The study evaluated clinicopathologic characteristics and treatment patterns in AML patients who were ineligible for standard intensive chemotherapy, who received systemic treatment with LDAC, HMA, or BSC. This chart review found that 62% of patients received HMA treatment (AZA or decitabine monotherapy), 15% patients received LDAC monotherapy, and the remaining 23% received other forms of treatment (cytarabine, aclarubicin, granulocyte colony stimulating factor combination regimen [CAG], gemtuzumab ozogamicin, FLT3 inhibitors, VEN, and enocitabine). The study highlighted the unmet need for novel therapies in AML patients who are ineligible for SIC (105, 106).

A retrospective chart review (2015-2018) of adult AML patients who were ineligible for SIC was undertaken in six Belgian centers. In this study, 91.9% of the patients received HMA treatment (29.7% AZA and 62.2% decitabine) and the remaining patients (8.1%) received other forms of treatment. A sub-analysis of the real-world study demonstrated consistent OS and CR/ complete remission with incomplete hematologic recovery (CRi) compared to previous clinical trials for all treatments; however, the outcomes for this patient population remained poor and recommendations for combination therapies with HMA or new agents were suggested to improve the outcomes, which is in line with global guidelines (107).

3.3 Unmet need in AML

Limited therapeutic options for AML and poor clinical outcomes, particularly in patients who are ineligible for SIC, suggest a need for innovative treatments that are more effective and better tolerated than currently available options. This is particularly relevant in the elderly population, where increased age is associated with poor prognosis (108) and greater mortality (109). 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 (54). 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) (6, 110, 111).

Several treatments for AML patients who are ineligible for intensive chemotherapy are being investigated in clinical trials; however, no interventions targeting patients with an IDH1 mutation are in late-stage development. Current treatment options for AML patients with an IDH1 mutation who are not considered suitable for SIC include HMAs (AZA or decitabine) or VEN-based therapy in combination with an HMA (112). Survival outcomes with these non-intensive treatments are poor for patients who are ineligible for SIC (113), with a median OS of 7.7, 10.4, 14.7, 7.2 or 8.3 months, respectively, for the above treatment options (84, 94, 114, 115).

In Europe, VEN (BCL-2 inhibitor), in combination with HMAs, has recently emerged as SoC in AML patients who are ineligible for SIC – including those with an IDH1 mutation, even though VEN does not specifically target this mutation (29). VEN, in combination with AZA, has demonstrated significant clinical benefit in newly diagnosed AML patients who are ineligible for SIC. It has also been associated with safety considerations and did not demonstrate an improvement in patient quality-of-life measures (116, 117). For example, in the VIALE-A clinical trial, 83% of patients treated with VEN combination therapy reported SAEs and fatal AEs occurred in 23% of patients (112). Furthermore, tumor lysis syndrome (TLS) was reported in three patients (1%) who received VEN combination therapy, compared to none in the comparator group (112). TLS is a concern as it may cause renal failure, resulting in death (112).

Another important safety concern with VEN is myelosuppression and infections. At final analysis of the VIALE-A trial, the most common Grade ≥3 AEs (venetoclax + azacitidine vs. azacitidine alone) were thrombocytopenia (45.9% vs. 39.6%), neutropenia (42.8% vs. 28.5%) and febrile neutropenia (42.8% vs. 19.8%) (118). Febrile neutropenia is also of particular importance as patients with febrile neutropenia at a high risk of complications should be hospitalized and treated without delay with broad spectrum antibiotics, according to the 2016 ESMO guidelines on management of febrile neutropenia. Serious infections, including sepsis with fatal outcome, has been reported (119). Accordingly, serious infections are mentioned as an important identified risk by the European Risk Management Plan for VEN (118).

Thus, although VEN has demonstrated significant benefits, it is also associated with a number of safety concerns. Therefore, despite the advances observed, there remains an unmet need for a targeted, efficacious, and tolerable therapy that can improve clinical outcomes in this patient population.

In addition to the high clinical burden, AML is associated with a high economic and humanistic burden as well as substantial HRU compared to other cancers (70, 73), despite being a rare disease with an incidence rate of 3.4 cases per 100,000 people in Finland (48). This is attributable in part to the heterogeneous characteristics at diagnosis, such as varied age distributions and cytogenetic or molecular abnormalities, combined with prolonged hospitalizations and high rates of infectious complications (61). In general, elderly AML patients (≥60 years) require more inpatient care, a longer length of hospital stay, and incur greater outpatient resource than younger patients (<60 years) (66-68).

Many patients with AML also frequently experience poor QoL due to the disease, along with therapy-related toxicities and inadequate psychosocial support (82). Symptom burden, hospitalization, and frequency of blood transfusions can have a substantial detrimental impact on the physical and psychosocial well-being of patients ineligible for intensive chemotherapy (61) and can also have an economic burden. At present, available treatments generally maintain QoL rather than improving it (82).

3.4 How Tibsovo® fulfils the unmet medical need in AML

The introduction of branded oral therapies, such as VEN and Tibsovo®, that are being used in combination with established generic options such as HMAs as SoC in this population are likely to substantially increase spending on medications and offset hospitalization costs (120). However, an increase in genetic and molecular profiling as recommended by the treatment guidelines may improve the allocation of healthcare resources to targeted patient populations by identifying patients most likely to benefit from new treatment options (e.g., IDH1 for Tibsovo®) (120).

Whilst most treatment options being evaluated in AML patients who are ineligible for SIC are mutation agnostic, recent molecular profiling has led to the development of targeted therapies for AML. As will be discussed in section 4.1, Tibsovo® in combination with AZA has demonstrated clinically meaningful and improved efficacy with favorable HRQoL in newly diagnosed AML patients with an IDH1 mutation who are ineligible for SIC (121). Tibsovo® also has a favorable safety profile. Tibsovo® plus AZA demonstrated a statistically robust and clinically relevant improvement in OS compared to placebo plus AZA (mOS = 29.3 versus 7.9 months; HR = 0.42, 95% CI, 0.27-0.65; p = 0.001) (122). Lower rates of febrile neutropenia (28.2 % vs. 34.2%) and infections (28.2% vs. 49.3%) were also achieved for Tibsovo® plus AZA versus placebo plus AZA (122).

Due to the significant benefits compared to currently available treatment options, Tibsovo® initially received EMA orphan drug designation (EU/3/16/1802) for AML on December 12, 2016 (123). The designation was maintained after receiving positive Committee for Medicinal Products for Human Use (CHMP) opinion in February 2023 (124), (125), and can be accessed via nominative ATU and compassionate use programs.

Tibsovo® is an oral therapy, allowing patients to self-manage their disease without the need for hospital admission, thus enabling them to better maintain their daily routine and quality of life (126). Based on the demonstrated improvements of Tibsovo®, the current National Comprehensive Cancer Network (NCCN) AML treatment guidelines include Tibsovo® plus AZA, or Tibsovo® monotherapy, as treatment options for adult patients with newly diagnosed AML with a susceptible IDH1 mutation who are ≥60 years old or who have comorbidities that preclude use of SIC (37). The 2022 ELN treatment guidelines only recommend Tibsovo® plus AZA, Tibsovo® monotherapy or BSC for patients with an AML IDH1 mutation not suitable for SIC (35).

In summary, Tibsovo®, a highly targeted therapeutic agent for the treatment of patients with IDH1-mutated cancers, demonstrates an important advancement in AML therapy by addressing the unmet need for a targeted, efficacious, and tolerable therapy that can improve clinical outcomes, including HRQoL, in this patient population (66-68, 117). It also

has the potential to lower costs associated with frequent blood transfusions in patients ineligible for intensive chemotherapy.

4 Clinical efficacy

4.1 AGILE – Key clinical trial evaluating Tibsovo® in IDH1-mutant untreated AML patients

At present, the development program for use in the AML indication encompasses one pivotal clinical trial, AGILE (NCT03173248), which is also used as source for the cost-effectiveness model. Several clinical practice and real-world evidence studies in AML are currently being developed and are further described in Table 36 in the Appendix 10.1.6. AGILE was a Phase 3, multicenter, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of Tibsovo® + AZA compared to placebo + AZA in newly diagnosed AML adult patients with an IDH1 mutation who are ineligible for SIC. Based on the recommendation of the Independent Data Monitoring Committee (IDMC), enrollment into the study was prematurely discontinued due to a clinically meaningful difference being observed between treatment arms (122).

After the recommendation of the data monitoring committee to stop accrual, fewer patients were recruited to the trial than initially planned, which limits data interpretation in some pre-planned subgroup analyses. Sample size estimations showed that this change allowed for a smaller (200 versus 398 patients) and more feasible trial in this rare patient population. Of the total 200 planned patients, a total of 146 patients were randomized: 72 in the Tibsovo® + AZA arm and 74 in the placebo + AZA arm (122). This section presents an overview of the study design and the main results from the AGILE trial. Additional outcomes are further described in Appendix 10.1.5.

OS has traditionally been regarded as a standard primary end point for trials in AML. However, preliminary safety and efficacy data from a previous phase 1 study (AG-221-AML-005) suggested that an earlier analysis of EFS in AGILE was justified. 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 treatment failure (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 SIC. OS was kept as a key secondary endpoint (122). For more information about the primary endpoint, please see section 4.1.2. Additional endpoints are described in Appendix 10.1.2.

The primary efficacy endpoint was met, with Tibsovo® + AZA demonstrating a statistically significant improvement in EFS compared to placebo + AZA (HR = 0.33; 95% CI, 0.16-0.69; p = 0.002) in patients with newly diagnosed IDH1m AML who were not eligible to receive SIC. Tibsovo® + AZA also demonstrated a statistically robust and clinically relevant improvement in OS compared to placebo + AZA (mOS = 24.0 versus 7.9 months; HR = 0.44, 95% CI, 0.27-0.73; p = 0.001) (122).

Patients treated with Tibsovo® + AZA demonstrated significantly higher CR rates (odds ratio of 4.76 [95% CI, 2.15-10.50]; p<0.001), CR + complete remission with partial hematologic recovery (CRh) rates (odds ratio of 5.01 [95% CI, 2.32-10.81]; p<0.001) and objective

response rate (ORR) (odds ratio of 7.15 [95% CI, 3.31-15.44]; p<0.001) compared to patients treated with placebo + AZA (122).

The safety profile of Tibsovo® in patients with previously untreated AML demonstrated the combination with AZA was well tolerated in these patients. The safety profile was manageable and similar to that attributed to treatment for AML. Many of the AEs were known risks associated with Tibsovo®, including electrocardiogram QT prolonged, differentiation syndrome, and leukocytosis (121).

All grade infections were more common in the placebo + AZA arm. Ninety-three percent of Tibsovo® + AZA treated patients experienced a Grade ≥3 versus 94.5% of placebo + AZA treated patients. An increase in absolute neutrophil count from baseline was found only with Tibsovo® + AZA over time, particularly during the first cycle of treatment. Please refer to Appendix 10.1.5.6 for detailed outcomes regarding hematologic recovery. The incidence of TEAEs leading to on-treatment deaths was higher in placebo + AZA -treated patients (21 [28.8%]) compared to those who received Tibsovo® + AZA (10 [14.1%]), with most deaths attributed to AEs and none designated as treatment-related (122).

The efficacy and safety findings were further supported by the HRQoL results which indicated patients who received Tibsovo® + AZA experienced stabilization of HRQoL, and in some cases, clinically meaningful improvements compared to the placebo + AZA arm. There were no clinically meaningful improvements in HRQoL in the placebo + AZA arm (122). Higher incidences of transfusion independence provide further support for the clinical benefit of Tibsovo® + AZA (122).

In this newly diagnosed IDH1m AML population, the combination of Tibsovo® + AZA demonstrated statistically robust and clinically meaningful improvements in the primary and all key secondary efficacy endpoints including EFS, OS, CR, CR + CRh, and ORR. This clinical benefit is supported by favorable HRQoL and incidences of transfusion independence. In addition, the combination therapy was tolerable, and the safety profile was manageable. These data demonstrate the clinical benefit of Tibsovo® + AZA in this difficult-to-treat AML population where outcomes remained poor despite recent advances in newer treatments (122).

4.1.1 Study design

Patients were randomized 1:1 to receive oral Tibsovo® or matched placebo, both administered in combination with SC or intravenous (IV) AZA. 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) (122). An overview of the AGILE study design is shown in Figure 2. Further details on the study design and methods and presented in Appendix 10.1.

