Joint Nordic HTA-Bodies

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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

Date for publication of report: 2024-12-18

Case number DMC: EMS-2024-00028
Case number Fimea: FIMEA/2024/002022
Case number Landspitali: IS240403
Case number NOMA: ID2022_128
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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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).

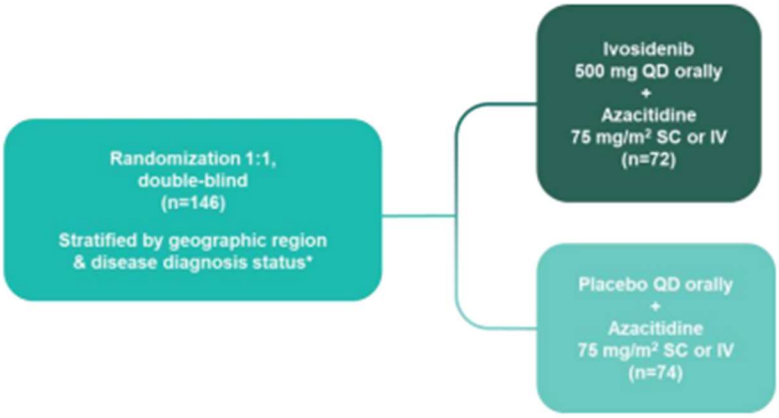


Figure 1 Study design AGILE

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.

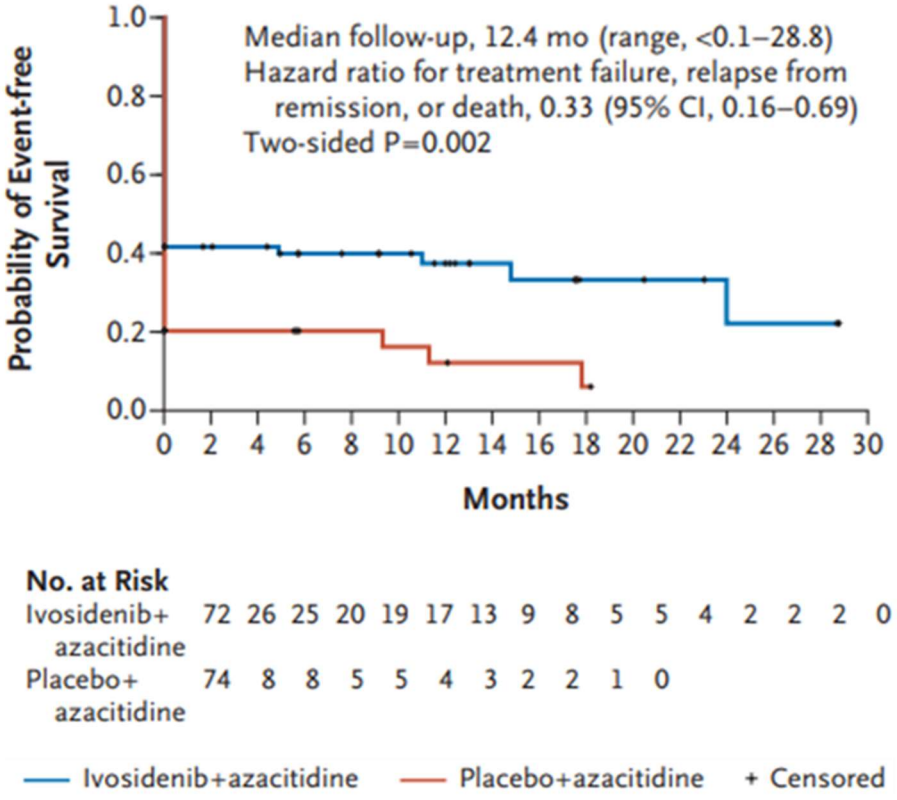


Figure 2 Kaplan-Meier plot of EFS, AGILE

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).

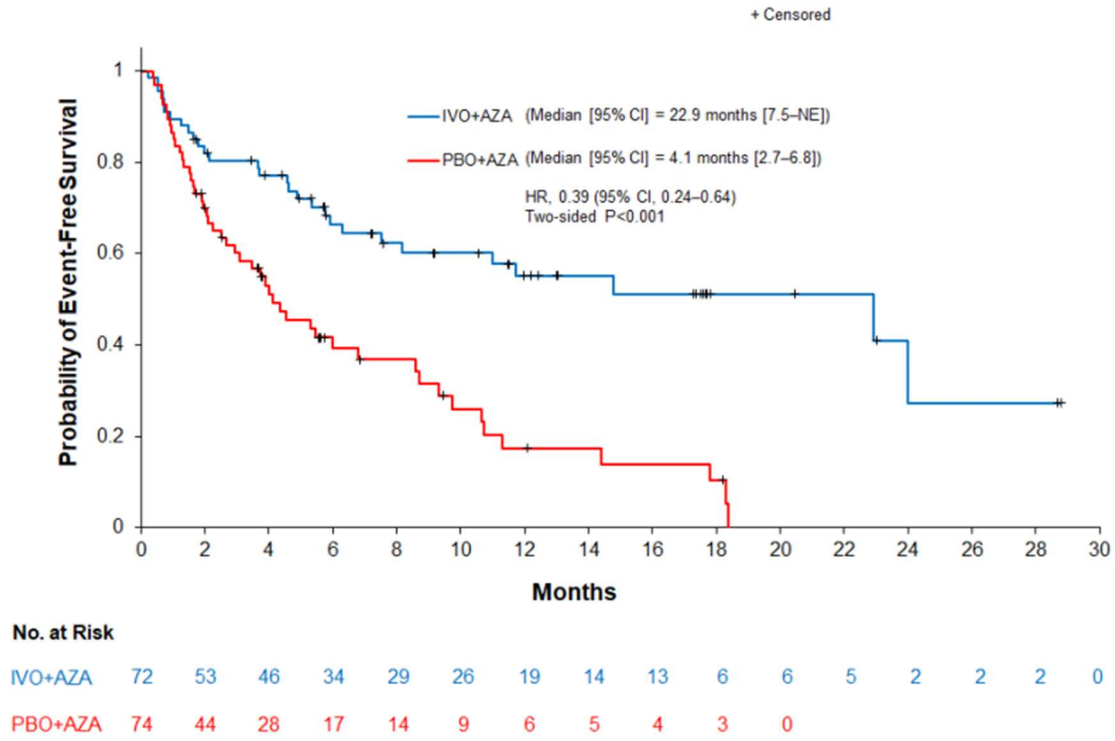


Figure 3 Kaplan-Meier plot of post-hoc EFS definition, AGILE

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.

