Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende venetoclax i kombination med azacitidin til behandling af akut myeloid leukæmi (AML)

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. venetoclax i kombination med azacitidin
2. Forhandlingsnotat fra Amgros vedr. venetoclax i kombination med azacitidin
3. Ansøgers endelige ansøgning vedr. venetoclax i kombination med azacitidin
4. Fagudvalgets svar på Rådets opfølgende spørgsmål vedr. venetoclax i kombination med azacitidin

AbbVie's comment to the DMC draft appraisal report

Secondary endpoint of transfusion independence
This endpoint of Viale-A is not at all mentioned in the draft report, although the high need for transfusions for AML patients was underlined. The endpoint is an important one, for the patients, but also for the understanding of how venetoclax works and how it can create more time for the patient outside the hospital. AbbVie insists that this endpoint is included in the final report.

Transfusion independence was defined as the absence of a red-cell or platelet transfusion for at least 56 days between the first and last day of treatment. Rates of post-baseline transfusion independence were significantly improved with venetoclax plus azacitidine compared with azacitidine plus placebo. The red blood cells independence rate improved by about 25 percentage points (59.8% vs 35.2%; p<0.001) and platelet transfusion independence improved with about 19 percentage points (68.5% vs 49,7%; p<0.001).

The need and relevance for cure modelling as a tool to estimate long-term survival in AML
Cure modelling is a technical tool to estimate long-term survival. It is not necessary to assume a cure to use cure modelling, as it can also be used as a method to achieve the modelling of survival patterns seen in a population. As presented in our submission, we are not including the assumption of a cure for venetoclax in combination with azacitadine. We are simply using the tool to estimate survival in a treated AML population, still assuming a higher death rate in the modelled population than in the general population after the time point the function is applied. DMC has itself used cure modelling in the appraisal of gilteritinib for AML. DMC assumed patients to be long-term survivors after two years in EFS but with the lower standardised mortality rate of 1.3 compared to 2 in our base-case for venetoclax + azacitidine. It is not explained in the draft report why DMC model AML differently in the case of venetoclax + azacitadine case compared to the gilteritinib case. DMC has referred to venetoclax + azacitidine not being a time-restricted chemotherapy, but the reason to that venetoclax + azacitidine is not time-restricted in the same way is because of much less toxicity and being better tolerated.

Other HTA agencies have recognised the usefulness and relevance of cure modelling as a way to estimate long-term survival in their appraisal of venetoclax + azacitadine for AML. TLV accepted the use of cure modelling and applied it at the time point of three years (as they did in their gilteritinib evaluation), and NICE explored the possibility of a proportion of patients being cured at three years. It was concluded in NICE final appraisal that "*The evidence for including a cure state in the model is uncertain, but it is plausible that some people may be cured*".

Use of anti-fungal azoles and corresponding dose intensity
DMC has in its draft report assumed a dose intensity of 60% for venetoclax based on an average use of four months of posaconazole. The discussions we have had with clinicians indicates that the use of concomitant pozaconazole in Denmark would be higher than this, as two out of three of the clinicians were expecting to use posaconazole throughout the whole treatment with venetoclax, as reflected in our base-case. The future generic pricing of posaconazole will likely also increase the probability of prescriptions (to more than 2/3 using pozoconazole through the whole treatment), which would lower the dose of venetoclax even more.

Scenario analysis with reduced health state utilities for ven+aza should be rejected and replaced
EQ-5D-5L data (and other quality of life data) was collected at baseline and, starting from treatment cycle 3 every other treatment cycle, in the time window of the first ten days of those cycles.

Since non-treatment specific utilities were estimated (i.e., pooled data from venetoclax + azacitidine and azacitidine arms), the impact of AEs on utility estimates were adjusted in the regression model. The grade 3 or 4 AEs that occurred in ≥ 5% in the Viale-A trial were included as covariates and coded as dummy variables to indicate the presence of specific AEs (1= presence, 0= not presence). Presence here means that the adverse event (of grade 3 or 4) was experienced at the time of the utility measurement. As can be seen in the table below, there are adequate numbers of observations to be able to observe the effect of the most common grade 3 or 4 adverse events.

Table 1: Observations of EQ-5D-5L with presence of a specific adverse events in Viale-A

AEs*	Number of observations with presence of AE
Neutropenia*	347
Thrombocytopenia	285
Anaemia	155
Leukopenia	135
Hypokalemia, hyponatraemia and hypophosphataemia	44
Pneumonia	18
Hypertension	18

* Grade 3/4 AEs that occurred in ≥ 5% patients were selected based on the incidence rates observed in Viale-A. Neutropenia included neutropenia and febrile neutropenia.

However, none of the disutilities for adverse event were statistically significant. Some of the adverse events are even associated with a numerically positive impact on utility. Looking at neutropenia, this was present to a higher degree at baseline for the ven + aza arm (72% vs. 62%), and was more frequently reported as an adverse event in Viale-A (42% vs 29%) keeping in mind that time on therapy was longer in the ven+ aza arm. Hence, neutropenia was common and expected in the experimental arm with the best clinical response to treatment. Looking at a regression analysis of utilities by treatment arms there is a tendency towards higher utility with ven + aza, maybe due to even deeper response, than the current three-state mixed-effects model could take into account.

Table 2: Mean utility per health state and treatment arm in Viale-A using UK value set[1]

	EFS with CR/CRi	EFS without CR/CRi	PD/RL
Ven + Aza	0,746	0,729	0,660
Placebo + Aza	0,73	0,717	0,576

The means are about 2% higher for ven + aza for the EFS states, and 14% for the PD/RL states. The same pattern was seen in Viale-C (Ven+LDAC vs. placebo+LDAC) with even higher differences to the advantage of the experimental arm. It is plausible that the positive utility estimate of neutropenia when specifying non-treatment specific utilities, could be a result of it being associated with a better treatment outcome in Viale-A, not completely captured by the three health states.

The scenario analysis regarding reduced health state utility in the ven+aza arm should therefore be replaced by one where the health state utility in the ven+aza arm is 2% higher in the EFS states.

Claiming that Viale-A utilities does not capture the impact of adverse events and then adjusting for this (with an arbitrary number) in only one of the treatment arms is not reasonable. The placebo + azacitidine arm also had a considerable rate of neutropenia and a higher rate of sepsis than the venetoclax arm.

[1] Analysis not available with the Danish value set. EQ-5D utility scores were estimated from data of the Viale-A trial (data cut 2020-01-04) based on individual dimension scores and using UK preference-weights. The EQ-5D 5L score in the trial data was transferred to EQ-5D 3L score using the UK cross-walk value set based on Van Hout et al. (2012). EQ-5D utility values for health states were estimated using a linear mixed-effects model to account for correlation within patients' repeated assessments.

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06/07-2022

MGK/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	31.08.2022
Leverandør	Abbvie
Lægemiddel	Venclyxto (venetoclax) + azacitidin
Ansøgt indikation	Voksne patienter med nylig diagnosticeret akut myeloid leukæmi (AML), som ikke er kandidater til behandling med intensiv kemoterapi.

Forhandlingsresultat

Amgros har opnået følgende pris på Venclyxto (venetoclax):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	AIP	Nuværende SAIP	Rabatprocent ift. AIP
Venclyxto (venetoclax)	100mg /400 mg dagligt/tabletter	112 stk.	39.010,08	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted]

Nedenstående tabel viser de årlige lægemiddelpriser for henholdsvis Venclyxto (venetoclax), Vidaza (azacitidin), samt kombinationen af Venclyxto (venetoclax) + Vidaza (azacitidin). Dosisjustering indgår ikke i nedenstående beregninger.

Tabel 2: Sammenligning af lægemiddelpriser til behandling af AML

Lægemiddel	Styrke/dosis/form	Pakningsstørrelse	Pakningspris SAIP	Antal pakninger/år	Årlig lægemiddelomkostning SAIP pr. år
Venclyxto (venetoclax)	100mg /400 mg dagligt (opstart: 100 mg dag 1, 200 mg dag 2/tabletter	112	[redacted]	13	[redacted]
Vidaza (azacitidin)	100 mg/ 100mg/m^2* dag 1-5 i 28 dages cykler/s.c.	1 stk.	[redacted]	118	[redacted]
Venclyxto (venetoclax) + Vidaza (azacitidin)					[redacted]

*1,81 m^2

Status fra andre lande

Norge: Under vurdering[1]
England: Anbefalet[2]

Konklusion

Det er Amgros vurdering, at vi ikke kan få en bedre pris på Venclyxto (venetoclax)
[redacted]

[1] https://nyemetoder.no/metoder/venetoklaks-venclyxto-indikasjon-vi
[2] https://www.nice.org.uk/guidance/ta765/chapter/1-Recommendations

Application for the assessment of Venclyxto in combination with a hypomethylating agent for treatment-naïve acute myeloid leukemia patients who are ineligible for intensive chemotherapy

March, 2022

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Venclyxto
Generic name	venetoclax
Marketing authorization holder in Denmark	AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Germany AbbVie A/S is representing the MAH in Denmark.
ATC code	L01XX52

Overview of the pharmaceutical	
Pharmacotherapeutic group	Other antineoplastic agents
Active substance(s)	venetoclax
Pharmaceutical form(s)	Film-coated tablet (tablet)
Mechanism of action	Venetoclax is a potent, selective inhibitor of B-cell lymphoma (BCL)-2
Dosage regimen	The recommended daily venetoclax dosing schedule (including dose titration) is: Day 1: 100mg Day 2: 200mg Day 3 and beyond: 400mg Venetoclax, in combination with a hypomethylating agent, should be continued until disease progression or unacceptable toxicity is observed. Venetoclax dosing may be interrupted as needed for management of haematologic toxicities and blood count recovery.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Venclyxto in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.
Other approved therapeutic indications	Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL). Venclyxto in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. Venclyxto monotherapy is indicated for the treatment of CLL: • in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or • in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor
Will dispensing be restricted to hospitals?	Yes.
Combination therapy and/or co-medication	Azacitidine should be administered at 75 mg/m2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. Decitabine should be administered at 20 mg/m2 intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1 Day 1. Combination therapy with a hypomethylating agent (azacitidine/decitabine). However, decitabine is not registered in Denmark, thus the submission will not include decitabine.

Overview of the pharmaceutical		
Packaging – types, sizes/number of units, and concentrations	Filmovertrukne tabletter 10 mg	14 stk. (blister)
	Filmovertrukne tabletter 50 mg	7 stk. (blister)
	Filmovertrukne tabletter 100 mg	7 stk. (blister)
	Filmovertrukne tabletter 100 mg	14 stk. (blister)
	Filmovertrukne tabletter 100 mg	112 stk. (blister)
Orphan drug designation	Venclyxto is no longer an orphan medicine. It was originally designated an orphan medicine on 6 December 2012. Venclyxto was withdrawn from the Community register of orphan medicinal products in October 2018 upon request of the marketing authorization holder.	

2. Abbreviations

17p	chromosome 17
AE	adverse event
AIC	Akaike information criterion
alloHSCT	allogeneic haematopoietic stem cell transplantation
ALT	alanine transaminase/alanine aminotransferase
AML	acute myeloid leukaemia
APL	acute promyelocytic leukaemia
AST	aspartate transaminase
AUC	area under curve
AZA	azacitidine
BC	base-case
BCL-2	B-cell lymphoma 2
BIC	Bayesian information criterion
BIM	Bcl-2-like protein 11, commonly called BIM. Other aliases: BCL2L11, BAM, BOD, BCL2 like 11.
BM	Bone Marrow
BSC	best supportive care
CBF	core-binding factor
CHF	congestive heart failure
CI	confidence interval
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CMML	chronic myelomonocytic leukemia
CMV	cytomegalovirus
CNS	central nervous system
CPD	chronic pulmonary disease
CR	complete response/complete remission
CRh	complete remission with partial haematologic recovery

Cri	complete remission with incomplete count recovery
cTTO	composite time trade-off
CYP3A	cytochrome P450, family 3, subfamily A
CYP3Ai	Inhibitor of CYP3A
DEC	decitabine
DLCO	diffusion capacity of carbon monoxide
DMC	Danish Medicines Council
DOR	duration of response
DSA	deterministic sensitivity analysis
DT	Distress Thermometer
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
ELN	European LeukaemiaNet
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D-3L	EuroQol - five dimensions - three levels
EQ-5D-5L	EuroQol - five dimensions - five levels
EQ-VAS	EuroQol visual analogue scale
ESMO	European Society for Medical Oncology
FACT	Functional Assessment of Cancer Therapy
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-Leu	Functional Assessment of Cancer Therapy - Leukemia
FEV1	forced expiratory volume in 1 second
FLT3	FMS-like tyrosine kinase 3
GHS	global health status
GVHD	graft versus host disease
HMA	hypomethylating agent
HR	hazard ratio
HRQL	health-related quality of life
HRQoL	health-related quality of life
HSCT	haematopoietic stem cell transplantation
ICER	incremental cost-effectiveness ratio
IPD	individual patient-level data
IPSS	International Prognostic Scoring System
IV	intravenous
IWG	International Working Group
K-M	Kaplan-Meier
LDAC	low-dose cytarabine
LSC	leukemia stem cell
LY	life year
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome

MM	multiple myeloma
MPN	myeloproliferative neoplasms
MRD	measurable residual disease (previously: minimal residual disease)
MRR	mortality rate ratio
NCCN	National Comprehensive Cancer Network
NICE	The National Institute for Health and Care Excellence
NoMA	Norwegian Medicines Agency
Nrf2	Nuclear factor erythroid 2-related factor 2 (NRF2), also known as nuclear factor erythroid-derived 2-like 2
ORR	overall response rate
OS	overall survival
PB	peripheral blood
PD/RL	progressive/relapsed disease
PH	proportional hazard
PR	partial response
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcome Measurement Information System
PS	performance status
PSA	probabilistic sensitivity analysis
PSM	partitioned survival model
QALY	quality-adjusted life year
QD	quaque die (every day)
QoL	quality of life
RBC	red blood cell
RBCs	red blood cells
RCT	randomized controlled trial
SC	subcutaneous
SE	standard error
SMR	standardized mortality ratio
SoC	standard of care
TACO	transfusion-associated circulatory overload
TLS	tumor lysis syndrome
TLV	Tandvårds- och läkemedelsförmånsverket
ToT	time on treatment
TP53	tumor protein 53
TRIALI	transfusion-related acute lung injury
TTD	delayed time to deterioration
TTO	time trade-off
ULN	The upper limit of normal
VAS	visual analogue scale
WHO	World Health Organization

3. Tables and Figures

Tables

Figures

4. Summary

Acute myeloid leukemia, AML, is a cancer that originates in the blood-forming cells of the bone marrow and quickly leads to death if left untreated. Among other things, the patient suffers from anemia, infections, and bleeding all of which greatly impair quality of life. AML is rapidly fatal if left untreated, with the lowest survival rate of all leukemias. It has particularly poor survival for patients ineligible for intensive chemotherapy, with a 1-year survival rate of 15–20% and a 5-year survival rate of just 5%. The impairment on quality of life is significant, with deterioration both due to AML symptoms, particularly fatigue, anemia, and infection, and due to treatment, which requires prolonged hospitalization. The need for repeated blood transfusions due to thrombocytopenia also leads to substantial clinical burden and healthcare resource use.

Intensive chemotherapy can be an option for the patient depending on biological age, co-morbidity, and whether the patient suffers from de novo or secondary AML (AML without known origin or originating from another blood disease). For those patients that are ineligible for intensive chemotherapy, the options are few, have poor response rates and, as a result, there is a high likelihood of relapse after initial remission. This means survival outcomes are poor and median OS is low. Until now, the preferred treatment has consisted of monotherapy with a hypomethylating drug such as azacitidine. There is a high need for new treatments that provide durable response rates, improve survival while maintaining HRQoL, and contribute to transfusion independence in patients with AML who are ineligible for intensive chemotherapy.

Earlier in 2021, Venclyxto was approved in combination with a hypomethylating drug for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

Venetoclax combined with a hypomethylating drug involves a new treatment option with a new mechanism of action to meet the major medical needs present in the care of those patients:

- Improved survival
- Improved quality of life
- Transfusion independence

Viale-A was a randomized (2:1), double-blind, placebo-controlled phase 3 trial evaluating the efficacy and safety of venetoclax combined with azacitidine in patients with newly diagnosed AML who were not suitable for intensive chemotherapy. In terms of population, according to different Danish AML experts, the baseline demographics of the Viale-A study are very similar and comparable to the Danish patient population that would be treated with Venclyxto + azacitidine. Further, the relevance and compatibility of the study is reflected in Aalborg University participation in the Viale-A study. Median survival was 14.7 months for venetoclax + azacitidine compared to 9.6 months for azacitidine alone. Venetoclax combined with azacitidine also produced faster responses and significantly more patients in remission, event-free survival, transfusion independence, and without residual measurable disease. The safety profile of venetoclax in combination with azacitidine is acceptable and manageable in a newly diagnosed AML patient population. Compared with azacitidine monotherapy, combination therapy with venetoclax was well tolerated. No new risks associated with venetoclax at the proposed doses in combination with azacitidine were identified in the entire AML development program.

AbbVie has developed a cost-utility model based on efficacy data from the clinical trial Viale-A. A partitioned survival model including the states event-free survival (EFS) with composite complete remission (CR/CRi), EFS without (CR/CRi) and progressed disease/relapse. The model has been validated and calibrated against Swedish registry data and long-term survival modelling has been carried out in line with DMC's previous assessments regarding how AML should be modelled. Utilities are based on the Viale-A EQ-5D-5L data, using the Danish value set recommended by DMC. The cost per quality-adjusted life year was shown to be low, approximately 90 000 DKK using AIP. The budget impact for

recommending Venclyxto in combination with azacitidine is [redacted] when using AIP.

There is a high probability of a different dosing scheme than in the clinical study making it likely that the cost per quality-adjusted year of life will effectively be even lower. The clinicians expect the actual dosing in clinical practice will be substantially lowered compared to the study dosing and label. The expectation is that the regime suggested will be overly tough on the patients without adding a balancing clinical benefit. This has also been supported by a more recent analysis of Viale-A data where it was concluded that "lower exposures associated with venetoclax dose reductions to manage cytopenias in patients who achieved CR/CRh did not appear to affect overall survival".

The results demonstrate that treatment with Venclyxto in combination with hypomethylating drugs produces great health gains with a low cost per quality-adjusted life year for patients with a very severe disease and where few treatment options are available.

Venclyxto also provides a treatment option with a distinct and new mechanism of action, addressing the high unmet need of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy and Venclyxto should therefore be reimbursed for the treatment of AML.

5. The patient population, the intervention, and choice of comparator

5.1 The medical condition and patient population

Table 1: Incidence and prevalence in the past 5 years

Year	2016	2017	2018	2019	2020
Incidence in Denmark (all AML patients, ALG 2020 report)		264	272	287	281
Incidence in Denmark (all AML patients, NORDCAN)	182	207	190	189	NA
Total prevalence in Denmark (all AML patients, NORDCAN)	996	1 027	1 048	1 072	NA

Table 2: Estimated number of patients eligible for treatment

Year	2021	2022	2023	2024	2025
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years		[redacted]	[redacted]	[redacted]	[redacted]

The incidence reported differs between the ALG (Akut Leukæmigruppen) 2020 report [2] and NORDCAN data [3]. Source of prevalence is NORDCAN (association of the Nordic Cancer Registries). More detailed ALG incidence and NORDCAN prevalence data can be found in Appendix K.

5.1.1 Patient populations relevant for this application

Approximately 250 new cases of AML are diagnosed annually in Denmark [4]. Average age at diagnosis is almost 70 years old [5]. According to the "Årsrapporter for Akut Leukæmigruppen" (ALG) 2018 report, the median age for newly diagnosed AML patients is 71 years, with the age varying between 71-73 years at the regional level [6]. According to the current Danish AML guidelines and the Danish AML database 2019 report [7, 8], patients can be treated according to 3 different treatment principles, described below:

a. Curatively intended treatment (eligible for intensive chemotherapy, mostly patients <60 years old).
b. Non-intensive/curative treatment (non-eligible for intensive chemotherapy mostly patients >60 years old).
c. Palliative/supportive care only

Overall, 48.3% of all AML patients diagnosed in 2018 (n = 230) are registered as being in remission-inducing treatment. Thus, around 51.7% are candidates for either non-intensive or palliative treatment.

Venclyxto in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy (group b from above). Danish AML physicians estimate that [redacted] of AML patients today are in group B, corresponding to [redacted].

5.1.2 Pathogenesis of AML

Acute myeloid leukemia (AML) is an aggressive and heterogeneous haematological malignancy of the myeloid cells. It is characterized by the accumulation of clonal, proliferative, poorly differentiated myeloid cells (myeloblasts) in the bone marrow, blood, and/or other tissue [9]. This accumulation of immature myeloblasts does not allow normal development of white blood cells, red blood cells, and platelets, thus complications from AML primarily include anemia, granulocytopenia, and thrombocytopenia. [10]. Infection-related death is a common cause of mortality if AML is left untreated [11].

5.1.3 Risk factors for developing AML

The exact cause of AML is unknown, but risk factors include age, race, smoking, presence of certain genetic syndromes and/or blood disorders, and exposure to chemicals and/or radiation, as summarized in Table 3 [12].

Table 3: Risk factors for AML

Risk factor	Causes
Demographics	Increasing age (>65) Non-Hispanic Caucasian race Male gender
Past medical history	Previous anti-cancer treatments Other blood disorders (i.e., myelodysplasia or myeloproliferative disorders)
Environmental exposure	Exposure to chemicals/radiation (i.e., benzene)
Lifestyle behavior	Smoking
Genetic	Concomitant genetic disorder (e.g., Down's syndrome)

Source: AML Mayo Clinic.

5.1.4 AML diagnosis and classification

The diagnostic workup of AML involves a combination of procedures and tests intended to assess patient history, cytology of nucleated cells in blood and bone marrow, immunophenotyping, cytochemistry, and cytogenetics markers [13]. Blast count plays a vital role in distinguishing acute leukemias from myelodysplastic syndromes (MDS).

The most recent developments in the diagnosis of AML are reflected in the 2016 World Health Organization (WHO) update [13]. According to the WHO, the diagnostic criteria of AML is based on any of the following:

- ≥20% blasts in blood or marrow (based on 200 nucleated cells from blood and 500 nucleated cells from bone marrow)
- clonal, recurring cytogenetic abnormalities t(8;21) (q22;q22), inv(16)(p13q22) or t(16;16)(p13;q22), and t(15;17)(q22;q12) (regardless of blast percentage)
- myeloid sarcoma (regardless of blast percentage)

AML can arise de novo or secondary to other treatments. Treatment-related AML is present in 5%-20% of all AML cases and has a worse prognosis[1] when compared to de novo AML, due to increased resistance to conventional AML therapies and unfavorable cytogenetics [9].

5.1.5 Prognostic factors in AML

Overall, prognostic factors in AML can be subdivided into 2 categories [14]

- Patient-associated factors, which include increasing age, coexisting conditions (comorbidities), and poor performance status.

- Disease-related factors, which include white-cell count, prior myelodysplastic syndrome or cytotoxic therapy for another disorder, and leukemic-cell genetic changes.

Age and performance status along with chromosomal and molecular aberrations are the most important variables for outcome prediction in AML. [15] Current treatment guidelines recognize validated prognostic groups categorized as favorable, intermediate, and adverse cytogenetics and molecular abnormalities [16].

Patients with AML aged 65 years and older tend to have worse baseline comorbidity scores and related complications than similar people without cancer [17]. In AML, the presence of a comorbid disease is significantly associated with overall mortality [18]. Age has been shown to have only a modest effect on treatment-associated mortality within the first 30 days of induction therapy, for patients with excellent ECOG performance (0 or 1). However, for elderly patients with an ECOG performance status of 2 or 3, age had a dramatic effect, with 82% of patients older than age 75 with a performance status of 3 dying within 30 days of the initiation of induction [19].

Patient-related factors are important for characterizing tolerability to intensive chemotherapy in the adult population when choosing a treatment strategy [15, 20-22]. Treatments suitable for older and frail patients include HMA (hypomethylating agents), LDAC (low-dose cytarabine), and BSC (best supportive care). Today, with current treatment options, OS ranges from 5 to 10 months for patients who are ineligible for intensive therapy [14].

[1] Except for therapy-related acute promyelocytic leukemia (APL) subtype or core binding factor (CBF) translocation.

5.1.6 Symptoms and Complications of AML

AML has a rapid onset and progression. However, some patients may have a history of illness over a slightly longer period of a few months, with more initial insidious symptoms [23].

The leukemic cells infiltrate the bone marrow and limit the maturation of normal cells. This leads to anemia, granulocytopenia, and thrombocytopenia. The signs and symptoms of AML reflect impaired bone marrow function and can include fatigue, fever, weakness, dizziness, headache, and shortness of breath due to anemia [24].

Complications from AML primarily include anemia, infections, and bleeding, and may be due to the condition itself or as a side effect of treatment [10].

Infections arising from AML are common due to deficiencies in immune cells, granulocytopenia, arising from the expansion of leukemic clones in the bone marrow [25]. Infection-related death is a common cause of mortality if AML is left untreated [11].

Bleeding disorders resulting from thrombocytopenia, such as frequent or severe nose bleeds, bleeding gums, and excess bruising, are also common [23, 26]. Serious bleeding can occur in patients with AML. As the AML advances patients are becoming more vulnerable and serious bleedings as intracranial hemorrhage, pulmonary hemorrhage, or gastrointestinal hemorrhage may be fatal [10].

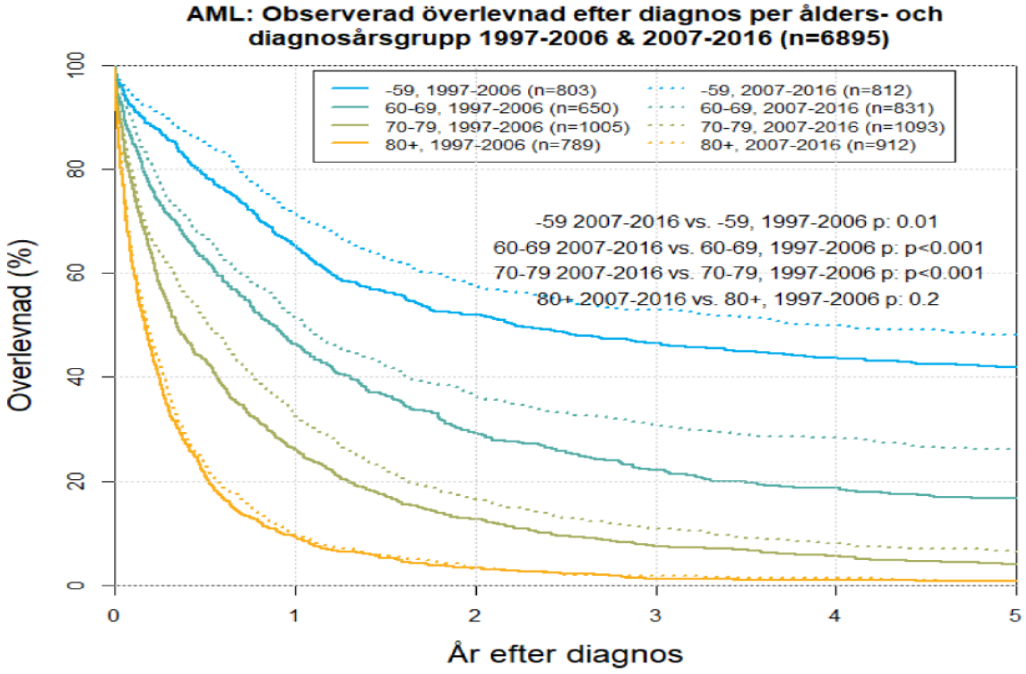
Anemia and thrombocytopenia, which require treatment with blood products may result in transfusion dependence. At least 85% of patients ineligible for intensive chemotherapy will require a transfusion [27]. Frequent and repeated red blood cell transfusions contribute to poor HRQL due to hospitalization, transfusion procedures, and associated adverse events [28]. Transfusion-associated complications include transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), alloimmunization, graft versus host disease (GVHD), transmission of viral infections (i.e. cytomegalovirus [CMV]), and iron overload [29]. Reducing anaemia symptoms and transfusion requirements may improve HRQL in patients with AML who are ineligible for intensive chemotherapy [28, 30].

5.1.7 Need for Improved Survival

AML is rapidly fatal if left untreated, with the lowest survival rate of all leukemias. It has particularly poor survival for patients ineligible for intensive chemotherapy, with a 1-year survival rate of 15–20% and a 5-year survival rate of just 5% [28, 30].

In the quality report from the Swedish AML registry, current registry data show that survival deteriorates for each older age cohort. Comparing patients diagnosed in 2007-2016 with those diagnosed in 1997-2006, there are differences. Looking at the 3 and 4-year survival there are substantial improvements in the two youngest age cohorts of <59 years and 60-69 years. For the 80+ group however, there seems to have been no increase at all, and for the 70-79 years old, only a very small increase in survival **Figure 1** [21].