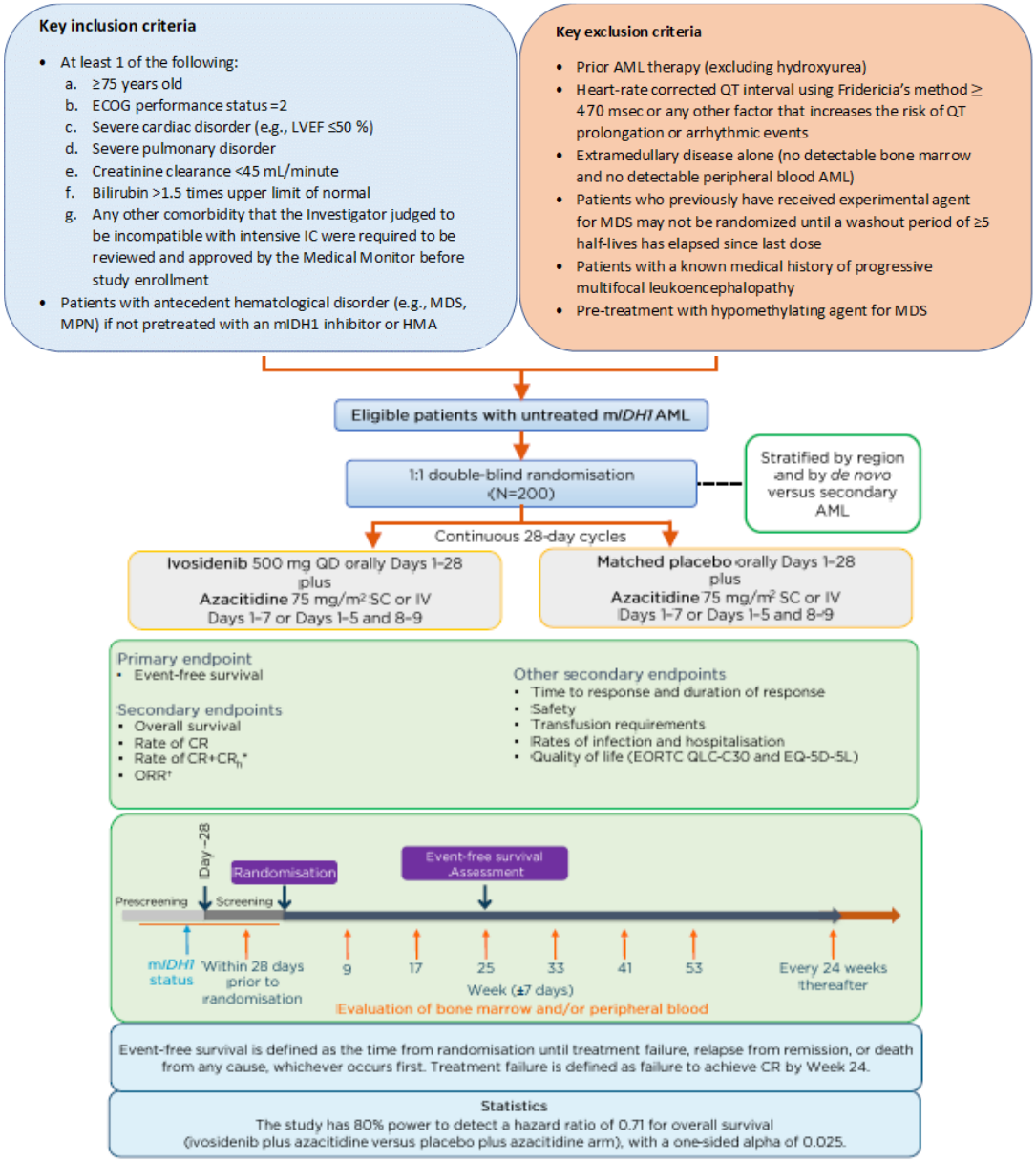


Figure 2. AGILE study schema

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) (127).

4.1.2 Primary endpoint

4.1.2.1 EFS: prespecified analysis

The primary objective was to compare EFS between Tibsovo® + AZA and placebo + AZA. EFS was defined as the time from randomization until TF, relapse from remission, or death from any cause, whichever occurred first. This definition of EFS was defined and aligned according to the United States (US) Food and Drug Administration (FDA) guidance due to improved association with OS, as outlined in the publication by Norsworthy et al (128). 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 (122).

The EFS definitions that was used in the AGILE trial is definition is different, and also more stringent, than that used in previous AML studies (129). This is exemplified in Table 3 below, comparing the EFS definitions in the AGILE trial to the main VEN trial, VIALE-A (116).

Table 3 Comparison of EFS definition from AGILE and VIALE-A

	AGILE	VIALE-A
Endpoint type	Primary	Secondary
Definition of EFS	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.*, (122)	Dinardo *et al,*. (94)

4.1.2.2 EFS: sensitivity analysis

An additional post-hoc EFS analysis was also undertaken using a modified definition similar to that used in other AML trials. 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 (122) (e.g., VIALE-A VEN study) (116). Treatment failure was defined as a lack of CR, complete remission with incomplete hematologic recovery, or morphologic clearance of leukemic 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 (122).

Additional endpoints used in the AGILE trial are described in Appendix 10.1.2

4.1.3 Study results

This section presents the main results from the AGILE trial. Further details on other outcomes are presented in Appendix 10.1.5.

4.1.3.1 Baseline demographics and 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 Tibsovo® + AZA arm and 38 patients [51%] in the placebo + AZA arm) and age (median age was 76.0 years and 75.5 years, respectively) (122).

In the Tibsovo® + AZA group, 54 patients (75%) had primary AML and 18 (25%) had secondary AML; in the placebo + AZA group, 53 (72%) had primary AML and 21 (28%) had secondary AML. A total of 16 patients (22%) in the Tibsovo® + AZA group had poor-risk cytogenetic characteristics, as compared with 20 (27%) in the placebo + AZA group (122).

Baseline demographics and disease characteristics are summarized in Table 4.

Table 4. AGILE – patient demographics and baseline characteristics (full analysis set - FAS)

Endpoints	Tibsovo® + 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)

Endpoints	Tibsovo® + AZA (N = 72)	Placebo + AZA (N = 74)	Total (N = 146)
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)
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; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set;; 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 Tibsovo® + AZA group and 1 [1%] in the placebo-and-AZA 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 Tibsovo® + AZA group and 3 patients (4%) in the placebo-and-AZA group.

Source: Montesinos et al. 2022 (122) & AGILE CSR – data cutoff date: 18 March 2021 [Data on file] (121).

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 (121).

4.1.3.2 Efficacy results

This section presents the results for the primary endpoint (EFS) and key secondary endpoints (OS, CR and CR + CRi) of the AGILE trial. Additional secondary endpoints are presented in appendix 10.1.2.1.

4.1.3.2.1 Primary endpoint: EFS

The primary efficacy endpoint was met with a significant improvement in EFS demonstrated for patients randomized to the Tibsovo® + AZA arm relative to the placebo + AZA arm (HR = 0.33; 95% CI, 0.16-0.69; p = 0.002) (Table 5). Because more than half the patients in each group did not have complete remission by week 24, the median EFS was the same in the two groups (see the definition of EFS in section 4.1.2 above). The median EFS in the Tibsovo® + AZA arm was 0.03 months (95% CI, 0.03-11.01 months) and 0.03 months (95% CI, not estimable [NE]-NE months) in the placebo + AZA arm (122).

However, the estimated probability that a patient would remain event-free was 40% at 6 months and 37% at 12 months in the Tibsovo® + AZA group, as compared with 20% at 6 months and 12% at 12 months in the placebo + AZA group (no patients in the placebo + AZA arm had EFS of ≥24 months by the data cutoff date) (122).The EFS benefit are summarized in Table 5 and a Kaplan-Meier (KM) plot of EFS is provided in Figure 3.

Table 5. AGILE – Summary of EFS (FAS)

	Tibsovo® + AZA (N = 72)	Placebo + AZA (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 + AZA 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 (122) & adapted from AGILE – data cutoff date: 18 March 2021 [Data on file] (121)

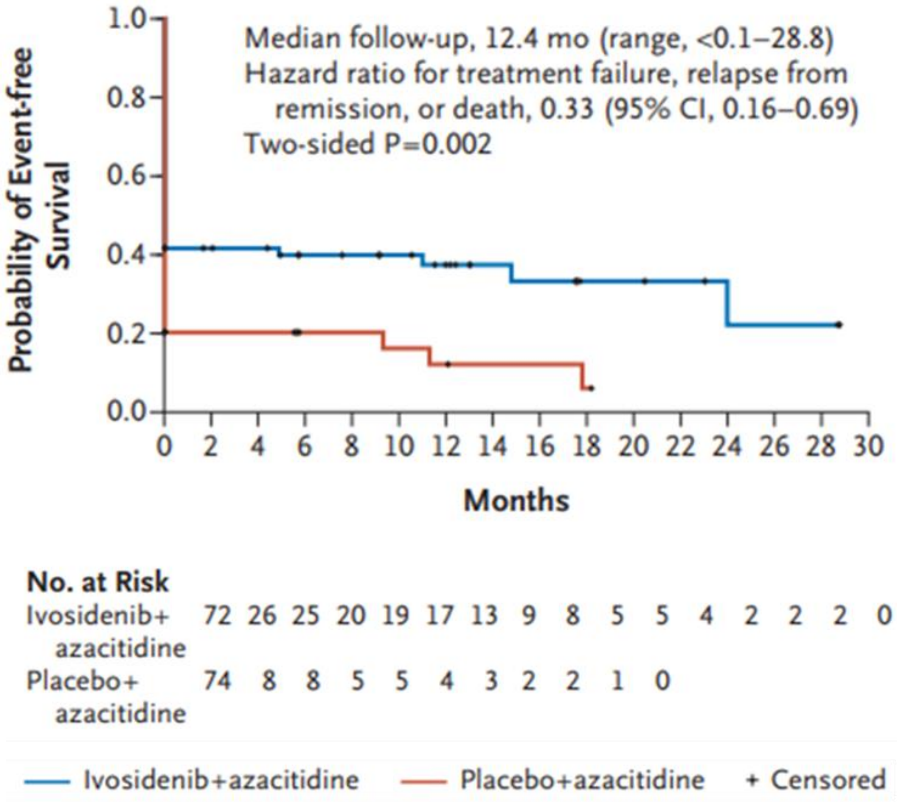


Figure 3. AGILE – KM plot of EFS (FAS)

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

Source: Montesinos et al. 2022 (122).

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 Tibsovo® + AZA arm versus eight patients in the placebo + AZA arm. CR rate by 24 weeks was 37.5% (95% CI, 26.4-49.7) in the Tibsovo® + AZA arm and 10.8% (95% CI, 4.8-20.2) in the placebo + AZA arm. Among patients who achieved CR by 24 weeks, median EFS was NE (95% CI, 14.8-NE months) in the Tibsovo® + AZA arm and 17.8 months (95% CI, 9.3-NE months) in the placebo + AZA arm (122) The EFS for patients who achieved CR by 24 weeks is summarized in Table 6.

The 12-month EFS rate was 89.8% (95% CI, 64.3%-97.4%) in the Tibsovo® + AZA arm versus 60.0% (95% CI, 12.6%-88.2%) in the placebo + AZA arm. The EFS rate at 24 months was 53.2% (95% CI, 8.9%-84.8%) with Tibsovo® + AZA and was NE in the placebo + AZA arm. The durability of the treatment effect was demonstrated in the Tibsovo® + AZA arm as higher EFS rates at 12, 18, and 24 months (122). The restricted mean survival time (RMST) calculated up to [redacted] months, was [redacted] months in the Tibsovo® + AZA arm and XXX months in the placebo + AZA arm. Difference in RMST, calculated by RMST (Tibsovo® + AZA) – RMST (placebo + AZA), was [redacted] months (95% CI, [redacted] months; one-sided p = [redacted] (121).

Table 6. AGILE – Summary of EFS for patients who achieved CR by 24 weeks (FAS)

	Tibsovo® + AZA (N = 72)	Placebo + AZA (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 (122) & adapted from AGILE – data cutoff date: 18 March 2021 [Data on file] (121)

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 4.

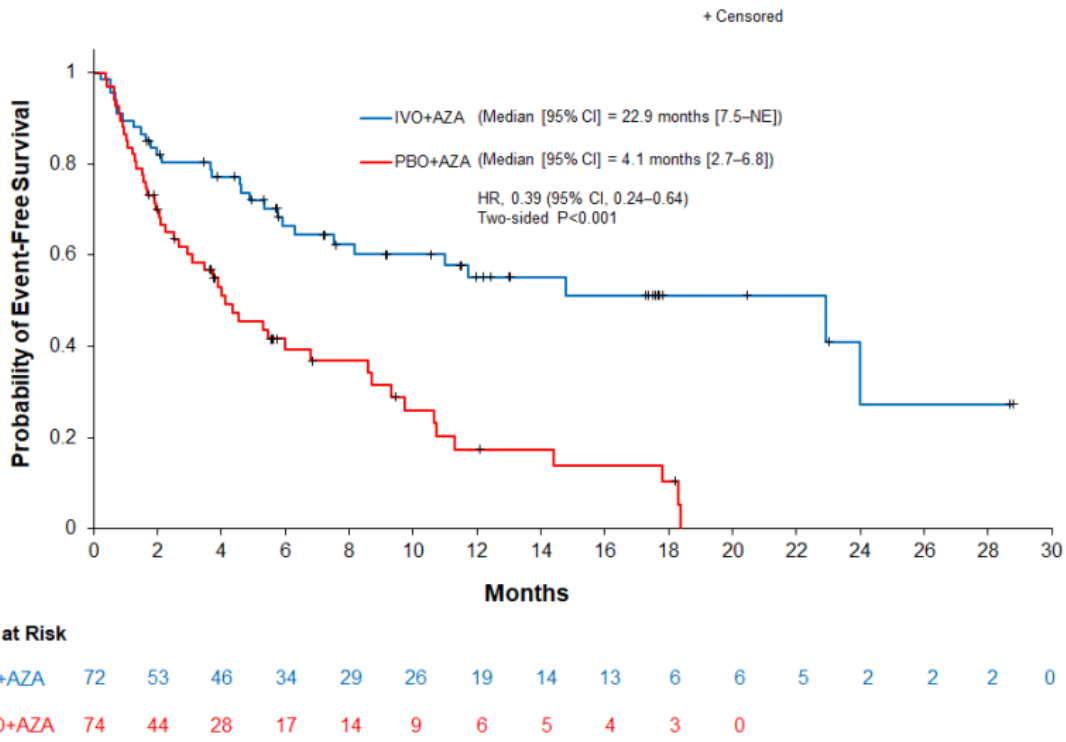


Figure 4 AGILE – EFS with treatment failure defined as failure to achieve CR, CRi, or MLFS after 24 weeks of treatment (FAS; sensitivity analysis)

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)

4.1.3.2.2 Secondary endpoint: Overall survival

OS was defined as the time from date of randomization to the date of death due to any cause (122).