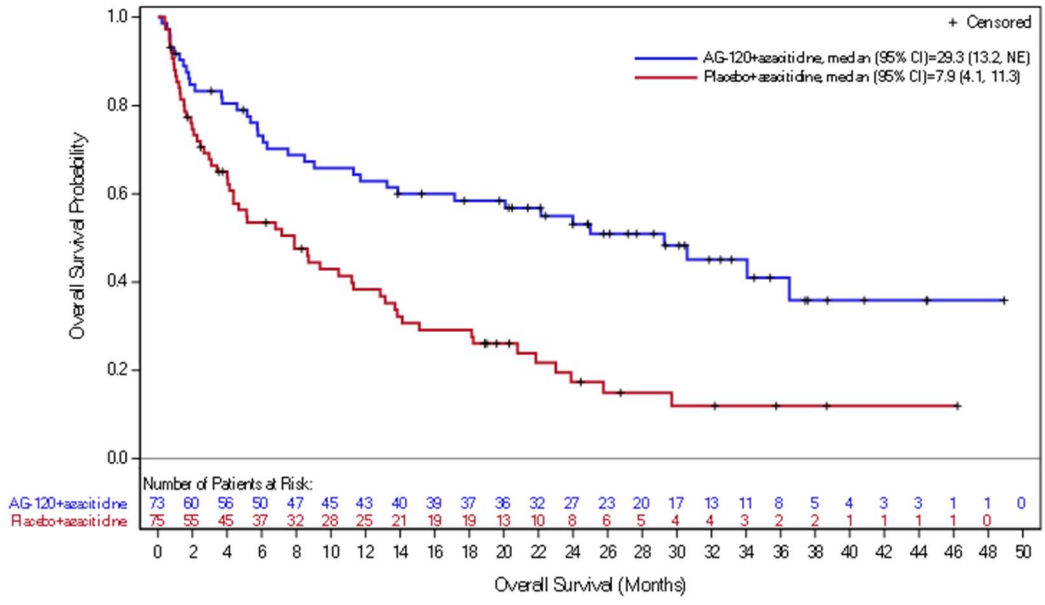


Figure 4 Kaplan-Meier plot of OS, AGILE

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.

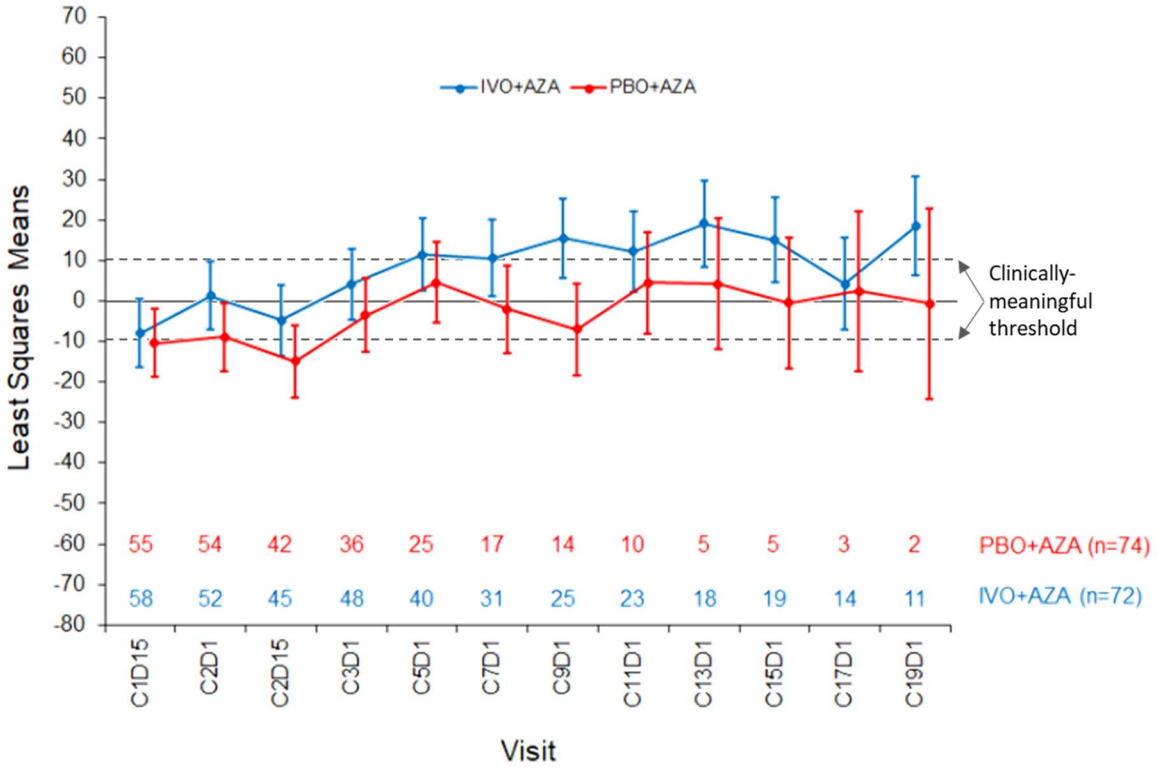


Figure 5 EORTC QLQ-C30 Global Health Status/QoL scorerom baseline (FAS), AGILE

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.

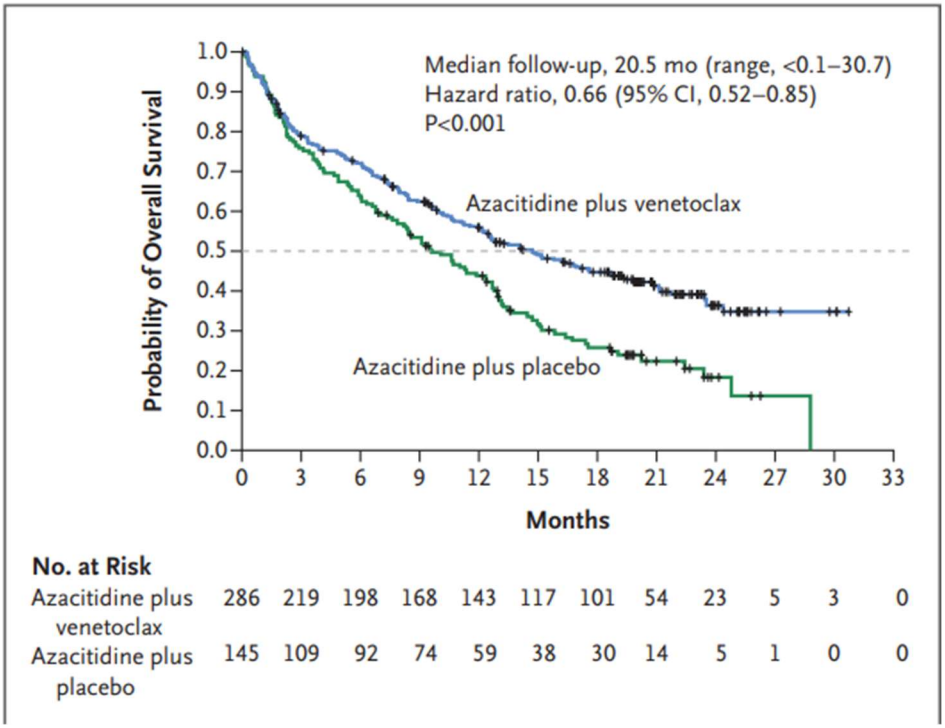
In total, 4,503 records were identified from the original literature search and a further 883 in the updated search. After removal of duplicate records and assessment for inclusion according to study eligibility criteria, 26 unique studies (reported in 69 publications) were prioritized for data extraction, 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].