Figure 1: Swedish National AML Registry Survival Data



5.1.8 Health-Related Quality of Life (HRQoL)

AML impacts many aspects of a patient's life throughout diagnosis, treatment, and recovery. Quality of life (QoL) and psychosocial well-being are among the most difficult challenges facing patients with AML and their caregivers [31]. Fatigue and diminished physical function are common in AML patients, and given the short life expectancy of AML patients, especially for older adults, patients are likely to prioritize general well-being and quality of life versus extending length of life [32]. Poor QoL is commonly observed after initial AML diagnosis and during induction treatment in patients receiving intensive chemotherapy. Irrespective of treatment stage or disease status, fatigue symptoms are reportedly the most burdensome to patients.[33] Severe fatigue prior to intensive chemotherapy is a prognostic factor for shorter survival in patients, regardless of age [34]. Additionally, psychological distress may be caused by the need for rapid treatment and the subsequent cognitive demand required to understand treatment pathways and options [34]. Achieving complete remission (CR) during first-line induction therapy has shown positive HRQL benefits [35] However, a haematologic improvement without CR can also yield clinical benefits, such as a reduction in transfusions and improved quality of life (QoL) [36].

HRQoL in AML vs. the general population

Leunis and colleagues reported that patients with AML have worse HRQoL than matched general population measures taken across various countries on all functioning scales of the EORTC QLQ-C30 and the EuroQol visual analogue scale (EQ-VAS).[21] Additionally, physical functioning, role functioning, cognitive functioning, and social functioning were all at least 10 points worse for patients with AML than the general population. In general, HRQoL, as measured by the EORTC QLQ-C30, is lower for patients with AML compared to reference values for other cancer types. [37]

Impact of disease diagnosis, age, and progression on HRQoL

HRQoL among AML patients is most negatively affected after diagnosis and during therapy.[33] Poor HRQoL at diagnosis has been associated with reduced overall survival.[28] After initial AML diagnosis, older patients (≥60 years) have reported clinical depression and anxiety symptoms at baseline with treatment leading to significantly improved

QoL over time [28]. Diminished quality of life is likely associated with disease progression and the need to rapidly treat at the onset of diagnosis. One study found that symptom burden with regards to fatigue, anxiety, and inability to engage in hard work or activity, measured by Functional Assessment of Cancer Therapy- General (FACT-G) scores, FACT-Leukemia (FACT-Leu) scores, and Distress Thermometer (DT) scores, worsened with proximity to death [38]. Achieving complete remission during induction therapy has also shown positive HRQoL benefits [39].

HRQoL in AML Patients Ineligible for Standard Induction Therapy

Forsyth and colleagues highlighted limited evidence with regards to HRQoL in AML patients ineligible for standard induction therapy [36]. Despite the limited data, HRQoL tended to worsen with an increased number of comorbid medical conditions, disease progression, and disease relapse. Similarly, Bosshard and colleagues concluded that HRQoL is poor in patients with AML who are ineligible for standard induction therapy and a negative association is observed between poorer HRQoL at diagnosis and overall survival [28]. Compared to newly diagnosed patients with AML receiving intensive (cytarabine/anthracycline combination) chemotherapy, older patients receiving non-intensive (hypomethylating agents) chemotherapy report similar QoL and mood at baseline and after 24-weeks after diagnosis [38]. Successful treatment may demonstrate improvements in HRQoL if adverse events and disease relapse can be avoided [36].

5.1.9 Transfusion Independence

Patients with AML who are ineligible for intensive chemotherapy have a high chance of developing anaemia and thrombocytopenia, which require treatment with blood products and may result in transfusion dependence. At least 85% of patients ineligible for intensive chemotherapy will require a transfusion [27]. Frequent and repeated red blood cell transfusions contribute to poor HRQoL due to hospitalization, transfusion procedures, and associated adverse events [28]. Transfusion-associated complications include transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), alloimmunization, graft versus host disease (GVHD), transmission of viral infections (i.e., cytomegalovirus [CMV]), and iron overload [29]. Reducing anaemia symptoms and transfusion requirements may improve HRQL in patients with AML who are ineligible for intensive chemotherapy [28, 30].

5.2 Current treatment options and choice of comparator

5.2.1 Current treatment options

According to the current Danish AML guidelines and the Danish AML database 2019 report [7, 8] patients can be treated according to 3 different treatment principles, described below:

a. Curatively intended treatment (mostly patients <60 years old), often intensive classical chemotherapy with the addition of newer biological agents as well as possibly consolidated with an allogeneic bone marrow transplant.
b. Non-curative treatment (mostly patients >60years old): Chemotherapy administered with some chance of remission but not with a view of achieving lasting health
c. Supportive care only

Venclyxto in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy (group b from above). Danish AML physicians estimate that [redacted] AML patients today are in group B, [redacted].

5.2.2 Choice of comparator

According to the current Danish guidelines, the intended treatment for group B includes:

1. Azacitidine 75-100 mg/m^2 s.c. daily for 5-7 days repeated every four weeks. Not recommended for proliferative AML. Response can be obtained up to after 9 series but is most often seen after 4-6 series. Treatment is given until treatment failure.

2. Low-dose cytarabine (LDAC) 20 mg s.c. Twice daily for 7-10 days possibly administered another 7 days if necessary, in the first course to check leukocyte counts. Thereafter every 4 to 6 weeks. Treatment is given until treatment failure.

According to Danish experts, LDAC is only used in limited cases. It is regarded as inferior to azacitidine and would be used only if azacitidine for some reason cannot be used for the patient. The treatment that would be replaced by the introduction of Venclyxto for AML is azacitidine in monotherapy. Because of this, azacitidine will be used as the relevant comparator, and it is also the comparator used in the head-to-head study. Azacitidine is today subject to generic competition.

5.2.3 Description of the comparator

Generic name (ATC-code)	Azacitidine (L01BC07) [40]
Mode of action	Azacitidine is believed to exert its antineoplastic effects by multiple mechanisms including cytotoxicity on abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may result from multiple mechanisms including inhibition of DNA, RNA, and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. Non-proliferating cells are relatively insensitive to azacitidine. Incorporation of azacitidine into DNA results in the inactivation of DNA methyltransferases, leading to hypomethylation of DNA. DNA hypomethylation of aberrantly methylated genes involved in normal cell cycle regulation, differentiation, and death pathways may result in gene re-expression and restoration of cancer-suppressing functions to cancer cells. The relative importance of DNA hypomethylation versus cytotoxicity or other activities of azacitidine to clinical outcomes has not been established.
Pharmaceutical form	Powder for suspension for injection, 25 mg/ml
Posology	Treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents. Patients should be premedicated with anti-emetics for nausea and vomiting
Method of administration	Subcutaneous
Dosing	SmPc: The recommended starting dose for the first treatment cycle, for all patients regardless of baseline haematology laboratory values, is 75 mg/m^2 of body surface area, injected subcutaneously, daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle). In Denmark, it is however administered at the dose of 100 mg/m^2 s.c. day 1–5 of the treatment cycle (confirmed by several experts).

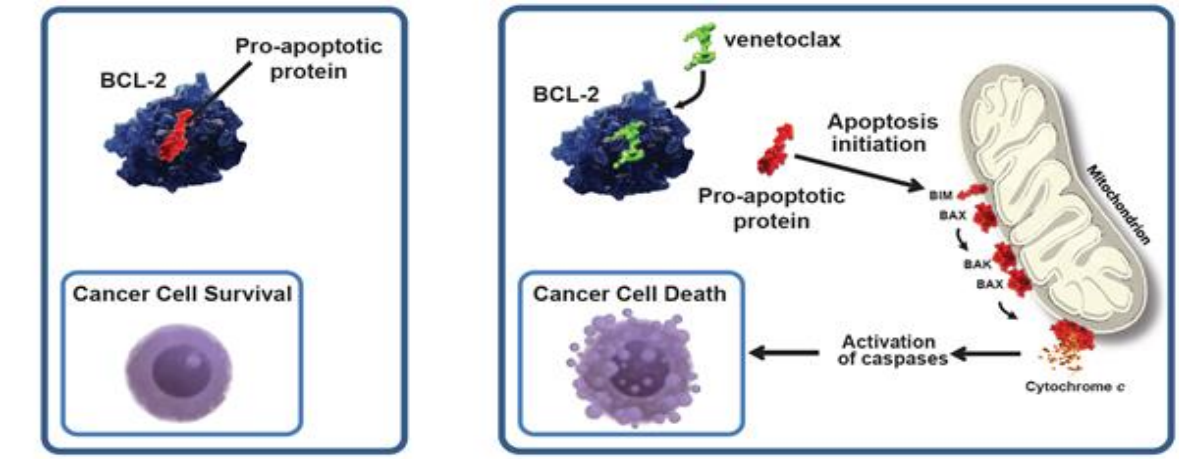
Should the pharmaceutical be administered with other medicines?	Monotherapy
Treatment duration/criteria for end of treatment	It is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued for as long as the patient continues to benefit or until disease progression.
Necessary monitoring, both during administration and during the treatment period	Patients should be monitored for haematologic response/toxicity and renal toxicities; a delay in starting the next cycle or a dose reduction may be necessary.
Need for diagnostics or other tests (i.e. companion diagnostics)	Liver function tests, serum creatinine and serum bicarbonate should be determined prior to initiation of therapy and prior to each treatment cycle. Complete blood counts should be performed prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle
Packaging	Each vial contains 100 mg azacitidine. After reconstitution, each mL of suspension contains 25 mg azacitidine.

5.3 The intervention

5.3.1 Mode of action

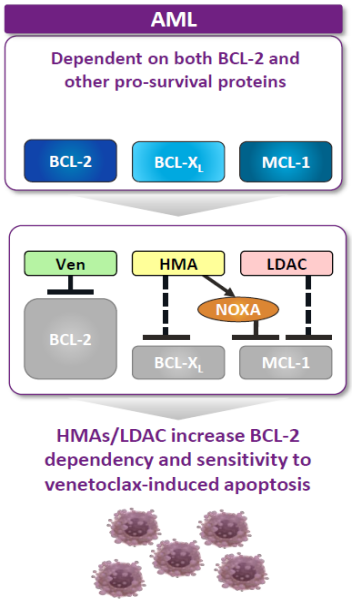
Venetoclax is a highly selective, potent, oral BCL-2 inhibitor that induces apoptosis in AML cells in combination with other therapeutic agents. [41-45] Overexpression of BCL-2 has been demonstrated in AML cells, where it mediates tumor cell survival and has been associated with resistance to chemotherapeutics. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing proapoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilization, and the activation of caspases.[41, 43, 44] In nonclinical studies, venetoclax has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2. The mechanism of action of venetoclax is illustrated in Figure 2.

Figure 2: Venetoclax mechanism of action: restoration of apoptosis through BCL-2 [1]



Sensitivity to venetoclax can be increased through a potentially synergistic combination with other therapeutic agents. Hypomethylating agents (HMAs) (e.g., azacitidine and decitabine) indirectly increase sensitivity to BCL-2 inhibition in AML cells by modifying the relative levels of BCL-2 family members. [46-48]

Figure 3: Venetoclax induces apoptosis alone or in combination with agents that enhance BCL-2 dependency [42]



In AML, the leukemia stem cell (LSC) population has different properties than the bulk AML population, making them challenging to eliminate, and therefore a source of disease progression, resistance, and relapse. By eliminating the LSC population, it is plausible to expect therapeutic deep and durable remissions with minimal risk of late relapse [49]. Recent data propose that the LSC population is efficiently targeted by venetoclax plus azacitidine, due to its specific disruption of amino acid-fueled oxidative phosphorylation, on which the LSC population is uniquely reliant. Resulting in promising clinical activity in a patient population with historically poor outcomes [50, 51]. This hypothesis is supported by the deep durable response that has been observed in the venetoclax clinical studies [52, 53]. Venetoclax modulates T-cells to increase their cytotoxicity to AML cells, while azacitidine demonstrates the potential to induce the susceptibility of AML cells to T-cell mediated cytotoxicity [54]. This suggests an immune-mediated mechanism of action compatible with the observed response depth and durability following venetoclax-azacitidine treatment in Viale-A.

5.3.2 Dosing and Administration of Venetoclax + HMA

The recommended venetoclax dosing schedule (including dose-titration) for use with a hypomethylating agent is shown in Table 4.

Table 4: Dose increase schedule in patients with AML

Day	Venetoclax daily dose
1	100 mg
2	200 mg
3 and beyond	400 mg

Azacitidine should be administered at 75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. If decitabine is used instead of azacitidine, it should be administered at 20 mg/m^2 intravenously on Days 1-5 of each 28-day cycle beginning on Cycle-1 Day 1.

Venetoclax dosing may be interrupted as needed for management of haematologic toxicities and blood count recovery. Venetoclax, in combination with a hypomethylating agent, should be continued until disease progression or unacceptable toxicity is observed.

If a CYP3A inhibitor must be used, the recommendations for managing drug-drug interactions summarized in Table 5 should be followed. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor. Further information regarding this and efficacy can be found in section 7.1.4.

Table 5: Management of potential Venclyxto interactions with CYP3A inhibitors

Inhibitor	Phase	Dose
Strong CYP3A inhibitor	Initiation and dose-titration phase	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg or less
	Steady daily dose (After dose-titration phase)	Reduce the Venclyxto dose to 100 mg or less (or by at least 75% if already modified for other reasons)
Moderate CYP3A inhibitor	All	Reduce the Venclyxto dose by at least 50%

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

As a head-to-head study with the relevant comparator for the relevant patient population with the relevant outcomes has been carried out, the literature search has been omitted.

6.2 List of relevant studies

Table 6: Trials within the development program

Study reference/ID	Available documentation	Status (ongoing/ completed)
Randomized controlled trials		
VIALE-A (NCT02993523)	DiNardo C, Jonas B, Pullarkat V, et al. A Randomized, Double-Blind, Placebo-Controlled Study Of Venetoclax With Azacitidine Vs Azacitidine In Treatmentnaive Patients With Acute Myeloid Leukemia Ineligible For Intensive Therapy-VIALE-A. European Hematology Association. 2020:LB2601.	Ongoing Est. completion September 2022

	DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med 2020;383:617-29 doi: 10.1056/NEJMoa2012971 Clinical study report from AbbVie 22 23	
Non-randomized controlled trials (supportive of VIALE-A)		
M14-358 (NCT02203773)	Pollyea D.A., Pratz K., Letai A., Jonas B.A., Wei A.H., Pullarkat V., Konopleva M., Thirman M.J., Arellano M., Becker P.S., Chyla B., Hong W.-J., Jiang Q., Potluri J., DiNardo C.D. Venetoclax with azacitidine or decitabine in patients with newly diagnosed acute myeloid leukemia: long term follow-up from a Phase 1b study. [Article in Press] American journal of hematology 2020. DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, Frankfurt O, Konopleva M, Wei AH, Kantarjian HM, Xu T, Hong WJ, Chyla B, Potluri J, Pollyea DA, Letai A. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019 Jan 3;133(1):7-17. doi: 10.1182/blood-2018-08-868752. Epub 2018 Oct 25.	Ongoing Est. completion: 27 September 2022

The Phase 1b (M14-358, venetoclax in combination with azacitidine or decitabine) trial confirmed the safety and efficacy of these combinations in the population of interest [55, 56].

The Phase 3 trial, VIALE-A, was designed to be as robust as possible: randomized, double-blind, placebo-controlled study versus the comparator considered to be the current SoC. It investigated venetoclax in combination with one HMA (azacitidine). Only one HMA was taken forward to Phase 3 due to the comparability of the azacitidine and decitabine combinations, consistent with their similar mechanisms of action [40, 52, 57, 58]. Specifically:

- Similarities in efficacy and safety profiles were reported across all subgroups evaluated with azacitidine and decitabine combination therapies in the non-randomized study, M14-358 [55]. Long-term follow-up data indicated not only a comparable median OS of 16.4 months and 16.2 months but also a comparable CR + CRi rate (71% vs. 74%) for venetoclax in combination with azacitidine and decitabine, respectively [53]. Key grade ≥3 adverse events were also comparable across combinations: febrile neutropenia (39% and 65%), anemia (30% and 26%), thrombocytopenia (25% and 23%), and neutropenia (20% and 10%) for venetoclax in combination with azacitidine and decitabine, respectively [53].
- The similar profiles between the two HMAs are also supported by network meta-analyses of randomized controlled trials. The authors concluded that neither shows superiority; both demonstrated enhanced outcomes in mortality, overall response rate, and haematological parameters compared with traditional treatments [59].
- The comparability of the two HMAs is further confirmed by real-world evidence from >2,000 elderly patients who were treated with either HMA. The authors reported no clinically meaningful differences in the context of prolonging OS or independence from RBC transfusions [60].

The azacitidine combination, and therefore azacitidine as a comparator, was chosen for Phase 3 in part due to the ELN guidelines favoring azacitidine over decitabine. Although ESMO guidelines recommend HMAs as the first-choice treatment for this patient population, ELN guidelines state that azacitidine may be particularly advantageous in AML with adverse cytogenetics [21]. In Denmark, azacitidine is the only HMA used.

Key characteristics of the AML development program studies for venetoclax in combination with an HMA are available in **Table** in the appendix.

7. Efficacy and safety

7.1 Efficacy and safety of venetoclax in combination with azacitidine compared to azacitidine in monotherapy for patients with AML that are ineligible for intensive chemotherapy

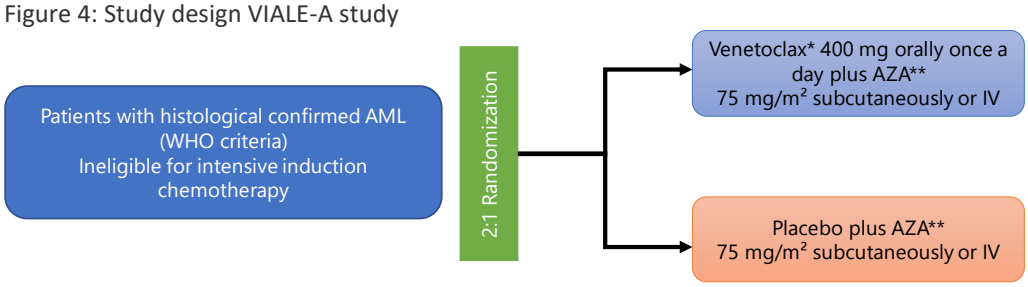
7.1.1 Relevant studies

The VIALE-A study (NCT02993523) [52] is a phase 3, randomized, double-blind, placebo-controlled, multicenter study comparing efficacy and safety of azacitidine plus either venetoclax or placebo among treatment-naïve patients with confirmed AML who were ineligible for standard induction therapy due to medical comorbidities and/or age ≥ 75 years. See Figure 4 for a simplistic representation of the study design for VIALE-A.

For mitigation of tumor lysis syndrome (TLS), venetoclax dosing was gradually increased in Cycle 1 from 100 mg on day 1 to 200 mg on day 2, and then to the target dose of 400 mg on day 3 which was continued until day 28, and then 400 mg daily in all subsequent 28-day cycles.

The primary study endpoint was to evaluate the OS between azacitidine plus venetoclax and control arms which was defined as the number of days from randomization to the date of death.

Figure 4: Study design VIALE-A study



*Venetoclax (oral) daily ramp-up in Cycle 1; 100 mg D1, 200 mg D2, 400 mg D3 until D 28; subsequent 28-day cycles at 400 mg.
**Azacitidine; 75 mg/m^2 IV or SC on days 1-7 for each 28-day cycle

For detailed study characteristics refer to appendix B. For baseline characteristics of patients included in each study refer to appendix C.

In addition to Viale-A, the phase 1b study M14-358 provides supportive evidence regarding the combination of venetoclax and an HMA.

7.1.2 Efficacy and safety – results per study

Study Results

Study Population

A total of 433 eligible patients were randomized and 431 patients were included in the intention to treat population: 286 patients in the azacitidine plus venetoclax arm and 145 in the azacitidine plus placebo arm. (see Figure 26 in appendix). Overall, the median age was 76 years, and the majority (60% patients) were male. One-fourth of the total patients had secondary AML. Bone marrow blast count was between 20%-30% in around one-third of patients in both azacitidine plus venetoclax and control arms, while poor cytogenetic risk was recorded in 36% and 39% patients,

respectively. Nearly half of the patients had >2 reasons for ineligibility for intensive therapies [52]. Key baseline and clinical characteristics are summarized in **Table 51** in the appendix.

Efficacy results

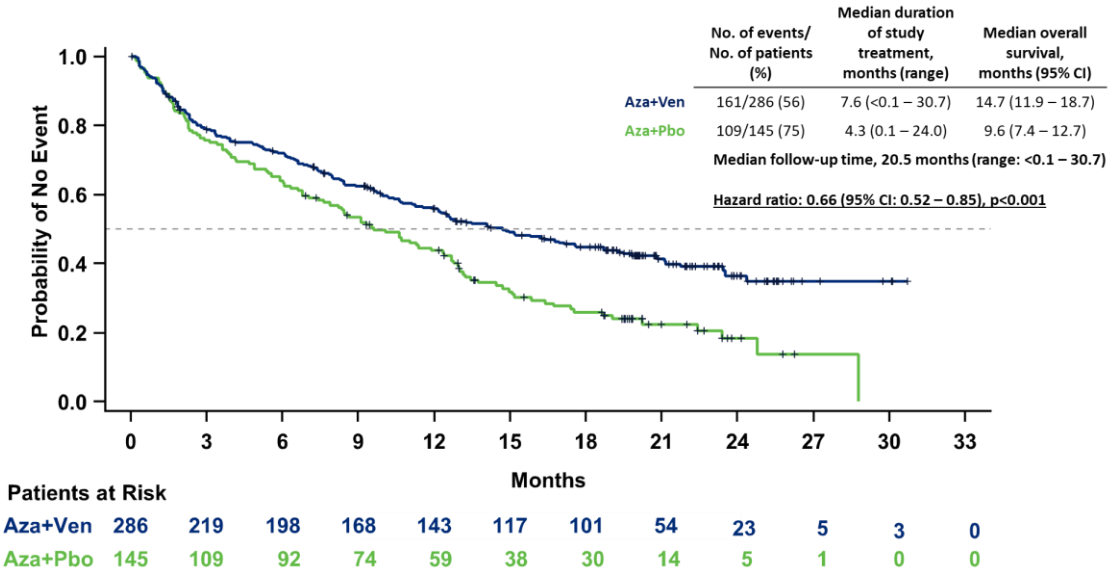
Overall survival (OS) (Primary endpoint)

The median duration of follow-up was 20.5 months (range: <0.1–30.7). At the time of analysis, 77 (27%) and 18 (12%) patients remained on treatment in the azacitidine plus venetoclax and control arms, respectively [52].

Venetoclax in combination with azacitidine led to a statistically significant and clinically meaningful reduction in the risk of death (HR 0.662 [95% CI: 0.518, 0.845]; p< 0.001). The median OS was 14.7 months in patients randomized to receive venetoclax plus azacitidine compared with 9.6 months in the azacitidine plus placebo arm.

This improvement in OS was not only significant but was consistent across most of the prognostic subgroups including blast count, type of AML (*de novo*, secondary) as well as several molecular and cytogenic subgroups. The results of a subgroup analysis with respect to overall survival are shown in **Figure 27** in the appendix.

Figure 5: Kaplan–Meier Estimates of Overall Survival in the Azacitidine and Venetoclax vs Azacitidine and Placebo Group



The distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk). The hazard ratio between treatment arms was estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test. Data included are subject to a cut-off date of 04 January 2020. The referenced dashed line indicates the 50% overall survival probability line, and the tick marks indicate censored data [52].

Response rate (Secondary endpoint)

Venetoclax in combination with azacitidine resulted in statistically significant increases in the remission rates (CR + CRi, CR, and CR + CRh) compared with patients treated with azacitidine and placebo.[2] Venetoclax plus azacitidine more than doubled CR + CRi compared to azacitidine and placebo (65% vs. 25%, p<0.001) [52].

[2] CRi: complete remission with incomplete count recovery, CRh: complete remission with partial hematologic recovery

More rapid achievement of CR + CRi, CR, and CR + CRh was observed with venetoclax, as measured by the response rates by the initiation of cycle 2 (43.4% vs. 7.6% p<0.001). Median time to first response (either CR or CR with incomplete count recovery) was also shorter (1.3 months vs 2.8 months). Responses were also durable; patients experienced sustained long-term benefits with ongoing treatment. The median duration for composite CR for venetoclax plus azacitidine was 17.5 months (95% CI: 13.6–not reached) in the venetoclax plus azacitidine arm compared to 13.4 months (95% CI: 5.8–15.5) in the control arm [52].

Venetoclax plus azacitidine treatment showed an improvement in CR + CRi for all patient subgroups stratified by various prognostic factors including bone marrow blasts and the presence of molecular mutations [52].

Definitions

- Complete remission (CR) was defined as an absolute neutrophil count of more than 1000 cells per cubic millimeter, a platelet count of more than 100,000 per cubic millimeter, red-cell transfusion independence, and bone marrow with less than 5% blasts.
- Complete remission with incomplete hematologic recovery (CRi) was defined as all the criteria for complete remission, except for neutropenia (absolute neutrophil count, ≤1000 per cubic millimeter) or thrombocytopenia (platelet count, ≤100,000 per cubic millimeter)
- Complete remission with partial hematologic recovery (CRh) was defined as all the criteria for complete remission, except that both the neutrophil and platelet counts were lower than the threshold designated for complete recovery (for neutropenia >500 per cubic millimeter and a platelet count of more than >50,000 per cubic millimeter).

Event-free survival

Event-free survival (EFS) was defined as the time from the date of treatment initiation to the date of first documented progression or relapsed from complete remission/complete remission with incomplete blood count recovery (CR/CRi), or treatment failure or death due to any cause. Venetoclax in combination with azacitidine significantly improved EFS compared with placebo plus azacitidine (HR 0.632 [95% CI 0.502, 0.796]; p<0.001). A total of 95 patients (33.2%) treated with venetoclax plus azacitidine were event-free compared with 23 patients (15.9%) in the azacitidine plus placebo arm. Median EFS was 9.8 months vs. 7.0 months, respectively. In patients with composite complete remission who achieved measurable residual disease $<10^{-3}$, overall survival at 24-months was 73.6% in the azacitidine plus venetoclax arm vs. 63.6% in the control arm [52].

Quality of Life

Patients receiving venetoclax in combination with azacitidine had a non-statistically significant trend to longer time to deterioration in GHS/QoL[3] (median in months [95% CI]: 16.5 [95% CI: 9.8, NE] vs. 9.3 [95% CI: 4.7, 16.6], P=0.066) and fatigue (9.3 [7.2, 16.6] vs. 8.6 [4.2, 16.6], P=0.189) compared with patients treated with azacitidine plus placebo. The patients also had significantly longer time to deterioration in PF[3] (9.7 [6.7, 16.0] vs. 6.2 [4.7, 9.5], P=0.028) and health status VAS[4] (10.7 [7.5, 18.6] vs. 3.9 [2.4, 7.4], P<0.001) than patients treated with azacitidine and placebo. [61]

Transfusion independence

Rates of post-baseline transfusion independence were significantly improved with venetoclax plus azacitidine compared with azacitidine plus placebo. The red blood cells (RBC) independence rate improved by about 25

[3] EORTC QLQ-C30 global health status (GHS)/QoL and physical functioning [PF] subscales

[4] EQ-5D-5L health status visual analog scale (VAS)

percentage points (59.8% vs 35.2%; p<0.001) and platelet transfusion independence improved with about 19 percentage points (68.5% vs 49,7%; p<0.001) [52].

Measurable Residual Disease (MRD)
In the clinical trials of venetoclax, a reduction in MRD levels below 1 leukemic cell in 1,000 ($<10^{-3}$) was shown to be prognostic for OS and risk of relapse after intensive chemotherapy, and therefore was considered a relevant metric to evaluate the quality of the remission (CR, CRi, or CRh) in response to treatment regimens.

Among patients who achieved CR + CRi (composite CR), MRD negativity was achieved in 23.4% of those receiving venetoclax plus azacitidine compared with 7.6% in the control arm (p<0.001) [52].

Safety Results

Overall, 427 patients were included in the safety analysis (azacitidine plus venetoclax n=283, control arm n=144). Patients received a median of 7.0 (range: 1.0–30.0) treatment cycles in the azacitidine plus venetoclax arm compared to 4.5 (range: 1.0–26.0) cycles in the control arm. The discontinuation rates seen showed that the percentage of patients discontinuing treatment due to AEs was similar for venetoclax plus azacitidine vs azacitidine alone (24.4% vs 20.1%) [52].

The most frequently reported grade ≥3 haematological adverse events (azacitidine plus venetoclax/control) included thrombocytopenia (45%/38%), neutropenia (42%/29%), febrile neutropenia (42%/19%), anemia (26%/20%), and leukopenia (21%/12%). Notable serious adverse events (grade≥3) in azacitidine plus venetoclax/control arm, respectively, were febrile neutropenia (30% vs.10%) and pneumonia (16% vs. 22%) [52]. (see Table 52 in appendix)

Tumor lysis syndrome was reported during venetoclax dose ramp-up in three (1%) patients in the azacitidine plus venetoclax arm and none in the control arm; all were transient biochemical changes that resolved with uricosuric agents and calcium supplements without treatment interruption [52].

The safety profile of venetoclax in combination with azacitidine is predictable and manageable in the newly diagnosed AML patient population. No new risks associated with venetoclax at the proposed doses in combination with azacitidine among patients with AML were identified and venetoclax in combination with azacitidine was well tolerated [52].