Primary analysis

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 Tibsovo® + AZA arm relative to the placebo + AZA 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 Tibsovo® + AZA arm and 7.9 months (95% CI, 4.1-11.3 months) in the placebo + AZA arm. The durability of the treatment effect was demonstrated at 3, 6, 9, 12, 18, and 24 months (122). The OS benefit observed with Tibsovo® + AZA compared with placebo + AZA was generally consistent across patient subgroups, with all point estimates favoring Tibsovo® + AZA (122). A summary of OS data is presented in Table 7. A KM plot of OS is provided in Figure 5.

Table 7. AGILE – Summary of OS (FAS)

	Tibsovo® + AZA (N = 72)	Placebo + AZA (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 + AZA 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 (122) & adapted from AGILE – data cutoff date: 18 March 2021 [Data on file] (121).

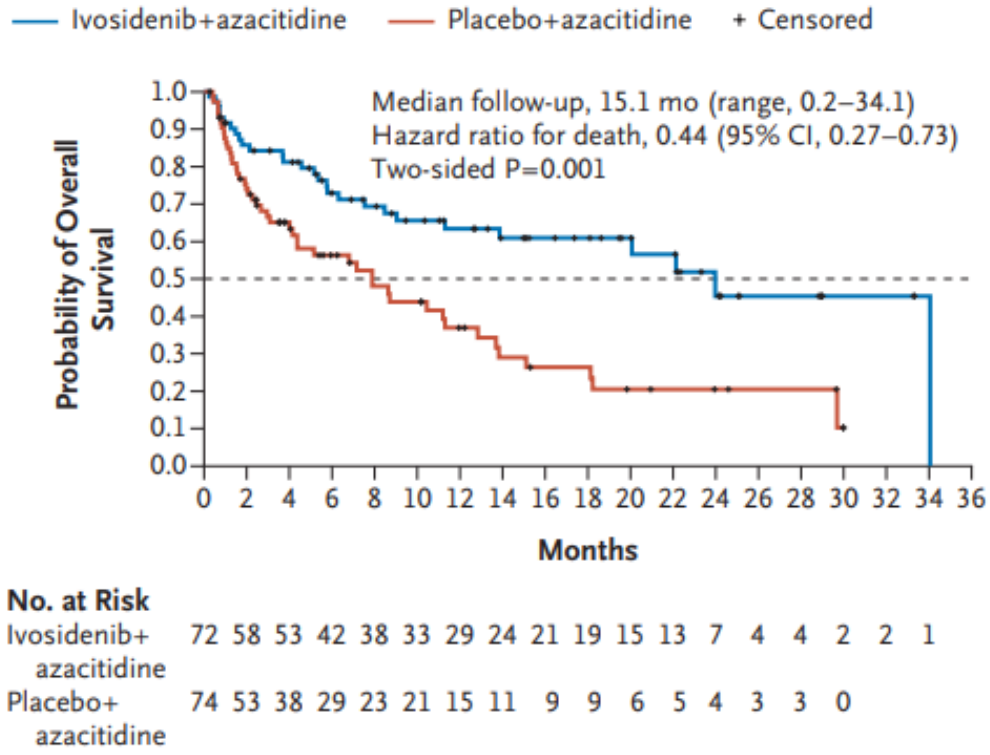


Figure 5. AGILE – KM plot of OS (FAS)

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

Source: Montesinos et al. 2022 (122).

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 Tibsovo® + AZA arm relative to the placebo + AZA 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 Tibsovo® + AZA arm and 7.9 months (95% CI, 4.1-11.3 months) in the placebo + AZA arm (130). 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 median OS gain of 21.4 months which is considered a meaningful clinical benefit (131).The updated OS data is presented in Figure 6 and Table 8 (128).

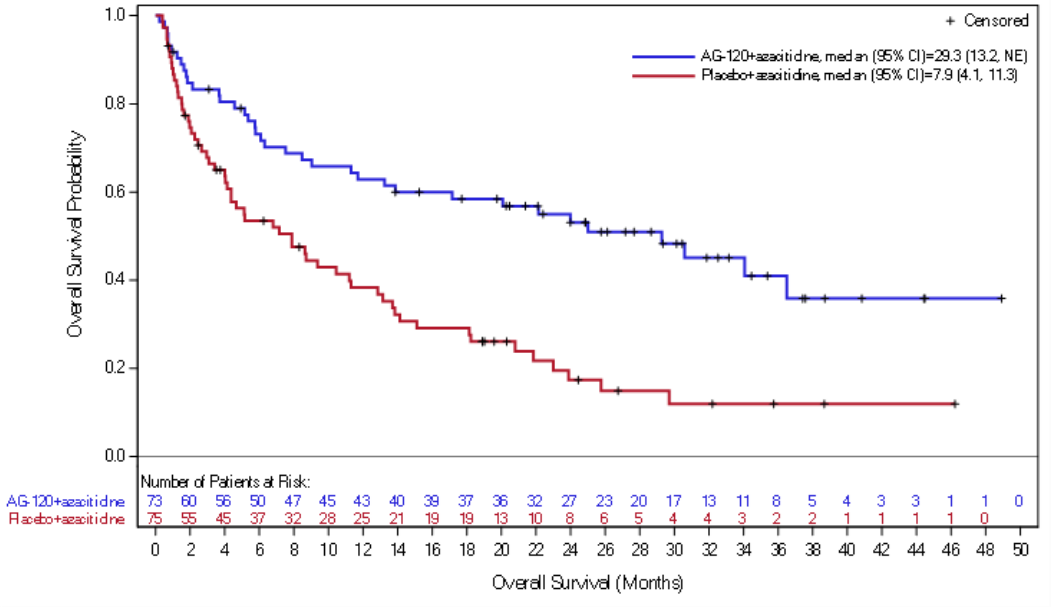


Figure 6.Updated AGILE analysis (data cut-off (DCO) 30th June 2022) – KM plot of OS (FAS)

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

Source: De Botton et al. (2023) (131)

Table 8. Updated AGILE analysis (DCO 30th June 2022) – Summary of OS (FAS)

	Tibsovo® + AZA (N = 73)	Placebo + AZA (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)		

	Tibsovo® + AZA (N = 73)	Placebo + AZA (N = 75)
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: De Botton et al. (2023) (131)

4.1.3.2.2.1 Secondary endpoint: Complete remission (CR)

The CR rate in the FAS was significantly higher in the Tibsovo® + AZA arm than in the placebo + AZA 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 Tibsovo® + AZA compared to 3.8 months with placebo + AZA (122).

The median duration of CR was not reached with Tibsovo® + AZA and was 11.2 months (95% CI, 3.2-NE) with placebo + AZA. Among patients with CR, the estimated probability that a patient would remain in CR at 12 months was 88% with Tibsovo® + AZA and 36% with placebo + AZA (122). The CR rates are summarized in Table 9.

Table 9. AGILE – Summary of CR (FAS)

	Tibsovo® + AZA (N = 72)	Placebo + AZA (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 (122).

4.1.3.2.2.2 Secondary endpoint: CR + CRi

CR + CRi was achieved in 54.2% (95% CI, 42.0-66.0) of the patients in the Tibsovo® + AZA arm and 16.2% (95% CI, 8.7-26.6) of the patients in the placebo + AZA arm. CR + CRi rate was more than three times higher in the Tibsovo® + AZA arm than in the placebo + AZA arm. CR + CRi was significantly higher in the Tibsovo® + AZA arm than in the placebo + AZA arm (odds ratio of 5.9 [95% CI, 2.69-12.97]; p<0.001) (121).

A summary of the CR + CRi outcomes are presented in Table 10.

Table 10. AGILE – Summary of CR + CRi rate (FAS)

	Tibsovo® + AZA (N = 72)	Placebo + AZA (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] (121).

4.1.3.3 Safety and tolerability

The AGILE trial demonstrated that the combination of Tibsovo® + AZA was associated with AEs similar to those attributed to treatment for AML. Overall, the incidence of any grade AE reported in each arm was comparable, occurring in 70 of 71 patients (99%) treated with Tibsovo® + AZA and 73 of 73 patients (100%) in the placebo + AZA arm.

The incidence of Grade ≥3 AEs reported in each arm were also very similar with 66 of 71 patients (93%) treated with Tibsovo® + AZA and 69 of 73 patients (94.5%) in the placebo + AZA arm (122). Grade ≥3 AE's that occurred in more than 15% of the patients in both the Tibsovo® + AZA arm and the placebo + AZA 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%) (122). A summary of common and Grade ≥3 adverse events is presented by preferred term in Table 34, in the Appendix 10.1.5.7.

Infection events were reported at a higher incidence for any grade, Grade ≥3, serious, and those leading to death in the placebo + AZA arm compared with Tibsovo® + AZA. Infections of any grade were reported in 28.8% patients in the Tibsovo® + AZA arm and 49.3% patients in the placebo + AZA arm. Grade ≥3 infections were reported in 21.1% patients in the Tibsovo® + AZA arm and 30.1% patients in the placebo + AZA arm (122). Consistent with improved infection rates versus placebo + AZA, an increase in absolute neutrophil count

from baseline was noted only with Tibsovo® + AZA over time, particularly during the first cycle of treatment (122).

Bleeding events were more frequent with Tibsovo® + AZA than with placebo + AZA (41% versus 29%) (122). However, baseline characteristics showed that median platelets count was lower in experimental arm compared to control arm. Furthermore, the incidence of bleeding events of grade 3 or higher were similar across both treatment arms, affecting 4 patients who received Tibsovo® + azacitidine (6%) and 5 patients who received placebo + azacitidine (7%). Bleeding events are not identified in the warnings and precautions for use sections of the EMA summary of product characteristics (49). Furthermore, the EMA marketing authorizations, nor the risk management plan specify additional monitoring of bleeding events in patients who receive Tibsovo®.

Serious adverse events (SAEs) were reported in fewer patients (49 of 71 patients; 69.0%) in the Tibsovo® + AZA arm compared with the placebo + AZA arm (60 of 73 patients; 82.2%) (Table 11) (122). Ten (14.1%) patients in the Tibsovo® + AZA arm had AEs that led to death, while 21 (28.8%) patients had an AE leading to death in the placebo + AZA arm (122).

The incidence of AEs leading to treatment discontinuations of the combination treatment was similar between arms (19 [26.8%] patients versus 19 [26.0%] patients in the Tibsovo® + AZA and placebo + AZA arms, respectively) (Table 11) (121). Treatment emergent adverse events (TEAEs) leading to dose reductions of both study drugs were infrequent in the Tibsovo® + AZA arm (4 [5.6%] patients), while no dose reductions occurred in the control arm. AEs leading to dose interruptions of both study medications occurred in 37 patients (52.1%) in the Tibsovo® + AZA arm and in 28 patients (38.4%) in the placebo + AZA arm. The most common AEs leading to drug interruption included neutropenia (23% with Tibsovo® + AZA and 4% with placebo + AZA), febrile neutropenia (10% and 8%, respectively), and pneumonia (8% and 7%) (122).

A description of the AEs of special interest is presented in the Appendix 10.1.5.7.1.

Table 11. AGILE – Summary of adverse events

N (%) of patients	Tibsovo® + AZA (N = 71) n (%)	Placebo + AZA (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†		

N (%) of patients	Tibsovo® + AZA (N = 71) n (%)	Placebo + AZA (N = 73) n (%)
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)
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)

N (%) of patients	Tibsovo® + AZA (N = 71) n (%)	Placebo + AZA (N = 73) n (%)
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 Tibsovo®+AZA arm and their corresponding frequencies in the placebo + AZA 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 Tibsovo®+AZA arm and their corresponding frequencies in the placebo + AZA arm are shown.

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

Source: Montesinos et al. 2022 (122)

4.1.3.4 Patient-reported outcomes:

Baseline scores from the EORTC QLQ-C30 were available for 69 patients (96%) who received Tibsovo® + AZA and 66 (89%) who received placebo + AZA (122). The results are presented in appendix 10.1.5.8.

Clinical benefits seen in the Tibsovo® + AZA arm (e.g., EFS, OS, responses) were supported by improvements in multiple HRQoL domains, including Global Health Status/QoL and Fatigue. Patients in the Tibsovo® + AZA arm experienced stabilization of HRQoL, and in some cases clinically meaningful improvements, through Day 1 of Cycle 19 (C19D1) compared to the placebo + AZA arm (122). 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 (122).

4.1.3.4.1 EuroQol-5 dimension 5-level health-related quality of life questionnaire (EQ-5D-5L)

A difference from baseline of at least seven points was considered clinically meaningful for EQ-5D-5L Visual Analogue Scale (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 Tibsovo® based on the summary of EQ-5D-5L VAS scores and index values. Between C5D1 and C19D1, there was clinically meaningful improvement in the Tibsovo® + AZA arm at most visits compared to baseline (Table 12 and Table 13).

In comparison, in the placebo + AZA 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 12). Clinically meaningful improvement in the index value were observed at C11D1, C13D1, and C19D1 (Table 13) (121).

Table 12. AGILE – EQ-5D-5L VAS scores and change from baseline (FAS)

Visit	Tibsovo® + AZA	Placebo + AZA
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);**	-6.40 (19.527);

Visit	Tibsovo® + AZA	Placebo + AZA
	n = 19	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: Adapted from AGILE - data cutoff date: 18 March 2021 [Data on file] (121).

Table 13. AGILE – EQ-5D-5L index values and score change from baseline (FAS)

Visit	Tibsovo® + AZA	Placebo + AZA
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);	0.0062 (0.15240);

Visit	Tibsovo® + AZA	Placebo + AZA
	n = 19	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.