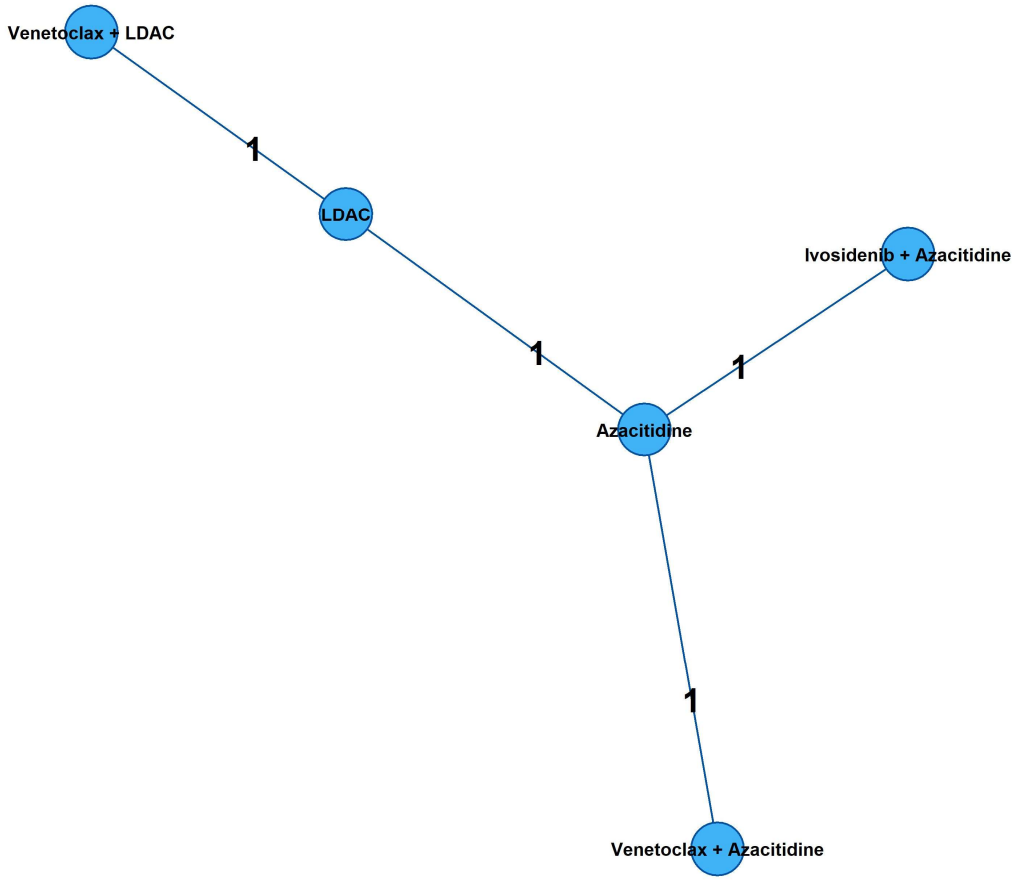


Figure 6 Evidence network for EFS

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).

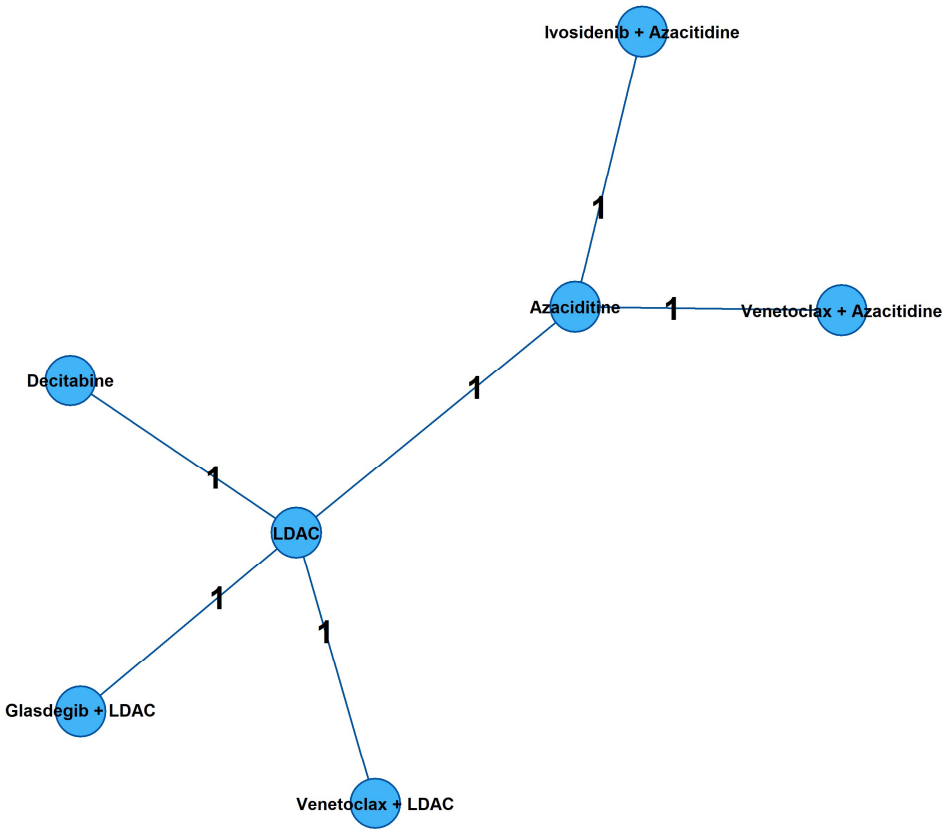


Figure 7 Evidence network for OS

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.

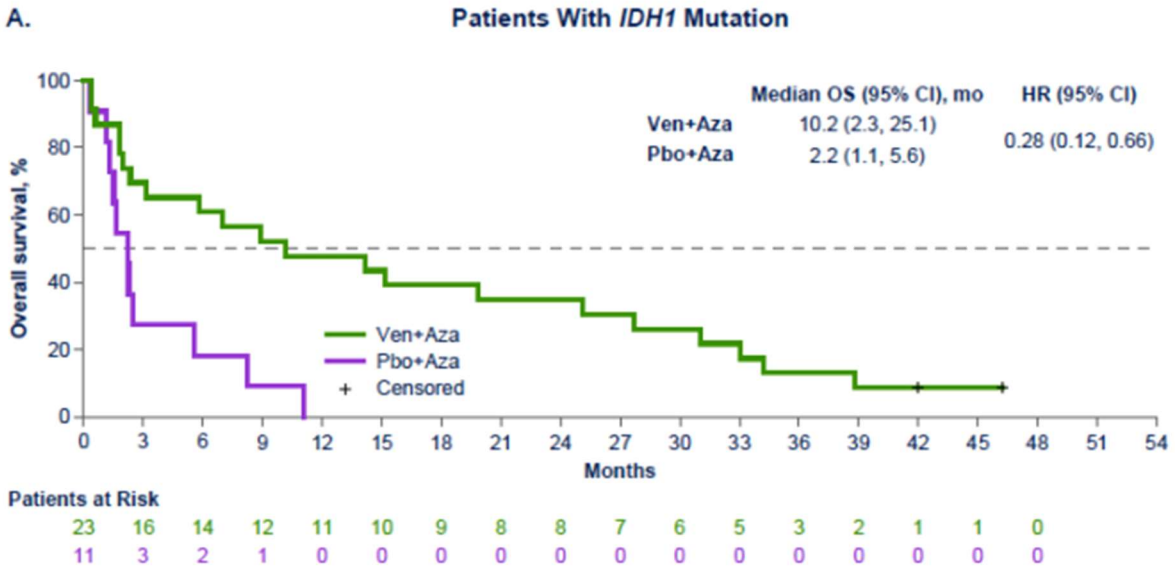


Figure 8 OS Kaplan-Meier from VIALE-A for *IDH1*-mutated patients (Pratz et al. 2022)

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.

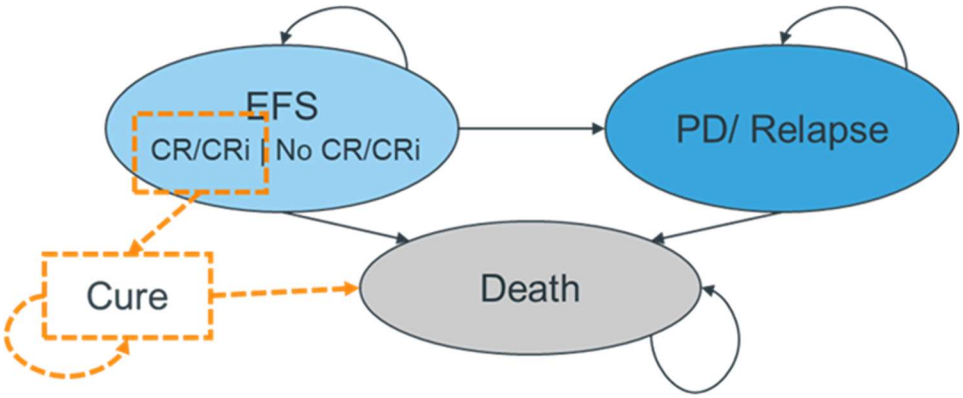


Figure 11 Servier's health economic model structure

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.