Supportive study

The study M14-358 provides supportive evidence to VIALE-A as part of the same development program.
M14-358 was a Phase 1b, open-label, non-randomized, multicenter study to evaluate the safety and pharmacokinetics of orally administered venetoclax combined with decitabine or azacitidine and the preliminary efficacy of these combinations. Patients (N = 145) were at least 65 years old with treatment-naive AML and were ineligible for intensive chemotherapy [52, 53, 55].

At a median duration of follow-up of 29 months, the median OS for venetoclax in combination with azacitidine was 16.4 months (95% CI: 11.3, 24.5). For patients treated with venetoclax in combination with decitabine, the median OS was 16.2 months (95% CI: 9.1, 27.8) at a median duration of follow-up of 40 months. Median OS for venetoclax in combination with azacitidine and venetoclax in combination with decitabine are consistent with each other in M14-358 and both are consistent with the median OS reported for venetoclax plus azacitidine arm of VIALE-A [53]. The long-term follow-up analysis of the phase 1b study supports previous data sets, including VIALE-A, and suggests that Ven+HMA leads to rapid and durable remissions in patients ineligible for intensive chemotherapy. [53]

Table 7: Comparison of phase 1b study (July 2019 data cut-off of 115 patients that were treated at the 400mg dose of venetoclax) and the Viale-A study [52, 53]

Ven+Aza (400mg)	M14- 358 (N=84)	Viale- A (N=286)
Design	Phase 1b, open-label, non-RCT	Phase 3, double-blinded, RCT
Follow up	29 months	20.5 months
Median OS	16.4 months (11.3 – 24.5)	14.7 months (11.9 – 18.7)
Median DOR*	21.9 months	17.5 months
CR/CRi	71% (61 - 81)	66.4% (60.6 – 71.9)
Median time for first response	1.2 months	1.3 months
MRD	48%	23.4%
Transfusion independence rates	64% (RBCs) 70% (platelets)	59.8% (RBCs) 68.5% (platelets)

*DOR: duration of response

For detailed efficacy and safety results, refer to appendices D and E.

7.1.3 Comparative analyses of efficacy and safety

Method of synthesis

As there is a head-to-head study comparing ven+aza to the relevant comparator and the comparator arm outcome is representative of clinical practice (see 8.3.6), there is no need for indirect analysis or other synthesis.

7.1.4 Dosing and efficacy of Venclyxto when CYP3A is inhibited

Venetoclax is largely eliminated through metabolization by cytochrome P450 3A (CYP3A). Co-administration with strong or moderate inhibitors of CYP3A (CYP3Ai) increase the exposure of venetoclax and consequently the dose of venetoclax should be reduced. Most relevant in the context of AML is concomitant prophylactic use of antifungal medication to neutropenic patients or patients otherwise at risk of infections. Several of the most commonly used antifungal drugs (prophylactic and therapeutic use) are moderate or strong inhibitors of CYP3A, most notably posaconazole and other antifungal therapies belonging to the azol-group. Of note the patient may also be exposed to CYP3Ai in the diet, hence it is recommended to avoid grapefruit products, seville oranges, and starfruit during treatment with venetoclax.

A phase 1b study compared the pharmacokinetics of venetoclax when adminstered alone (400 mg/day) vs. reduced doses of venetoclax (50 mg/day or 100 mg/day) co-administered with posaconazole, a strong CYP3i. Posaconazole was calculated to increase venetoclax C_{max} and AUC_{0-24} by 7.1- and 8.8-fold, respectively. The authors conclude ”Posaconazole can be used for antifungal prophylaxis in patients with acute myeloid leukemia receiving venetoclax after reducing the venetoclax dose by at least 75%”. Both the 50- and 100-mg venetoclax doses coadministered with posaconazole were well tolerated and resulted in drug exposure higher or comparable to 400 mg venetoclax administered without concomitant CYP3Ai [62].

Additionally, an analysis of patients receiving a reduced venetoclax dose due to concomitant use of moderate or strong CYP3A-inhibitors resulted in overall similar composite remission (CR+CRi) rates [63]. Jonas et al. report that the CR+CRi rates in the ven+aza arm was 67 % in the absence of concomitant CYP3Ai and corresponding dose reduction, while comparable CR+CRi rates of 61 % and 64% where reported for patients on reduced dose due to concomitant use of moderate or strong CYP3Ai, respectively. Also, time to CR+CRi was comparable (Table 8).

Table 8: Efficacy outcomes in patients treated with and without concomitant anti-infective moderate or strong CYP3A-inhibitor profylaxis, with coresponding venetoclax dosereduction, in the first 2 cycles of therapy – subanalysis of the Viale-A trial. Table based on Jonas et al [63]

	Ven+Aza (n=286)			**Pbo+Aza (n=145)**		
CYP3Ai (patients)	None (n=230)	Moderate (n=41)	Strong (n=22)	None (n=115)	Moderate (n=18)	Strong (n=13)
CR+CRi, n (%) (95% CI)	153 (67) (60-72,6)	25 (61) (44,5-75,8)	14 (64) (40,7-82,8)	32 (28) (19,9-37,0)	3 (17) (3,6-41,4)	6 (46) (19,2-74,9)
CR	90 (39)	10 (24)	6 (27)	20 (17)	2 (11)	4 (31)
CRi	63 (27)	15 (37)	8 (36)	12 (10)	1 (6)	2 (15)
Median time to CR+CRi (range), months	1,2 (0,6-9,9)	1,4 (1,0-5,5)	1,4 (0,9-5,4)	2,8 (0,8-13,2)	2,8 (1,1-6,3)	2,8 (1,0-5,3)

Pharmacokinetic analyses from a phase 3-trial evaluating the combination of venetoclax + LDAC (FDA label) also demonstrated that the recommended venetoclax dose reduction, while receiving concomitant CYP3Ai, result in venetoclax exposures comparable to standard dosing in the setting where no concomitant CYP3Ai is used [57].

As can be seen in Table 5 in section 5.3.2, EMA has recognized the effects of CYP3A inhibition on venetoclax.

7.1.5 Value of Venclyxto in AML

AML is rapidly fatal if left untreated, with the lowest survival rate of all leukemias. It has particularly poor survival for patients ineligible for intensive chemotherapy, with a 1-year survival rate of 15–20% and a 5-year survival rate of just 5%. The impairment on quality of life is significant, with deterioration both due to AML symptoms, particularly fatigue, anemia, and infection, and due to treatment, which requires prolonged hospitalization. The need for repeated blood transfusions due to thrombocytopenia also leads to substantial clinical burden and healthcare resource use.

AML is also a heterogeneous disorder characterized by different cytogenetic and molecular profiles, which makes it difficult to treat and many patients with AML are not candidates for standard induction therapy due to age, comorbidities, disease status, cytogenetic/molecular risk stratification, and toxicity.

Several unmet needs exist in AML treatment such as the need for improved survival, need for improved HRQoL, need for transfusion independence, and need for more treatment options for patients who are ineligible for intensive chemotherapy. Venclyxto in combination with azacitidine meets all of those unmet needs;

- The need for an improved survival
  - *Venetoclax in combination with azacitidine resulted in significant longer OS, more rapid and durable responses with significant and clinically meaningful improvements in response rates, compared with azacitidine monotherapy.*
  - *Venetoclax in combination with azacitidine resulted in a significantly deeper response among patients who achieved remission of CR + CRi (composite CR), MRD negativity was achieved in 23.4% of those receiving venetoclax plus azacitidine compared with 7.6% in the control arm (p<0.001).*

- The need for an improved HRQoL and treatments with an acceptable side effect profile
  - *Venetoclax in combination with azacitidine resulted in longer EFS and improved patient-reported outcomes compared with azacitidine monotherapy.*

- The need for transfusion independence
  - *Venetoclax in combination with azacitidine resulted in greater transfusion independence rates.*

Furthermore, the safety profile of venetoclax in combination with azacitidine is acceptable and manageable in a newly diagnosed AML patient population. Compared with azacitidine monotherapy, combination therapy with venetoclax was well tolerated. No new risks associated with venetoclax at the proposed doses in combination with azacitidine were identified in the entire AML development program.

Venetoclax in combination with a an HMA provides an alternative treatment option with a distinct and new mechanism of action, addressing the high unmet need of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

8. Health economic analysis

A de novo partitioned survival model was constructed to assess the cost-effectiveness of venetoclax with azacitidine compared with azacitidine for the treatment of newly diagnosed adult patients with acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy.

The cost-utility model was developed and populated in line with Danish health care context.

8.1 Model

8.1.1 Model overview

Table 9: Model overview

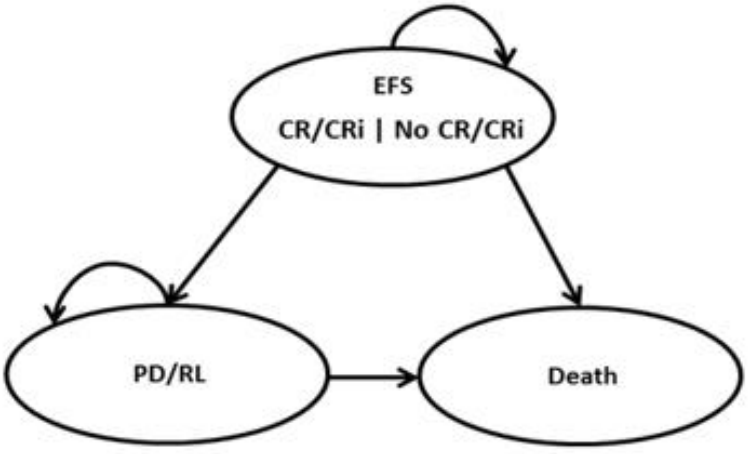
Population	Adults with newly diagnosed AML for whom intensive chemotherapy is unsuitable
Intervention	Venclyxto co-administered with azacitidine Venclyxto Day 1: 100mg Day 2: 200mg Day 3 and beyond: 400mg Azacitidine, 100 mg/m^2 s.c. day 1–5 of the 28-day treatment cycle
Comparator	Azacitidine, 100 mg/m^2 s.c. day 1–5 of the 28-day treatment cycle
Perspective	Limited societal
Time horizon	Lifetime
Discount rate	Costs and effectiveness are discounted at 3.5% annually during the years 0-35, 2.5 percent during the years 36-70, and 1.5% after year 70.
Model type	Partitioned survival model with cure modelling for extrapolation
Cycle length	28 days
Model outputs	• Costs ○ Initial treatment drug cost ○ Initial treatment administration cost ○ Subsequent pharmacological treatment costs (including drug and administration) ○ Adverse events costs associated with initial treatments ○ Medical costs associated with health states (i.e. hospitalization, blood transfusion, and other monitoring costs) ○ Terminal care costs ○ Patient time ○ Patient transport • Effectiveness

    - Life years
    - Quality-adjusted life years
- Incremental cost-effectiveness
    - Cost per LY
    - Cost per QALY
- Budget impact

8.1.2 Model Structure

The cost-effectiveness model was developed in Microsoft Excel®. A three-state partitioned survival model (PSM) was used for the economic modelling, which is a typical approach in modelling oncology therapies. The model comprised of three mutually exclusive health states: (i) event-free survival (EFS), (ii) progressive/relapsed disease (PD/RL), and (iii) death (Figure 6). EFS was defined as the time from the date of treatment initiation to the date of first documented progression or relapsed from complete remission/complete remission with incomplete blood count recovery (CR/CRi), or treatment failure or death due to any cause. All patients began in EFS at the model start. The proportion of patients in the EFS health state of the model was set to be equal to the EFS curve of each treatment. Within EFS, a proportion of time will be assumed in CR/CRi and it was estimated by applying the proportion of patients in CR/CRi over time to the EFS curve. CR/CRi is clinically relevant and is related to improved OS [64]. The PD/RL state included alive patients who progressed or relapsed. The proportion of patients in the PD/RL health state was set to be equal to the difference between the proportion of living patients, which was based on the OS curve, and the proportion of EFS patients. During each cycle, patients were redistributed among the three health states, with death being the absorbing state. Half-cycle correction is applied.

Figure 6. Partitioned survival model structure



8.1.3 Model assumptions

Table 10 summarizes the key assumptions of the model.

Table 10. Key assumptions of the model

Parameter	Assumption
Health states and utilities by health states	At the start of each cycle, patients were redistributed among the three health states, with death being the absorbing state. Utilities of health states were assumed to be dependent only on health state and independent on treatment arm. Utilities are derived from EQ-5D-5L Viale-A data using the Danish hypothetical value set [65].
AE disutility	The model considered disutility associated with grade 3/4 AEs. Disutilities are derived from EQ-5D-5L Viale-A data using the Danish hypothetical value set [65]. An estimator model is used to distinguish the AE disutility from utility by health state.
Subsequent treatments	Subsequent pharmacological treatments after the initial treatment are considered in the model for patients who had either progressive or relapsed disease to reflect the natural treatment course patients experienced. Costs will be applied to the proportion of patients who receive subsequent treatments, as relevant in the Danish context. Effectiveness of subsequent treatments on EFS and OS are assumed to be reflected in the clinical trial results.
Efficacy	CR/CRi, EFS, and OS were separately estimated for the intervention and comparator arms. Efficacy was extrapolated using the clinically most relevant curves.
Long-term survival assumption	Long-term survival assumption (technical term being a cure model) applied to patents in EFS state after year 2 in the base-case. • Patients who remained in EFS in the model at year 2 were considered to be functionally cured; these patients were associated with a risk of death equivalent to twice of that of the general population (SMR=2). • After year 2, all patients who remained in EFS state were assumed to incur health state costs and utilities associated with long-term AML survivors.
Treatment costs	Patients were treated based on the treatment schedule specified in the Viale-A trial. Time on treatment data from the clinical trial was used to estimate time on treatment.
Medical costs and AE costs	Costs of grades 3 or 4 AEs were considered in the model. Only AEs with a prevalence rate greater than 5% in any of the arms were considered. AE costs were added as one-time costs in the model for both treatment arms. In addition to treatment and AE costs, the model considered additional medical costs including hospitalization, blood transfusion, and other monitoring costs associated with each health state (i.e., EFS with CR/CRi, EFS without CR/CRi, PD/RL) and terminal care costs. All patients incur one-time terminal care costs before death.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

Efficacy inputs included OS, EFS and CR/CRi. OS, EFS and CR/CRi inputs for venetoclax in combination with azacitidine and azacitidine were based on data from the Viale-A trial (data cut-off: January 4, 2020). Viale-A is a multicentre and randomized double-blind placebo-controlled phase 3 trial, in which patients were assigned in a 2:1 ratio either to the venetoclax combination therapy or to the control group. The individual patient-level data (IPD) from the Viale-A trial were used to derive the OS and EFS of venetoclax with azacitidine and azacitidine.

The key patient characteristics and the design of the data source considered for venetoclax with azacitidine and azacitidine are summarized in Table 11.

Table 11. Clinical data sources for base-case analysis

Comparator Arm	Source	Patient Population	Main Patient Characteristics	Sample Size	Follow-up
Venetoclax with azacitidine	Viale-A	Adult patients with newly diagnosed AML who were ineligible for intensive chemotherapy	Median age: 76; >30% bone marrow blast count: 72% Prior HMA use: 0%	286	Median: 20.5 months (Data cut-off date: January 4, 2020)
Azacitidine			Median age: 76; >30% bone marrow blast count: 74% Prior HMA use: 0%	145	

Abbreviations: AML: acute myeloid leukemia; HMA: hypomethylating agents

In the base-case analysis, the efficacy inputs for OS, EFS and ToT were predicted using parametric survival models estimated based on the Viale-A trial data. Over time, patients remaining in EFS with CR/CRi are defined as long-term survivors and assumed to have a higher mortality rate than the general population. This assumption is discussed further below in section 8.3.6.

8.2.2 Relationship between the clinical documentation, data used in the model, and Danish clinical practice

8.2.2.1 Patient population

The Danish patient population is the same as in the clinical documentation and health economic analysis submitted: adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy.

Table 12: Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc.	Used in the model	Danish clinical practice
Age (years)	(Viale-A)		
Average	75	75	The Viale-A population is corresponding well to Danish clinical practice according to expert opinion.
Median (range)	76 (49-91)		
≥75 years (%)	61%		
ECOG status	(Viale-A)	Not used as an input per se, but inputs are from Viale-A, reflecting the baseline ECOG status in the study.	The Viale-A population is corresponding well to Danish clinical practice according to expert opinion.
0-1	55%		
2-3	45%		
Secondary AML (%)	11% (Viale-A)	Not used as an input per se, but inputs are from Viale-A, reflecting that proportion of secondary AML.	The Viale-A population is corresponding well to Danish clinical practice according to expert opinion.

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice (as defined in section 2.2): Venclyxto + azacitidine
Intervention in the clinical documentation submitted: Venclyxto + azacitidine
Intervention as in the health economic analysis submitted: Venclyxto + azacitidine

Table 13: Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice
Posology	Treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents. Patients should be premedicated with anti-emetics for nausea and vomiting.	20% of patients receive first treatment as inpatients (expert opinion). First treatment in the cycle uses additional patient time due to monitoring etc.	20% of patients receive first treatment as inpatients (expert opinion). First treatment in the cycle uses additional patient time due to monitoring etc.
Dosing	Day 1: 100mg Day 2: 200mg Day 3 and beyond: 400mg Venetoclax dosing may be interrupted as needed for management of haematologic toxicities and blood count recovery. Also, dose reduction when using CYP3A-inhibitor.	Venetoclax as per SmPC and azacitidine 100 mg/m^2 s.c. day 1–5 of the treatment cycle. Dose intensity of ven [redacted] in base-case (dynamic) compared to full dose for venetoclax and [redacted] of azacitidine full dose due to expected Danish clinical practice of anti-fungal treatment and dose	In a higher scenario: As per SmPC but 2/3 patients receive strong CYP3Ai during the whole course of treatment and 1/3 for the first three cycles and dose interruptions as in Viale-A, and dose intensity of azacitidine as in Viale-A but 100 mg/m^2 s.c. day 1–5 of the treatment cycle.

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice
	Azacitidine administered at 75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1 Day 1. Dose intensity: [redacted] (Viale-A and SmPC)	interruptions and modifications seen in Viale-A due to other reasons than anti-fungal treatment.	In a lower scenario: Clinical practice will not use venetoclax for all 28 days as standard, but rather 7-21 days. CYP3Ai and dose intensity as above. (clinical opinion)
Length of treatment (time on treatment) (mean/median)	Treatment was made until disease progression or unacceptable toxicity (9.9/7.6 months) (Viale-A)	Parametric function based on Kaplan-Meier ToT data from Viale-A where treatment was made until disease progression or unacceptable toxicity.	Treating until disease progression or unacceptable toxicity (expert opinion). It can be noted that this differed from expert opinion outside Denmark where treatment would be assumed to stop after a long time (2-3 years) in remission, and it might therefore be a conservative assumption.
Criteria for discontinuation	**According to SmPC:** Venetoclax, in combination with a hypomethylating agent, should be continued until disease progression or unacceptable toxicity is observed. **Per Viale A study protocol**, each subject has the right to withdraw from the study at any time. In addition, the investigator will discontinue a subject from the study at any time if the investigator considers it necessary for any reason including: ● The investigator believes it is in the best interest of the subject. ● The subject's response to therapy is unsatisfactory, as evidenced by the progression of the disease as defined per ELN criteria while on study drug. ● Treatment failure, defined as failure to achieve CR, CRi, PR, or	Treating until disease progression or unacceptable toxicity as per Viale-A data and with parametric functions for extrapolation.	Treating until disease progression or unacceptable toxicity (expert opinion). It can be noted that this differed from expert opinion outside Denmark where treatment would be assumed to stop after a long time (2-3 years) in remission and it might therefore be a conservative assumption.

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice
	MLFS after at least 6 cycles of study treatment. ● The subject experiences toxicities related to study drug that require more than a 4-week (1 cycle) dose interruption of venetoclax or azacitidine, in the absence of clinical benefit. ● The subject requires any radiotherapy or chemotherapy agents during the study period (apart from hydroxyurea allowed during Cycle 1). ● The occurrence of an adverse event that precludes further azacitidine drug administration. ● Noncompliance with the protocol. ● The subject becomes pregnant while on study drug.		
The pharmaceutical's position in Danish clinical practice	Adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy (Viale-A)	Adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy	Adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy

8.2.2.3 Comparators

The current Danish clinical practice: Azacitidine monotherapy
Comparator in the clinical documentation submitted: Placebo + azacitidine
Comparator in the health economic analysis submitted: Azacitidine monotherapy

Table 14: Comparator

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	Treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents. Patients should be premedicated with anti-emetics for nausea and vomiting. (SmPC)	20% of patients receive first treatment as inpatients (expert opinion). First treatment in the cycle uses additional patient time due to monitoring etc.	20% of patients receive first treatment as inpatients (expert opinion). First treatment in the cycle uses additional patient time due to monitoring etc.

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Dosing	Azacitidine 75-100 mg/m^2 s.c. daily for 5-7 days repeated every four weeks. (Danish guidelines)	100 mg/m^2 s.c. day 1–5 of the treatment cycle repeated every four weeks.	100 mg/m^2 s.c. day 1–5 of the treatment cycle (expert opinion) repeated every four weeks.
Length of treatment	It is recommended that patients should be treated for a minimum of 6 cycles. Treatment should be continued for as long as the patient continues to benefit or until disease progression. (SmPC)	Parametric function based on ToT data from Viale-A where treatment was made until disease progression or unacceptable toxicity.	Response can be obtained up to after 9 cycles but is most often seen after 4-6 cycles. Treatment is given until treatment failure. (Danish guidelines)
The comparator's position in the Danish clinical practice	Adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy (Viale-A)	Adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.	Non-curative treatment (mostly patients >60years old) (Danish guidelines)

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation: OS, EFS, CR/CRi.
Relevance of the documentation for Danish clinical practice: OS and EFS are relevant clinical outcomes and have previously been used also in evaluations within AML by DMC [66]. CR/CRi is clinically relevant and is related to improved OS [64].

Parametric functions derived from the OS and EFS Kaplan-Meier data are as expected following the data very well, and which distribution used has importance for the extrapolated values. In Table 15 the difference between the arms in median value from the Viale-A results are compared to the difference in the median model values. The differences are small and are also affected by that interpolation within the cycles were used to find the median model value for both arms.

Table 15 Summary of clinical values from documentation and used in the HE model

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint in the study		
Overall survival (OS)	+5.1 months difference in medians observed (Viale-A)	Parametric functions with a difference in medians of +5.7 and average (area under the curve) of +36.3 months
Secondary endpoint		
Composite complete remission (CR/CRi)	+40 percentages (65% vs 25%)	For economic modelling, the proportion of patients in CR/CRi per timepoint is relevant.

Event-free survival (EFS)	+2.8 months difference in medians	This is modelled by using Kaplan-Meier data as described in section 8.3.5. Parametric functions with +3.6 months difference in medians and average (area under the curve) of +17.7 months

8.2.2.5 Adverse reaction outcomes

The adverse event rate inputs are obtained from Viale-A. Only grade 3/4 AEs with ≥ 5% rate in any of the arms were considered. The AE costs are estimated based on clinical input/price lists/DRG costing. Disutilities were obtained from Viale-A. Note that several adverse events listed do not have disutility associated with them as per the result of the analysis presented in section 8.4.2.

Table 16: Adverse reaction outcomes

Grade 3/4 AEs ≥ 5%	Venetoclax + azacitidine	Azacitidine	AE Cost per event (2021 DKK)	AE Disutility per event
Anemia	26,1%	20,1%	3 114 kr.	0,006
Atrial fibrillation	5,7%	2,1%	1 153 kr.	0,000
Febrile neutropenia	41,7%	18,8%	3 114 kr.	0,022
Hypertension	6,0%	4,2%	14 155 kr.	-0,040
Hypokalemia	10,6%	10,4%	1 518 kr.	-0,028
Hypophosphataemia	7,4%	7,6%	1 518 kr.	-0,028
Leukopenia	20,5%	11,8%	3 114 kr.	-0,007
Neutropenia	42,0%	28,5%	3 114 kr.	0,022
Pneumonia	17,7%	25,0%	36 514 kr.	-0,049
Sepsis	5,7%	6,9%	42 770 kr.	0,000
Thrombocytopenia	44,5%	38,2%	35 483 kr.	-0,026
Urinary tract infection	3,9%	5,6%	24 431 kr.	0,000
Total AE Cost (2021 DKK)	**30 889.42 kr**	**30 360.52 kr**		
Total AE Disutility	**-0,0003**	**-0,0006**		
Notes & References	M15-656 trial	M15-656 trial		M15-656 trial

8.3 Extrapolation of relative efficacy

8.3.1 Time to event data – summarized:

In the base-case analysis, the efficacy inputs for OS and EFS were predicted using parametric survival models estimated based on the Viale-A trial data. Over time, patients remaining in EFS with CR/CRi are defined as long-term survivors but are assumed to have a higher mortality rate than the general population. This assumption is discussed

further below in section 8.3.6. Table 17 provides a summary of extrapolation methods for ToT, EFS, remission, and OS efficacy inputs used in the base-case.

Table 17: Summary of efficacy data sources and base-case extrapolation approach

Efficacy inputs	Treatments	Extrapolation method
OS	Venetoclax with azacitidine	Weibull + cure modelling
	Azacitidine	Exponential + cure modelling
EFS	Venetoclax with azacitidine	Gompertz + cure modelling
	Azacitidine	Exponential + cure modelling
CR/CRi (as proportion of EFS)	Venetoclax with azacitidine	-
	Azacitidine	Adjustments made based on Ven+aza arm
ToT	Venetoclax with azacitidine	Exponential
	Azacitidine	Log-normal

Abbreviations: BSC, best supportive care; EFS, event-free survival; HR, hazard ratio; OS, overall survival

Methods are described below. A complete description of extrapolation methods can be found in Appendix G.

8.3.2 Extrapolation of data and curve fitting

Following the survival model selection process algorithm recommended by NICE DSU TSD14, a range of methods, when appropriate, were used to assess the suitability of parametric survival models for all efficacy inputs [67]. Specifically, the model fit was evaluated based on the following steps:

- **Akaike information criterion (AIC)/Bayesian information criteria (BIC) tests:** The AIC and the BIC provide useful statistical tests of the relative fit of different parametric survival models. These tests weigh the improved fit of models with the potentially inefficient use of additional parameters. Lower AIC and BIC values indicate a better fit of the selected model.
- **Visual inspection:** the visual inspection could evaluate how well a parametric survival model fits with the observed K-M curve visually. The parametric survival model that most closely follows the K-M curve could be considered the best fit.
- **Examination of the log-cumulative hazard plots:** Log-cumulative hazard plots were constructed to compare the hazards observed in the clinical trial and hazards estimated by different parametric survival models over time. Since different parametric survival models incorporate different hazard functions (e.g., exponential for constant hazard, Gompertz for monotonic hazard), the hazard plots could be used to select the suitable parametric survival models that had the most consistent hazard function with observed hazard patterns.
- **Clinical input and external validation:** Extrapolations were compared and fitted to Swedish registry data. Clinical input influenced the choice of parametric function.

As is often done, we are using different types of parametric models for the different treatment arms based on the steps above. The difference in mode of action and efficacy, such as the proportion of patients in CR/CRi over time justifies this approach, as we will explain below.

Mode of action (MoA) and time to onset of effect is described in sections 5.3.1 and 7.1.2, respectively.

Briefly, hypomethylating agents (HMAs) such as azacitidine has long been considered standard therapy for AML patients ineligible for intensive chemotherapy. Aberrant DNA methylation patterns are thought to be involved in driving the pathobiology of AML. Azacitidine incorporates into the DNA/RNA of highly proliferating cells leading to demethylation. The MoA of azacitidine likely involves additional effects such as direct cytotoxicity, activation of DNA-damage pathways and immunomodulatory effects. The full understanding of the MoA remains unclear [68].

Venetoclax is a selective, potent, oral BCL-2 inhibitor that induces apoptosis, programmed cell death, in AML cells in combination with other therapeutic agents, including azacytidine and other HMA [41-45]. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins, triggering mitochondrial outer membrane permeabilization, and the activation of caspases, eventually leading to cell death [41, 43, 44]. HMAs (e.g., azacitidine and decitabine) indirectly and synergistically increase sensitivity to BCL-2 inhibition in AML-cells by modifying the relative levels of proteins in the BCL-2 family [46-48]. MoA of venetoclax including synergies with HMAs has been reviewed relatively recently in the scientific literature [69]. Leukemic stem cells (LSC) is a source of disease progression, resistance, and relapse in AML. By targeting the LSC population, it is plausible to achieve deep and durable responses with reduced risk of late relapse [49]. Venetoclax in combination with azacitidine effectively targets the LSC population via disruption of amino acid-fueled oxidative phosphorylation, on which the LSC population is uniquely reliant. This hypothesis is supported by the deep and durable responses observed in clinical trials [52, 53]. In addition to restoration of apoptosis and targeting LSCs, a third element of venetoclax MoA in AML is immunomodulation. Venetoclax modulates T-cells to increase their cytotoxicity to AML cells, while azacitidine demonstrates the potential to induce the susceptibility of AML cells to T-cell mediated cytotoxicity [54]. This suggests an immune-mediated mechanism of action compatible with the observed response depth and durability following venetoclax-azacitidine treatment in Viale-A [52].