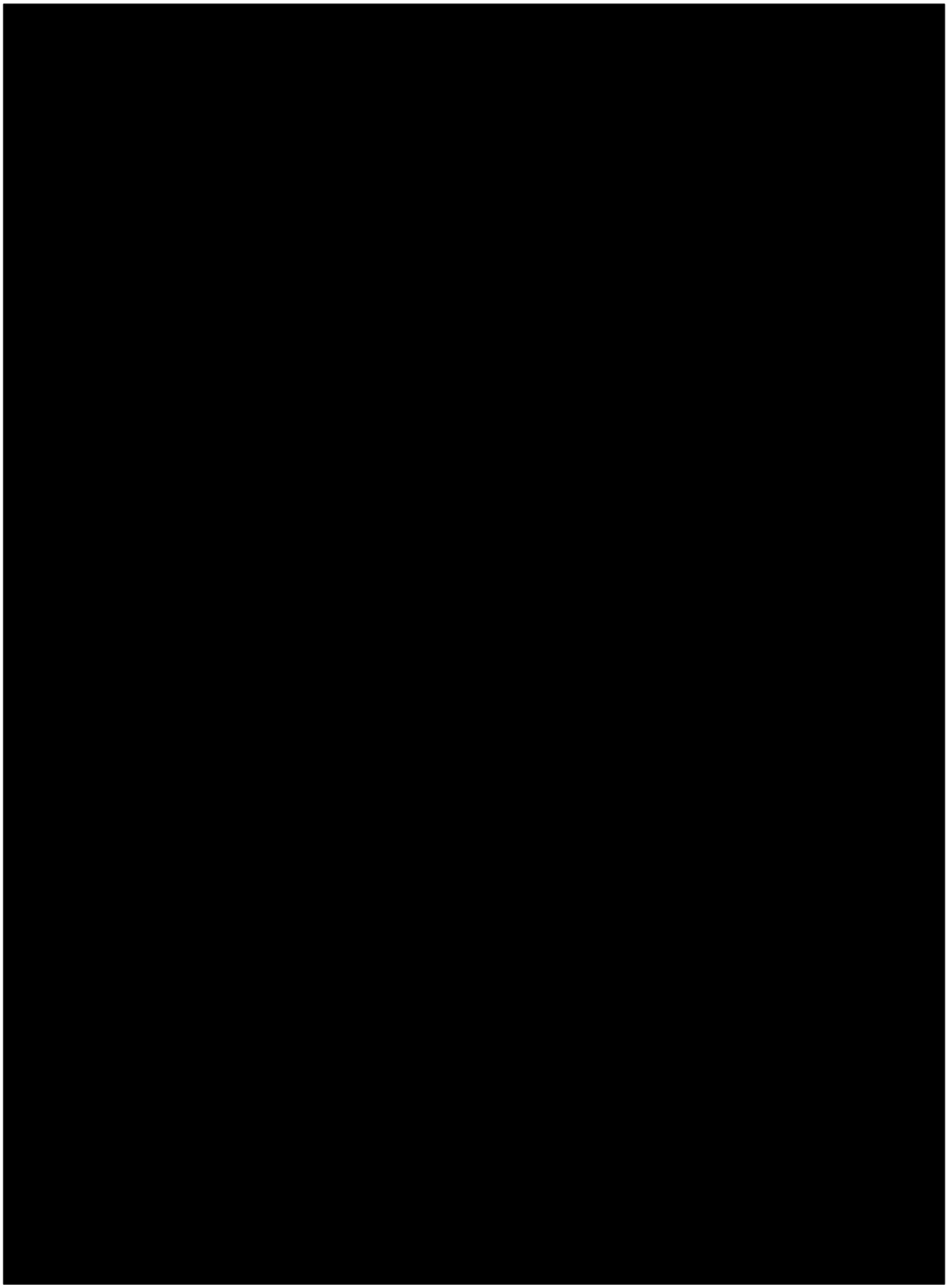
Baseline is defined as most recent measurement on or before the date of randomization. If there is no value available on or before the date of randomization, the last measurement on or before the start of study treatment will be used as baseline. Unscheduled visits are excluded from the analysis. Bold 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] (121).

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 (122).

4.2 [redacted]

[redacted]



NMA results

4.2.1.1 Event-free survival

The network of evidence for the EFS NMA consisted of four studies (94, 114, 127, 133) which reported estimates for five interventions (Figure 7).

Figure 7. Network for evidence for EFS

Source: Servier (data on file) (129)

Tibsovo® + AZA was estimated to improve EFS compared with AZA (HR [redacted]) and VEN + AZA (HR [redacted]) (Figure 8 and Table 14). Furthermore, Tibsovo® + AZA was ranked as the first treatment option with a 98% probability according to the SUCRA values (Table 15). An overview of the treatment ranking probabilities for EFS is provided in Figure 9.

Figure 8. [redacted]

Abbreviations: CrI, credible interval; HR, hazard ratio; LDAC, low dose cytarabine.

Source: Servier (data on file) (129)

Table 14. [redacted]

Comparison	AZA	VEN + AZA	Tibsovo® + AZA
AZA	[redacted]	[redacted]	[redacted]
VEN + AZA	[redacted]	[redacted]	[redacted]
Tibsovo® + AZA	[redacted]	[redacted]	[redacted]

Abbreviations: AZA, azacitidine.

Source: Servier (data on file) (129)

Table 15. NMA EFS SUCRA values

Treatment	SUCRA
Tibsovo® + AZA	[redacted]
VEN + AZA	[redacted]
AZA	[redacted]

Abbreviations: AZA, azacitidine; SUCRA, surface under the cumulative ranking curve.

Source: Servier (data on file) (129)

Figure 9. Ranking probabilities for NMA EFS

Abbreviations: LDAC, low dose cytarabine.

Source: Servier (data on file) (129)

4.2.1.2 Overall survival

The network of evidence for the OS NMA consisted of six studies (94, 114, 115, 127, 133, 134) which reported estimates for seven interventions (

Figure 10).

Figure 10. Network of evidence for OS

Abbreviations: LDAC, low dose cytarabine.

Note: comparators of interest for the Swedish context are AZA and VEN + AZA

Source: Servier (data on file) (129)

Tibsovo® + AZA was estimated to improve OS compared with AZA (HR [redacted]) and VEN + AZA (HR [redacted]) ([redacted]

Figure 11 and Table 16). Furthermore, Tibsovo® + AZA was ranked as the first treatment option with a XXX probability according to SUCRA (surface under the cumulative ranking curve) values (Table 17). An overview of the treatment ranking probabilities for OS is provided in

Figure 12. As described in section 10.2.3, the ranking probabilities graphs show the probabilities a treatment would rank in different places whereas SUCRA values represent an overall ranking for a treatment.

Figure 11. NMA OS forest plot

Abbreviations: CrI, credible interval; HR, hazard ratio; LDAC, low dose cytarabine.

Note: comparators of interest for the Swedish context are AZA and VEN + AZA

Source: Servier (data on file) (129)

Table 16. NMA OS hazard ratios (HR) and 95% credible intervals

Comparison	AZA	VEN + AZA	Tibsovo® + AZA
AZA	[redacted]	[redacted]	[redacted]
VEN + AZA	[redacted]	[redacted]	[redacted]
Tibsovo® + AZA	[redacted]	[redacted]	[redacted]

Abbreviations: AZA, azacitidine.

Source: Servier (data on file) (129)

Table 17. NMA OS SUCRA values

Treatment	SUCRA
Tibsovo® + AZA	[redacted]
VEN + AZA	[redacted]
AZA	[redacted]

Abbreviations: AZA, azacitidine.

Source: Servier (data on file) (129)

Figure 12 [redacted]

Abbreviations: LDAC, low dose cytarabine.

Note: comparators of interest for the Swedish context are AZA and VEN + AZA

Source: Servier (data on file) (129)

4.2.1.3 Overall survival with new data cut from AGILE and VIALE-A

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) remains the same with that for OS and is presented in

Figure 10. Tibsovo® + AZA was estimated to improve OS compared with AZA (HR 0.43; 95% CrI 0.28-0.65) and VEN + AZA (HR 0.74; 95% CrI 0.46-1.18) (Figure 13 and Table 18).

The ranking probabilities graph is presented in Figure 14 and the SUCRA values in Table 19. Based on the ranking probabilities graph and the SUCRA values, Tibsovo® + AZA was ranked as the first treatment option with a 94% probability of being the preferred treatment.

Figure 13 [redacted]

Abbreviations: CrI, credible interval; HR, hazard ratio; LDAC, low dose cytarabine.

Note: comparators of interest for the Swedish context are AZA and VEN + AZA

Source: Servier (data on file) (129)

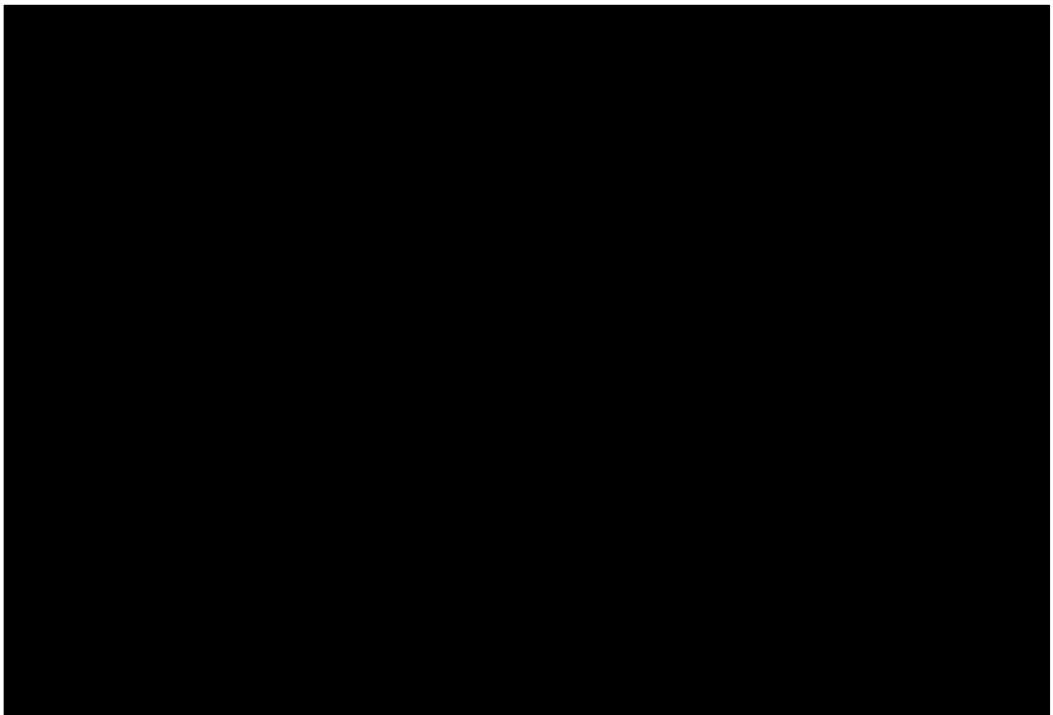


Table 18. [redacted]

Comparison	AZA	VEN + AZA	Tibsovo® + AZA
AZA	[redacted]	[redacted]	[redacted]
VEN + AZA	[redacted]	[redacted]	[redacted]
Tibsovo® + AZA	[redacted]	[redacted]	[redacted]

Abbreviations: AZA, azacitidine.

Source: Servier (data on file) (129)

Table 19. SUCRA values for overall survival with new data cut from AGILE and VIALE-A

Treatment	SUCRA
Tibsovo® + AZA	[redacted]
VEN + AZA	[redacted]
AZA	[redacted]

Abbreviations: AZA, azacitidine.

Source: Servier (data on file) (129)

Figure 14 [redacted]

4.3 Clinical assessment report

Tibsovo® was granted a marketing authorization in the EU on 4 May 2023 (1). The assessment report by EMA's CHMP is attached to this application. Tibsovo® was granted orphan medicine designation for both indications, and in the case of AML, this was based on a significant benefit compared to currently authorised treatment options for frontline SIC-ineligible patients.

As described in the report, AG120-C-002 (AGILE) was found to support the efficacy of Tibsovo® in combination with AZA in treating adult patients with newly diagnosed AML and IDH1 R132 mutation who are ineligible for SIC (135). Tibsovo® in combination with AZA has shown significant clinically relevant improvements in several key endpoints including EFS, OS and CR/CRh rates when compared to the control group (135). Notably, the OS data revealed a substantial 16-month improvement in patients receiving Tibsovo®, representing a tripling of median OS in the primary OS analysis (March 2021). This is indicative of a meaningful clinical benefit, particularly in individuals with a fragile and poor-prognosis status (135). The safety profile of Tibsovo® in combination with AZA in patients with newly diagnosed AML primarily revolves around concerns related to QT prolongation, differentiation syndrome, as well as hematological and gastrointestinal toxicity (135). These safety concerns are mitigated through detailed product information, including contraindications for at-risk patients, comprehensive warnings, and precautions. Thus, the CHMP concluded that the overall benefit/risk balance of Tibsovo® is positive, subject to conditions outlined in the report (135).

5 Tibsovo® – product information

Tibsovo® was developed for the targeted treatment of hematological and solid malignancies harbouring IDH1 mutations, including r/r AML, CCA, and glioma. Tibsovo® (ivosidenib; previously known as AG-120) is a first-in-class, non-cytotoxic, selective, orally active small-molecule inhibitor of mutated isocitrate dehydrogenase 1 (IDH1), making it a highly targeted therapeutic agent for the treatment of patients with IDH1-mutated cancers (9, 126, 136). Tibsovo® has received EMA orphan drug designation for AML in 2016 and CCA in 2018 (137, 138) which was maintained following CHMP opinion in March 2023.