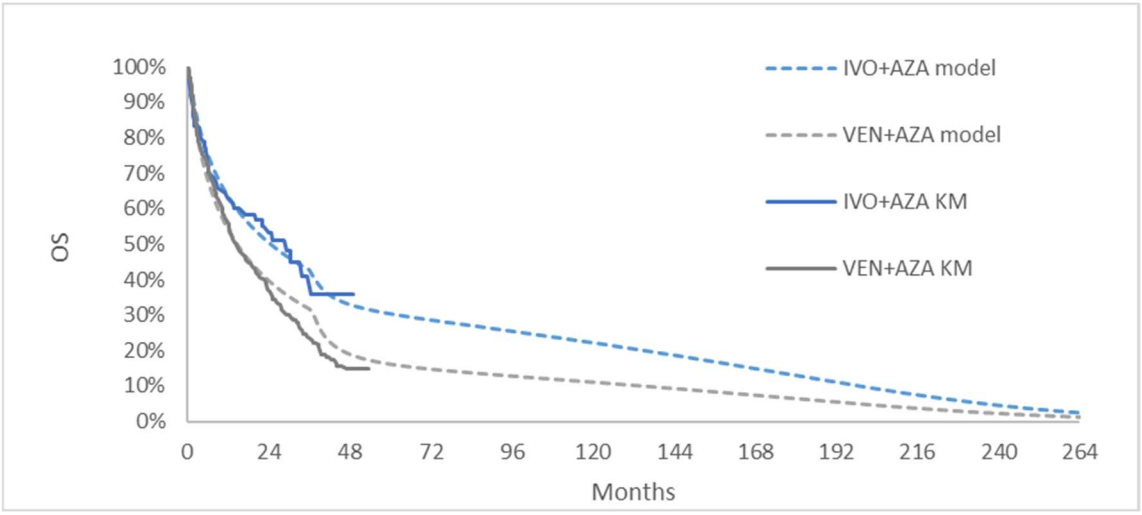


Figure 12 Servier's base case extrapolation of OS using log-normal distribution.

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.

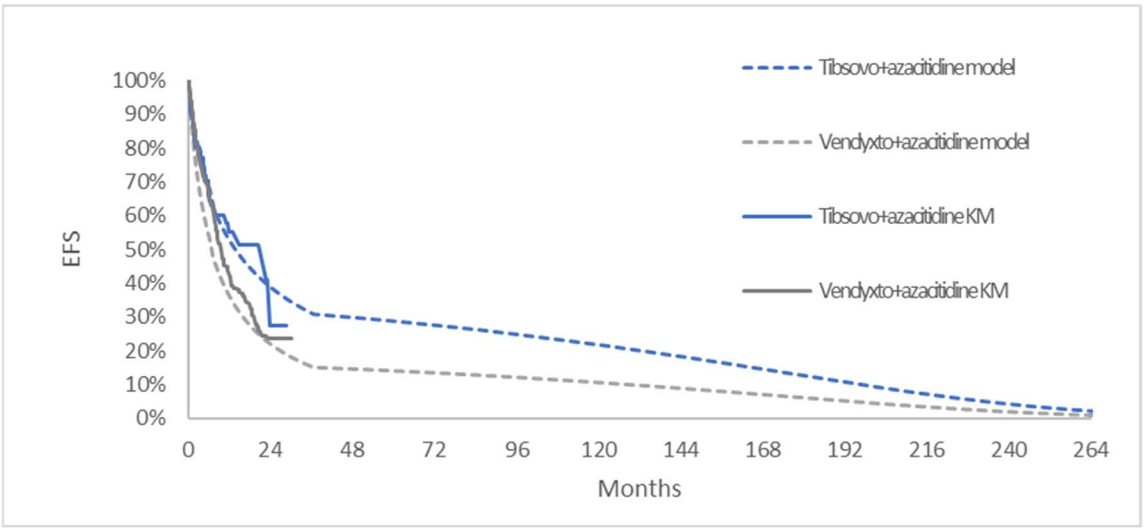


Figure 13 Servier's base case extrapolation of EFS

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.

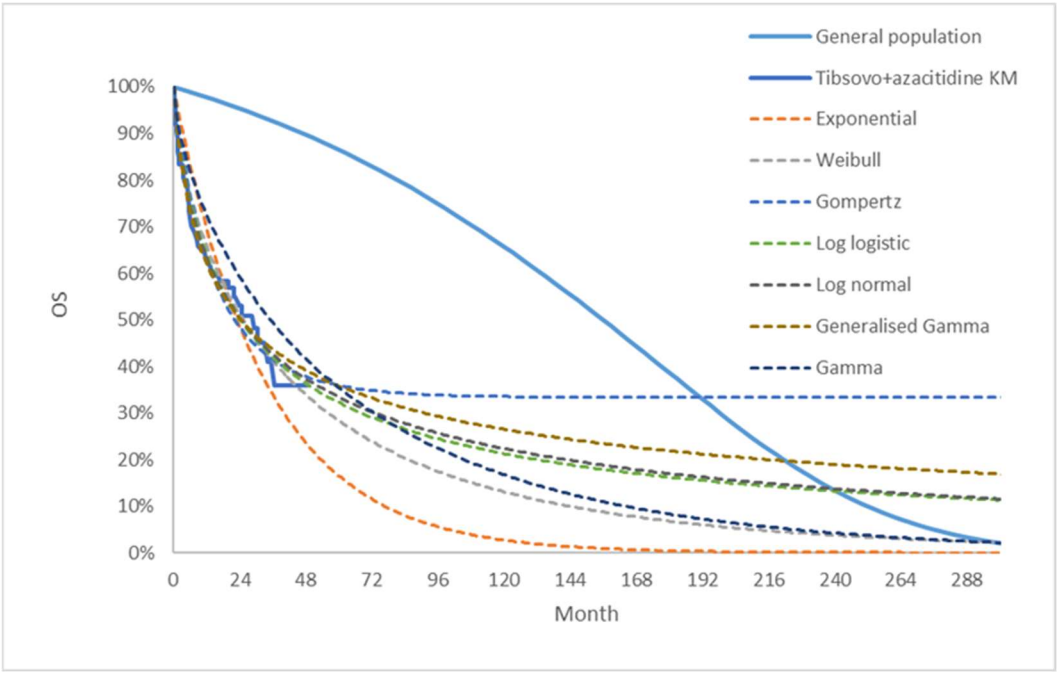


Figure 14 Extrapolated OS curves for Tibsovo+AZA in Servier's model when not assuming cure

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.