In the Viale-A trial, the median time to first response (CR or CRi) was shorter for patients treated with venetoclax in combination with azacitidine compared to patients receiving azacitidine monotherapy (1.3 months vs 2.8 months). By the initiation of the second treatment cycle, the rates were 43.4% vs. 7.6% for venetoclax in combination with azacitidine vs. azacitidine monotherapy [52]. In addition to faster time to response and a larger population reaching CR/CRi, venetoclax combined with azacitidine resulted in significantly higher proportion of patients achieving deep responses with measurable residual disease (MRD) negativity compared to the control group [52]. The impact of response depth (MRD < 10^{-3} vs. MRD ≥ 10^{-3} was demonstrated in a sub-analysis concluding that duration of response, event-free survival (EFS), and overall survival (OS) were all significantly longer in patients who achieved CR/CRi with MRD < 10^{-3}, further supporting the prognostic value of MRD-negativity on key clinical outcomes in AML [70].

In summary, venetoclax in combination with azacitidine resulted in longer OS, more rapid and durable as well as deeper responses, compared with azacitidine monotherapy. Venetoclax and azacitidine act synergistically to kill AML cells and display combinatorial antitumor activity. This includes initiation of apoptosis of AML-cells, targeted effects on the critical LSC population and immunomodulatory effects driving the above-mentioned clinical benefits and providing a mechanistic rationale for long-term efficacy. MoA, time to response, and the quality of the biological response, evidenced by different potential to produce deep responses (high level of MRD-negativity), varies between the two treatment groups (venetoclax + azacitidine vs. azacitidine monotherapy).

The much higher rate and earlier onset of CR/CRi with ven+aza that this MoA results in means that the proportion of patients with CR/CRi over time was higher within EFS, OS (**Figure 12** and **Figure 13**) and ToT in the ven+aza arm in Viale-A, as well as having a different shape (**Figure 13**). These very different dynamics make it reasonable to account for different risk patterns between the arms by using different parametric functions. Due to the low and slow onset of CR/CRi in the aza arm, a constant hazard over time (exponential function) would seem reasonable for azacitidine EFS

and OS, while allowing for decreasing hazards over time for ven+aza EFS and OS (Gompertz and Weibull) due to the difference in MoA and the quick onset and high rate of CR/CRi.

The methodology for parametric extrapolation and the selection of survival models is described in more detail in the following sections.

8.3.3 Overall survival

Based on input from an expert haematologist, the Weibull distribution was chosen in the base case for venetoclax with azacitidine. The exponential model was chosen for azacitidine.

8.3.4 Event-free survival

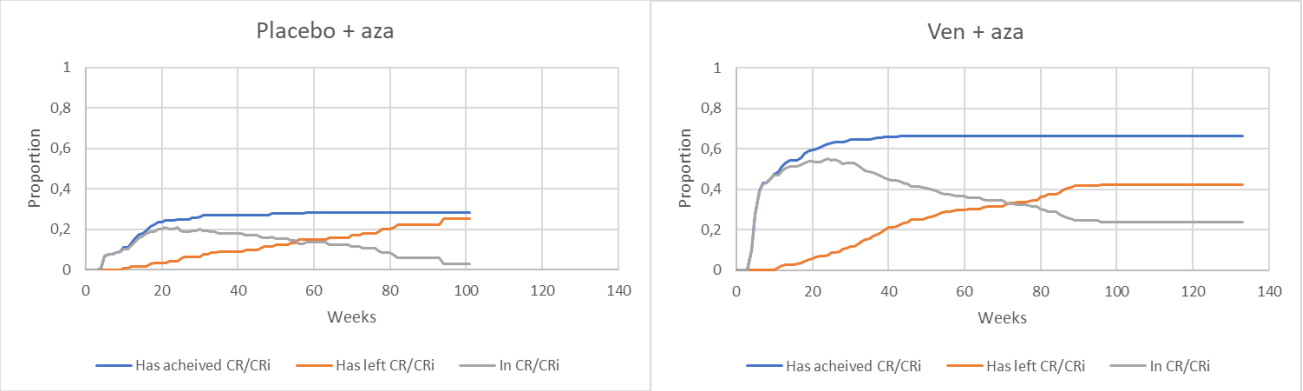
The EFS for venetoclax with azacitidine and azacitidine in monotherapy were predicted using parametric survival models estimated based on the Viale-A trial data [71]. The Gompertz and exponential models were chosen as the best fit models for venetoclax with azacitidine and azacitidine, respectively.

8.3.5 CR/CRi

Proportion of patients in CR/CRi was modelled using Viale-A data. Kaplan-Meier curves of patients achieving CR/CRi as well as leaving the CR/CRi state (for any reason, including death) were developed. These were used to calculate the

probability over time of any patients in the study being in CR/CRi. This was done for both venetoclax + azacitidine and for the azacitidine arm (Figure 11).

Figure 11: Proportion of patients in CR/CRi over time



Looking at CR/CRi, EFS and OS together (**Figure 12**) we can see that the CR/CRi curves are over time converging with the EFS curve. In the ven+aza arm, all patients remaining in EFS at two years after treatment initiation have CR/CRi. The trend can also be visualised by looking at the proportion over time of patients in EFS that have achieved CR/CRi (**Figure 13**).

Figure 12: Proportion of patients in CR/CRi, EFS and OS over time

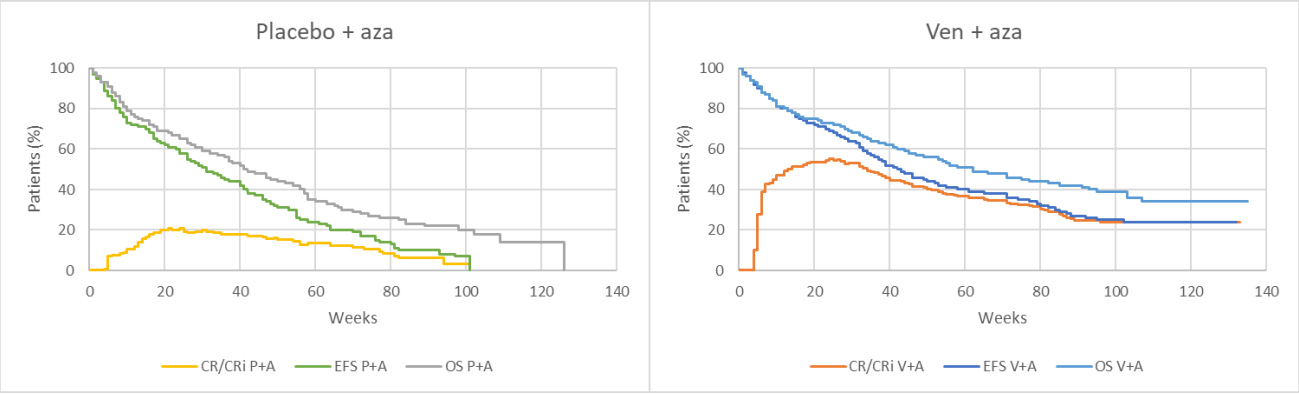
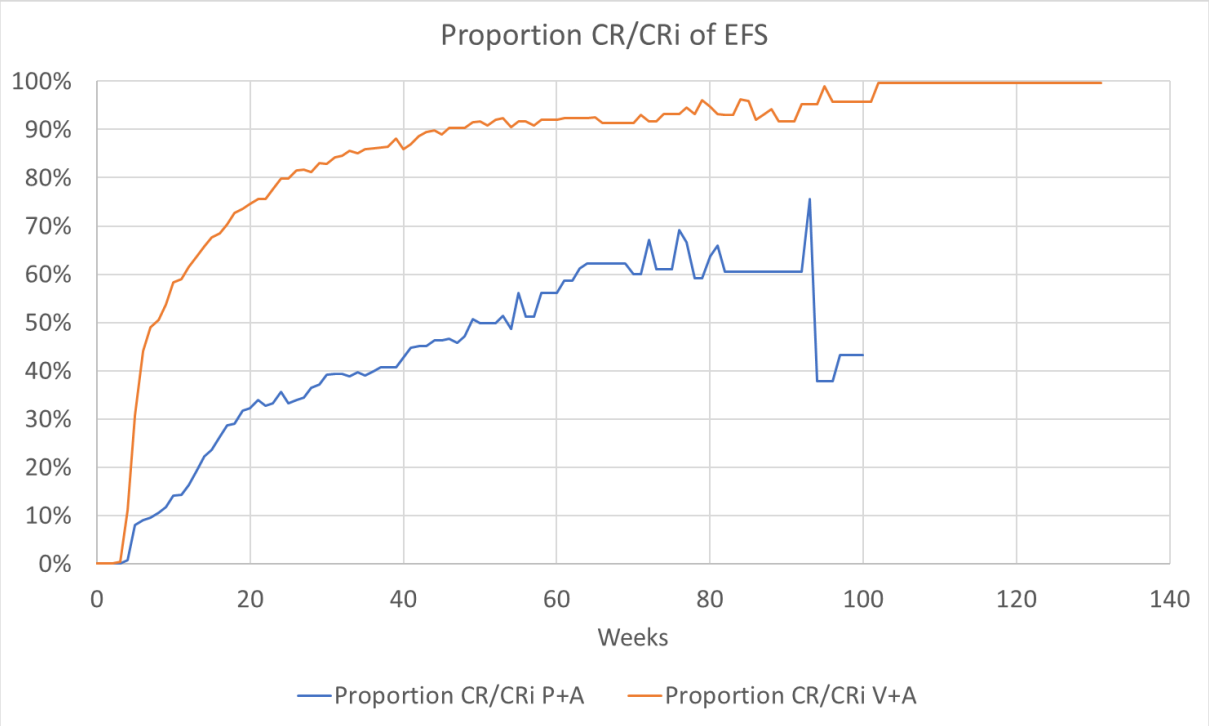


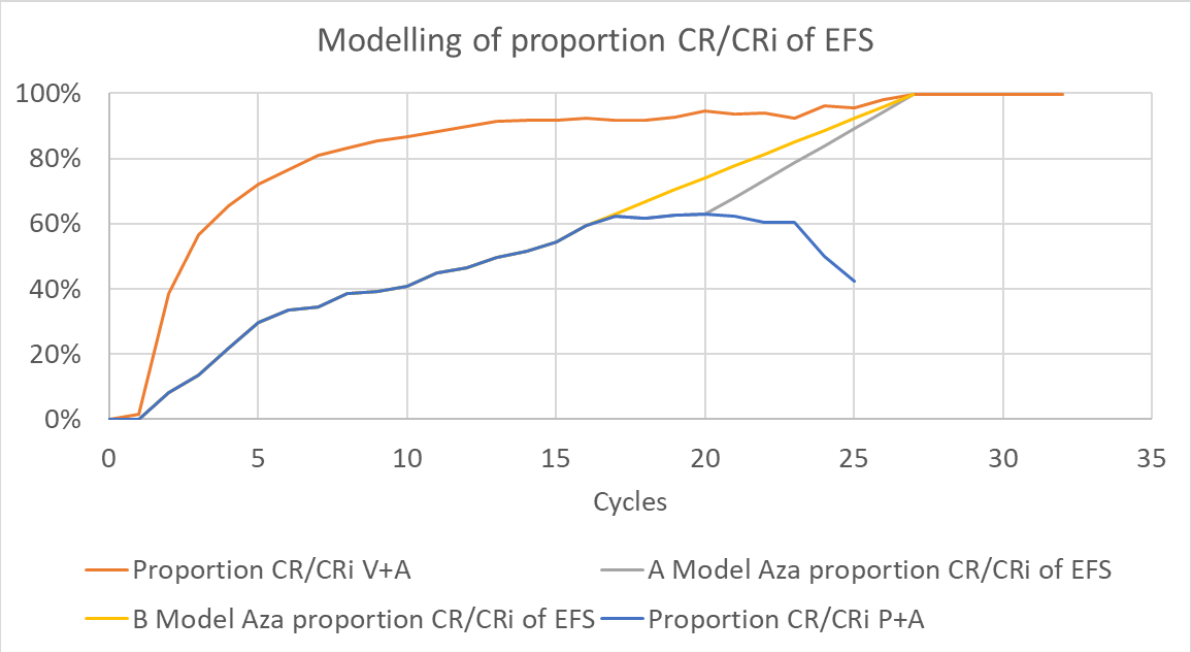
Figure 13: Proportion of patients in EFS that are in CR/CRi over time



The trend is less clear for the azacitidine arm after 70-80 weeks. We believe however this to be due to few observations.

The proportion of patients in CR/CRi of all patients in EFS was used to model the proportion of patients in CR/CRi in the model. Half-cycle adjustment was performed on week data after which the values for 28-day cycles were calculated by taking the average of the four corresponding weeks. The result was then applied in the CUA model. Due to the shape of the azacitidine curve however, an adjustment had to be done, as a downwards trend after some time in the azacitidine arm did not seem plausible. A linear increase was modelled to reach 100% at the time of functional cure assumed in the model. Two models (A and B) were looked at, where model B, where the linear increase would start already after cycle 16 (**Figure 14**) was chosen. To choose model B results in a more conservative incremental effectiveness estimate for ven+aza compared to azacitidine alone and can thereby be a source of overestimation of the ICER.

Figure 14: Modelling of proportion of CR/CRi of EFS over time



8.3.6 Long-term survival

In the base-case model, patients who remain in EFS in the model after a certain time point were considered to be long-term survivors. There are several reasons why AbbVie has chosen this approach.

Assumptions regarding long-term survival in AML using cure modelling have been evaluated and accepted in multiple HTA evaluations and by several HTA agencies, including TLV, NICE and NoMA [72-81]. There are some differences between the evaluated populations, including the rates of HSCT, however, a biological rationale for long-term survival in AML is also present in the treatment pathway for venetoclax and the rationale and assumptions are supported as plausible by clinical experts.

Most relapses following standard treatment with intensive induction chemotherapy for AML occur within the first 18 months, and late relapses are infrequent [82, 83].

The leukemia stem cell (LSC) population has different properties than the bulk AML population, making them challenging to eliminate, and therefore a source of disease progression, resistance and relapse. By eliminating the LSC population, it is plausible to expect therapeutic deep and durable remissions with minimal risk of late relapse [49]. Recent data propose that in AML, the LSC population is efficiently targeted by venetoclax with azacitidine, due to its specific disruption of amino acid-fueled oxidative phosphorylation, on which the LSC population is uniquely reliant. Resulting in promising clinical activity in a patient population with historically poor outcomes [50, 51]. This hypothesis is supported by the deep durable response that has been observed in the venetoclax clinical studies [52, 53].

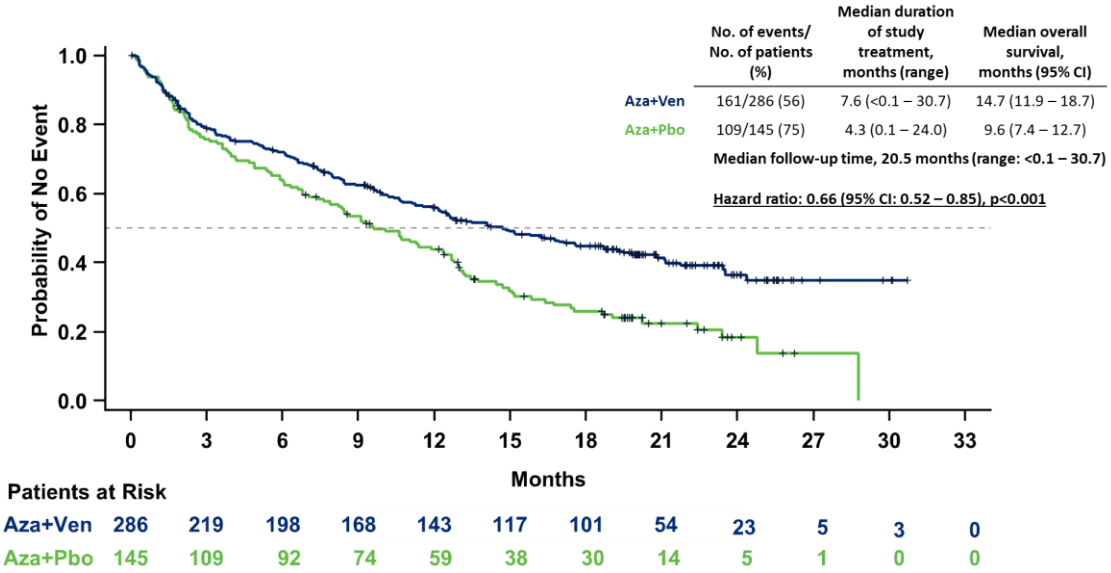
Venetoclax modulates T cells to increase their cytotoxicity to AML cells, while azacitidine demonstrates the potential to induce the susceptibility of AML cells to T-cell mediated cytotoxicity [54]. This suggests an immune-mediated mechanism of action compatible with the observed response depth and durability following venetoclax-azacitidine treatment in Viale-A.

In Viale-A, the venetoclax - azacitidine group achieved a rapid response with a median time to first response of 1.3 months. In this group, composite complete remission was achieved in around 2/3 of the patients, and achieving complete response is related to the deep response of the treatment. For venetoclax – azacitidine it is therefore a plausible assumption that a number of patients would remain in remission for years with minimal risk of late relapse.

Visual inspection of the K-M curves for OS from Viale-A shows a clear and continuous separation of the curves (shown below in Figure 15.

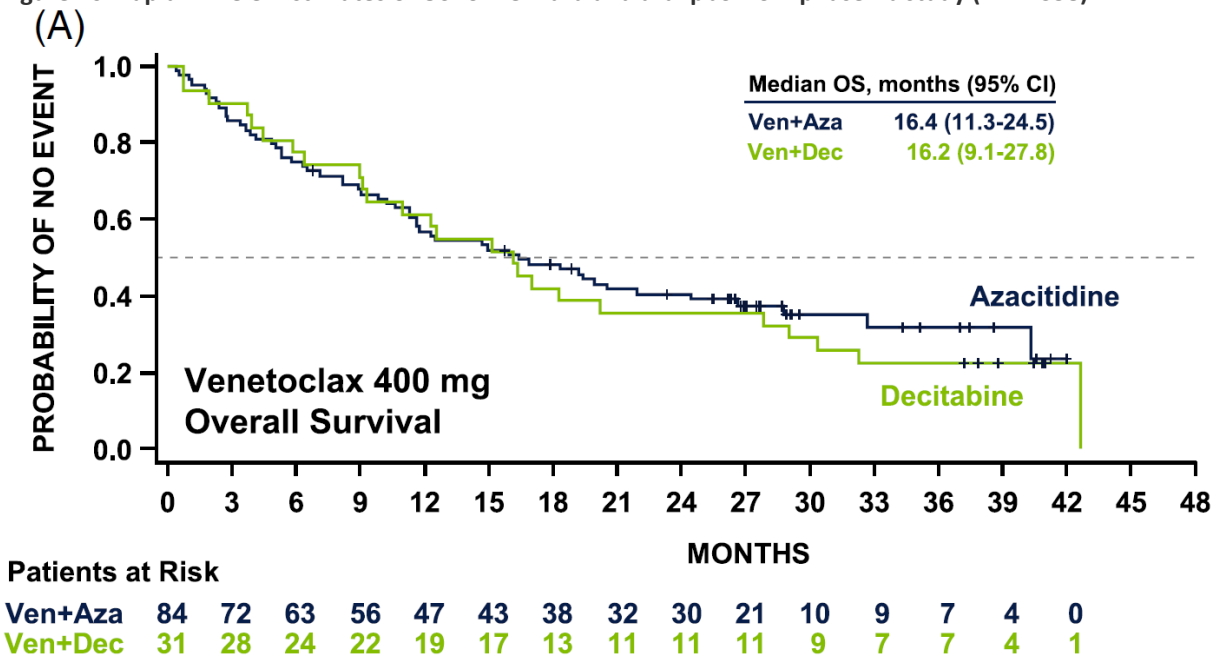
It is not unreasonable to interpret the curve as showing a beginning plateau based on a clinical rationale. This assumption is also supported by Wei et al. [57] who commented on an apparent survival plateau after 18 months.

Figure 15: Kaplan–Meier Estimates of OS for ven+aza and aza+pbo from Viale-A



The notion of a survival plateau is further supported by data from the phase 1b study of venetoclax + HMA agent, see figure below (Figure 16).

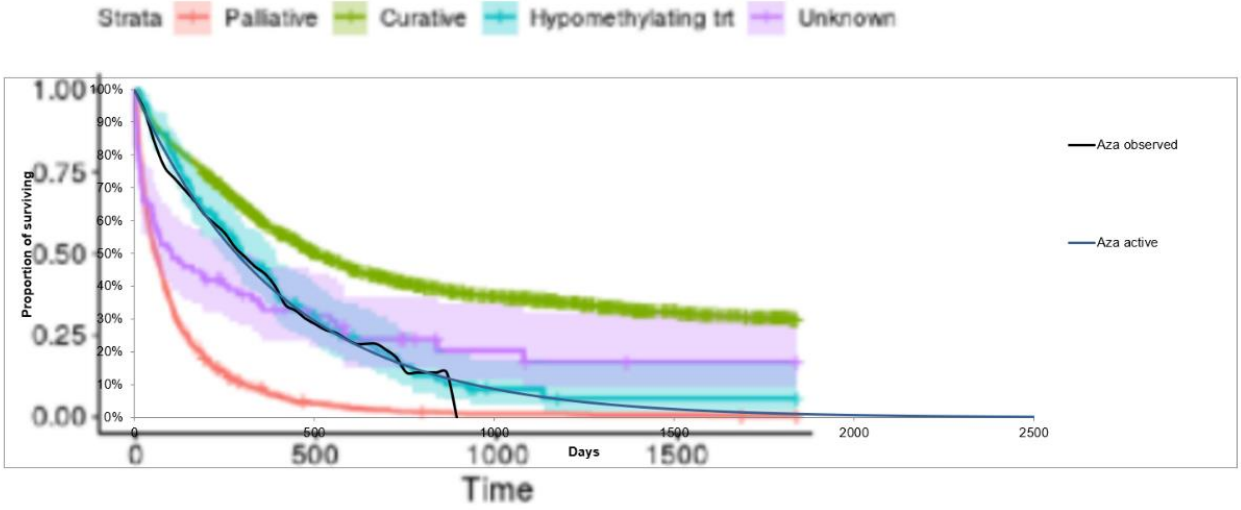
Figure 16: Kaplan–Meier Estimates of OS for ven+aza and aza+pbo from phase 1b study (M14-358)



As described earlier, more rapid achievement of CR + CRi, CR, and CR + CRh was observed with ven+aza than with aza+pbo in Viale-A, and also at a higher rate. These responses were durable, and patients experienced sustained long-term benefits. This is also supported by data of CR/CRi over time from Viale-A, which clearly show that over time the EFS and CR/CRi curves have completely converged after around two years. The interpretation is that after around two years the patients who are still in EFS are also in sustained complete remission. Data from the literature demonstrate that most relapses following standard treatment with intensive induction chemotherapy for AML occur within the first 18 months which also supports calculating with a sustained long-term benefit after two years in EFS [82, 83].

Further, AbbVie has calibrated the model extrapolations using data from the Swedish AML registry [84]. Comparison of the chosen parametric survival model for azacitidine OS with registry data [85] demonstrates a very good fit to the data until after 1000 days, when the model is underestimating OS.

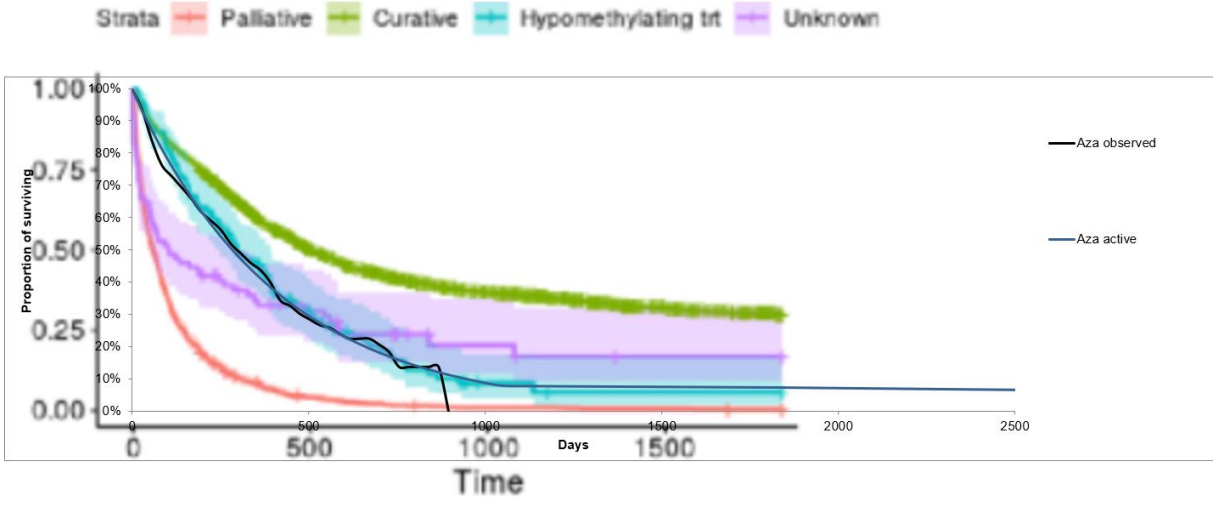
Figure 17: Modelled OS for azacitidine arm versus registry outcomes without cure modelling



One could argue that there are very few patients at risk at that timepoint in the registry data, and that the number of patients that would still be alive in that way would be uncertain. However, the fact that a patient in the registry is alive at the latest time point in the presented registry data while the model function is close to zero if no adjustment is made, proves that the modelling in the figure above is underestimating the long-term survival.

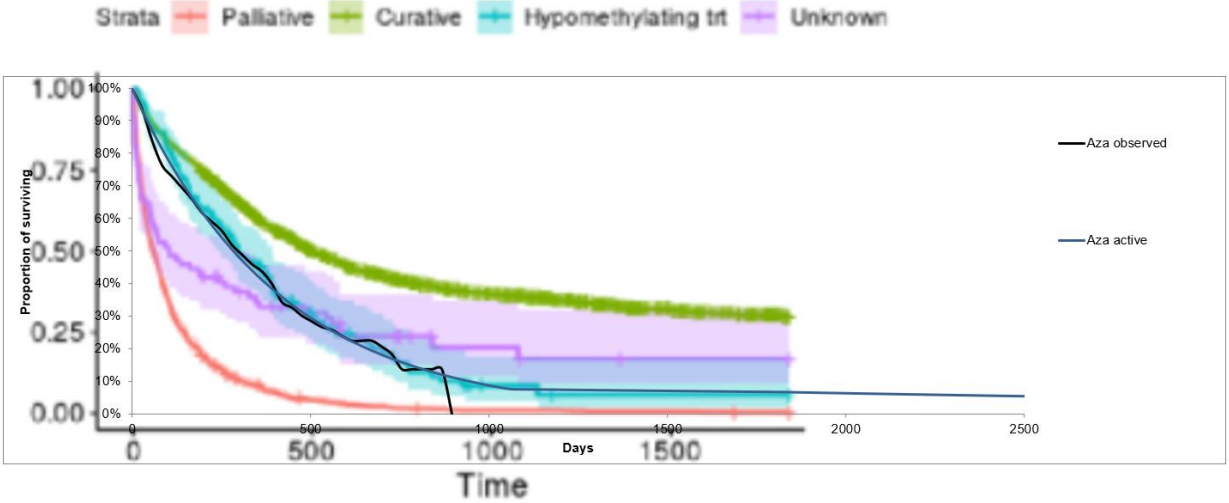
Using an assumption on long-term survival applied to EFS patients, patients who remained in EFS in the model after a certain time point were considered to be long-term survivors. Setting the risk of death equal to the general population mortality after the selected time point, and assuming that all patients still in EFS at the time of two years are long-term survivors, the fit to registry data is improved, although it now looks slightly overestimated.

Figure 18: Modelled OS fit improved with cure modelling



If we in addition to the approach above apply a standardized mortality ratio (SMR) adjustment to the general population mortality, an SMR of 2 for the long-term survivors, the fit is improved.

Figure 19: Modelled OS fit with cure modelling and an SMR of 2



Obviously, the registry data demonstrate that there are patients living longer than the model predicts without adjustments – so calibration is a justified approach. These assumptions are also similar to those made by DMC in the gilteritinib assessment [66], although the SMR in the base case was 1.3 and it is not clear to us if the assumption of cure at two years were applied to the whole of the population or only those modelled to be in CR.