5.1 Indications

In the EU , Tibsovo® has received a marketing authorization from the EMA for the following indication (1):

- In combination with AZA for the treatment of adult patients with newly diagnosed AML with an IDH1 mutation who are not eligible to receive SIC.
- as monotherapy for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma (CCA) with an IDH1 mutation who were previously treated by at least one prior line of systemic therapy.

5.2 Mechanism of action

Tibsovo® is a small-molecule inhibitor that targets the mutant IDH1 enzyme. Mutant IDH1 converts α-KG to 2-HG. Increased 2-HG levels results in epigenetic alterations that impairs myeloid differentiation, increases proliferation of myeloblast and blocks cellular differentiation (8, 139, 140).

Inhibition of the mutant IDH1 enzyme by Tibsovo® led to decreased 2-HG levels and restored cellular differentiation, as illustrated in Figure 15 (8, 17, 139, 141). In blood samples from patients with AML with mutated IDH1, Tibsovo® decreased 2-HG levels ex-vivo, reduced blast counts, and increased percentages of mature myeloid (126). Tibsovo® is not myelosuppressive and is associated with a low rate of severe cytopenia (141, 142).

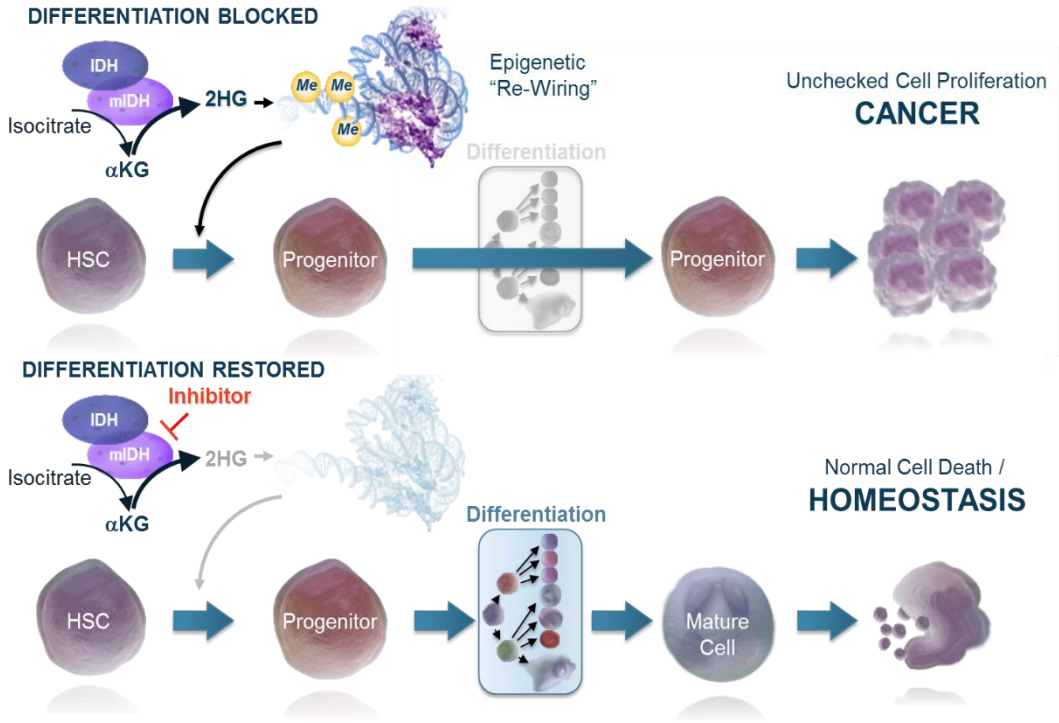


Figure 15. Mechanism of action of Tibsovo®
Abbreviations: αKG, alpha-ketoglutarate; 2-HG, 2-hydroxyglutarate; HSC, hematopoietic stem cells; IDH, isocitrate dehydrogenase; mIDH, mutant isocitrate dehydrogenase.
Source: Cairns 2013 (139)

5.2.1 Monitoring

An electrocardiogram (ECG) should be performed prior to treatment initiation. ECGs should be monitored at least weekly during the first three weeks of therapy and then at least once monthly for the duration of therapy. Any abnormalities should be managed promptly (126).

For patients with AML, blood counts for leucocytosis and blood chemistries for abnormalities associated with electrolyte imbalances or tumour lysis syndrome should be assessed prior to treatment initiation. Blood counts and chemistries should be monitored periodically according to institutional standards of care and any abnormalities managed promptly (126).

6 Intervention and relevant comparators in AML

6.1 Relevant comparators in AML

As discussed in section 3, the AML treatment guidelines in each country discuss the use of AZA or VEN + AZA for the treatment of AML. Tibsovo® in combination with AZA aims to provide a cost-effective treatment alternative for AML patients with IDH1 mutation who may receive AZA or VEN + AZA. Therefore, AZA and VEN + AZA were selected as relevant comparators.

6.2 Most common daily dose

6.2.1 Tibsovo®

The recommended dose is 500 mg ivosidenib (2 x 250 mg tablets) taken orally once daily in combination with AZA during a cycle of 28 days (140). The treatment can be as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (140). The dose of AZA in the treatment combination matches the dose of AZA when administered as monotherapy.

A recommended dose has not been determined for patients with severe renal or hepatic impairment. Tibsovo® should be used with caution in patients with severe renal or hepatic impairment and this patient population should be closely monitored (140).

See the SmPC for full dosing recommendations (130).

6.2.2 AZA

In general, the recommended dosage of AZA according to the SmPC is 75 mg/m2 body surface area once-per-day for 7 days, during a cycle of 28 days (143).

6.2.3 VEN + AZA

The recommended dose of VEN is an initial dose titration of 100 mg day 1, 200 mg day 2, 300 mg day 3, followed by 400 mg daily from day 4. VEN is administered orally once daily in

combination with AZA during a cycle of 28 days (144). The recommended dosage of AZA in the treatment combination matches the dose of AZA when administered as monotherapy.

6.3 Treatment costs

Drug treatment costs of Tibsovo® + AZA and VEN + AZA combinations are presented for each country, in the tables under Section 6.3. AZA is only reimbursed in Norway (H-resept) whilst VEN is recommended/reimbursed in all FINOSE countries. According to the authorities' guidelines the lowest listed price has been used for AZA in Norway, Denmark, and Finland, whereas the price presented for AZA in Sweden is the procured price (145-148). On the other hand, the lowest list prices of VEN were used in the CEM.

The wholesale prices of Tibsovo® presented under Section 1.1 were used to derive the appropriate intervention prices for each country specific cost-effectiveness analysis. Considering the local HTA guidelines, the per cycle cost of each treatment does not account for drug wastage in Sweden (145). However, the per cycle costs presented for Denmark, Finland, and Norway account for the possible drug wastage (146-148). The prices are presented as "per package" and "per 28-day cycle". Per cycle costs account for the relative dose intensity of the products. For the detailed per cycle calculation, please refer to the CEM.

- In Finland, the price of VEN and Tibsovo® was set to the products' retail price excluding VAT, as requested by HILA (147). The retail prices were calculated based on the wholesale price of Tibsovo®, in accordance with the regulation on pharmaceutical tariffs (149). Both wholesale and retail prices are presented in Table 20 and Table 21.
- In Sweden, the price of AZA was set to the weighted average procurement price of AZA in accordance with the approach in the Venclyxto TLV decision (97). The price of VEN and Tibsovo® was set to the pharmacy retail price (AUP).
- In Norway, the retail prices ("Maksimal utsalgspris for apotek"), excluding 25% VAT, were added to the CEM as requested in the Norwegian guideline (148).
- In Denmark, the price of VEN, AZA, and Tibsovo® was set to the products' apotekets indkøbspris (AIP) in accordance with the Danish guideline (146).

6.3.1 Treatment costs in Finland

Table 20: Treatment cost of Tibsovo® + AZA in Finland

Drug	Dosing	Strength & package	Wholesale price		Retail price incl. VAT	
			Price per pack	Cost per 28-day cycle	Price per pack	Cost per 28-day cycle
Tibsovo®	500 mg, once daily,7 days per 28 days	250 mg per tablet, 60 tablets	[redacted]	[redacted]	[redacted]	[redacted]
AZA (99)	75 mg/m2, once daily for 7 days per 28 days	25 mg/ml, 100 mg	[redacted]	[redacted]	[redacted]	[redacted]

Table 21: Treatment cost of VEN + AZA in Finland

Drug	Dosing	Strength & package	Wholesale price		Retail price incl. VAT	
			Price per pack	Cost per 28-day cycle	Price per pack	Cost per 28-day cycle
VEN (99)	400 mg once daily	100 mg per tablet, 112 tablet	[redacted]	[redacted]	[redacted]	[redacted]
AZA (99)	75 mg/m2, once daily for 7 days per 28 days	25 mg/ml, 100 mg	[redacted]	[redacted]	[redacted]	[redacted]

6.3.2 Treatment costs in Sweden

Table 22 - Treatment cost of Tibsovo® + AZA in Sweden

Drug	Dosing	Strength & package	Price per pack	Cost per 28-day cycle
Tibsovo®	500 mg, once daily,7 days per 28 days	250 mg per tablet, 60 tablets	[redacted]	[redacted]
AZA	75 mg/m2, once daily for 7 days per 28 days	25 mg/ml, 100 mg	[redacted]	[redacted]

* Pharmacy retail price (AUP)
**Procured price from the regions, weighted by sales data from IQVIA

Table 23 – Treatment cost of VEN + AZA in Sweden

Drug	Dosing	Strength & package	Price per pack	Cost per 28-day cycle
VEN (150)	400 mg once daily	100 mg per tablet, 112 tablet	[redacted]	[redacted]
AZA	75 mg/m2, once daily for 7 days per 28 days	25 mg/ml, 100 mg	[redacted]	[redacted]

* Pharmacy retail price (AUP)
**Procured price from the regions, weighted by sales data from IQVIA

6.3.3 Treatment costs in Norway

Table 24 - Treatment cost of Tibsovo® + AZA in Norway (retail price excl. VAT)

Drug	Dosing	Strength & package	Price per pack	Cost per 28-day cycle
Tibsovo®	500 mg, once daily,7 days per 28 days	250 mg per tablet, 60 tablets	[redacted]	[redacted]
AZA (151)	75 mg/m2, once daily for 7 days per 28 days	25 mg/ml, 100 mg	[redacted]	[redacted]

Table 25 – Treatment cost of VEN + AZA in Norway (retail price excl. VAT)

Drug	Dosing	Strength & package	Price per pack	Cost per 28-day cycle
VEN (152)	400 mg once daily	100 mg per tablet, 112 tablet	[redacted]	[redacted]
AZA (151)	75 mg/m2, once daily for 7 days per 28 days	25 mg/ml, 100 mg	[redacted]	[redacted]

6.3.4 Treatment costs in Denmark

Table 26 - Treatment cost of Tibsovo® + AZA in Denmark (pharmacy purchase price)

Drug	Dosing	Strength & package	Price per pack	Cost per 28-day cycle
Tibsovo®	500 mg, once daily,7 days per 28 days	250 mg per tablet, 60 tablets	[redacted]	[redacted]
AZA (153)	75 mg/m2, once daily for 7 days per 28 days	25 mg/ml, 100 mg	[redacted]	[redacted]

Table 27 – Treatment cost of VEN + AZA in Denmark (pharmacy purchase price)

Drug	Dosing	Strength & package	Price per pack	Cost per 28-day cycle
VEN (154)	400 mg once daily	100 mg per tablet, 112 tablet	[redacted]	[redacted]
AZA (153)	75 mg/m2, once daily for 7 days per 28 days	25 mg/ml, 100 mg	[redacted]	[redacted]

7 Treatment duration

In the AGILE trial, the median duration of treatment was 6.0 months (range, 0.1 to 33.5) with Tibsovo® and AZA, and 2.8 months (range, 0.1 to 19.8) with placebo and AZA (122).

8 Patient numbers

Based on the AML incidence numbers, the assumption of 10% prevalence of mIDH1 in AML patients and an estimation that approximately 50% of AML patients are ineligible for SIC (and excluding patients that are not fit for active treatment), the patient numbers that are estimated to be eligible for treatment with Tibsovo® in combination with AZA are presented in Table 28.

Table 28 - Patient numbers

Country	Sweden	Denmark	Finland	Norway
AML patients eligible for treatment with Tibsovo in combination with azacitidine	18	13	9	9

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10 Appendices

10.1 AGILE

10.1.1 Study treatments

Tibsovo®, or matched placebo, was administered orally, once-daily (QD), combined with AZA (75 mg per square meter of body-surface area SC or IV) for 7 days in 28-day cycles (122).

All patients received AZA 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 Tibsovo® or placebo QD on each day of the 4-week cycle (122). 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 (122).

10.1.1.1 Dose modifications and delays

10.1.1.1.1 Tibsovo® or placebo dose modification

Dose modifications of Tibsovo® 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, Tibsovo® or placebo was dose-reduced to 250 mg. This differs from the dosing instructions in the SmPC, which state that in certain cases dose could be resumed if toxicity resolves (130). Re-escalation was allowed with approval from the medical monitor (122).

10.1.1.1.2 AZA 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 AZA demonstrated a benefit then that dose was maintained during subsequent cycles unless toxicity developed. The medical monitor was contacted, when necessary, for guidance on AZA dose modification (122).

10.1.2 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 (122).

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 (122).