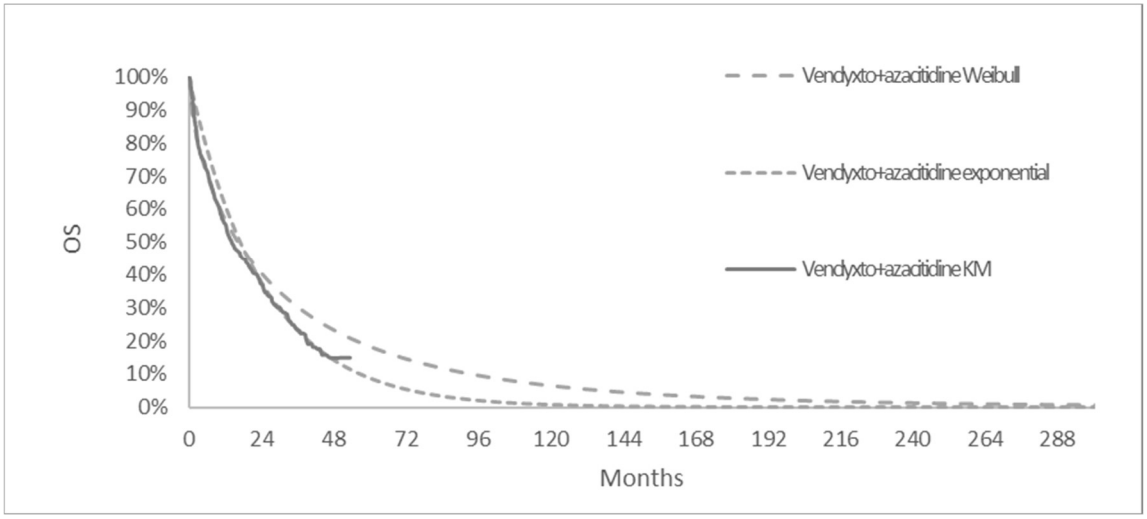


Figure 15 Extrapolated OS curves for Venclyxto+AZA in Servier's model when not assuming cure

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.

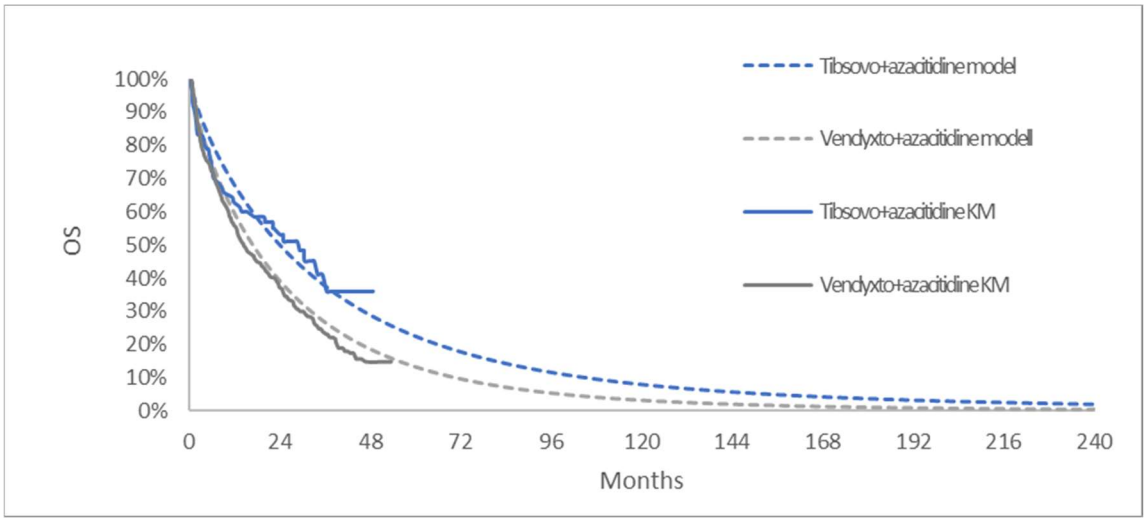


Figure 16 JNHB OS without cure. Weighted extrapolation of exponential and Weibull distribution

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.

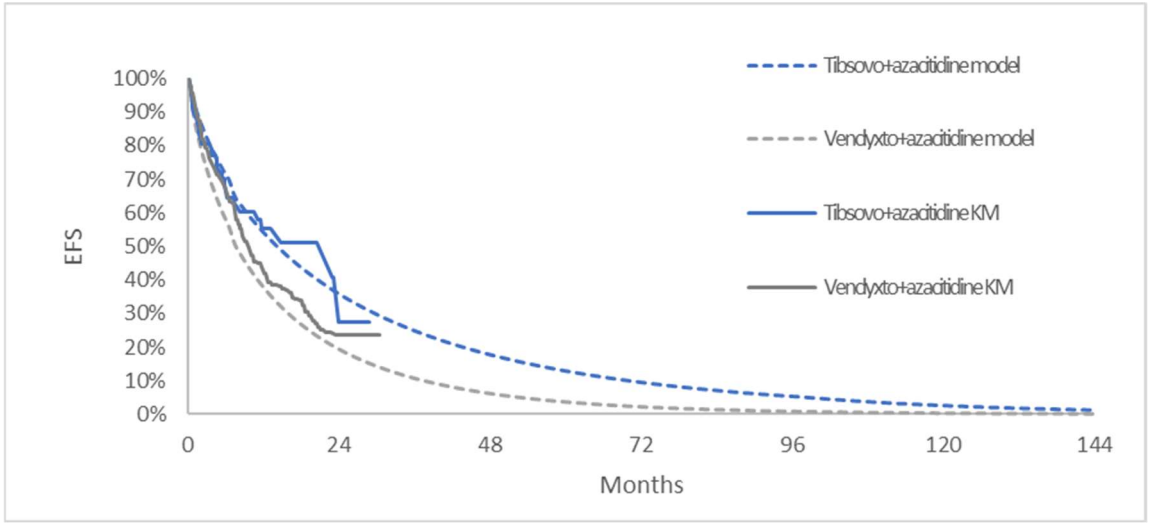


Figure 17 JNHB EFS with Weibull extrapolation

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.

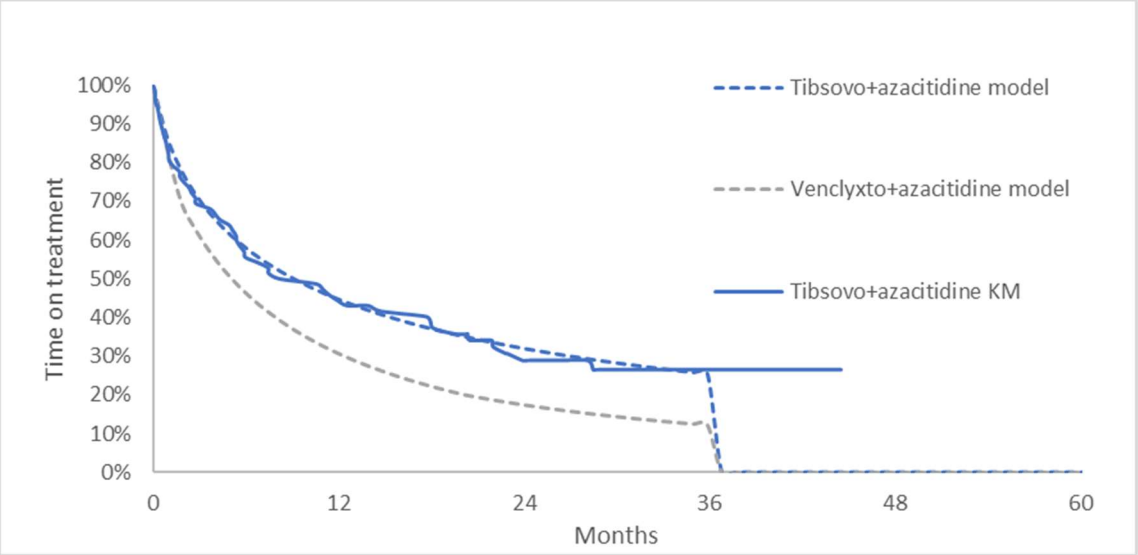


Figure 18 Servier´s modelled time on treatment

[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.