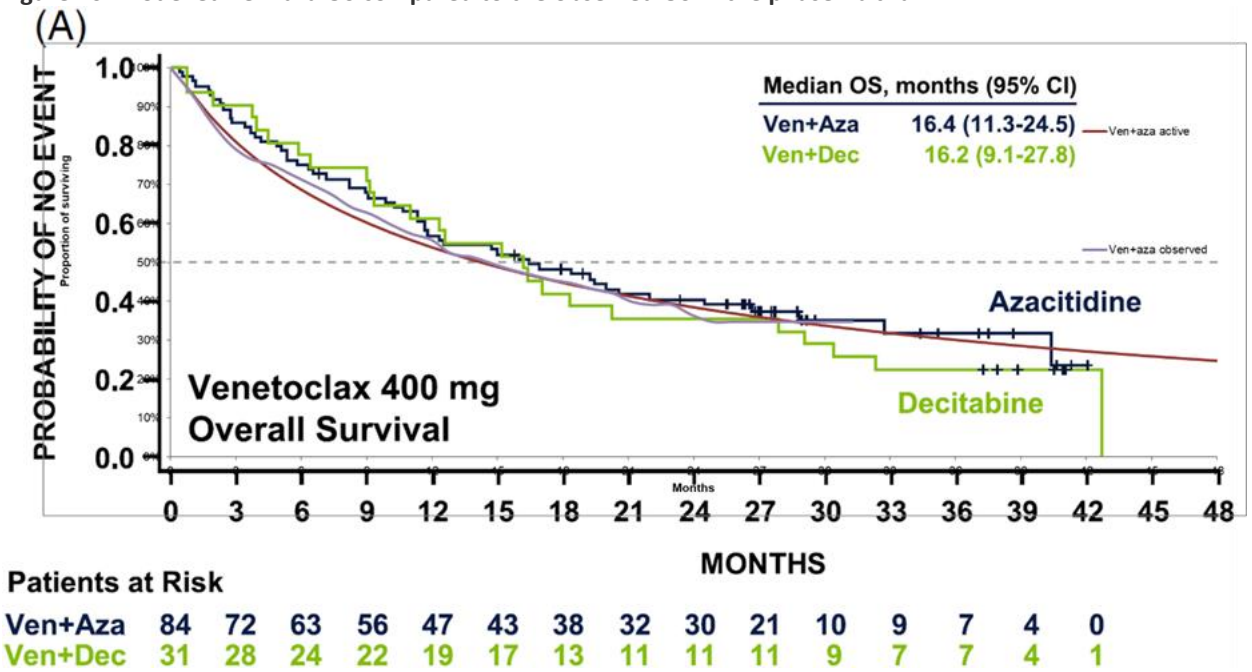
The year 2-5 has been considered in previous AML submissions, representing a clinically important time point for patients to reach while still being in remission, given the limited risk of relapses for those patients [75-77].

To sum up, the patients are expected to have a high rate of progression initially, but over time this is assumed to change. Due to the AML pathophysiology and the mode of action of the treatment, a strong patient selection will occur, and the patients remaining will be well controlled and in complete remission. This is based on the preclinical/clinical rationale, the Swedish clinical registry, input from Norwegian AML clinicians, and also from the data on CR/CRi over time from Viale-A, which clearly show that over time the patients remaining in EFS are in complete remission.

In our base-case model settings, two years is selected as the time point for long-term survival (input is user changeable in the sheet “Base Case”). When two years is selected, the patients are then associated with a risk of death double that of the general population mortality. Note that this is related to the choice of two years only as the assumption is built upon calibration to the Swedish registry. Other settings should handle this explicitly and the input is user changeable in the sheet “Life table”.

Using the same modelling for the venetoclax + azacitidine arm also provides a good fit to the observed OS in the phase 1b study (7) (Figure 20) which is a validation of the extrapolation beyond Viale A follow up.

Figure 20: Modelled ven+aza OS compared to the observed OS in the phase 1b trial



The dark blue line is OS for ven+aza in the phase 1b. The light green line is OS for ven+dec in the phase 1b. The red line is the modelled ven+aza OS. The light purple is observed ven+aza OS in Viale-A. The figure is composed of the figure from the phase 1b publication with the excel diagram from the model put on top of it. OS = Overall survival

8.3.7 Time on treatment

Time on treatment was estimated based on Kaplan-Meier data on time on treatment in Viale-A. Parametric survival models were used. Log-normal models were found to have the best fit, but based on input from an expert haematologist, the exponential distribution was chosen in the base case for venetoclax with azacitidine.

In addition to this, it was assumed that none of the initial treatments would continue in the PD/RL state. Based on feedback from Danish clinical expertise, there was no assumption on a time point where all treatment would have ended, although such functionality is available in the model and has been used in other countries. Such an assumption

would be based on experience from other cancer areas and related to the biological rationale on long-term survival (see section 8.3.6) as patients with a good control of their disease, i.e. EFS and deep response for two years and more will likely not continue with their treatment and hence be treatment free. Treating patients outside of a clinical trial protocol obviously provides the treating haematologist with more freedom to judge when it is more beneficial for a patient to stop treatment.

8.3.8 Proportion of patients at relevant timepoints

A tabular presentation of the proportion of patients in each state for different time points for the different parametric functions and the modelling in use in the base-case, taking cure modelling into account, are presented below for both the intervention and the comparator. Please note that the values presented below are those that are not half-cycle corrected, meaning they represent values at the end of each cycle.

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

In accord with the DMC guidelines [86], utilities were calculated based on EQ-5D-5L data from Viale-A using the Danish value set [65].

8.4.2 Health state utility values used in the health economic model

In the Viale-A trial, the EuroQol Group-5 Dimension-5 Level Instrument (EQ-5D-5L) was used to measure patients' health-related quality of life [71, 87]. It was administered at cycle 1 day 1 and on day 1 of every other cycle as well as the last visit after patients discontinue the treatment. The final visit was defined as the last assessments on or after the date of disease progression, relapse from CR/CRi, or treatment failure.

Descriptive statistics on the utility values generated using patient-level EQ-5D data from the data trial were calculated by the following categories corresponding to the model health states including:

- **EQ-5D measures for EFS:** any EQ-5D assessments when patients are in the EFS state, i.e., any assessment on or after the treatment start date and before the date of relapse, disease progression, treatment failure, or death. EFS definition is consistent with the EFS definition used in the Viale-A trial protocol.

- **EQ-5D measures for EFS with CR/CRi:** any EQ-5D assessments when patients are in the EFS state with CR/CRi, i.e., any assessment on or after the date of CR/CRi
- **EQ-5D measures for EFS without CR/CRi:** any EQ-5D assessments when patients are in the EFS state without CR/CRi, i.e., any assessment before the date of CR/CRi

- **EQ-5D measures for PD/RL:** any EQ-5D assessment when patients are in "progressive disease" or "relapsed disease" categories. PD/RL was defined as any assessments on or after the date of disease progression, relapse from CR/CRi, or treatment failure.

Patients who were included in the analysis have [redacted] missing scheduled visits on average. The analysis did not impute values for missing evaluations and thus a subject who did not have an evaluation on a scheduled visit would be excluded from the analysis for that visit. Information regarding compliance is available in Appendix J.

EQ-5D-5L utility scores were calculated based on the individual dimension scores using the different value sets. Below we present the values using the hypothetically based Danish value set [65] recommended by DMC [86]. Means and standard deviation of EQ-5D value for EFS, EFS with CR/CRi, EFS without CR/CRi, PD/RL are reported. A linear mixed-effects model was developed to estimate patient utility scores with a robust variance estimator to account for correlation within patients' repeated assessments. Within the model, the grade 3 or 4 AEs that occurred in ≥5% were adjusted. Atrial fibrillation, sepsis or urinary tract infection were not included in the mixed-effects model because of the low event rates (i.e., less than 10 number of visits with each AE), which would lead to non-convergence issue of the model if included. The results are summarized in Table **24** and Table **25** and are inputs used in the analysis. Utility values in the model were assumed to be dependent on health state and independent of treatment arm. AML long-term survivors were assumed to have the same utility as EFS with CR/CRi.

Table 24. EQ-5D utility estimates by health states

Health States	Mean	SE	95% CI
EFS with CR/CRi	0.820	0.015	(0.776, 0.840)
EFS without CR/CRi	0.808	0.016	(0.791, 0.850)
PD/RL	0.713	0.022	(0.670, 0.756)

Abbreviations: CR, complete remission; CRi, complete remission with incomplete blood count recovery; EFS, event-free survival; SE, standard error; PD/RL, progressive/relapsed disease; CI, confidence interval

Table 25: Impact on utility of selected adverse events in Viale-A

Adverse Events	Number of Visits With Each AE	Impact on Utility (95% CI)	P-value
Neutropenia (including febrile neutropenia)	347	0.022 (-0.011, 0.055)	0,194
Thrombocytopenia	285	-0.026 (-0.062, 0.010)	0,157
Anaemia	155	0.006 (-0.043, 0.055)	0,807
Leukopenia	135	-0.007 (-0.060, 0.046)	0,790
Hypokalemia, hyponatraemia and hypophosphataemia	44	-0.028 (-0.116, 0.059)	0,527
Pneumonia	18	-0.049 (-0.129, 0.030)	0,222
Hypertension	18	-0.040 (-0.127, 0.048)	0,370

Abbreviations: AE: Adverse event, CI: Confidence interval

None of the disutilities for adverse event were statistically significant. Some of the adverse events are associated with a numerically positive impact on utility. Looking at neutropenia, this was present to a higher degree at baseline for the ven + aza arm (72% vs. 62%), and was more frequently reported as an adverse event in Viale-A (42% vs 29%) keeping in mind that time on therapy was longer in the ven+ aza arm. Hence, neutropenia was common and expected in the experimental arm with the best clinical response to treatment. Looking at an analysis of utilities by treatment arms (Table 59 in Appendix J) there also seem to be a tendency towards higher utility with ven + aza, maybe due to even deeper response, than the current three-state mixed-effects model could take into account. One could speculate that the positive utility estimate of of neutropenia could be a result of it being associated with a better treatment outcome, not completely captured by the three health states.

8.5 Resource use and costs

The model considered the following cost components: initial treatment costs (including drug and administration), subsequent pharmacological treatment costs (including drug and administration), adverse event costs associated with initial treatments, medical costs associated with health states (i.e. hospitalization, blood transfusion, and other monitoring costs), patient time and transportation costs, and terminal care costs. The resource use specific to venetoclax with azacitidine and azacitidine in monotherapy was obtained from the Viale-A (data cut-off: January 4, 2020) to the extent possible.

8.5.1 Drug and administration costs

For as long as the patient is on treatment, drug (AIP) and administration costs are applied as can be seen in Table 26. The cost of subcutaneous administration used is from Danish DRG tariffs DRG 17MA98. The price of azacitidine is the lowest price from medicinpriser.dk. Dosing schedule of azacitidine is matched to clinical practice and guideline recommendation as has been described in section 5.2.3. Anti-fungal treatments are also used for these patients. The input used for these can be seen in Table 27 and Table 28.

Dose intensity is assumed to be the same as in Viale-A (data cut-off of January 4, 2020) regarding azacitidine. For Venclyxto, the dose intensity is very much affected by the use of antifungal treatment, as these are inhibitors of CYP3A, which leads to a higher concentration of venetoclax in the blood, meaning that lower doses must be used in order to not get a too high concentration of the drug in the blood (see Table 5 in section 5.3.2 and section 7.1.4). The dose intensity in Viale-A was but use of antifungal treatment is expected to be higher in Denmark than it was in

Viale-A. Our calculations on dose intensity for Venclyxto is therefore based both on the expected clinical use of anti-fungal treatment in Denmark and the effect on dose intensity for other reasons than anti-fungal treatment (such as dose interruptions) that were observed in Viale-A (calculated to correspond to a dose intensity of The expected clinical use of anti-fungal treatment is based on opinions from different Danish haematologist experts at University hospitals from different regions. The majority (2/3) of physicians strongly believe that they would use posaconazole (a strong inhibitor of CYP3Ai) as an antifungal prophylactic treatment for the complete treatment course of Ven+aza and thus using a venetoclax dosage between 50-100 mg (modelled as 25%). However, one of the physicians believed that a strong CYP3Ai would be used for the three first cycles followed by occasional strong/intermediate CYP3Ai anti-fungal prophylactic treatment as needed. The assumption in the model is therefore that 2/3 of patients receive strong CYP3Ai throughout the course of treatment, while the remaining third receive a strong CYP3Ai only the first three cycles of treatment. This means that the modelled dose intensity is dynamic, depending on the length of treatment that is modelled. In the base-case, the resulting dose intensity is The modelling is in this way completely in line with the SmPC/Viale-A dosing schedule and the expected use of concomitant anti-fungal treatment in Denmark.

There is however a high probability that, in addition to this, the dosing schedule used in clinical practice will differ from the one in Viale-A. Haematologists from the Scandinavian countries have notified AbbVie of their proposed study protocol and plans to study a dosing schedule where venetoclax is not administered all days in the 28-day cycle. The Swedish guidelines [16] states that the venetoclax treatment duration can be discussed and that there is experience of treating only 7-14 days per each 28-day treatment cycle while still achieving a high response frequency and that is a current discussion also in the Danish AML society.

This possible practice is also supported by a more recent analysis of Viale-A data [88], where it is concluded that "lower exposures associated with venetoclax dose reductions to manage cytopenias in patients who achieved CR/CRh did not appear to affect overall survival".

In addition to this, an analysis of patients receiving a reduced venetoclax dose due to concomitant use of moderate or strong CYP3A-inhibitors resulted in overall similar composite remission rates [63]. An interpretation of this is that if there are clinically motivated reasons to use of CYP3Ai, there seems not to be any reason to hold back such treatment as long as the venetoclax dose is lowered accordingly.

The effect on the cost-effectiveness for different dosing schedules will be explored and discussed in sensitivity analyses.

Table 26: Drug and administration costs

Treatment	Dosing schedule[1]	Price per package/ tablet/ vial	Package /tablet/ vial size (mg)	Number of tablets/vials per administration	Number of administrations per cycle	Dose intensity (base-case)	Admin cost per administration
Venetoclax + azacitidine							
Venetoclax [First cycle: treatment initiation]	100 mg, 200 mg, 400 mg on Days 1, 2, 3	357,24 kr.	100	3,00	3		- kr.
Venetoclax [First cycle: post treatment initiation]	400 mg daily on Days 4-28	357,24 kr.	100	4,00	25		- kr.

Venetoclax [Subsequent cycles]	400 mg daily for 28 days	357,24 kr.	100	4,00	28		- kr.
Azacitidine	100 mg/m² daily for 5 days	2 140,00 kr.	100	2,00	5		3 203,00 kr.
Azacitidine	100 mg/m² daily for 5 days	2 140,00 kr.	100	2,00	5		3 203,00 kr.

Based on clinical input on how the care for these patients are currently organised, it is assumed that a third of patients can self-administer (inject themselves with) azacitidine for three out of five days.

Table 27: AIP of anti-fungal treatments

	Strength	Tablets	Company	AIP	AIP per tablet	Price per tablet in use	Daily dose	Cost per day
Posaconazole	100 mg	96	Stada Nordic	16800,00	175,00	1,66	300 mg	4,98
Fluconazole	200 mg	28	Krka AB	46,50	1,66	1,66	400 mg	3,32

Posaconazole has relatively recently been exposed to generic competition. This is still not fully reflected in the AIP. In comparison with fluconazole, the AIP per tablet is at the moment still high, and cannot be representative of the cost during the relevant time frame for the decision of Venclyxto at hand. For instance in Sweden, the AIP per tablet was 1.75 SEK during November 2021 for posaconazole 100 mg[5]. In order for the analysis to be relevant for a relevant time-frame, we have instead used the same AIP per posaconazole tablet as there is today for a fluconazole tablet (1.66 DKK). In a scenario analysis, we use the current AIP for posaconazole.

Table 28: Anti-fungal use in base-case

CYP3Ai	Proportion of patients administered CYP3Ai	
	Venetoclax + azacitidine	**Azacitidine**
Strong	100,00%	15,00%
Moderate	0,00%	45,00%
For the above patients, the proportion of time on treatment when CYP3Ai is also administred		
Strong	73,39%	100,00%
Moderate	0,00%	100,00%

The use of anti-fungal treatment (Table 28) is based on clinical input. The use of posaconazole for Ven+Aza is expected to be high due to low posaconazole prices as well as being clinically relevant. For azacitidine arm, one clinician did typically not use anti-fungals, while one stated that fluconazole is typically used, but that the lowering price of posaconazole might change this, and a third one expected only fluconazole to be used, but to a lesser degree when the patient is not severely neutropenic or not presenting recurrent infection. Our interpretation of this input is presented in the column for azacitidine.

[5] The AIP per tablet was indeed in Denmark 175.00 DKK, and in Sweden 1.75 SEK. The number similarity is is a coincidence.

Table 29: Drug and administration costs per cycle

Treatment	Venetoclax Drug Costs for the First Cycle (2021 DKK)	Venetoclax Drug Costs for Subsequent Cycles (2021 DKK)	Azacitidine Drug Costs per Cycle (2021 DKK)	Azacitidine Administration Costs per Cycle (2021 DKK)	Anti-fungal Drug Cost per Cycle (2021 DKK)
Venetoclax + azacitidine					102,37 kr.
Azacitidine					62,78 kr.

The model assumed patients could also receive subsequent pharmacological treatments once they experienced progressive or relapsed disease after the initial treatment, which reflected the natural treatment course patients experienced. As per clinical opinion, it was assumed that ten percent of patients would receive treatment with hydroxycarbamide regardless of treatment arm. The opinion was also that cytarabine is and will be used. For cytarabine, the proportions seen in Viale-A were deemed reasonable by the clinical expert.

The dosing schedule used for low-dose cytarabine was that from the Viale-C trial protocol [87] and for hydroxycarbamide from NHS shared care guidelines [89]. The unit drug costs were obtained from medicinpriser.dk (hydrea and cytarabine). The cost of intravenous administration used is from Danish DRG tariffs DRG 17MA98. The mean treatment duration was assumed to be 4.33 cycles, derived from Stahl 2018, which is a retrospective database study that evaluated hypomethylating agents, including azacitidine, in relapsed/refractory (RR) AML patients [90]. The resulting undiscounted cost for subsequent treatment in the ven + aza arm was in this way calculated to 9 784 kr. and for aza to 17 157 kr.

Table 31 presents the dosing schedule and drug acquisition and administration cost of subsequent treatment. Table 30 presents the proportion of patients receiving subsequent treatments by each arm.

Table 30: Subsequent treatment rates

Subsequent Treatment Rates	First-line Treatment	
	Venetoclax + azacitidine	Azacitidine
Cytarabine	6,6%	11,7%
Hydroxycarbamide	10,0%	10,0%

Table 31: Subsequent treatment costs

Subsequent treatment	Dosing schedule	Price per package/ tablet/vial	Package/ tablet/ vial size (mg)	Number of tablets/vials per administration	Number of administrations per cycle	Administration Costs per Cycle
Cytarabine	20 mg/m² daily for 10 days	150.00 kr.	100	1	10	32 030 kr.
Hydroxy-carbamide	20–30 mg/kg daily	2.95 kr.	500	4	28	0 kr.

Cost (and disutility) of HSCT was not modelled since there was no difference in treatment rate between the arms in Viale-A (0.7% in both arms).

8.5.2 Resource Use and Costs associated with treatment initiation and health states

At treatment initiation, many patients stay in inpatient care due to their poor health state at that time. It could be argued that using the more effective venetoclax + azacitidine could lead to patients being able to leave the hospital

earlier than when treated with azacitidine alone. We have however assumed the same numbers for venetoclax + azacitidine as for azacitidine alone (Table 32).

Table 32: In-patient hospitalization during treatment-initiation

Treatment	% patients hospitalized	Total cost	Reference
Venetoclax + azacitidine	20%	8780.20 kr.	Clinical opinion that probably similar to aza.
Azacitidine	20%	8780.20 kr.	Clinical opinion
Total cost calculated by using 43 901 kr. per hospital admission (17MA01: Malign hæmatologisk sygdom uden specifik behandling, pat mindst 18 år)			

Resource use and cost per item in different health states in the base case scenario are presented in Table 33. Resource use was based on clinical input. For the 'Long-term survivors' state, clinical input has confirmed a lower resource use for the long-term survivors, and that the patient visits could be half of that in the CR/CRi state. The resulting resource use cost per health state per cycle is presented in Table 34. Specification of the blood test cost can be seen in Table 35.

Table 33: Resource use by health state for all treatments during subsequent cycles and blood transfusion by health state for all cycles

Resource	EFS with CR/CRi	EFS without CR/CRi	PD/RL	Long-term survivors	Cost	Cost reference
Visit Haematologist	0,92	0,92	0,5	0,46	3 203 kr.	17MA98: MDC17 1-dagsgruppe, pat. mindst 7 år
Phone call	0	3	0	0	129 kr.	65TE01 Telefon- og email konsultation, samt skriftlig kommunikation ved prøvesvar
Blood test	1	4	4	0,5	684 kr.	Table 35
Hospital admission	0	0,33	0,33	0,00	43 901 kr.	17MA01: Malign hæmatologisk sygdom uden specifik behandling, pat mindst 18 år
Transfusion, erythrocytes, allogeneic	0	4,00	6,00	0,00	4 628 kr.	16PR02
Transfusion, thrombocytes, allogeneic	0	1,00	0,50	0,00	4 628 kr.	16PR02
Transfusion, plasma, allogeneic	0	0,00	0,00	0,00	6 042 kr.	16PR01

Table 34: Total resource use cost per health state per cycle

EFS with CR/CRi	EFS without CR/CRi	PD/RL	Long-term survivors
3 624,46 kr.	43 690,79 kr.	48 906,83 kr.	1 812,23 kr.

Table 35: Blood test specification and cost

Labka code	Name	Price (DKK)
HB	B-hæmoglobin	37
Lymfomik	B-leukocytter	17
Neutromik	B-neutrofilocytter	17
THROMMIK	B-trombocytter	25
ASAT	P-ASAT	29
ALAT	P-ALAT	29
BILI	P-Bilirubiner	29
GGT	P-gamma-Glutamyltransferase	29
BASP	P-basisk fosfatase	29
ALB	P-Albumin	29
CA	P-calcium	29
CRP	P-CRP	29
CREA	P-kreatinin	29
CARB	P-karbamid	29
GLU	P-glukose	29
K	P-kalium	17
CL	P-klorid	31
MG	P-magnesium	29
NA	P-natrium	17
PHOS	P-phosphat	29
URAT	P-Urat	29
APTT	P-koagulation, tid	22
CREACLEA	Nye-Kreatinin-clearance	95
Total		684
Costs from Rigshospitalet labportal (https://labportal.rh.dk/Metodeliste.asp)		

8.5.3 Terminal care and adverse events

All patients were assigned the cost of terminal care, regardless of whether they were long-term survivors or not and regardless of treatment arm. This can be a source of overestimating the cost of terminal care in the venetoclax + azacitidine arm, as the probability of dying from something else than AML in that arm should be higher. The effect the

terminal care costs have on the total incremental costs is then only a discounting effect. The terminal care cost used was 43 687 kr. (26MP46, "Specialiseret Palliativ indsats, Mellem" from Danish DRG tariffs).

Adverse events of grade three and four (using frequencies in Table 16) were costed as per Table 36 and resulting in costs as per Table 37.

Table 36: Cost per adverse event

Grade 3/4 AEs ≥ 5%	Cost in DKK	Source
Anemia	3 114,00 kr.	16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år
Atrial fibrillation	1.153,00 kr.	05MA98: MDC05 1-dagsgruppe, pat. mindst 7 år
Febrile neutropenia	3 114,00 kr.	16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år
Hypertension	14 155,00 kr.	05MA11: Hypertension
Hypokalemia	1 518,00 kr.	10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år
Hypophosphataemia	1 518,00 kr.	10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år
Leukopenia	3 114,00 kr.	16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år
Neutropenia	3 114,00 kr.	16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år
Pneumonia	36 514,00 kr.	04MA13: Lungebetændelse og pleurit, pat. mindst 60 år
Sepsis	42 770,00 kr.	18MA01: Sepsis
Thrombocytopenia	35 483,00 kr.	16MA03: Granulo- og trombocytopeni
Urinary tract infection	24 431,00 kr.	11MA07: Infektioner i nyrer og urinvej, pat. mindst 16 år

Table 37: Total cost of AEs per treatment

Ven+ Aza	Aza
30 889.42 kr.	30 360.52 kr.

8.5.4 Patient cost and transportation

The cost of patient time was DKK 179 per hour and transportation cost is 100 DKK based on the Medicine council catalogue of unit cost and applied throughout the model. Assumptions on time expenditure and number of transports were based on clinical opinion.

Subcutaneous administration of azacitidine was assumed to take 240 minutes the first day in the treatment cycle. Administrations 2-5 took 30 minutes per treatment if done in the clinic and 10 minutes if done at home.

The following was assumed regarding patient cost and transportation per type of resource event.

Table 38: Time expenditure and number of transports per resource type

Resource	Time spent per resource (min)	Transport (number)
Visit Haematologist	120	1
Phone call	15	0
Blood test	15	0
Hospital admission	23616 (16.4 days)	1
Transfusion, erythrocytes, allogeneic	120	1
Transfusion, thrombocytes, allogeneic	120	0
Transfusion, plasma, allogeneic	0	0

This resulted in the cost per health state described in Table 39.

Table 39: Cost of patient time and transport per health state

EFS with CR/CRi	EFS without CR/CRi	PD/RL	Long-term survival
465,21 kr.	26 420,27 kr.	26 831,56 kr.	232,60 kr.

Cost due to subsequent treatment was calculated using subsequent treatment rates (Table 30) and assumptions and resulting costs per cycle as per Table 40 leading to a cost of 379 kr. for the ven+aza arm and 670 kr. for the aza arm per patient before discounting.

Table 40: Cost of patient time and transport for subsequent treatments

	Patient time (min)	Transport	Cost per cycle PD
Cytarabine	1680	7	5 712,00 kr.
Hydroxycarbamide	0	0	- kr.
Decitabine	300	5	1 395,00 kr.

Costs due to adverse events were calculated as per assumptions in Table 41 and frequencies in Table 16.

Table 41: Time expenditure and transportation per adverse event

	Patient time (min)	Transport
Anemia	120	1
Atrial fibrillation	120	2
Febrile neutropenia	10080	1

Hypertension	30	1
Hypokalemia	30	1
Hypophosphataemia	30	1
Leukopenia	30	1
Neutropenia	30	1
Pneumonia	10 080	1
Sepsis	14 400	1
Thrombocytopenia	60	1
Urinary tract infection	120	1

Total patient cost due to adverse events is 20 834 kr. for the ven + aza arm and 16 541 kr. for the aza arm.

8.6 Results

8.6.1 Base case overview

Table 42: Base case overview

Comparator	Azacitidine
Type of model	Partitioned survival model with cure modelling for extrapolation
Time horizon	25 years (lifetime)
Treatment line	1st line. Costs of subsequent treatment lines included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in Viale-A. The Danish value set was used to estimate health-state utility values.
Included costs	Initial treatment drug cost Initial treatment administration cost Subsequent pharmacological treatment costs (including drug and administration) Adverse events costs associated with initial treatments Medical costs associated with health states (i.e., hospitalization, blood transfusion, and other monitoring costs) Terminal care costs Patient time Patient transport
Dosage of pharmaceutical	As per SmPC from expected Danish use of CYP3Ai
Parametric function for ToT	Intervention: Exponential

	Comparator: Log-normal
Parametric function for EFS	Intervention: Gompertz Comparator: Exponential
Parametric function for OS	Intervention: Weibull Comparator: Exponential
First-line treatment after event/progression	No
Long-term extrapolation approach	After 2 years in EFS and still in CR/CRi, population SMR=2.

8.6.2 Base case results

In the base-case, the total incremental cost per patient is 93 541 kr. and the total incremental QALY's are 1.02, resulting in an ICER of 92 000 kr (Table 43). Incremental cost increases can be found in pharmaceutical costs and administration costs, while there is a reduction in medical costs, patient time, and transport costs. That medical costs are decreased despite the longer survival time is due to more time in the EFS with CR/CRi health state. The increase in QALYs is explained by the longer survival and longer time spent in EFS health states.

Table 43: Base case results

Per patient	Venetoclax + azacitidine	Azacitidine	Difference
Costs (2021 DKK)			
Pharmaceutical Costs	409 209 kr.	221 101 kr.	188 108 kr.
Administration Costs	186 153 kr.	142 285 kr.	43 868 kr.
Subsequent Treatment Costs	9 112 kr.	16 696 kr.	-7 584 kr.
Subsequent HSCT Costs	- kr.	- kr.	- kr.
Adverse Event Costs Associated with Initial Treatment	30 889 kr.	30 361 kr.	529 kr.
Medical Costs	416 202 kr.	491 646 kr.	-75 445 kr.
Event-Free with CR/CRi Costs	68 827 kr.	22 821 kr.	46 006 kr.
Event-Free without CR/CRi Costs	153 668 kr.	276 078 kr.	-122 411 kr.
Post-Progression Costs	153 419 kr.	150 587 kr.	2 833 kr.
Terminal Care Costs	40 288 kr.	42 160 kr.	-1 873 kr.
Indirect Costs	- kr.	- kr.	- kr.
Patient time and transport	225 433 kr.	282 158 kr.	-56 725 kr.
Total Costs	1 278 486 kr.	1 184 945 kr.	93 541 kr.
Effectiveness			
Total QALYs	2,16	1,13	1,02
QALYs: Event-free survival with CR/CRi	1,78	0,59	1,19
QALYs: Event-free survival without CR/CRi	0,21	0,38	-0,17
QALYs: PD/RL	0,17	0,17	0,00
Total LYs	2,66	1,42	1,24
LYs: Event-free survival	2,42	1,18	1,24
LYs: PD/RL	0,24	0,24	0,00
Incremental cost-effectiveness ratio (ICER) (2021 DKK)			
Incremental Cost per QALY Gained			91 533,82 kr.
Incremental Cost per LY Gained			75 280,01 kr.