10.1.2.1 Secondary endpoints

The key secondary objectives were to characterize the safety profile and to compare CR, OS, CRh and ORR between Tibsovo® + AZA and placebo + AZA. 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 Tibsovo® + AZA and placebo + AZA (122).

An overview of the primary and secondary endpoints and their definitions is presented in Table 29.

Table 29. 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* Treatment failure defined as failure to reach CR by week 24 treated as experiencing an event on Day 1.
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 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)

Primary endpoint	Definition
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)
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; 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 occurs first.

Source: Montesinos et al. 2022 (122).

10.1.3 Inclusion and exclusion criteria

AGILE was conducted in adult patients with newly diagnosed AML with an IDH1 mutation who were ineligible for SIC (122). The key inclusion and exclusion criteria for patients enrolled in AGILE are presented in Figure 2 in section 4.1.1.

10.1.4 Statistical analysis

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 (122).

The 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 (122).

On the basis of the recommendation of the IDMC, whose members noted a difference in the number of deaths favoring Tibsovo® + AZA, 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 (122).

In addition, a number of subgroup analyses were completed. Hazard ratios were calculated from the unstratified Cox regression model, with placebo and AZA as the denominator and with two-sided 95% CIs (122).

10.1.5 Results

10.1.5.1 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 Tibsovo® + AZA arm and 74 patients to the placebo + AZA arm. Twenty-seven patients in the Tibsovo® + AZA arm, and 12 patients in the placebo + AZA arm, were still receiving treatment as of the primary data cutoff date (122). Among patients assigned to receive Tibsovo® and AZA, 25 continued to receive both Tibsovo® and AZA, one who discontinued ivosidenib continued to receive AZA alone, and one who discontinued AZA continued to receive ivosidenib alone (27 patients overall in the Tibsovo® -and-AZA group).

Reasons for treatment discontinuation were similar between the treatment arms, however a numerically higher number of patients discontinued treatment in the placebo + AZA arm due to patient withdrawal, clinical progression, or lack of treatment benefit. A total of 106 patients discontinued Tibsovo® or placebo: 45 (62.5%) in the Tibsovo® + AZA arm, and 61 (82.4%) in the placebo + AZA 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 + AZA 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 AZA treatment (122). A summary of patient disposition is provided in Figure 16.

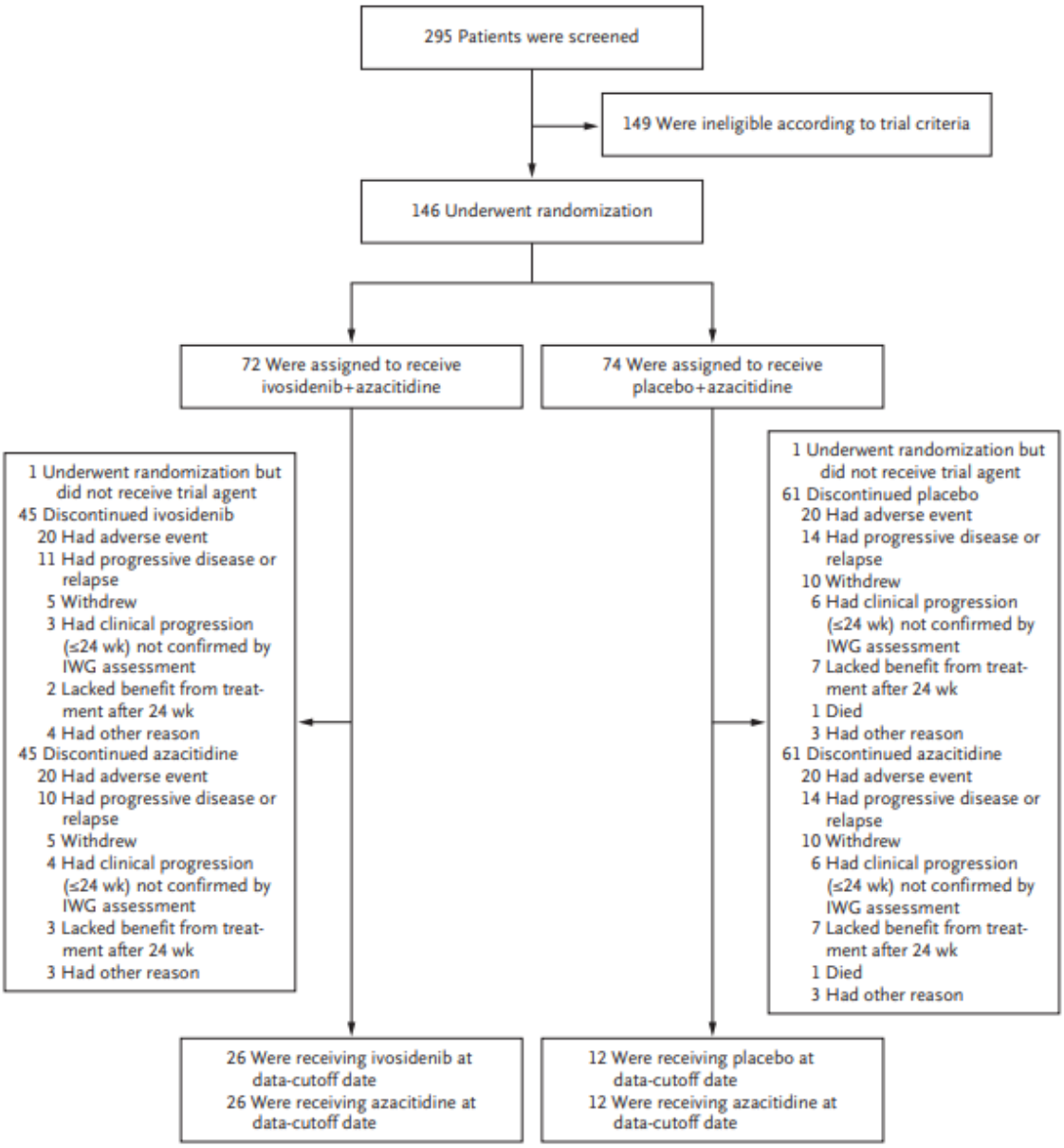


Figure 16. AGILE – Screening and randomization

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

Source: Montesinos et al. 2022 (122).

[redacted]

Table 30. [redacted]

[redacted]

10.1.5.2 Secondary endpoint: CR + CRh

The CR + CRh rate was significantly higher in the Tibsovo® + AZA arm than in the placebo + AZA 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) (122). A summary of CR + CRh rates is presented in Table 31.

Table 31. AGILE – Summary of CR + CRh rates (FAS)

	Tibsovo® + AZA (N = 72)	Placebo + AZA (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 (122).

10.1.5.3 Secondary endpoint: 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 Tibsovo® + AZA arm and 18.9% (95% CI, 10.7-29.7) of the patients in the placebo + AZA arm. ORR was significantly higher in the Tibsovo® + AZA arm than in the placebo + AZA arm (odds ratio of 7.15 [95% CI, 3.31-15.44]; p<0.001). Additionally, seven (9.7%) patients in the Tibsovo® + AZA arm and 27 (36.5%) in the placebo + AZA arm had stable disease at the time of data cutoff (122). A summary of ORR is presented in Table 32.

Table 32. AGILE – Summary of ORR (FAS)

	Tibsovo® + AZA (N = 72)	Placebo + AZA (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 (122).

10.1.5.4 Secondary endpoint: Duration of response

10.1.5.4.1 DOR

Median duration of response (DOR) was 22.1 months in the Tibsovo® + AZA arm (95% CI, 13.0-NE) and 9.2 months in the placebo + AZA arm (95% CI, 6.6-14.1). The durability of the Tibsovo® + AZA treatment effect was demonstrated at 9, 12, 18, and 24 months (122).

10.1.5.4.2 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 Tibsovo® + AZA arm and was [redacted] months in the placebo + AZA arm (95% CI [redacted]). The durability of the Tibsovo® + AZA treatment effect was demonstrated at 6, 9, 12, 18, and 24 months (121).

10.1.5.4.3 DOCRh

Median DOCRh was [redacted] as of the data cutoff date in the Tibsovo® + AZA arm and was XXX months in the placebo + AZA arm (95% CI, [redacted]). The durability of the Tibsovo® + AZA treatment effect was demonstrated at 3, 6, 9, 12, 18, and 24 months (121).

10.1.5.4.4 DOCRi

Median DOCRi was [redacted] as of the data cutoff date in the Tibsovo® + AZA arm and was [redacted] months in the placebo + AZA arm (95% CI, [redacted]). The durability of the Tibsovo® + AZA treatment effect was demonstrated at 6, 9, 12, 18, and 24 months (121).

10.1.5.5 Secondary endpoint: Time to response

Time to response, defined as TTCR, TTCRh and TTCRi, is reported in Table 33. The median time to first CR was 4.2 months (range, 1.7 to 9.2) in the Tibsovo® + AZA arm and 3.8 months (range, 1.9 to 8.5) in the placebo + AZA arm. The median time to first CR + CRh was 4.0 months (range, 1.7 to 8.6 months) in the Tibsovo® + AZA arm and 3.9 months (range, 1.9 to 7.2 months) in the placebo + AZA arm. The median TTR was 2.1 months (range, 1.7 to 7.5 months) in the Tibsovo® + AZA arm and 3.7 months (range, 1.9 to 9.4 months) in the placebo + AZA arm (122). The median time to first CR +CRi was [redacted] months (range, [redacted] months) in the Tibsovo® + AZA arm and [redacted] months (range, [redacted] months) in the placebo + AZA arm (121).

Table 33. AGILE – Summary of time to CR, CR + CRh, first response and CR +CRi (TTCR, TTCRh, TTR, TTCRi) (FAS)

	Tibsovo® + AZA (N = 72)	Placebo + AZA (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
sTime to first response (months)***		
n	45	14
Mean (SD)	2.8 (1.320)	3.9 (1.985)
Median	2.1	3.7

	Tibsovo® + AZA (N = 72)	Placebo + AZA (N = 74)
Min, max	[redacted]	[redacted]
Time to CR +CRi(months)****		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]

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 (122) & adapted from AGILE – data cutoff date: 18 March 2021 [Data on file] (121).

Overall, the median duration of treatment was more than two times longer in the Tibsovo® + AZA arm (6.0 months [range, 0.1 to 33.5]) than in the placebo + AZA arm (2.8 months [range, 0.1 to 19.8]) (122).

10.1.5.6 Secondary endpoint: Hematologic 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 Tibsovo® + AZA and placebo + AZA arms (54.2% versus 54.1%, respectively). Among patients who were transfusion dependent at baseline, a higher proportion who received Tibsovo® + AZA (18 [46.2%] patients) experienced RBC and PLT transfusion independence compared with those who received placebo + AZA (7 [17.5%] patients) (two-sided p = 0.006). Furthermore, regardless of baseline transfusion status, a greater proportion of patients in the Tibsovo® + AZA arm (45 [62.5%] patients) experienced RBC and/or PLT transfusion independence compared with the placebo + AZA arm (38 [51.4%] patients), however this difference was not statistically significant (two-sided p = 0.21) (122).

Consistent with improved infection rates versus placebo + azacitidine, an increase in absolute neutrophil count from baseline was noted only with Tibsovo® + azacitidine over time, particularly during the first cycle of treatment, with the advantage maintained over time (34). Absolute neutrophil count change from baseline through C11D1 among patients in the Tibsovo® + azacitidine arm compared with those in the placebo + azacitidine arm is shown in Figure 17.

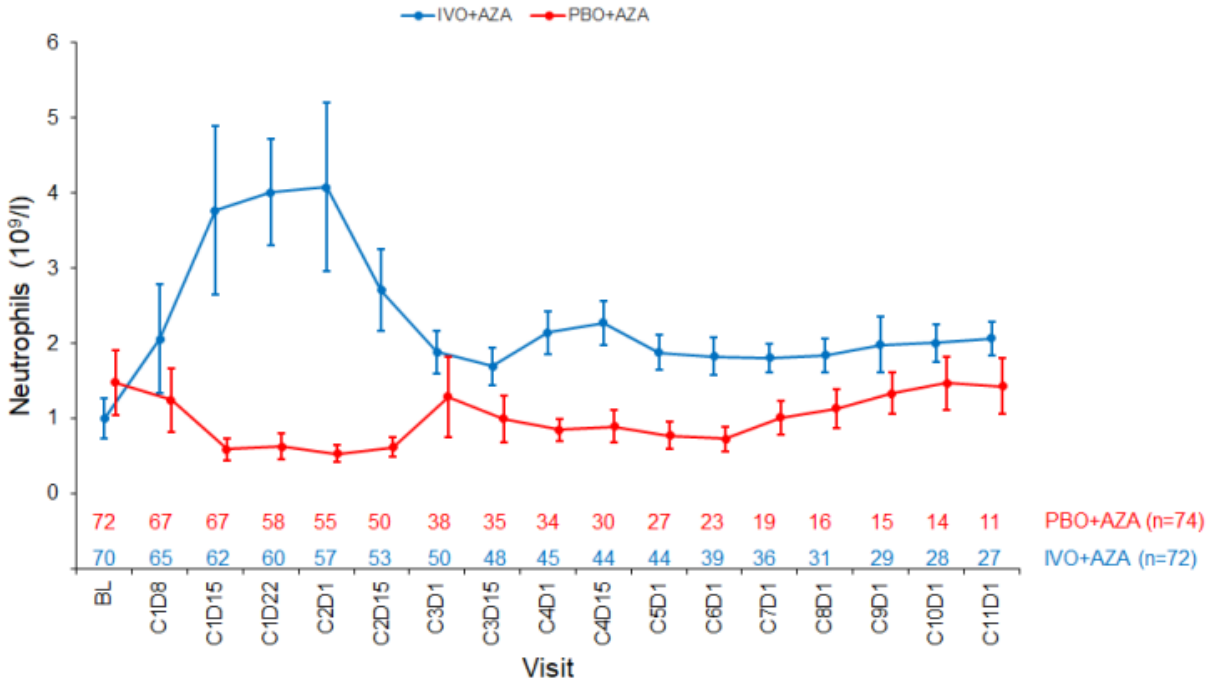


Figure 17. AGILE – Change in absolute neutrophil count from baseline with Tibsovo® + azacitidine compared with placebo + azacitidine

Abbreviations: AZA, azacitidine; BL, baseline; CxDy, cycle x day y; IVO, ivosidenib -Tibsovo®; n, number; PBO, placebo.
Source: Montesinos et al. 2022 (122)

10.1.5.7 Safety and tolerability

A summary of common and Grade ≥3 adverse events is presented by preferred term in Table 34.