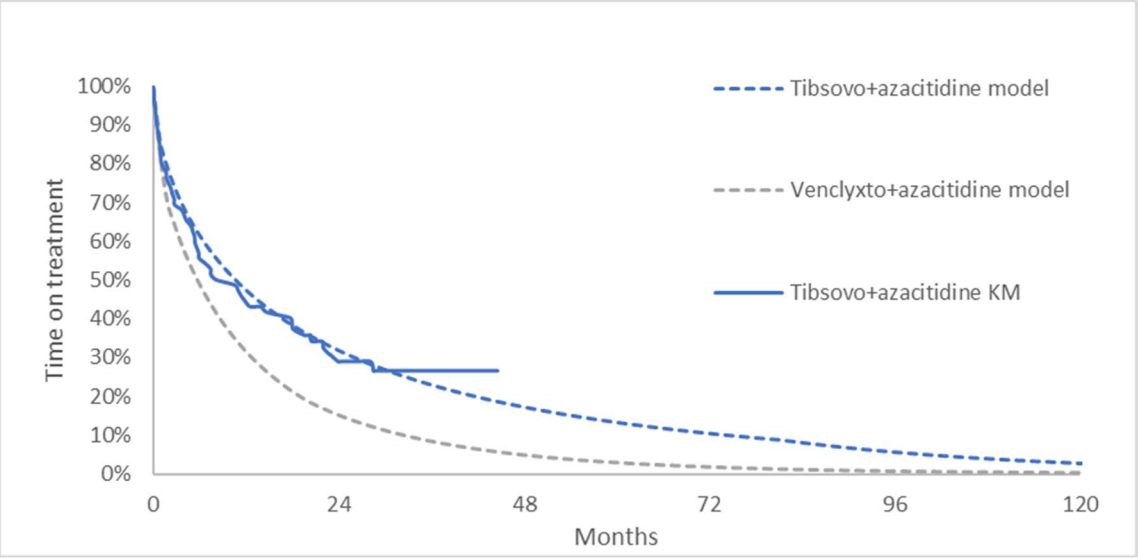


Figure 19 JNHB´s extrapolated time on treatment

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

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Appendix A Hazard of the different OS extrapolation distributions

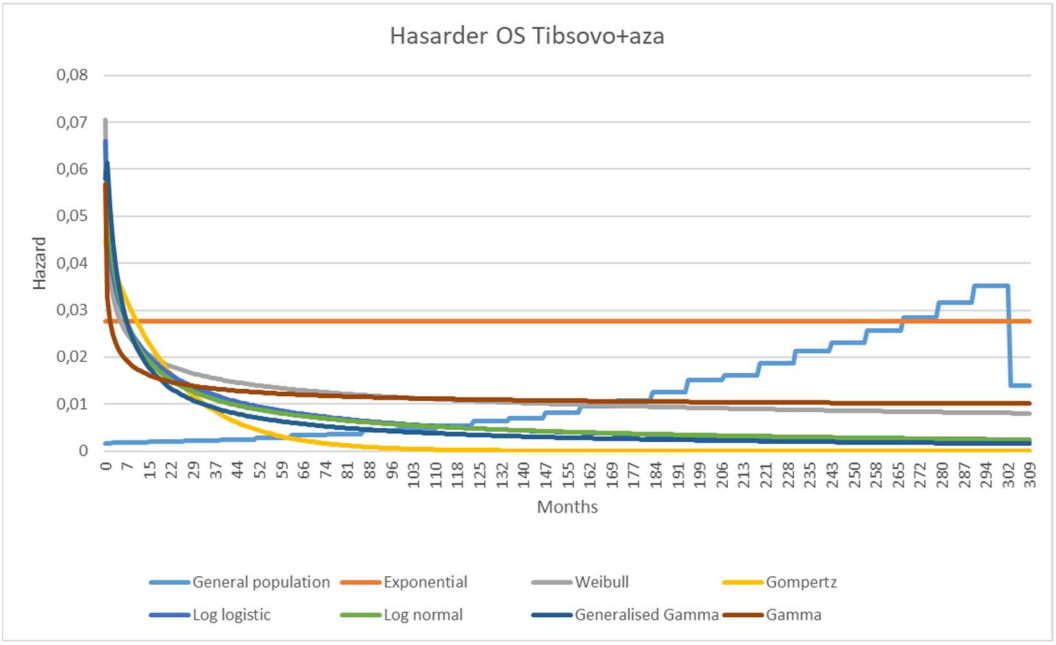

Figure A1 Hazard in different OS curves in Servier's model

Appendix B EFS and OS in sensitivity analyses

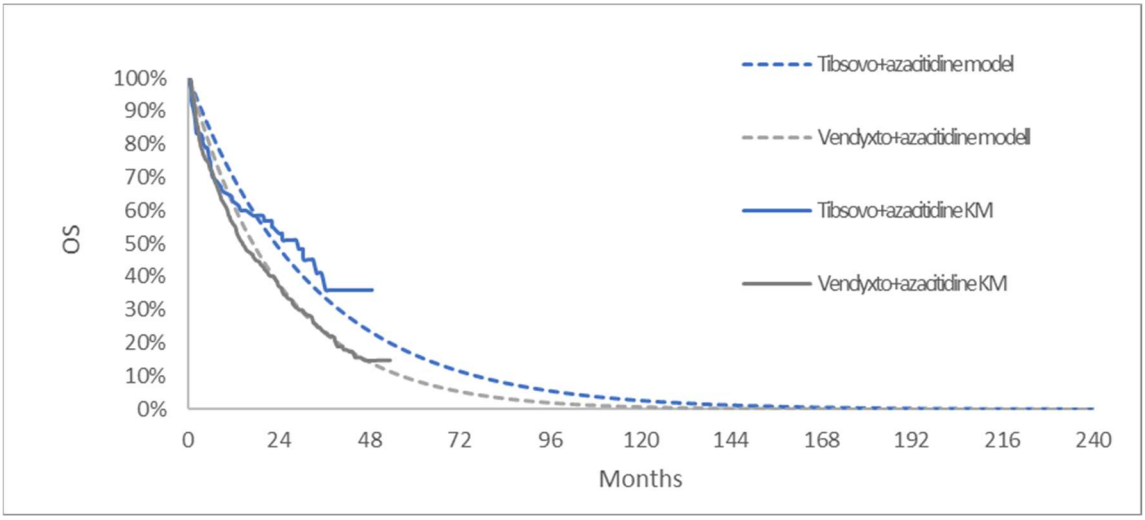

Figure B1 JNHB sensitivity analysis OS exponential distribution.

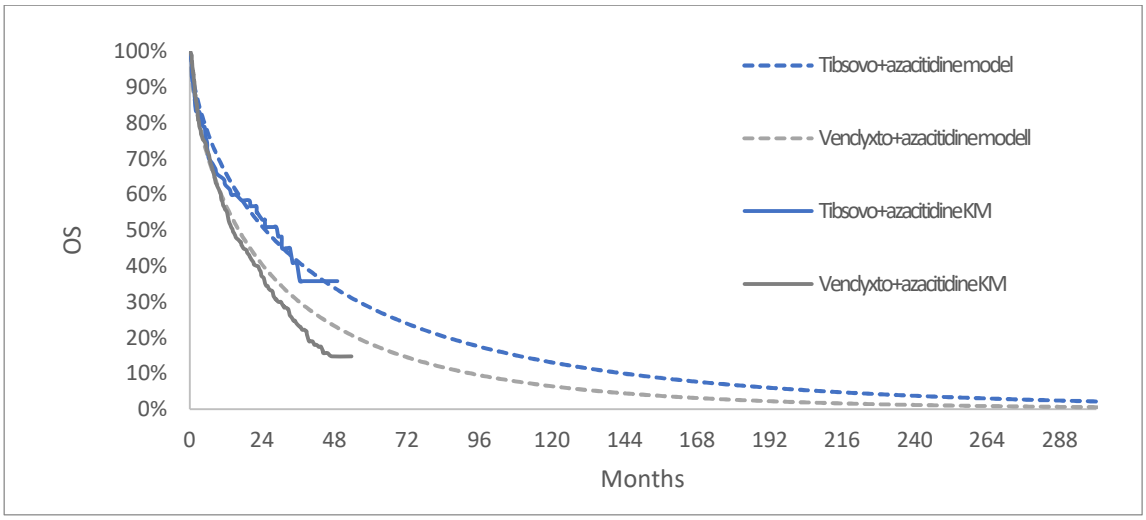

Figure B2 JNHB sensitivity analysis OS Weibull distribution.