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

Deterministic sensitivity analyses have been performed, and these are presented in the sheet "DSA" in the model. The DSA and scenario analysis reveal that the results are relatively sensitive to the cost of treating with venetoclax as well as choice of parametric functions for ToT and OS. In the tornado diagram (Figure 23), the 20 parameters/scenarios affecting the ICER the most are presented. DSA and scenario analyses are listed in Table 44 and Table 45. It can be worth noting that using the combination of an SMR of 1.3 as in DMC's appraisal of gilteritinib, the ICER is lowered to .

DSA = Deterministic sensitivity analysis, ICER = incremental cost-effectiveness ratio, QALY = Quality-adjusted life year, ToT = Time on treatment, EFS = Event-free survival, CR = complete response/complete remission, CRi = complete remission with partial haematologic recovery. The parameters impacting the ICER the most are time on treatment and dosing parmaters.

Scenarios regarding different dosing schedules for venetoclax are included, looking at administering venetoclax only 7, 14, or 21 days out of a 28-day treatment cycle. These are included as we are aware of an AML study being planned in the nordic countries to investigate different dosing schedules and due to a recent analysis of data from Viale-A (see section 2.7.1). Clinicians we have been in contact with believe that the current dosing schedule could be optimised further to lower the number of cytopenias while maintaining the efficacy of the drug.

Table 44: One-way Sensitivity Analyses

Table 45: Scenario analyses

	ICER	% Change vs. Base-case
Base case	91 534 kr	-
Efficacy based on alternative parametric functions for both treatment arms		
EFS		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
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[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

8.7.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis has been conducted using 3000 iterations and is presented in the model sheet “PSA”. All the model parameters that were varied in PSA and their associated distributions are presented in the model, on sheet “PSA_Setup”. Whenever available, the standard error (SE) of the model input was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around a parameter, the SE for each parameter was assumed to be equal to the mean value divided by four.

Looking at the 3 000 iterations from the PSA plotted in the cost-effectiveness plane, all the results indicate very low ICERs. The cost-effectiveness acceptability curve indicates very high probabilities of being cost-effective at very low ICERs.

Figure 24: Scatterplot

Figure 25: CEAC

9. Budget impact analysis

A budget impact was carried out as per DMC recommendation. Patient costs are not included and the costs are not discounted.

Approximately 250 new cases of AML are diagnosed annually in Denmark [4]. Danish AML physicians estimate that around 20-30% of AML patients today are patients "Non-intensive/curative treatment (non-eligible for intensive chemotherapy mostly patients >60 years old)", see section 5.1.1. In this group, there are yearly. Based on this, we have assumed that about will be eligible for VEN + AZA, see Table 46 and Table 47. Market uptake the first

Number of patients

Table 46 Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
VEN + AZA					

	Year 1	Year 2	Year 3	Year 4	Year 5
AZA					
Total number of patients					

Table 47 Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
VEN + AZA					
AZA					
Total number of patients					

Expenditure per patient

Table 48 Costs per patient starting year 1 -, DKK AIP

	Year 1	Year 2	Year 3	Year 4	Year 5
VEN+ AZA, costs per patient					
AZA, cost per patient					

Budget impact

Table 49: Expected budget impact of recommending VEN + AZA, DKK AIP

	Year 1	Year 2	Year 3	Year 4	Year 5
VEN+ AZA recommended					
Drug costs					
Administrative costs					
Hospital costs					
Adverse reaction costs					
Minus: **VEN + AZA NOT recommended**					
Drug costs					
Administrative costs					
Hospital costs					
Adverse reaction costs					
Budget impact of the recommendation					

The budget impact result in extra cost of .

10. Discussion on the submitted documentation

AML is rapidly fatal if left untreated, with the lowest survival rate of all leukemias. It has particularly poor survival for patients ineligible for intensive chemotherapy, with a 1-year survival rate of 15–20% and a 5-year survival rate of just 5%. The impairment on quality of life is significant, with deterioration both due to AML symptoms, particularly fatigue, anemia, and infection, and due to treatment, which requires prolonged hospitalization. The need for repeated blood transfusions due to thrombocytopenia also leads to substantial clinical burden and healthcare resource use.

Current treatment options for patients ineligible for intensive chemotherapy are few, have poor response rates and, as a result, there is a high likelihood of relapse after initial remission. This means survival outcomes are poor and median OS is low.

There is a high need for new treatments that provide durable response rates, improve survival while maintaining HRQoL, and contribute to transfusion independence in patients with AML who are ineligible for intensive chemotherapy.

Venetoclax in combination with azacitidine has shown significant improvement versus azacitidine in monotherapy, the current standard of care in Danish clinical practice, in a randomized, placebo-controlled, and double-blind trial, Viale-

A. The median overall survival was 14.7 months in patients randomized to receive venetoclax plus azacitidine compared with 9.6 months in the azacitidine monotherapy arm. The venetoclax combination provides an alternative treatment option with a distinct mechanism of action, addressing the high unmet need of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy - an important step forward for the treatment of AML. Furthermore, the safety profile of venetoclax in combination with azacitidine is acceptable and manageable in a newly diagnosed AML patient population. Compared with azacitidine monotherapy, combination therapy with venetoclax was well tolerated. No new risks associated with venetoclax at the proposed doses in combination with azacitidine were identified in the entire AML development program.

In the economic analysis, the results from the Viale-A trial are extrapolated beyond the time in the currently available data cut. Based on a biological rationale, Swedish registry data and clinical input, AbbVie has assumed a reduction in risk for patients with good disease control and being in complete remission beyond the second year on treatment, defined here as long-term survivors. The AML pathophysiology and the mode of action of the treatment indicates that the assumption of a significant long-term impact is reasonable. Assumptions on long-term survivors in line with this is common in AML and has been discussed and accepted by several HTA agencies, as DMC, TLV, NoMA and NICE, among others, and is supported by clinical expertise.

The base-case ICER of about 90 000 DKK using Venclyxto AIP is very low, especially when considering the severity of the disease. A budget impact of [redacted] in year five, if VEN+AZA is recommended by Medicinrådet, must also be seen as manageable.

An important factor is however that the clinicians expect the actual dosing in clinical practice will be substantially lowered compared to the study dosing and label. The expectation is that the regime suggested will be overly tough on the patients without adding a balancing clinical benefit. This has also been supported by a more recent analysis of Viale-A data where it was concluded that “lower exposures associated with venetoclax dose reductions to manage cytopenias in patients who achieved CR/CRh did not appear to affect overall survival”. Clinicians we have talked to also saw a parallel to other therapeutic areas, such as chronic myeloid leukemia, CML, where a lower dosing in clinical practice (than in studies and label) had little consequence for patient outcomes. The high probability of administering Venclyxto maybe as seldom as 7-14 days per cycle, compared to 28 in the Viale-A study clearly points in the direction of the presented ICER being overestimated. If calculating with administering Venclyxto 7-14 days per cycle the results are close to cost-neutral or dominant.

Other sensitivity analyses made point in both directions. Using different parametric distributions has the highest effect on the results. As expected, shorter time horizons do not affect the results much. Using similar settings as in DMC evaluation of gilteritinib in AML lowered the ICER somewhat. The PSA results are also indicating a very high probability of cost-effectiveness already at very low willingness-to-pay levels.

In summary, Venclyxto in combination with azacitidine is a highly cost-effective treatment meeting an urgent unmet medical need in a disease with a very high severity of illness. The cost-utility analysis has several strengths; directly comparative data from the pivotal study, utility weights using EQ-5D-5L data from the pivotal study, a comprehensive model, validation against Swedish registry data and OS from the separate phase 1b study. The data and input from clinicians highlight that venetoclax is an important evolution of the treatment of AML patients, and the high cost-effectiveness and very low cost to society in terms of budget impact leads to the conclusion that Venclyxto should be made available to Danish clinicians and patients for the treatment of AML.

11. List of experts

Danish physicians from University hospitals in different regions have provided clinical feedback and input.

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Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

Omitted as there was no literature search carried out.

Appendix B Main characteristics of included studies

Table 50: Key characteristics of venetoclax AML studies

Study reference/ID	VIALE-A, M15-656 (NCT02993523)	M14-358 (NCT02203773)
Objective	To compare the efficacy and safety of venetoclax plus AZA to placebo + AZA in previously untreated AML patients ineligible for intensive chemotherapy due to medical comorbidities and/or were ≥75 years old	To evaluate the safety and pharmacokinetics of orally administered venetoclax combined with DEC or AZA and the preliminary efficacy of these combinations
Study design	Phase 3, randomized, double-blind, placebo-controlled, multicenter	Phase 1b, open-label, non-randomized, multicenter study

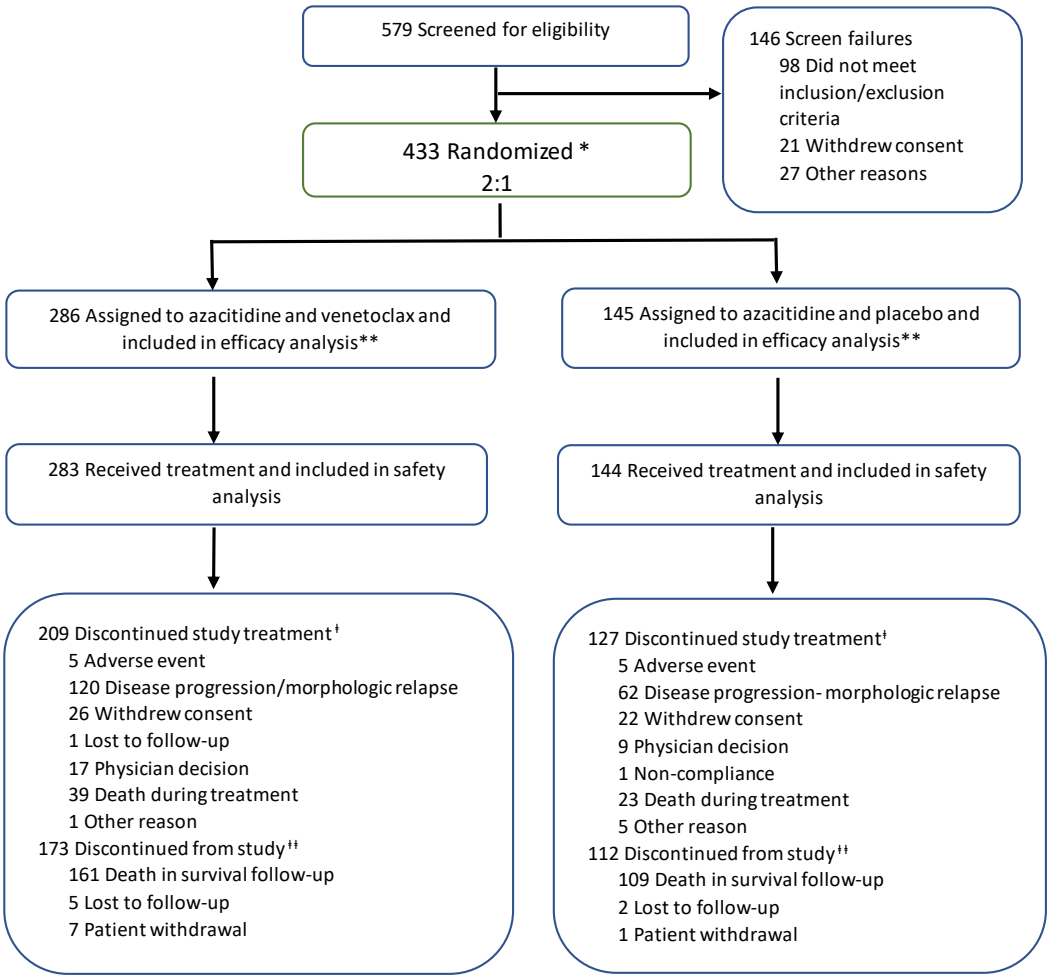
Eligibility criteria	**Key inclusion criteria:**
	- Patients aged ≥18 years with previously untreated AML confirmed by WHO criteria.
	- Patients must be considered ineligible for treatment with a standard cytarabine and anthracycline induction regimen due age or comorbidities as defined by the following:
	  ○ ≥75 years of age; or
	  ○ ≥18 to 74 years of age with at least one of the following comorbidities:
	  ▪ ECOG PS 2 or 3
	  ▪ Cardiac history of CHF requiring treatment or ejection fraction ≤50% or chronic stable angina DLCO ≤65% or FEV1 ≤65%
	  ▪ Creatinine clearance ≥30 mL/min to <45 ml/min
	  ▪ Moderate hepatic impairment with total bilirubin >1.5 to ≤3.0 × ULN
	  ▪ Any other comorbidity that was physician judged to be incompatible with intensive chemotherapy.
	- Patients must have a projected life expectancy of at least 12 weeks.
	- Patients must have an ECOG PS:
	0 to 2 for patients ≥75 years; or
	0 to 3 for patients ≥18 to 74 years.
	- Patients must have adequate renal function as demonstrated by a creatinine clearance ≥30
		Key inclusion criteria:
		- Confirmed AML by WHO criteria
		- Ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to comorbidity or other factors
		- Received no prior treatment for AML with the exception of hydroxyurea
		- ECOG PS of 2 for subjects ≥75 years of age, or 0 to 3 for subjects ≥60 to 74 years of age
		- Adequate kidney and liver function as described in the protocol
		
		Key exclusion criteria:
		- Received treatment with an HMA and/or chemotherapeutic agent for an antecedent hematologic disorder
		- History of Myeloproliferative Neoplasm
		- Favorable risk cytogenetics as categorized by the NCCN Guidelines Version 2, 2014 for AML t(8;21), inv(16), t(16;16) or t(15;17) karyotype abnormalities
		- Acute promyelocytic leukemia.
		- Active CNS involvement with AML
		- Received a strong and/or moderate CYP3A inducer within 7 days prior to the initiation of study treatment

	mL/min; calculated by the Cockcroft Gault formula or measured by 24-h urine collection. - Patients must have adequate liver function as demonstrated by: AST ≤3.0 × ULN* ALT ≤3.0 × ULN* bilirubin ≤1.5 × ULN* *Unless considered due to leukemic organ involvement. Patients who are <75 years may have a bilirubin of ≤3.0 × ULN. **Key exclusion criteria:** - Prior receipt of any hypomethylating agent, venetoclax, or chemotherapy for myelodysplastic syndrome. - Patients with favorable cytogenetic risk as per the AML NCCN Guidelines.	
Intervention and Comparator (N enrolled)	Venetoclax QD, ramp-up in Cycle 1; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3 until Day 28; subsequent 28-day cycles at 400 mg plus AZA 75 mg/m2, SC or IV, on days 1–7 every 28-day cycle **(N = 286)** versus Placebo QD plus AZA 75 mg/m2, SC or IV, on days 1–7 every 28-day cycle **(N = 145)**	**Dose escalation:** Venetoclax QD, ramp-up in Cycle 1; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3, until maximum dose is reached (400, 800, or 1,200 mg); max dose until D28; subsequent 28-day cycles at 400 mg or 800 mg or 1,200 mg plus AZA (75 mg/m2, days 1–7, IV or subcutaneously) or DEC (20 mg/m2, days 1–5, IV) **Expansion:** Venetoclax QD, ramp-up in Cycle 1; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3, (600 mg Day 4, 800 mg Day 5) until Day 28; subsequent 28-day cycles at 400 mg or 800 mg plus AZA 75 mg/m2, SC or IV, on days 1–7 every 28-day cycle or DEC (20 mg/m2, days 1–5, IV) **All treated patients (N = 145)** Venetoclax 400 mg (N = 60; 29 with AZA, 31 with DEC) Venetoclax 800 mg (N = 74; 37 each AZA or DEC) Venetoclax 1,200 mg (N = 11; 6 AZA, 5 DEC)

Primary outcome measure and follow-up time point	**Dual primary endpoint:** **OS (months)** All patients were followed for survival information (date/cause of death) every 2 months after the last study visit or as needed until the end of the study. **Composite CR rate (CR + CR with incomplete hematologic recovery; CR + CRi)** Bone marrow assessments were performed at screening, at the end of cycle 1, and every three cycles thereafter until two consecutive samples confirmed a CR or CRi. Disease assessments were performed with the use of the modified International Working Group response criteria for AML.	**Response** - CR - Cri - ORR (CR + CRi + PR) Determined by the number of subjects who achieve a CR/CRi. - Responses were evaluated per the International Working Group criteria for AML. Time frame: Measured up to 1 year after the last subject last dose. **Pharmacokinetics** - AUC from 0 to the time of the last measurable concentration - AUC from 0 to the time of the last measurable concentration. - Half-life - Cmax - Maximum observed concentration, occurring at Tmax. - Clearance is defined as the rate at which a drug is cleared from the blood. - AUC over a 24-hour dose interval. - Time to Cmax - AUC from 0 to infinity Time frame: For approximately 5 days following a single dose of venetoclax **OS** Defined as the number of days from the date of enrolment to the date of death. Time frame: Measured up to 1 year after the last subject last dose

Secondary outcome measures and follow-up time points	- CR rate - CR + CRh rate - Proportion of patients achieving composite CR by the initiation of cycle 2 - Rates of RBC and platelet transfusion independence - CR rates and OS in molecular and cytogenetic subgroups - EFS - MRD response rate - HRQL - Safety Bone marrow assessments were performed at screening, at the end of cycle 1, and every three cycles thereafter until two consecutive samples confirmed a CR or CRi. Disease assessments were performed with the use of the modified International Working Group response criteria for AML. Patients were followed for safety and tolerability from the first dose of the study drug until 30 days after the last dose of the study drug. PRO assessments were collected on or within 3 days prior to Cycle 1 Day 1 and then on Day 1 of every other cycle throughout the trial, including the Final Visit.	Percent of subjects who move on to stem cell transplant. Duration of Response defined as the number of days from the date of first response per the IWG criteria for AML to the earliest recurrence or PD. EFS defined as the number of days from the date of the first dose to the date of earliest evidence of relapse, subsequent treatment other than stem cell transplant while in composite complete response (CR + CRi), or death. Time frame: Measured up to 1 year after the last subject last dose.

Figure 26: Patient disposition in Viale-A study



*2 patients were not stratified by cytogenetic risk. They were excluded from efficacy analysis but included in the safety analysis. Six patients who did not receive treatment were excluded from the safety analysis set.

** 2 patients randomized to receive Aza+Ven and 1 patient randomized to receive Aza+Pbo did not receive any treatment due to deterioration of pre-existing medical illness

† Patients who discontinued treatment but were followed for survival

†† Patients who were no longer observed for survival follow-up

2 patients in Aza+Ven arm and 1 patient in the Aza+Pbo arm underwent transplantation after discontinuing study treatment

SOURCE: DiNardo et al, 2020

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 51: Baseline characteristics of patients in VIALE-A and M14-358 studies

	Viale-A		M14-358	
Characteristic	**Azacitidine and venetoclax n= 286**	**Azacitidine and placebo n = 145**	**Venetoclax 400 mg + azacitidine n = 84**	**Venetoclax 400 mg + decitabine n = 31**
Age				
Median (range) years	76 (49–91)	76 (60–90)	75 (61–90)	72 (65–86)
≥75 years, n (%)	174 (61)	87 (60)	42 (50)	8 (26)
Male, n (%)	172 (60)	87 (60)		
AML type, n (%)				
De novo	214 (75)	110 (76)	63 (75)	22 (71)
Secondary	72 (25)	35 (24)	21 (25)	9 (29)
Secondary AML				
Post MDS, CMML	46 (64)	26 (74)		
Therapy-related AML	26 (36)	9 (26)		
ECOG performance status, n (%)				
0-1	157 (55)	81 (56)	58 (69)	27 (87)
2-3	129 (45)	64 (44)	26 (31)	4 (13)
Bone marrow blast count, n (%)				
<30%[#]	85 (30)	41 (28)	24 (29)	7 (23)
≥30–<50%	61 (21)	33 (23)	29 (34)	14 (45)
≥50%	140 (49)	71 (49)	31 (37)	10 (30)
AML with Myelodysplasia related Changes, n (%)	92 (32)	49 (34)		
Cytogenetic risk category, n (%)				
Intermediate*	182 (64)	89 (61)	50 (60)	16 (52)
Normal karyotype	128	62		
Trisomy 8; + 8 alone	13	10		
Poor*	104 (36)	56 (39)	33 (39)	15 (48)
del 7 or 7q	20	11		
del 5 or 5q	46	22		
Complex (≥3 clonal abnormalities)	75	36		
Somatic mutations, n/N (%)				
IDH1/2	61/245 (25)	28/127 (22)	20/74 (27)	5/22 (23)
FLT3-ITD/TKD	29/206 (14)	22/108 (20)	12/74 (16)[§]	4/22 (18)

NPM1	27/163 (17)	17/86 (20)	14/74 (19)	3/22 (14)
TP53	38/163 (23)	14/86 (16)	20/74 (27)	7/22 (32)
Baseline Cytopenia Grade[1] ≥ 3, n (%)				
Anemia	88 (31)	52 (36)		
Neutropenia	206 (72)	90 (63)		
Thrombocytopenia	145 (51)	73(50)		
Baseline transfusion dependence[2], n (%)				
Red blood cells	144 (50)	76 (52)		
Platelets	68 (24)	32 (22)		
≥ 2 Reasons for ineligibility to receive intensive therapy, n (%)	141 (49)	65 (45)		
Reasons for being ineligible for standard induction therapy[†]– n(%)				
≥75 years of age	80 (55.2)	165 (57.7)		
≥18 years to 74 years of age	65 (44.8)	121 (42.3)		
ECOG Performance status of 2 or 3	50 (34.5)	95 (33.2)		
History of congestive heart failure requiring treatment	3 (2.1)	2 (0.7)		
Ejection fraction ≤50%	3 (2.1)	5 (1.7)		
Chronic stable angina	1 (0.7)	5 (1.7)		
DLCO ≤65%	12 (8.3)	11 (3.8)		
FEV-$_1$ ≤65%	7 (4.8)	12 (4.2)		
Creatinine clearance ≥30mL/min to <45 mL/min	5 (3.4)	11 (3.8)		
Moderate hepatic impairment with total bilirubin >1.5 to ≤3.0 X ULN	2 (1.4)	3 (1.0)		

[¤]For M14-358 all were 2 [#]Bone marrow blast counts were between 20-30% in Viale-A *Includes only cytogenetics of interest [†]A patient can report more than one reason. Therefore, the sum of the reasons may be greater than the overall number of patients. [§]Included 1 FLT3-other and 2 FLT3-ITD and FLT3 other mutations.
AML: acute myeloid leukemia; CMML: Chronic myelomonocytic leukemia; ECOG: Eastern Cooperative Oncology Group; HMA: hypomethylating agent; MDS: Myelodysplastic syndrome; ULN: upper limit of normal; DLCO: diffusion capacity of carbon monoxide; FEV1: Forced expiratory volume in 1 second.
[1] Common Terminology Criteria for Adverse Events Grade
[2] Transfusion within 8 weeks prior to the first dose of study drug or randomization
SOURCE: DiNardo et al, 2020 and Pollyea et al. 2018

Comparability of patients across studies

The VIALE-A study (NCT02993523) [67] is a phase 3, randomized, double-blind, placebo-controlled, multicenter study comparing efficacy and safety of azacitidine plus either venetoclax or placebo among treatment-naïve patients with confirmed AML who were ineligible for standard induction therapy due to medical comorbidities and/or age ≥ 75 years.

M14-358 was a Phase 1b, open-label, non-randomized, multicenter study to evaluate the safety and pharmacokinetics of orally administered venetoclax combined with decitabine or azacitidine and the preliminary efficacy of these combinations. Patients (N = 145) were at least 65 years old with treatment-naive AML and were ineligible for intensive chemotherapy.

The M14-358 is phase 1b/2 studies, that provides supportive evidence to VIALE-A as part of the same development program.

Comparing baseline characteristics between the two ven-aza 400 mg arms between the studies, differences are small. However, compared to patients in the Viale-A study, patients in M14-358 appear to (numerical differences):

- have been slightly younger
- had the same proportion with secondary AML
- to a higher degree have ECOG status of 0-1
- have lower bone marrow blast count
- higher proportion in the poor cytogenic risk category
- be similar in somatic mutations

It should be noted that any differences noted between the studies have only been noted as numerical differences, and no statistical analysis has been carried out.

Comparability of the study populations with Danish patients eligible for treatment

In terms of population, according to different Danish AML experts, the baseline demographics of the Viale-A study are very similar and comparable to the Danish patient population that would be treated with Venclyxto + azacitidine. Further, the relevance and compatibility of the study is reflected in Aalborg University participation in the Viale-A study. We also want to highlight the very high similarity of the placebo + azacitidine OS data with the Swedish registry data demonstrating the validity of the study data and the modelling for Scandinavian purposes (section**Error! R eference source not found.** 8.3.6).

In terms of comparison, according to Danish guidelines as well as different expert opinion, azacitidine monotherapy is the main option for patients ineligible for intensive treatment, which is the comparator arm in the phase 3, randomized, double-blind, placebo-controlled, multicenter Viale-A study.

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures (per Viale A study)

Outcome measure	Definition	Validity	Clinical relevance
Overall survival (months) **(primary outcome)**	All patients were followed for survival information (date/cause of death) every 2 months after the last study visit or as needed until the end of the study.	OS is the main outcome used across different studies and in previous Danish Medical council submission	Increased survival is the main optimal goal of physicians treating AML patients
Composite Complete remission (CR) rate (CR + CR with incomplete haematologic recovery; CR + CRi) **(Primary outcome)**	Bone marrow assessments were performed at screening, at the end of cycle 1, and every three cycles thereafter until two consecutive samples confirmed a CR or CRi. Disease assessments were performed with the use of the modified International Working Group response criteria for AML	CR is one of the main outcomes used across different studies and in previous Danish Medical council submission	Inducing remission is the main immediate goal in treatment for AML
Health-related quality of life (HRQoL) **(secondary outcome)**	To evaluate if venetoclax in combination with azacitidine reduces fatigue and improves global health status/quality of life (GHS/QoL) based on patient-reported outcome (PRO) assessments (Patient-Reported Outcomes Measurement Information System [PROMIS] Cancer Fatigue Short Form [SF] 7a and European Organization for Research and Treatment of Cancer Quality of Life m Questionnaire Core [EORTC QLQ-C30]). PRO assessments were collected on or within 3 days prior to Cycle 1 Day 1 and then on Day 1 of every other cycle throughout the trial, including the Final Visit.	HRQoL is used across different studies and in previous Danish Medical council submission	Improving the quality of life is especially important for elderly patients with limited expected added life expectancy

Outcome measure	Definition	Validity	Clinical relevance
Safety **(secondary outcome)**	Patients were followed for safety and tolerability from the first dose of the study drug until 30 days after the last dose of study drug. A safety analysis will be performed for all dosed subjects unless otherwise indicated. For the study, AEs will be evaluated and summarized. Laboratory test results and vital signs wer explored for trends and summarized as appropriate.	Safety is an essential outcome to be balanced considering efficacy profile	A mild/controlled safety profile balanced with an expected efficacy profile is especially important for elderly patients with limited expected added life expectancy
Event-free survival **(EFS)** **(secondary outcome)**	EFS was defined as the number of days from the date of randomization to the date of earliest evidence of relapse, subsequent treatment other than stem cell transplant while in composite complete remission (CR/CRi), or death. If the specified event (relapse, start of subsequent treatment, or death) does not occur, subjects will be censored at the date of last disease assessment. Data for subjects without any disease assessments performed after randomization will be censored at the time of randomization plus 1 day	EFS is a known and used outcome across most AML studies	EFS is especially important for elderly patients with limited expected added life expectancy as well as decreasing resource usage.
Time to first composite complete remission (CR or CRi) **(secondary outcome)**	Time to first composite complete remission will be defined as the number of days from the date of randomization to the date of earliest CR or CRi. For subjects who do not achieve CR or CRi, their data will be censored at the date of last disease assessment. Data for subjects without any disease assessments performed after randomization will be censored at the time of randomization plus 1 day.	Time to response is a known and used outcome across most AML studies	Time to response is a clinically important tool to guide physicians treating AML on how and when to change treatment regimen for optimal care.