Table 34. AGILE – Summary of adverse events (SAS)

Event	Tibsovo® + AZA (N = 71) n (%)		Placebo + AZA (N = 73) n (%)	
	Any grade	Grade 3 or higher	Any grade	Grade 3 or higher
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)

Event	Tibsovo® + AZA (N = 71) n (%)		Placebo + AZA (N = 73) n (%)	
	Any grade	Grade 3 or higher	Any grade	Grade 3 or higher
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 Tibsovo® + AZA group.

Source: Montesinos et al. 2022 (122) & adapted from AGILE – data cutoff date: 18 March 2021 [Data on file] (121).

10.1.5.7.1 Adverse events of special interest

Differentiation syndrome

The percentage of patients with differentiation syndrome of any grade was 14.1% (10 patients) with Tibsovo® + AZA treatment and 8.2% (six patients) with placebo + AZA. The majority of differentiation syndrome AEs in the Tibsovo® + AZA arm were Grade 2 (seven [9.9%] patients), with only three (4.2%) patients experiencing a grade 3 event. In the placebo + AZA 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 35). Serious

AEs of differentiation syndrome were reported in six (8.5%) patients in the Tibsovo® + AZA arm and one (1.4%) patient in the placebo + AZA arm (121).

All cases were managed with glucocorticoids, diuretics, and hydroxyurea. The median time to onset of investigator-reported differentiation syndrome of any grade in the Tibsovo® + AZA group was 19.5 days (range, 3.0 to 33.0). No deaths due to differentiation syndrome were noted in either group (122).

QT prolongation

Adverse events of QT interval prolonged on ECG of any grade were reported in 14 (19.7%) patients in the Tibsovo® + AZA arm compared to five (6.8%) of patients in the placebo + AZA arm. The frequency of grade ≥3 QT prolongation was 9.9% (seven patients) with Tibsovo® + AZA compared to 4.1% (three patients) with placebo + AZA. All QT prolongation AEs were Grade 3 events (Table 34).

Leukocytosis

Leukocytosis was reported in eight (11.3%) patients in the Tibsovo® + AZA arm and one (1.4%) patient in the placebo + AZA arm. There were no grade ≥3 AE's of leukocytosis reported in either arm. None of the events of leukocytosis were assessed as serious (Table 35).

Table 35. AGILE – Summary of adverse events of special interest (SAS)

	Tibsovo® + AZA (N = 71) n (%)	Placebo + AZA (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] (121).

10.1.5.8 Patient reported outcomes: 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 (122).

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 Tibsovo® + AZA arm, with no statistically significant or clinically meaningful differences (i.e., difference in subscale score change exceeding 10 points) in favor of the placebo + AZA arm at any visits (Figure 18 and Figure 19) (122).

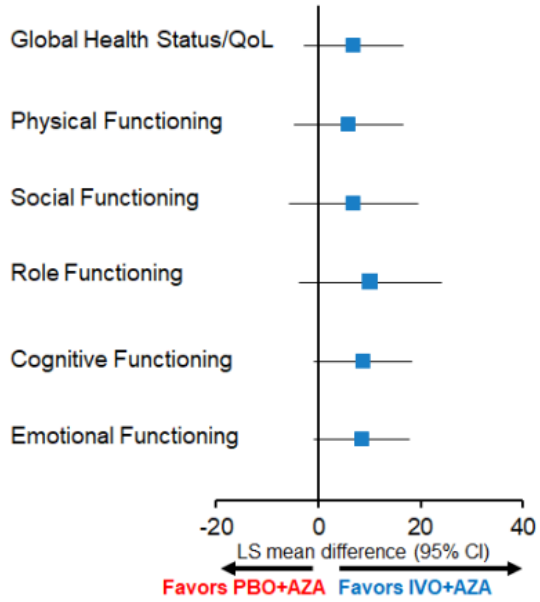


Figure 18. AGILE – EORTC QOQ-C30 Global Health Status/QoL and functional subscales change scores between arms at C5D1 (FAS)

Abbreviations: AZA, AZA; 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 -Tibsovo®; 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 (122)

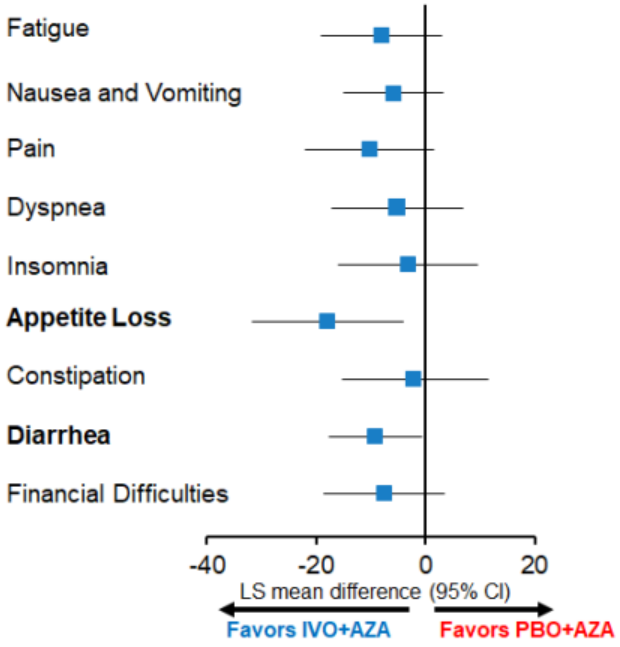


Figure 19. AGILE – EORTC QOQ-C30 symptom subscales change scores between arms at C5D1 (FAS)

Abbreviations: AZA, AZA; 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 -Tibsovo®; LS, least squares; PBO, placebo

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

Source: Montesinos et al. 2022 (122)

Following an initial, similar decline from baseline to C3D1 in both arms, HRQoL for remaining patients in the Tibsovo® + AZA arm was similar to baseline or showed improvement across many EORTC QLQ-C30 subscales from C5D1 until C19D1 (after which no placebo + AZA HRQoL data were available). The decline was consistent with time to response of about 4 months. Notably, from C5D1 to C19D1, patients in the Tibsovo® + AZA arm experienced clinically meaningful improvements in the Global Health Status/QoL subscale (exceeding the 10-point threshold) at all visits except C17D1 (Figure 20). In contrast, patients in the placebo + AZA 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 Tibsovo® + AZA arm versus

the placebo + AZA 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) (122, 155).

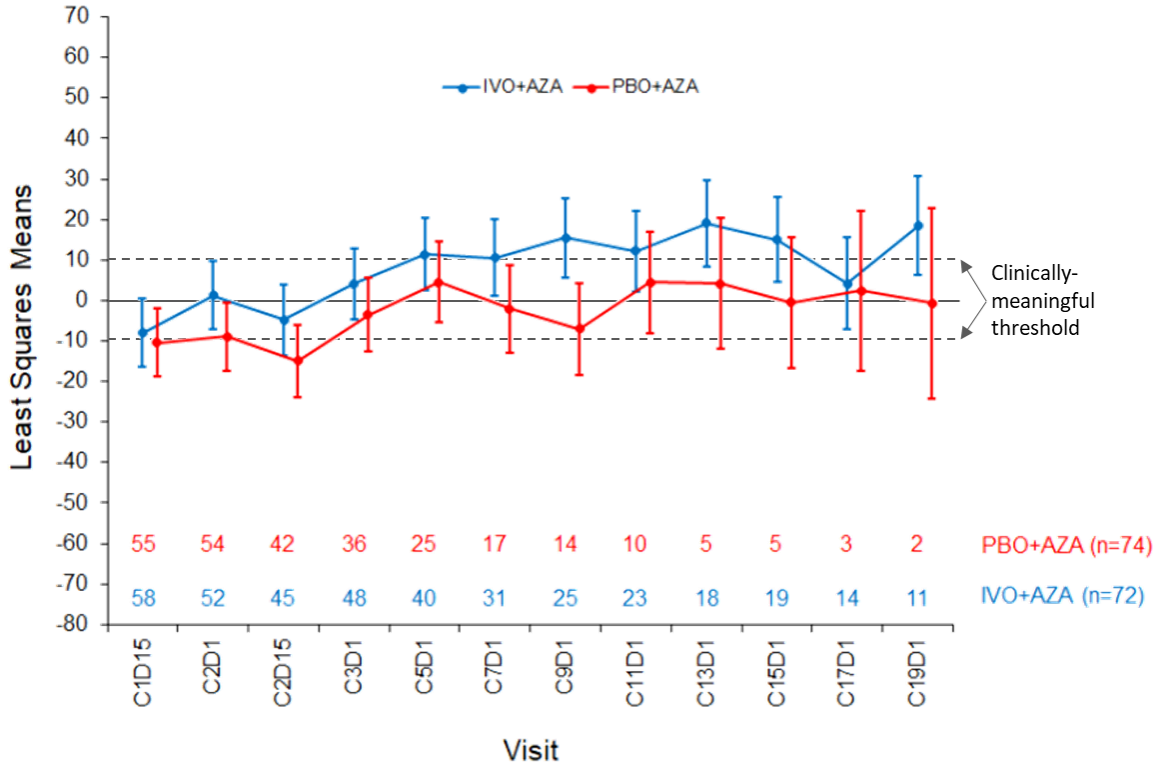


Figure 20. AGILE – EORTC QOQ-C30 Global Health Status/QoL score change from baseline through C19D1 (FAS)

Abbreviations: AZA, AZA; 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 -Tibsovo®; 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 (122)

Similar trends were observed on the Fatigue subscale (Figure 21). From C5D1-C19D1, improvements in the Tibsovo® + AZA arm were clinically meaningful at all visits except for C5D1, whereas Fatigue scores were similar to baseline in the placebo + AZA 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 Tibsovo® + AZA arm versus the placebo + AZA arm at C7 (12.7), 9 (15.0), 11 (11.1), 13 (24.1), 15 (13.1), and 19 (13.1) (122, 155).

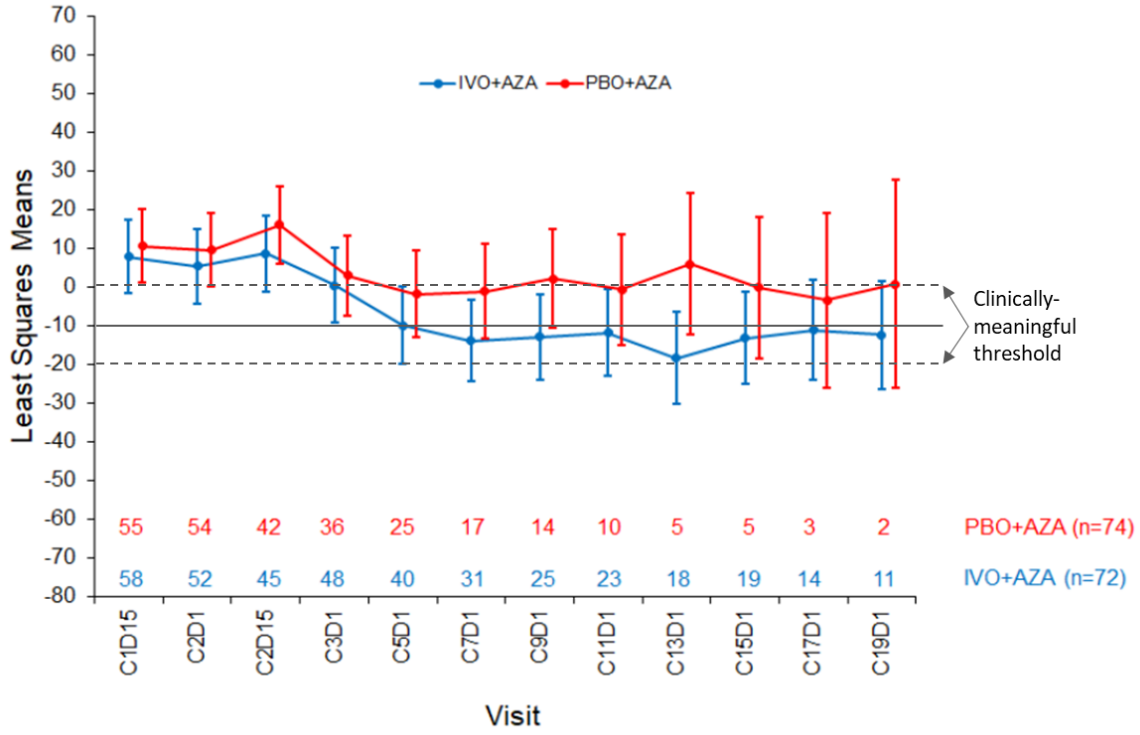


Figure 21. AGILE – EORTC QOQ-C30 Fatigue score change from baseline through C19D1 (FAS)

Abbreviations: AZA, AZA; 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 -Tibsovo®; 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 (41).