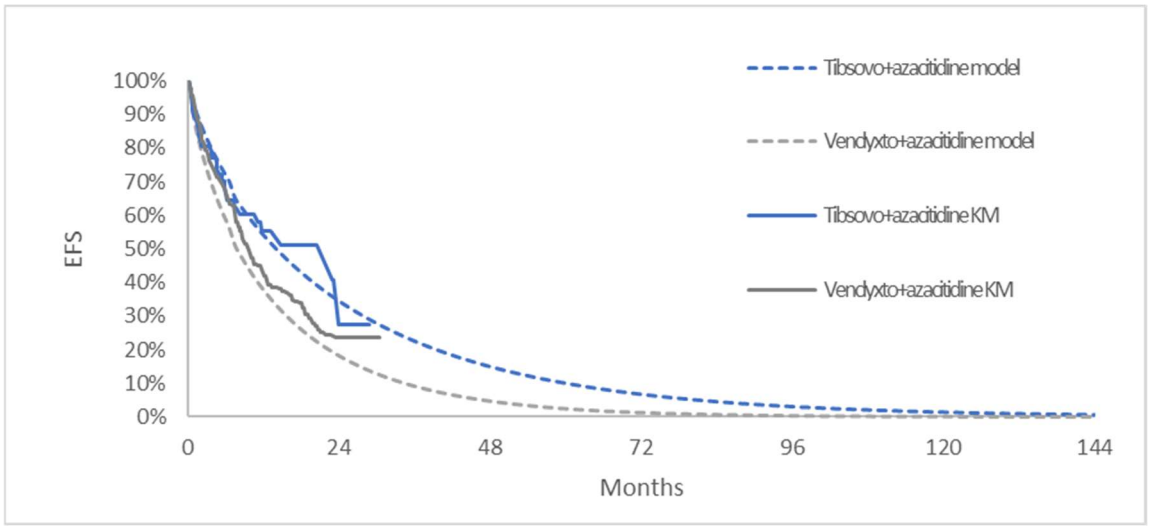

Figure B3 JNHB sensitivity analysis EFS Gamma distribution.

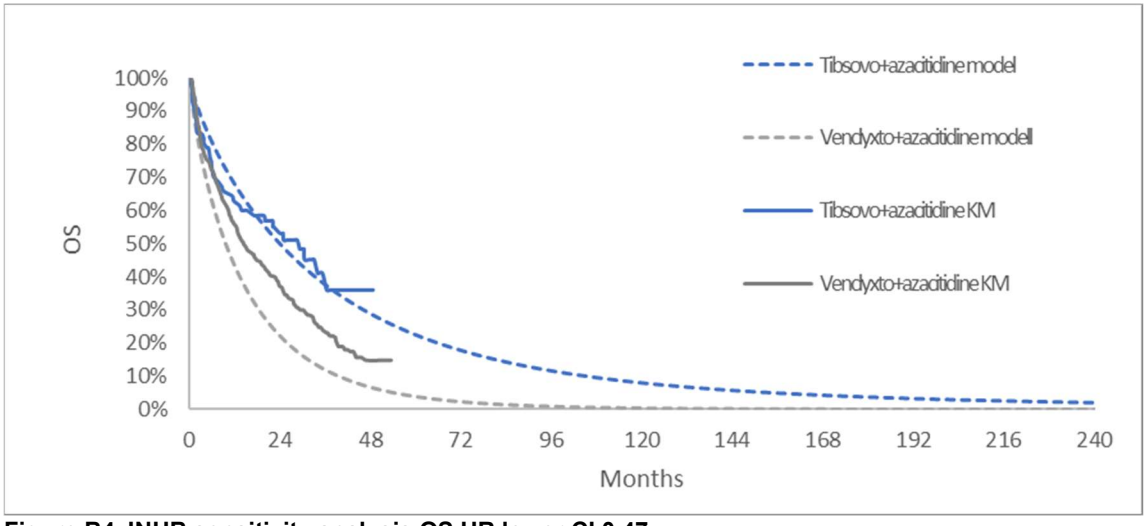

Figure B4 JNHB sensitivity analysis OS HR lower CI 0,47.

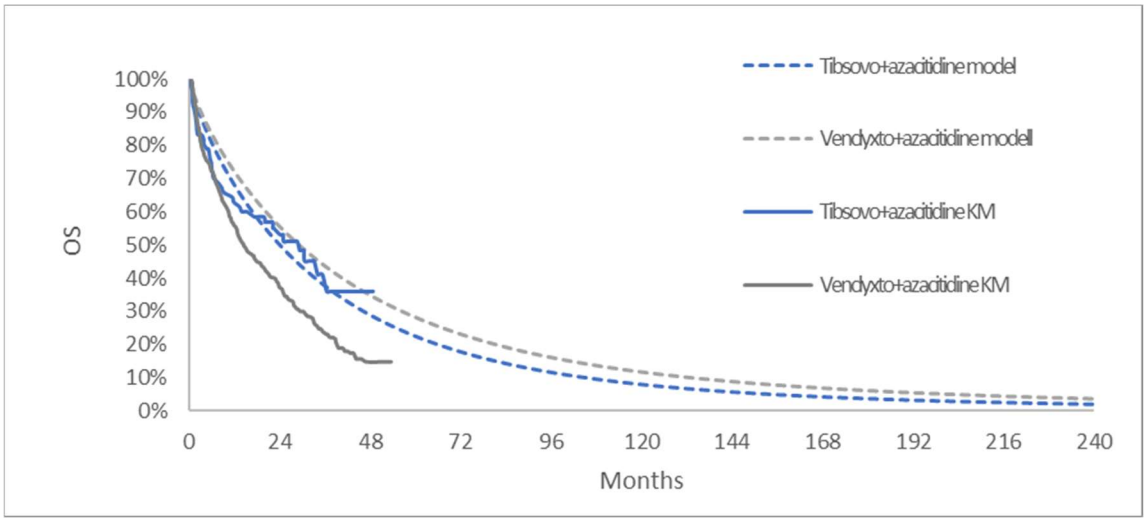

Figure B5 JNHB sensitivity analysis OS HR upper CI 1,18.