Results per study

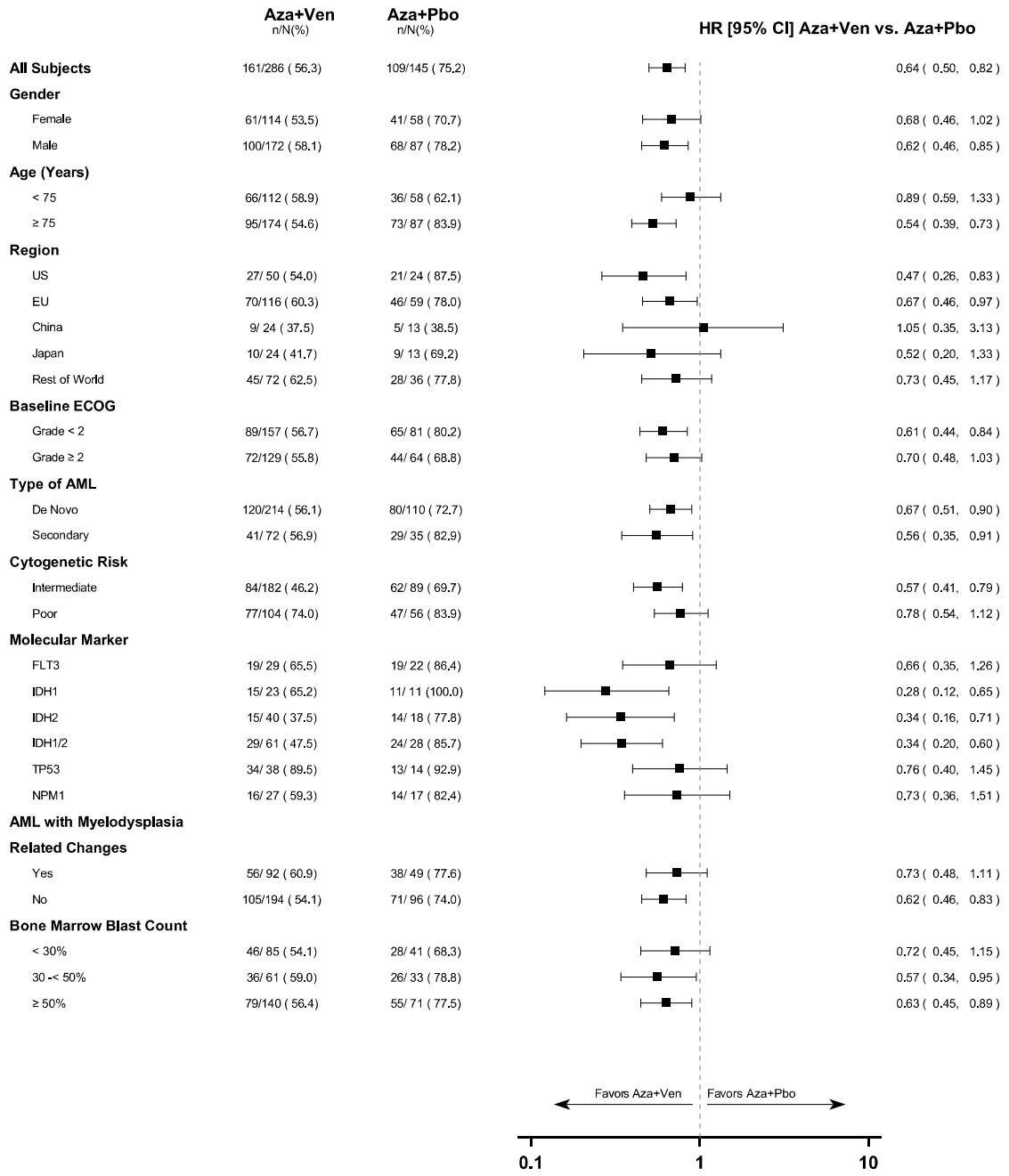
Table A3a Results of VIALE-A - M15-656 (NCT02993523)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P-value***		
Median overall survival	Ven+Aza	161/286	14.7 months (11.9 – 18.7)	5.1 months			HR: 0.66	0.52-0.85	<0.001	*The distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk). The hazard ratio between treatment arms was estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test. Data included are subject to a cut-off date of 04 January 2020.*	
	placebo+Aza	109/145	9.6 (7.4 -12.7)								
CR	Ven+Aza	286	36.7% (31.1, 42.6)	18.78%	10.4-27.16		2.05	1.40-2.99		*Relative difference was estimated using Mantel-Haenszel risk ratio with a 95% confidence interval.* *Absolute difference was estimated using Mantel-*	
	placebo+Aza	145	17.9% (12.1, 25.2)								

Table A3a Results of VIALE-A - M15-656 (NCT02993523)									
								Haenszel risk difference with 95% confidence interval.	
CR+CRi	Ven+Aza	286	66.4% (60.6, 71.9)	38.16%	29.01- 47.31	2.35	1.79-3.08	Relative difference was estimated using Mantel-Haenszel risk ratio with 95% confidence interval. Absolute difference was estimated using Mantel-Haenszel risk difference with 95% confidence interval.	
	placebo+Aza	145	28.3% (21.1, 36.3)						
CR+CRh	Ven+Aza	286	64.7% (58.8, 70.2)	41.93%	33.14-50.72	2.84	2.08-3.88	Relative difference was estimated using Mantel-Haenszel risk ratio with a 95% confidence interval. Absolute difference was estimated using Mantel-Haenszel risk difference with 95% confidence interval.	
	Placebo+Aza	145	22.8% (16.2, 30.5)						
Median time to first response	Ven+Aza	286	1.3 months (range: 0.6-9.9)	-1.5 months					
	placebo+Aza	145	2.8 months (range: 0.8-13.2)						

Table A3a Results of VIALE-A - M15-656 (NCT02993523)									
Event-free survival (EFS)	Ven+Aza	95/286	9.8 months (8.4, 11.8)	2.8 months	HR: 0.63	0.5-0.8	<0.001	The distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk). The hazard ratio between treatment arms was estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test.	
	placebo+Aza	23/145	7.0 months (5.6, 9.5)						

Figure 27: Subgroup Analysis of Overall Survival



Note: For this analysis, the hazard ratio for death was estimated with the unstratified Cox proportional-hazards model.

SOURCE: DiNardo et al, 2020

Appendix E Safety data for intervention and comparator(s)

Table 52: Summary of treatment-emergent adverse events (AEs) * in VIALE-A study

Adverse events, n (%)	**Azacitidine and venetoclax**		**Azacitidine and placebo**	
	All grades**	Grade ≥ 3***	All grades**	Grade ≥ 3***
number of patients (percent)				
All AEs	283 (100)	279 (99)	144 (100)	139 (97)
Haematologic AEs	236 (83)	233 (82)	100 (69)	98 (68)
Thrombocytopenia	130 (46)	126 (45)	58 (40)	55 (38)
Neutropenia	119 (42)	119 (42)	42 (29)	41 (29)
Febrile neutropenia	118 (42)	118 (42)	27 (19)	27 (19)
Anemia	78 (28)	74 (26)	30 (21)	29 (20)
Leukopenia	58 (21)	58 (21)	20 (14)	17 (12)
Non-haematologic AEs	47 (17)	46 (17)	44 (31)	44 (31)
Nausea	124 (44)	5 (2)	50 (35)	1 (1)
Constipation	121 (43)	2 (1)	56 (39)	2 (1)
Diarrhea	117 (41)	13 (5)	48 (33)	4 (3)
Vomiting	84 (30)	6 (2)	33 (23)	1 (1)
Hypokalemia	81 (29)	30 (11)	41 (29)	15 (10)
Peripheral edema	69 (24)	1 (0)	26 (18)	0
Pyrexia	66 (23)	5 (2)	32 (22)	2 (1)
Fatigue	59 (21)	8 (3)	24 (17)	2 (1)
Decreased appetite	72 (25)	0	25 (17)	0
Infections	239 (85)	180 (64)	97 (67)	74 (51)
Pneumonia	65 (23)	56 (20)	39 (27)	36 (25)
Serious AEs**	235 (83)	232 (82)	105 (73)	102 (71)
Febrile neutropenia	84 (30)	84 (30)	15 (10)	15 (11)
Anemia	14 (5)	14 (5)	6 (4)	6 (4)
Neutropenia	13 (5)	13 (5)	3 (2)	3 (2)
Atrial fibrillation	13 (5)	10 (4)	2 (1)	2 (1)
Pneumonia	47 (17)	46 (16)	32 (22)	31 (22)
Sepsis	16 (6)	16 (6)	12 (8)	12 (8)

* Includes all patients who received at least one dose of either of the treatments.

**Adverse events shown were reported in ≥20% of patients in either treatment arms.

*** Adverse events of grade 3 or higher that were reported in at least 10% of patients in either treatment group are listed.

**** Serious adverse events that were reported in at least 5% of patients in either treatment group are listed.

SOURCE: table 2 published in DiNardo et al, 2020 [52]

Table 53: Treatment-emergent adverse events in M14-358

	Venetoclax + AZA (n = 84)		Venetoclax + DEC (n=31)	
AEs in ≥30% of patients, n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Anemia	26 (31)	26 (31)	8 (26)	8 (26)
Platelet count decreased	25 (30)	22 (26)	15 (48)	14 (45)
WBC count decreased	28 (33)	28 (33)	14 (45)	14 (45)
Febrile neutropenia	33 (39)	33 (39)	20 (65)	20 (65)
Pneumonia	23 (27)	23 (27)	12 (39)	10 (32)
Decreased appetite	24 (29)	2 (2)	10 (32)	1 (3)
Constipation	42 (50)	3 (4)	16 (52)	0
Diarrhea	49 (58)	2 (2)	14 (45)	2 (6)
Nausea	54 (64)	2 (2)	20 (65)	0
Vomiting	32 (38)	0	12 (39)	0
Fatigue	28 (33)	5 (6)	14 (45)	3 (10)
Edema peripheral	34 (41)	1 (1)	10 (32)	0
Hypokalemia	28 (33)	5 (6)	11 (36)	5 (16)

Abbreviations: AE: adverse events; AZA: azacitidine; DEC: decitabine; n: number of patients;

SOURCE: Pollyea et al. 2018[91]

Table 54: Serious AEs, dose interruptions, and early mortality data in M14-358

Serious AEs in ≥5% of patients, n (%)	**Venetoclax + AZA (n = 84)** , n (%)	**Venetoclax + DEC (n = 31)** , n (%)
Febrile neutropenia	26 (31)	14 (45)
Pneumonia	19 (23)	9 (29)
Bacteremia	3 (4)	5 (16)
Sepsis	3 (4)	2 (6)
Respiratory failure	3 (4)	2 (6)
Early Deaths		
≤30 days after beginning treatment	2 (2)	2 (7)
≤60 days after beginning treatment	7 (8)	3 (10)
Any AE leading to:		
Dose interruption*	56 (67)	20 (65)
Dose reduction†	1 (1)	2 (6)

Abbreviations: AE, Adverse events; AZA, Acacitidine; DEC, Decitabine

* Dose interruption between treatment cycles was implemented to allow peripheral count recovery once leukemia clearance was confirmed

† Dose reductions due to neutrophil count decreased (n=2) and neutropenia (n=1)

Anti-infective prophylaxis was implemented per institutional standards

SOURCE: Pollyea et al. 2018[91]

Appendix F Comparative analysis of efficacy and safety

Omitted as no meta-analyses have been used.

Appendix G – Extrapolation

12.1 Extrapolation of data and curve fitting

Following the survival model selection process algorithm recommended by NICE DSU TSD14, a range of methods, when appropriate, were used to assess the suitability of parametric survival models for all efficacy inputs [67]. Specifically, the model fit was evaluated based on the following steps:

- **Akaike information criterion** (**AIC)/Bayesian information criteria (BIC) tests:** The AIC and the BIC provide useful statistical tests of the relative fit of different parametric survival models. These tests weigh the improved fit of models with the potentially inefficient use of additional parameters. Lower AIC and BIC values indicate a better fit of the selected model.
- **Visual inspection:** the visual inspection could evaluate how well a parametric survival model fits with the observed K-M curve visually. The parametric survival model that most closely follows the K-M curve could be considered the best fit.
- **Examination of the log-cumulative hazard plots:** Log-cumulative hazard plots were constructed to compare the hazards observed in the clinical trial and hazards estimated by different parametric survival models over time. Since different parametric survival models incorporate different hazard functions (e.g., exponential for constant hazard, Gompertz for monotonic hazard), the hazard plots could be used to select the suitable parametric survival models that had the most consistent hazard function with observed hazard patterns.
- **Clinical input and external validation:** Extrapolations were compared and fitted to Swedish registry data. Clinical input influenced the choice of parametric function.

As is often done, we are using different types of parametric models for the different treatment arms based on the steps above. The difference in mode of action and efficacy, such as the proportion of patients in CR/CRi over time justifies this approach, as we will explain below.

Mode of action (MoA) and time to onset of effect is described in sections 5.3.1 and 7.1.2, respectively.

Briefly, hypomethylating agents (HMAs) such as azacitidine has long been considered standard therapy for AML patients ineligible for intensive chemotherapy. Aberrant DNA methylation patterns are thought to be involved in driving the pathobiology of AML. Azacitidine incorporates into the DNA/RNA of highly proliferating cells leading to demethylation. The MoA of azacitidine likely involves additional effects such as direct cytotoxicity, activation of DNA-damage pathways and immunomodulatory effects. The full understanding of the MoA remains unclear [68].

Venetoclax is a selective, potent, oral BCL-2 inhibitor that induces apoptosis, programmed cell death, in AML cells in combination with other therapeutic agents, including azacytidine and other HMA [41-45]. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing pro-apoptotic proteins, triggering mitochondrial outer membrane permeabilization, and the activation of caspases, eventually leading to cell death [41, 43, 44]. HMAs (e.g., azacitidine and decitabine) indirectly and synergistically increase sensitivity to BCL-2 inhibition in AML-cells by modifying the relative levels of proteins in the BCL-2 family [46-48]. MoA of venetoclax including synergies with HMAs has been reviewed relatively recently in the scientific literature [69]. Leukemic stem cells (LSC) is a source of disease progression, resistance,

and relapse in AML. By targeting the LSC population, it is plausible to achieve deep and durable responses with reduced risk of late relapse [49]. Venetoclax in combination with azacitidine effectively targets the LSC population via disruption of amino acid-fueled oxidative phosphorylation, on which the LSC population is uniquely reliant. This hypothesis is supported by the deep and durable responses observed in clinical trials [52, 53]. In addition to restoration of apoptosis and targeting LSCs, a third element of venetoclax MoA in AML is immunomodulation. Venetoclax modulates T-cells to increase their cytotoxicity to AML cells, while azacitidine demonstrates the potential to induce the susceptibility of AML cells to T-cell mediated cytotoxicity [54]. This suggests an immune-mediated mechanism of action compatible with the observed response depth and durability following venetoclax-azacitidine treatment in Viale-A [52].

In the Viale-A trial, the median time to first response (CR or CRi) was shorter for patients treated with venetoclax in combination with azacitidine compared to patients receiving azacitidine monotherapy (1.3 months vs 2.8 months). By the initiation of the second treatment cycle, the rates were 43.4% vs. 7.6% for venetoclax in combination with azacitidine vs. azacitidine monotherapy [52]. In addition to faster time to response and a larger population reaching CR/CRi, venetoclax combined with azacitidine resulted in significantly higher proportion of patients achieving deep responses with measurable residual disease (MRD) negativity compared to the control group [52]. The impact of response depth (MRD < 10^{-3} vs. MRD ≥ 10^{-3} was demonstrated in a sub-analysis concluding that duration of response, event-free survival (EFS), and overall survival (OS) were all significantly longer in patients who achieved CR/CRi with MRD < 10^{-3}, further supporting the prognostic value of MRD-negativity on key clinical outcomes in AML [70].

In summary, venetoclax in combination with azacitidine resulted in longer OS, more rapid and durable as well as deeper responses, compared with azacitidine monotherapy. Venetoclax and azacitidine act synergistically to kill AML cells and display combinatorial antitumor activity. This includes initiation of apoptosis of AML-cells, targeted effects on the critical LSC population and immunomodulatory effects driving the above-mentioned clinical benefits and providing a mechanistic rationale for long-term efficacy. MoA, time to response, and the quality of the biological response, evidenced by different potential to produce deep responses (high level of MRD-negativity), varies between the two treatment groups (venetoclax + azacitidine vs. azacitidine monotherapy).

The much higher rate and earlier onset of CR/CRi with ven+aza that this MoA results in means that the proportion of patients with CR/CRi over time was higher within EFS, OS (Figure 37 and Figure 38) and ToT in the ven+aza arm in Viale-A, as well as having a different shape (Figure 38). These very different dynamics make it reasonable to account for different risk patterns between the arms by using different parametric functions. Due to the low and slow onset of CR/CRi in the aza arm, a constant hazard over time (exponential function) would seem reasonable for azacitidine EFS and OS, while allowing for decreasing hazards over time for ven+aza EFS and OS (Gompertz and Weibull) due to the difference in MoA and the quick onset and high rate of CR/CRi.

The methodology for parametric extrapolation and the selection of survival models is described in more detail in the following sections.

12.2 Overall survival

The OS associated with venetoclax in combination with azacitidine and azacitidine in monotherapy were based on the IPD data from the Viale-A clinical trial data (data cut-off: January 4, 2020).[71] The OS was evaluated from the date of randomization.
Following the survival model selection process specified in **section 12.1**, the following criteria were considered to select the best-fit parametric survival model:

- The goodness-of-fit criteria (including AIC and the BIC) were estimated for each parametric model to evaluate model fit for OS based on statistical test results (**Table 55**)
- An overlay of the K-M curves of OS from the trial and the predicted curves based on each parametric survival model is presented in Figure 29 for visual inspection of the survival prediction.

Log cumulative hazard plots for OS were generated for venetoclax with azacitidine and azacitidine based on the OS K-M curves to assess the hazard pattern over time (Figure 30 and **Figure 31**)

The OS for venetoclax with azacitidine and azacitidine in monotherapy were predicted using parametric survival models estimated based on the Viale-A trial data. The log-normal and exponential model seemed the best fit model for venetoclax with azacitidine and azacitidine, respectively, based on the following consideration: 1) it has the lowest AIC and BIC values among all survival models; 2) it demonstrates a good fit with the observed curves based on visual inspection; 3) the log cumulative hazard plots of the parametric model indicate consistent hazard patterns with the observed hazard plots. However, based on input from an expert haematologist, the Weibull distribution was chosen in the base case for venetoclax with azacitidine.

Figure 28 Parametric models for OS - venetoclax with azacitidine

Figure 29: Parametric models for OS - azacitidine

Figure 30: Log cumulative hazard plot for OS - venetoclax with azacitidine

Figure 31. Log cumulative hazard plot for OS - azacitidine

12.3 Event-free survival

The EFS associated with venetoclax in combination with azacitidine and azacitidine in monotherapy were based on the IPD data from the Viale-A clinical trial data (data cut-off: January 4, 2020).

Following the survival model selection process specified in **section 12.1**, the following criteria were considered to select the best-fit parametric survival model:

- The goodness-of-fit criteria (including AIC and the BIC) were estimated for each parametric model to evaluate model fit for EFS based on statistical test results (**Table 56**)
- An overlay of the K-M curves of EFS from the trial and the predicted curves based on each parametric survival model is presented in **Figure 32** for visual inspection of the survival prediction
- Log cumulative hazard plots for EFS were generated based on the EFS K-M curves to assess the hazard pattern over time (**Figure 34**)

The EFS for venetoclax with azacitidine and azacitidine in monotherapy were predicted using parametric survival models estimated based on the Viale-A trial data [71]. The Gompertz and exponential models were chosen as the best fit models for venetoclax with azacitidine and azacitidine, respectively, based on the following consideration: 1) it has the lowest AIC and BIC values among all survival models; 2) it demonstrates a good fit with the observed curves based on visual inspection; 3) the log cumulative hazard plots of the parametric model indicate consistent hazard patterns with the observed hazard plots.

Figure 32. Parametric models for EFS - venetoclax with azacitidine

Figure 33. Parametric models for EFS - azacitidine

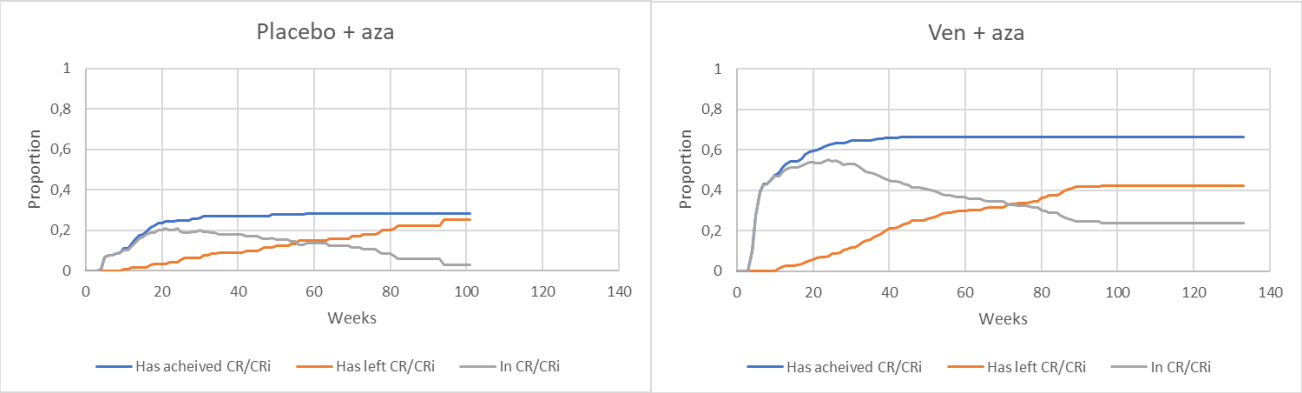
Figure 34. Log cumulative hazard plot for EFS - venetoclax with azacitidine

Figure 35. Log cumulative hazard plot for EFS - azacitidine

12.4 CR/CRi

Proportion of patients in CR/CRi was modelled using Viale-A data. Kaplan-Meier curves of patients achieving CR/CRi as well as leaving the CR/CRi state (for any reason, including death) were developed. These were used to calculate the probability over time of any patients in the study being in CR/CRi. This was done for both venetoclax + azacitidine and for the azacitidine arm (Figure 36).

Figure 36: Proportion of patients in CR/CRi over time



Looking at CR/CRi, EFS and OS together (Figure 37) we can see that the CR/CRi curves are over time converging with the EFS curve. In the ven+aza arm, all patients remaining in EFS at two years after treatment initiation have CR/CRi. The trend can also be visualised by looking at the proportion over time of patients in EFS that have achieved CR/CRi (Figure 38).

Figure 37: Proportion of patients in CR/CRi, EFS and OS over time

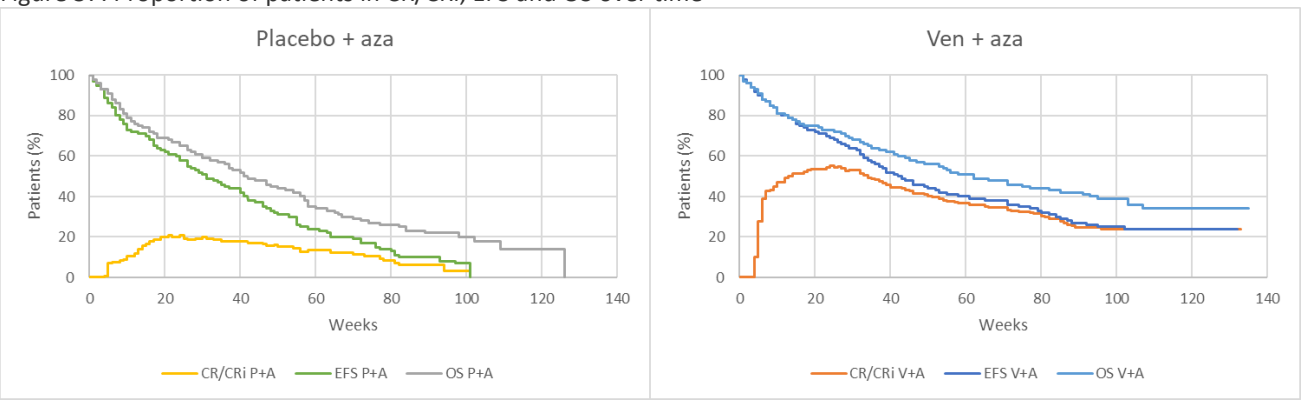
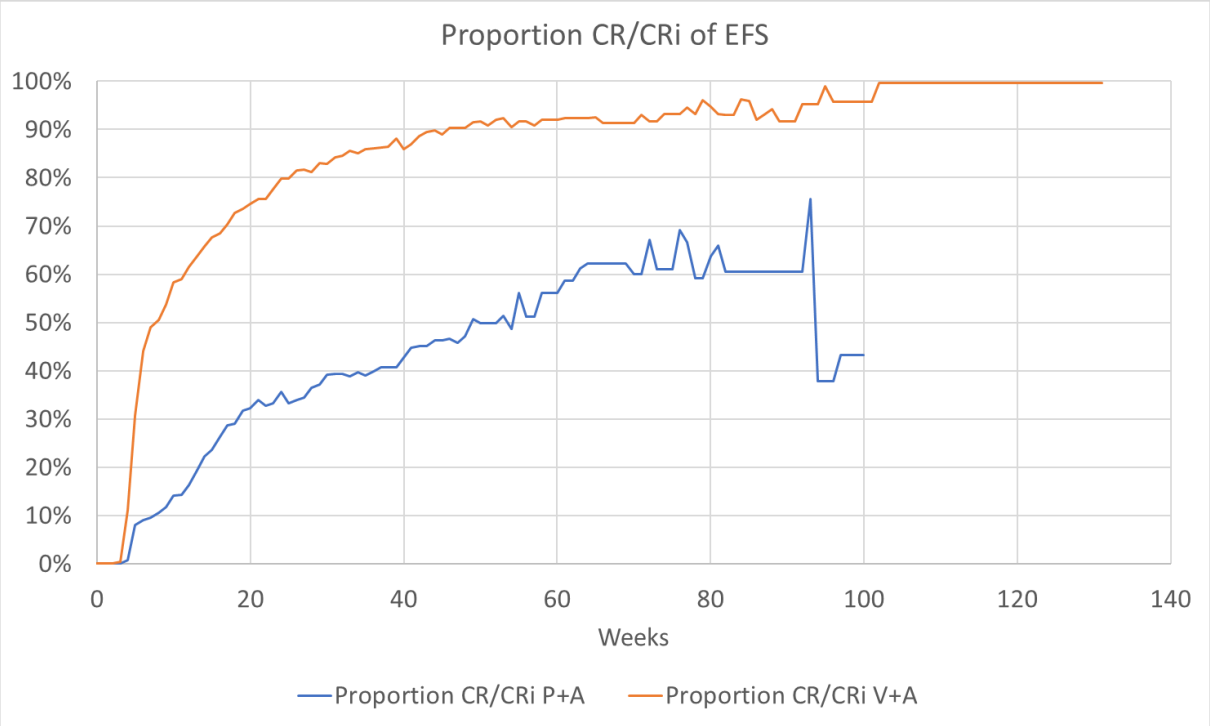


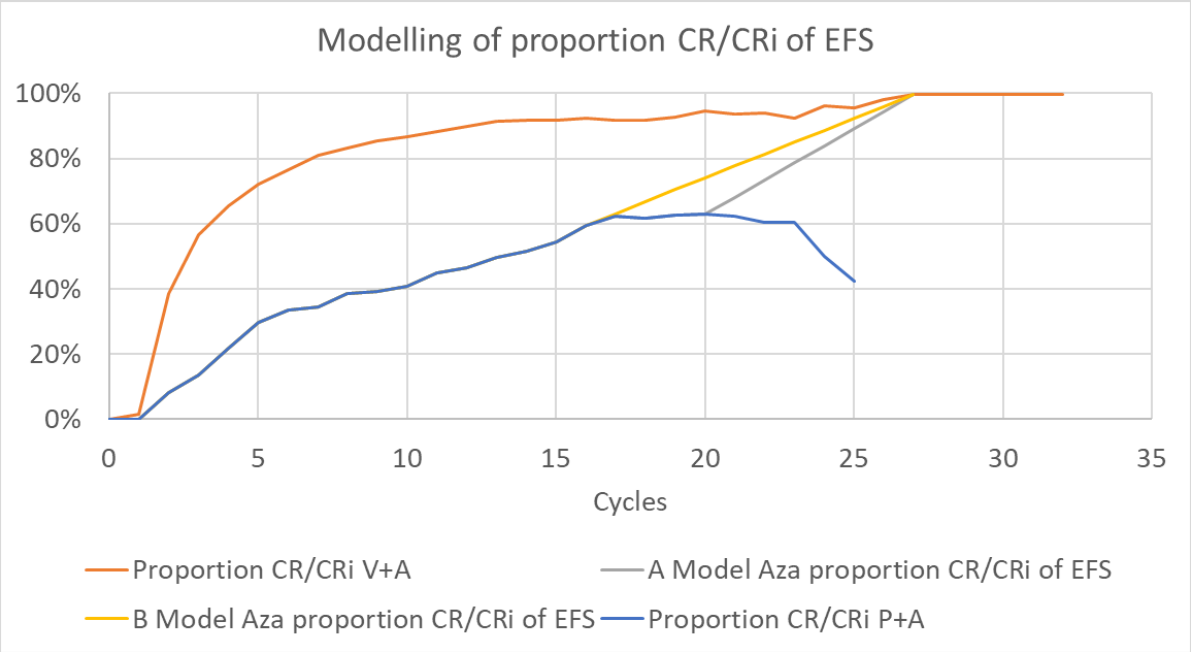
Figure 38: Proportion of patients in EFS that are in CR/CRi over time



The trend is less clear for the azacitidine arm after 70-80 weeks. We believe however this to be due to few observations.