Source: Montesinos et al. 2022 (122)

In addition, clinically meaningful differences between arms, favoring Tibsovo® + AZA, in appetite loss and nausea and vomiting symptoms subscales were observed at most visits from C5D1 to C19D1 (155). Scores remained worse than baseline in the Tibsovo® + AZA and placebo + AZA arms for the insomnia Figure 20 and constipation subscales, with meaningful deterioration at multiple visits for both arms.

Patients in the placebo + AZA 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 + AZA 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) (122).

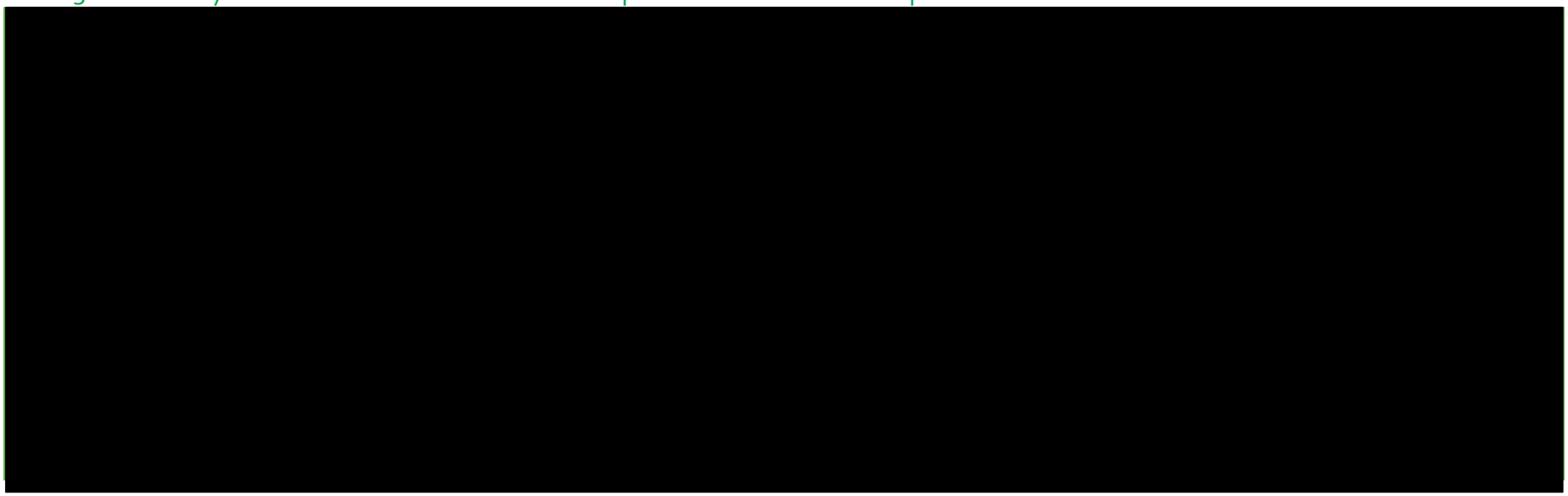
Score change from baseline for each EORTC QLQ-C30 subscale was analyzed with mixed models for repeated measures. Results favored Tibsovo® + AZA across all EORTC QLQ-C30 subscales (122).

In summary, the clinical benefit Tibsovo® + AZA 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 diarrhea, HRQoL results also favored Tibsovo® + AZA over placebo across the remaining symptoms subscales. Patients in the Tibsovo® + AZA arm experienced stabilization of HRQoL, and showed clinically meaningful improvements in Global Health Status/QoL at most visits.

10.1.6 Supporting studies

As part of the clinical development programme for Tibsovo®, several clinical practice and real-world evidence studies in AML are currently being developed or are already available. An overview of the key studies in development for Tibsovo® are included in Table 36.

Table 36. Summary of real-world evidence and clinical practice studies in development for Tibsovo®



Abbreviations: 2-HG, 2-hydroxyglutarate; AE, adverse events; AESI, adverse event of special interest; Allo-HSCT Hematopoietic stem cell transplantation; AML, Acute myeloid leukemia; AZA; CR, complete remission; CRi, Complete Remission with Incomplete Count Recovery; EFS, event-free survival; FDA, Food and drug administration; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; IWG, International Working Group; MRD, Minimal Residual Disease; ORR, objective response rate; OS, overall survival

Notes: *Data similar to AGILE in clinical practice setting; **Complementary data; † Quality of life; †† Work with patients

Source: Servier Pharmaceuticals 2022 (157)

10.2 Comparative effectiveness

10.2.1 Evidence base and studies included in the ITC

The SLR (previously mentioned in section **Fel! Hittar inte referenskälla.**) was conducted on 28th October 2021 and updated on 31st of January 2023 with the aim to identify relevant clinical trials that investigated the efficacy and safety of therapies in adults with previously untreated (including secondary) AML who are ineligible for intensive chemotherapy (158). 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 NITA (159, 160). The approach complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (161). The literature searches, which were conducted through the OVID platform, included the MEDLINE®, Embase® and Cochrane Central Register of Controlled Trials databases (129). Hand-searches of the proceedings for key oncology conferences (between 2019 and 2021) and clinical trial registries (Clinicaltrials.gov, International Clinical Trials Registry Platform and Clinicaltrialsregister.eu) were also included. For full details see the ITC report (129).

In total, 4,503 records were identified from the original literature search and a further 883 in the updated search. After removal of duplicate records and assessment for inclusion according to study eligibility criteria, a total of 26 unique studies (reported in 69 publications) were prioritized for data extraction, based on a requirement for a randomized controlled trial (RCT) design and total study sample size (N) ≥20, as possibly relevant for ITC. Following screening of the 26 extracted studies, 10 studies were included in the ITC feasibility assessment, including the AGILE study (127) and the publication by Pollyea et al. reporting on VEN efficacy (132).

It should be noted that none of the identified studies, apart from AGILE, solely recruited patients with IDH1 mutations. However, it was decided to include 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 ITC; however, it was deemed appropriate to be more inclusive to establish the comparative efficacy of available treatments. Furthermore, the prognostic impact of IDH1m on patients with AML has been assessed in several studies, with no clear evidence for an important difference in prognosis. Therefore, an ITC comparing Tibsovo® as studied in a molecularly selected population to VEN as studied in molecularly unselected populations is justifiable and valid (22, 25, 27, 28, 162). Results specific to patients with IDH1 mutations have been reported for VEN + AZA in DiNardo et al. 2020 (VIALE-A) (94) and Pollyea et al. 2022 (132) (pooled data from VIALE-A and a single-arm phase Ib study) however are based on post-hoc subgroup analyses with small sample sizes (specifically, <20 mIDH1 patients were enrolled in the AZA arm in VIALE-A, which did not meet the sample size inclusion criterion above).

10.2.2 ITC feasibility assessment

An assessment was undertaken to determine whether an ITC was feasible for outcomes of interest based on the relevant clinical evidence identified from the SLR (129). Key objectives of the feasibility assessment were to:

1. Determine whether the evidence for a given outcome of interest could be pooled across the studies within each treatment group by checking availability of reported data for each outcome of interest, consistency of outcome definitions and methods of outcome measurement
2. Determine whether the comparability/transitivity assumption was held across trials by investigating the presence and extent of between-study heterogeneity (based on comparison of baseline patient characteristics, outcome definitions and measurement and study design characteristics that could affect the outcomes of interest)

The target population for the ITC was based on the population of the AGILE trial. It included patients with 1L/treatment naïve/newly diagnosed AML/sAML (AML-MRC, t-AML) who were ineligible for intensive chemotherapy. The target population was not limited to subjects with IDH1 mutation alone due to lack of comparative evidence in the literature for patients specifically with IDH1 mutation status.

Interventions included in the ITC encompassed treatments that have been recommended for the treatment for first-line AML patients ineligible for intensive chemotherapy, specifically HMAs (decitabine, AZA), LDAC, VEN in combination with other agents, glasdegib in combination with other agents and BSC. The intervention used in the AGILE trial was Tibsovo® + AZA.

The outcomes considered for this ITC analysis were OS, EFS, DoR, CR, CR + CRi, CR +CRh, TI and transfusion burden, as these outcomes were deemed most relevant for demonstration of treatment benefit and to provide outputs amenable to economic modelling.

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, results for the mIDH1 population were based on post hoc analyses with small patient numbers (indirect comparisons using these data are not feasible)
- Population baseline characteristics for the IDH1 subgroup were not available for VEN + AZA (i.e., DiNardo et al. 2020 (94), Pollyea et al. 2022 (132)); in addition, the IDH1/2 baseline characteristics reported in the Pollyea et al. 2022 (132) publication were unbalanced between VIALE-A treatment arms
- Notable differences in placebo arm efficacy rates were observed across placebo-controlled studies (i.e., AGILE (127) and the IDH1m subgroup from VIALE-A as reported in Pollyea et al. 2022 (132)), which raised concerns about the comparability of the underlying patient populations

For the reasons listed above, results from any ITC should be interpreted within the context of these limitations. In addition, the study by Mohammed et al. 2021 (163) was not considered for evidence synthesis due to serious quality concerns. These included concerns across several domains in the risk of bias assessment, unplausible values for several baseline characteristics and erroneous results. Among the remaining studies, the patient populations were generally comparable, and a low-to-moderate degree of heterogeneity was identified. IDH1 mutation status was reported in only four comparative

studies, in which only a small proportion of the patient population was IDH1m positive; in contrast, the AGILE was conducted specifically in IDH1m positive patients.

10.2.3 NMA methodology

Analyses were run in a Bayesian framework (129). Using this approach posterior densities for the unknown parameters were estimated using Markov chain Monte Carlo (MCMC) simulations for each model and convergence assessed as per National Institute for Health and Care Excellence (NICE) guidance (164). As none of the evidence networks used in the NMA had closed loops a consistency assessment was not required according to NICE guidance.

The conducted analyses consisted of binary (CR, CR + CRi, TI) and continuous (hazard rates for OS and EFS) outcomes following NICE guidance (164). Both fixed effects (FE) and random effects (RE) models were considered for each analysis, however only one model was chosen to draw any inferences (129). The Deviance Information Criterion (DIC) was reported to choose the appropriate model for the data. Following the feasibility assessment, meta-regression was not carried out to adjust for differences in study level effect modifiers due to lack of data.

The analysis was conducted using OpenBUGS v3.2 (OpenBUGS Foundation) and R 4.1.0 (or higher) software packages (129). The models used were based on those suggested by NICE Decision Support Unit (DSU) (164). Odds ratios (ORs) were used to reflect the relative treatment effects between interventions for categorical outcomes, while HRs were used for time to event outcomes. The 2.5th and 97th percentiles to capture the 95% credible interval (CrI) of OR/HR were also calculated (note that a 95%CRI is interpreted differently to a 95% CI – the 95%CRI is interpreted that there is a 95% probably that the true estimate would lie within the interval, given the evidence provided by the observed data). For time to event outcomes (OS and EFS), median HR <1 indicates a favourable result for Tibsovo® + AZA versus the comparator. However, for categorical outcomes median OR >1 indicates a favourable result for Tibsovo® + AZA. In addition, ranking probabilities graphs and SUCRA values showing the performance of different treatments on each outcome were generated. The ranking probabilities graphs show the probabilities a treatment would rank in different places whereas SUCRA values represent an overall ranking for a treatment. The higher the SUCRA value, and the closer to 100%, the higher the likelihood that a therapy is in the top rank or one of the top ranks; the closer to 0% the SUCRA value, the more likely that a therapy is in the bottom rank, or one of the bottom ranks.

10.2.4 Additional NMA outcomes

10.2.5 NMA limitations

One of the limitations of the NMA analyses is heterogeneity in the analysis population arising from lack of published data for patients with IDH1m (129). 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 six studies reported the baseline IDH1m proportions, where the proportion of patients with the IDH1m ranged from 12.4% to 40.7% across studies, indicating differences in genetic disposition. Whether or not IDH1m status is an effect modifier for one or more of the comparator treatments is currently unknown, and therefore the NMA results should be interpreted within this context. Heterogeneity across studies was also observed in the baseline bone marrow blast count threshold that was used as a study inclusion criterion. The extent to which bone marrow blast levels are a potential effect modifier is also unknown, however, the EFS and OS HRs in AGILE did not vary significantly by baseline bone marrow blast levels. This was also the case for OS in VIALE-A, and several other included studies. In addition, heterogeneity in other patient demographic and disease characteristics was observed for gender, type of AML diagnosis, cytogenic risk, ECOG 0-1 performance status and median bone marrow blast. In addition, following the feasibility assessment, meta-regression was not carried out to adjust for differences in study level effect modifiers due to lack of data.

Another limitation of the NMA is the heterogeneity in EFS, CR + CRh, TI and conditional TI outcome definitions (129). The AZA-AML-001 study reported by Dombret et al. 2015 did not include treatment failure as part of the EFS definition; this less restrictive definition could have resulted in prolonged EFS compared to the remaining studies. The median EFS estimate for AZA in Dombret et al. 2015 (6.7 months) was higher than the median EFS estimate for AZA in AGILE (4.1 months), which could be attributed to the different definition of EFS between the studies. Although CR + CRh definitions were similar across AGILE and VIALE-A, VIALE-C included absence of circulating blasts and blasts with Auer Rods as well as absence of extramedullary disease in the CR + CRh definition. An overall limitation of CR outcomes (CR either as a single or a combined endpoint) is that the rates capture the treatment effect only partially, and they can only be fully understood when CR duration is taken into consideration. Given that CR duration typically varies between studies and could not be captured in the NMA, the CR findings should be interpreted within this limiting factor. In addition, findings for TI and conditional TI should be interpreted with caution considering the different definitions used across studies.