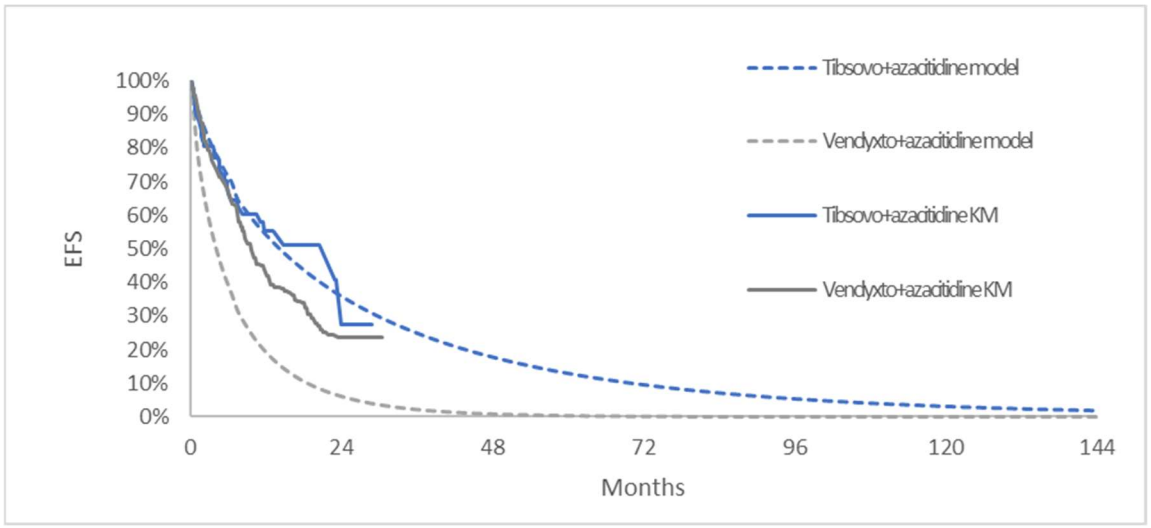

Figure B6 JNHB sensitivity analysis OS HR upper CI 0,26.

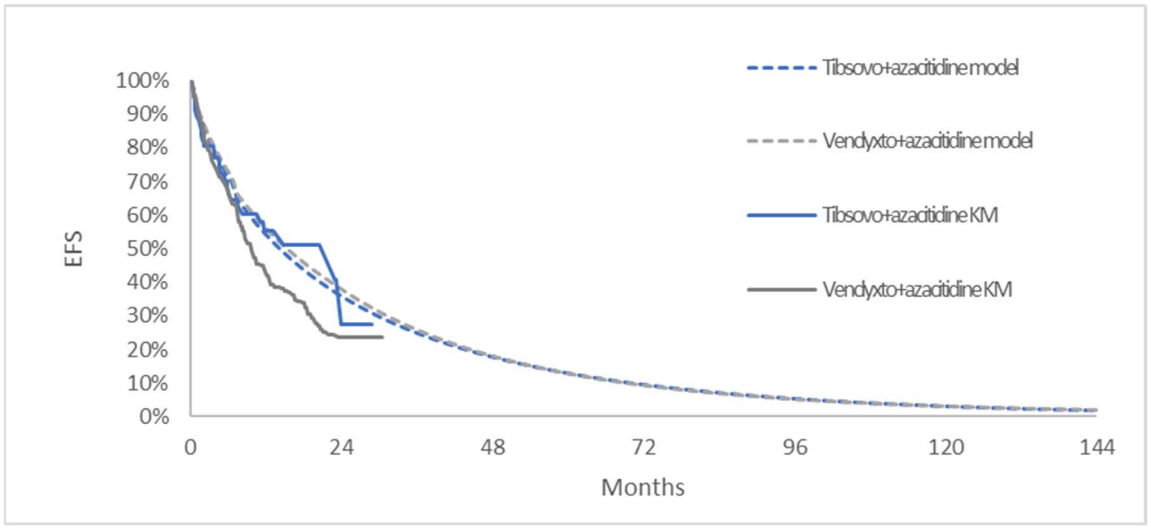

Figure B7 JNHB sensitivity analysis EFS HR upper CI 1,06.

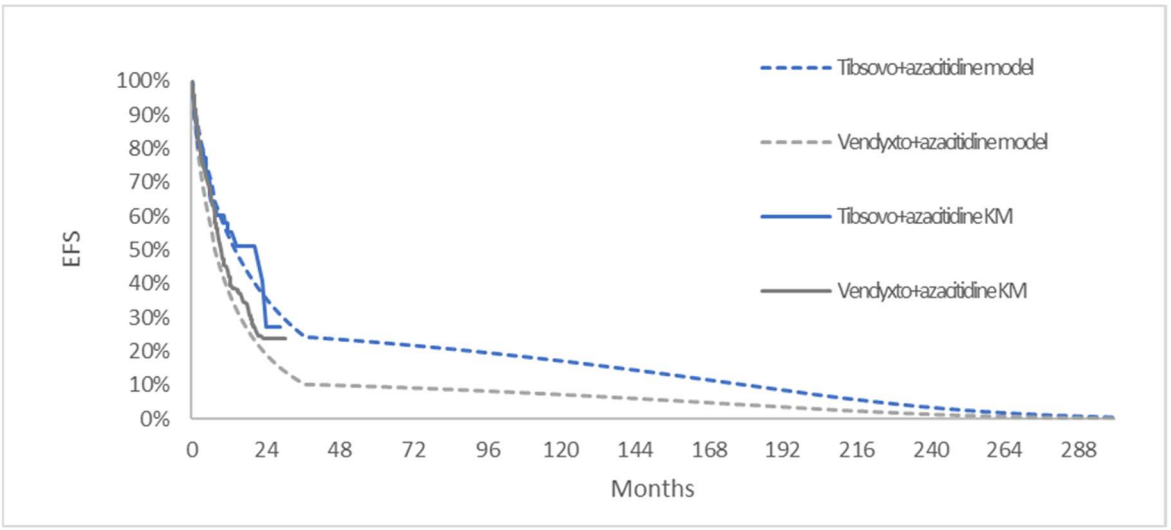

Figure B8 JNHB sensitivity analysis assuming cure after 3 years remission, EFS.

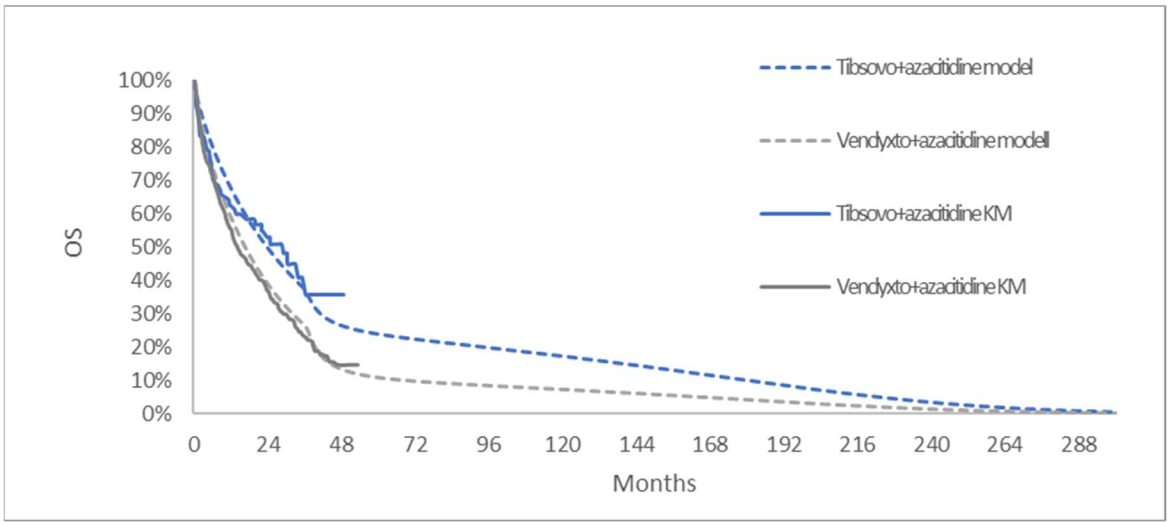

Figure B9 JNHB sensitivity analysis after 3 years remission, OS.