The proportion of patients in CR/CRi of all patients in EFS was used to model the proportion of patients in CR/CRi in the model. Half-cycle adjustment was performed on week data after which the values for 28-day cycles were calculated by taking the average of the four corresponding weeks. The result was then applied in the CUA model. Due to the shape of the azacitidine curve however, an adjustment had to be done, as a downwards trend after some time in the azacitidine arm did not seem plausible. A linear increase was modelled to reach 100% at the time of functional cure assumed in the model. Two models (A and B) were looked at, where model B, where the linear increase would start already after cycle 16 (Figure 39) was chosen. To choose model B results in a more conservative incremental effectiveness estimate for ven+aza compared to azacitidine alone and can thereby be a source of overestimation of the ICER.

Figure 39: Modelling of proportion of CR/CRi of EFS over time



12.5 Long-term survival

In the base-case model, patients who remain in EFS in the model after a certain time point were considered to be long-term survivors. There are several reasons why AbbVie has chosen this approach.

Assumptions regarding long-term survival in AML using cure modelling have been evaluated and accepted in multiple HTA evaluations and by several HTA agencies, including TLV, NICE and NoMA [72-81]. There are some differences between the evaluated populations, including the rates of HSCT, however, a biological rationale for long-term survival in AML is also present in the treatment pathway for venetoclax and the rationale and assumptions are supported as plausible by clinical experts.

Most relapses following standard treatment with intensive induction chemotherapy for AML occur within the first 18 months, and late relapses are infrequent [82, 83].

The leukemia stem cell (LSC) population has different properties than the bulk AML population, making them challenging to eliminate, and therefore a source of disease progression, resistance and relapse. By eliminating the LSC population, it is plausible to expect therapeutic deep and durable remissions with minimal risk of late relapse [49]. Recent data propose that in AML, the LSC population is efficiently targeted by venetoclax with azacitidine, due to its specific disruption of amino acid-fueled oxidative phosphorylation, on which the LSC population is uniquely reliant. Resulting in promising clinical activity in a patient population with historically poor outcomes [50, 51]. This hypothesis is supported by the deep durable response that has been observed in the venetoclax clinical studies [52, 53].

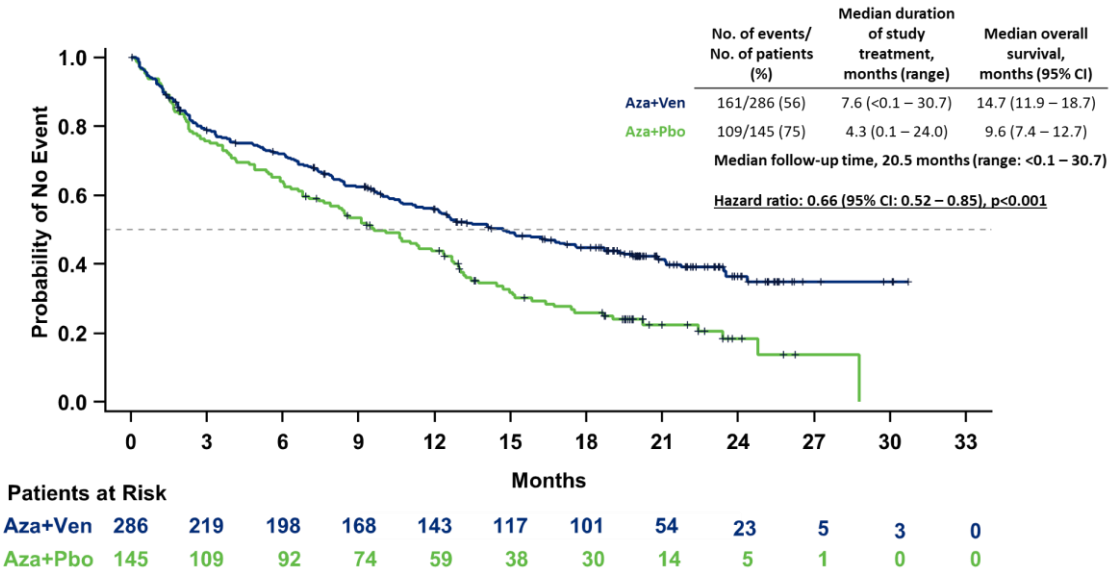
Venetoclax modulates T cells to increase their cytotoxicity to AML cells, while azacitidine demonstrates the potential to induce the susceptibility of AML cells to T-cell mediated cytotoxicity [54]. This suggests an immune-mediated mechanism of action compatible with the observed response depth and durability following venetoclax-azacitidine treatment in Viale-A.

In Viale-A, the venetoclax - azacitidine group achieved a rapid response with a median time to first response of 1.3 months. In this group, composite complete remission was achieved in around 2/3 of the patients, and achieving complete response is related to the deep response of the treatment. For venetoclax – azacitidine it is therefore a plausible assumption that a number of patients would remain in remission for years with minimal risk of late relapse.

Visual inspection of the K-M curves for OS from Viale-A show a clear and continuous separation of the curves (shown below in **Figure 40**)

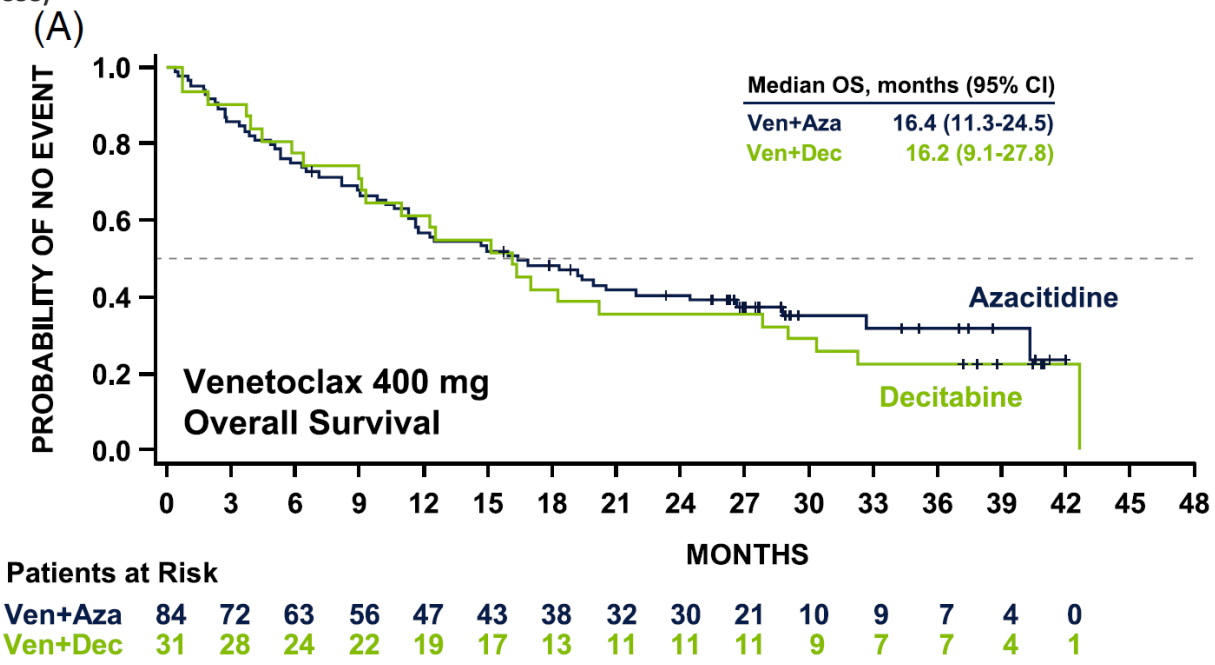
It is not unreasonable to interpret the curve as showing a beginning plateau based on a clinical rationale. This assumption is also supported by Wei et al. [57] who commented on an apparent survival plateau after 18 months.

Figure 40: Kaplan–Meier Estimates of OS for ven+aza and aza+pbo from Viale-A



The notion of a survival plateau is further supported by data from the phase 1b study of venetoclax + HMA agent, see figure below (**Figure 41**).

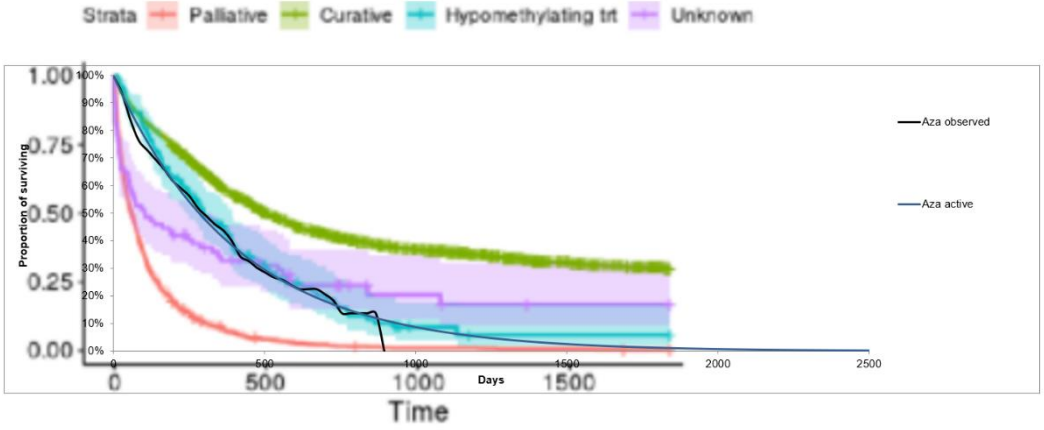
Figure 41: Kaplan–Meier Estimates of OS for ven+aza and aza+pbo from phase 1b study (M14-358)



As described earlier, more rapid achievement of CR + CRi, CR, and CR + CRh was observed with ven+aza than with aza+pbo in Viale-A, and also at a higher rate. These responses were durable, and patients experienced sustained long-term benefits. This is also supported by data of CR/CRi over time from Viale-A, which clearly show that over time the EFS and CR/CRi curves have completely converged after around two years. The interpretation is that after around two years the patients who are still in EFS are also in sustained complete remission. Data from the literature demonstrate that most relapses following standard treatment with intensive induction chemotherapy for AML occur within the first 18 months which also supports calculating with a sustained long-term benefit after two years in EFS [82, 83].

Further, AbbVie has calibrated the model extrapolations using data from the Swedish AML registry [84]. Comparison of the chosen parametric survival model for azacitidine OS with registry data [85] demonstrates a very good fit to the data until after 1000 days, when the model is underestimating OS.

Figure 42: Modelled OS for azacitidine arm versus registry outcomes without cure modelling

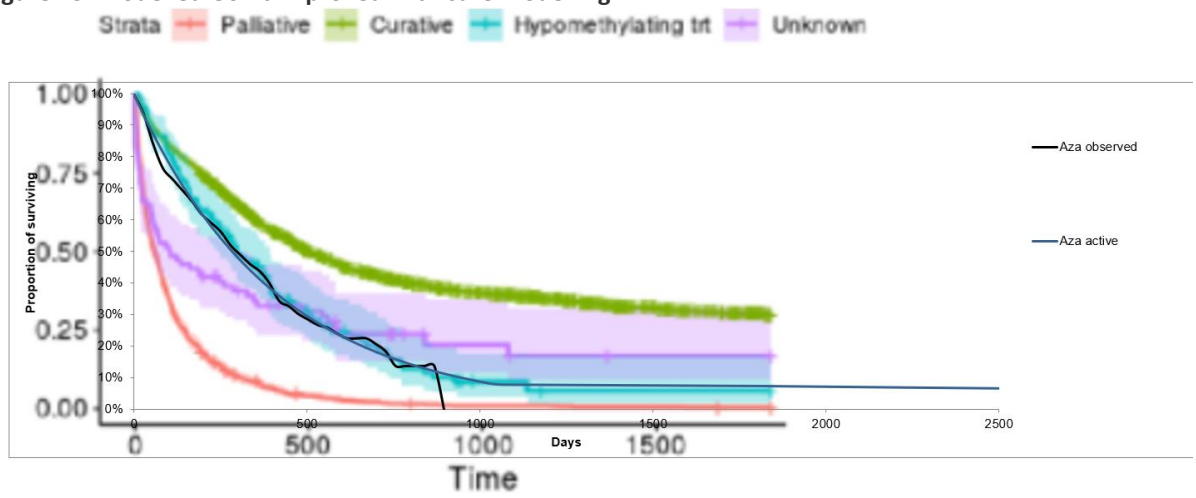


One could argue that there are very few patients at risk at that timepoint in the registry data, and that the number of patients that would still be alive in that way would be uncertain. However,

the fact that a patient in the registry is alive at the latest time point in the presented registry data while the model function is close to zero if no adjustment is made, proves that the modelling in the figure above is underestimating the long-term survival.

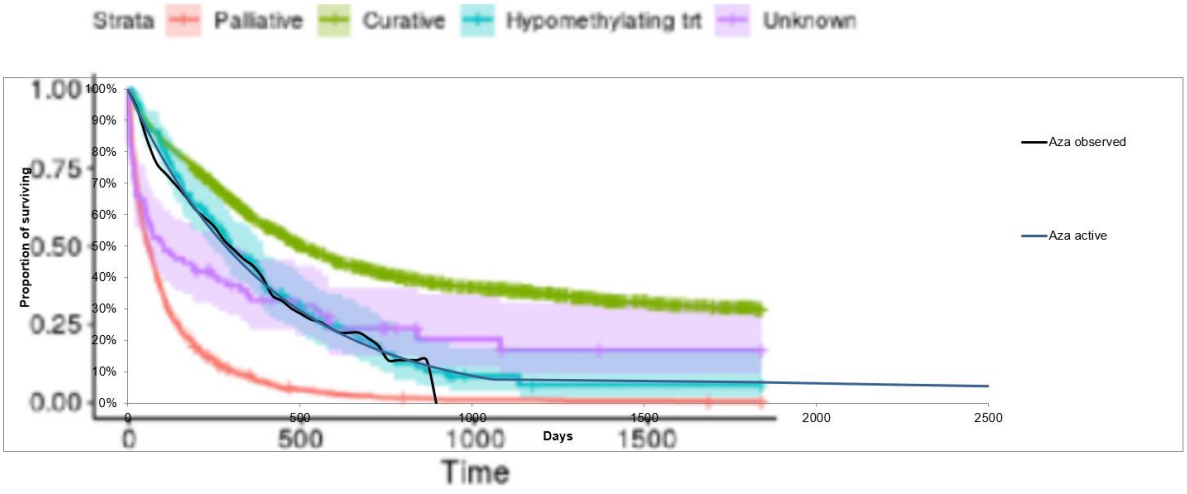
Using an assumption on long-term survival applied to EFS patients, patients who remained in EFS in the model after a certain time point were considered to be long-term survivors. Setting the risk of death equal to the general population mortality after the selected time point, and assuming that all patients still in EFS at the time of two years are long-term survivors, the fit to registry data is improved, although it now looks slightly overestimated.

Figure 43: Modelled OS fit improved with cure modelling



If we in addition to the approach above apply a standardized mortality ratio (SMR) adjustment to the general population mortality, an SMR of 2 for the long-term survivors, the fit is improved.

Figure 44: Modelled OS fit with cure modelling and an SMR of 2



Obviously, the registry data demonstrate that there are patients living longer than the model predicts without adjustments – so calibration is a justified approach. These assumptions are also similar to those made by DMC in the gilteritinib assessment, although the SMR in the base case was 1.3 and it is not clear to us if the assumption of cure at two years were applied to the whole of the population or only those modelled to be in CR.

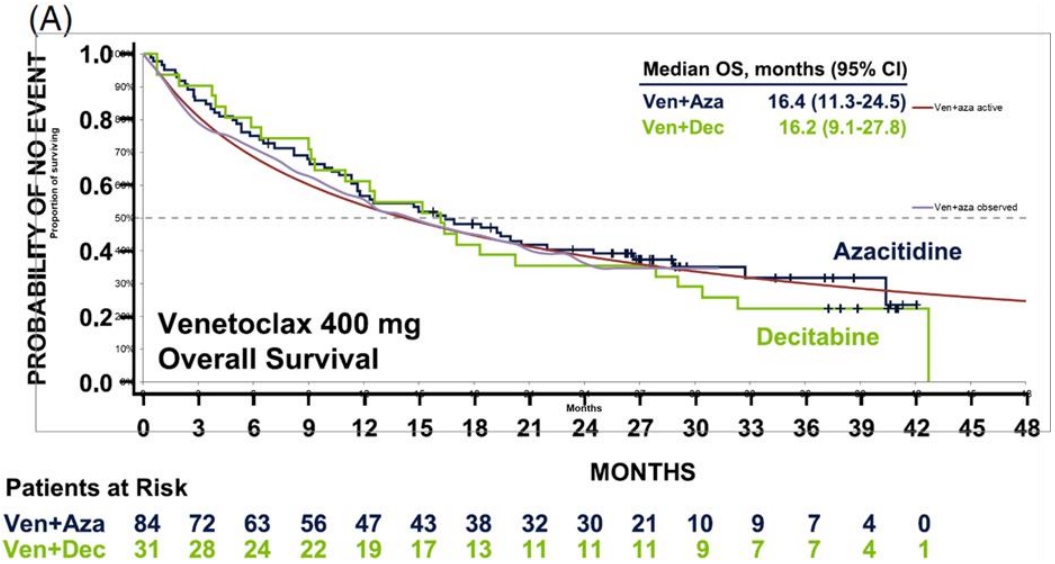
The year 2-5 has been considered in previous AML submissions, representing a clinically important time point for patients to reach while still being in remission, given the limited risk of relapses for those patients. [75-77].

To sum up, the patients are expected to have a high rate of progression initially, but over time this is assumed to change. Due to the AML pathophysiology and the mode of action of the treatment, a strong patient selection will occur, and the patients remaining will be well controlled and in complete remission. This is based on the preclinical/clinical rationale, the Swedish clinical registry, input from Norwegian AML clinicians, and also from the data on CR/CRi over time from Viale-A, which clearly show that over time the patients remaining in EFS are in complete remission.

In our base-case model settings, two years is selected as the time point for long-term survival (input is user changeable in the sheet "Base Case"). When two years is selected, the patients are then associated with a risk of death double that of the general population mortality. Note that this is related to the choice of two years only as the assumption is built upon calibration to the Swedish registry. Other settings should handle this explicitly and the input is user changeable in the sheet "Life table".

Using the same modelling for the venetoclax + azacitidine arm also provides a good fit to the observed OS in the phase 1b study (7) (**Figure 45**) which is a validation of the extrapolation beyond Viale A follow up.

Figure 45: Modelled ven+aza OS compared to the observed OS in the phase 1b trial



12.6 Time on treatment

Time on treatment was estimated based on Kaplan-Meier data on time on treatment in Viale-A. Parametric survival models were used. Log-normal models were found to have the best fit looking at AIC and BIC numbers (**Table 57**). It also demonstrates a good visual fit with the observed curves (**Figure 46** and **Figure 47**). The log cumulative hazard plots of the parametric model also indicate consistent hazard patterns with the observed hazard plots (**Figure 48** and **Figure 49**). However, based on input from an expert haematologist, the exponential distribution was chosen in the base case for venetoclax with azacitidine.

Figure 46: Parametric models for ToT - venetoclax with azacitidine

Figure 47: Parametric models for ToT - azacitidine

Figure 48: Log cumulative hazard plot for ToT - venetoclax with azacitidine

Figure 49: Log cumulative hazard plot for ToT - azacitidine

In addition to this, it was assumed that none of the initial treatments would continue in the PD/RL state. Based on feedback from Danish clinical expertise, there was no assumption on a time point where all treatment would have ended, although such functionality is available in the model and has been suggested in other countries. Such an assumption would be based on experience from other cancer areas and related to the biological rationale on long-term survival (see section 12.5) as patients with a good control of their disease, i.e. EFS and deep response for two years and more might not continue with their treatment and hence be treatment free. Treating patients outside of a clinical trial protocol obviously provides the treating haematologist with more freedom to judge when it is more beneficial for a patient to stop treatment.

Appendix H – Literature search for HRQoL data

Omitted, since not relevant in this submission.

Appendix I Mapping of HRQoL data

Omitted, since EQ-5D-5L data is available in the clinical study.

Appendix J Probabilistic sensitivity analyses

The assumptions for the probabilistic analysis are found in the tab PSA Setup.

Appendix J Additional Utility Analyses

Notes:

1. EQ-5D utility scores were estimated from data of the Viale-A trial (data cut 2020-01-04) based on individual dimension scores and using UK preference-weights. The EQ-5D 5L score in the trial data was transferred to EQ-5D 3L score using the UK cross-walk value set based on Van Hout et al. (2012). (Reference: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/)
2. EQ-5D utility values for health states were estimated using a linear mixed-effects model to account for correlation within patients' repeated assessments.

Compliant responses

The table below shows the number of patients who were still on treatment, and how many patients that provided valid questionnaire responses. Some patients were excluded due to unknown health at the time of measurement, ie whether they were in EFS with or without CR / CRi or PD / RL. In this analysis, it was not a requirement to have answered the questionanaire more than once, so that all information available was included in the analysis.

Appendix K Additional prevalence and incidence figures

Table 61: Prevalence figures from NORDCAN [3]

Year	Total	1-year	3-years	5-years	10-years
2015	975	122	268	378	563
2016	996	120	264	360	553
2017	1027	125	271	378	565
2018	1048	125	266	378	572
2019	1072	116	269	380	581

Table 62: Detailed incidence figures from ALG 2020 report [2]

	2020		2019		2018		2017	
	AML	ALL	AML	ALL	AML	ALL	AML	ALL
Danmark	281	29	287	36	272	17	264	27
Hovedstaden	70	8	85	9	83	6	68	8
Sjælland	38	5	41	5	43	#	46	0
Syddanmark	78	4	65	12	68	3	61	3
Midtjylland	60	10	71	9	42	6	61	12
Nordjylland	35	#	25	#	36	#	28	4
Hovedstaden	70	8	85	9	83	6	68	8
Rigshospitalet	33	7	38	7	42	5	28	7
Herlev	37	#	47	#	41	#	40	#
Sjælland	38	5	41	5	43	#	46	0
Roskilde	38	5	41	5	43	#	46	0
Syddanmark	78	4	65	12	68	3	61	3
Odense	75	3	61	12	64	3	56	3
Esbjerg	#	0	3	0	#	0	3	0
Vejle	#	#	#	0	3	0	#	0
Midtjylland	60	10	71	9	42	6	61	12
Århus	54	10	67	9	39	6	59	12
Holstebro	6	0	4	0	3	0	#	0
Nordjylland	35	#	25	#	36	#	28	4
Ålborg	35	#	25	#	36	#	28	4

 # Resultatet er af diskretionshensyn fjernet, da der er under tre observationer i tæller eller nævner

AbbVie replies to questions submitted in the e-mail of January 21, 2022

Table 1:

- Inkluder gerne prævalenstal for AML (findes bl.a. på cancer.dk)

AbbVie's reply: We have updated tables and added Appendix K.

QoL:

- Mangler HR? (desuden fuldstændig samme værdier for HRQL?)

AbbVie's reply: There was an unneccesary repetition. We have removed the piece " Health-related quality of life (HRQL)" from within 7.1.2.

Table 19:

- Hvorfor har man valgt en SMR=2?

AbbVie's reply: We are calibrating the model so that it fits the registry data for hypomethylating treatment (azacitidine). See section 8.3.6, Long-term survival. Compare figure 18 and 19. However, the difference is very small, and we agree that since the difference is so small, and in order to not complicate things unnecessarily, one could also keep it at SMR=1.

Figur 20:

- Ikke forklaret hvad der er hvad?

AbbVie's reply: We have added a text " The dark blue line is OS for ven+aza in the phase 1b. The light green line is OS for ven+dec in the phase 1b. The red line is the modelled ven+aza OS. The light purple is observed ven+aza OS in Viale-A. The figure is composed of the figure from the phase 1b publication with the excel diagram from the model put on top of it. OS = Overall survival"

Figur 23:

- ikke forklaret

AbbVie's reply: We added an explaining text " DSA = Deterministic sensitivity analysis, ICER = incremental cost-effectiveness ratio, QALY = Quality-adjusted life year, ToT = Time on treatment, EFS = Event-free survival, CR = complete response/complete remission, CRi = complete remission with

partial haematologic recovery. The parameters impacting the ICER the most are time on treatment and dosing parmaters”

Table 49:

- AML-type for M14-358 summer ikke til 100% (der er kun vist én kategori)

AbbVie’s reply: The corresponding numbers for ”de novo” has been added.

Table A3a:

- CI mangler for CR andele - added
- Tid til første respons har modsat fortegn end OS/EFS (skal være minus, idet der er kortere til første respons) - adjusted
- CI for absolut risikodifference er Wald CI, dvs. det er ikke beregnet baseret på CI for relativ risiko, som metodebeskrivelsen kunne indikere. – text adjusted

Also added ”months” where appropriate

Figur 27:

- Svær at læse pga. lav opløsning (det synes, at HR for All subjects ikke passer med tabellen, forskelligt datacut?)

AbbVie’s reply: Resolution improved (not saved as a tracked change). The difference in HR is due to a difference in calculation, just as in the DiNardo publication there are two different values for HR. A note has been added below the figure to describe method used for calculating HR in that figure.

CRh og CRi:

- Beskriv den anvendte definition af CR og CRi

AbbVie's reply: Added a text square in 7.1.2 with definitions

Definitions

- Complete remission (CR) was defined as an absolute neutrophil count of more than 1000 cells per cubic millimeter, a platelet count of more than 100,000 per cubic millimeter, red-cell transfusion independence, and bone marrow with less than 5% blasts.
- Complete remission with incomplete hematologic recovery (CRi) was defined as all the criteria for complete remission, except for neutropenia (absolute neutrophil count, ≤1000 per cubic millimeter) or thrombocytopenia (platelet count, ≤100,000 per cubic millimeter)
- Complete remission with partial hematologic recovery (CRh) was defined as all the criteria for complete remission, except that both the neutrophil and platelet counts were lower than the threshold designated for complete recovery (for neutropenia >500 per cubic millimeter and a platelet count of more than >50,000 per cubic millimeter).

Dosis og effekt:

- I bedes inkludere data som underbygger, at venetoclax har samme effekt, når det gives i mindre dosis. Hvis ikke dette er tilgængeligt, bedes I argumentere for denne antagels

AbbVie's reply:

We added a new section, 7.1.4. regarding dosing and efficacy of Venclyxto when CYP3A is inhibited.

We want to be clear about that the assumptions in our base-case is completely in line with the SmPC/Viale-A dosing schedule and the expected use of concomitant anti-fungal treatment in Denmark.

We are also inserting a segment from our application that is describing why it is also relevant to look at scenarios with treatment schedule where venetoclax is not administered every day:

> *There is however a high probability that, in addition to this, the dosing schedule used in clinical practice will differ from the one in Viale-A. Haematologists from the Scandinavian countries have notified AbbVie of their proposed study protocol and plans to study a dosing schedule where venetoclax is not administered all days in the 28-day cycle. The Swedish guidelines [16] states that the venetoclax treatment duration can be discussed and that there is experience of treating only 7-14 days per each 28-day treatment cycle while still achieving a high response frequency and that is a current discussion also in the Danish AML society.*

This possible practice is also supported by a more recent analysis of Viale-A data [85], where it is concluded that "lower exposures associated with venetoclax dose reductions to manage cytopenias in patients who achieved CR/CRh did not appear to affect overall survival".

Fortrolighed:

- I bedes markere hvilke resultater, som I mener er fortrolige

AbbVie's reply: We will attach a copy of the document with those things highlighted.

Ekstrapolering:

OS:

- I tester for proportional hazard mellem venetoclax + azacitidin og azacitidin uden at forholde jer til betydningen af resultatet. Hvorfor vælger I at lave individual fit på data i stedet for joint fit?

AbbVie's reply:

We mistakenly included the following text in our submission (highlight added):

- **Testing the proportional hazards assumptions:** The proportional hazard (PH) assumptions were evaluated when hazard ratios were estimated and applied to a base survival curve to compare different comparator arms with the same reference case. In most cases, one HR is applied to the entire modelled period. In this scenario, Schoenfeld residuals test was used to test the proportional hazards assumption to ensure the treatment effect is proportional over time and the survival curves fitted to each treatment arm have a similar shape.

The text is from a technical report which included comparisons of "external" treatment arms, meaning treatment arms that did not exist in Viale-A, such as BSC. For such a comparison, indirect comparisons would have to be carried out, using a reference case to estimate hazard ratios. For this reason, tests regarding proportional hazards were carried out for those cases, as can be read out by the highlighted text above. For the comparison of ven+aza versus aza, however, we have data for both arms from the same trial, so then the individual fit can be used.

We have removed the text from the submission document.

- Hvad er jeres argumenter for at vælge at ekstrapolere data for venetoclax + azacitidin og azacitidin med to forskellige parametriske funktioner?

AbbVie's reply:

Testing for the fit, using AIC and BIC, they typically rank the distributions differently between ven+aza and aza, regardless of whether we are looking at OS/EFS/ToT – so it seems there is no statistical

reason to support the use of the same parametric functions. Medically speaking, the venetoclax component adding the BCL-2-inhibition makes the two treatments very different in terms of mode of action, which also would not indicate a similar shape of the survival curves.

- Redegør for den kliniske plausibilitet af de valgte ekstrapoleringer

AbbVie's reply: The survival is still low, which would be expected for this serious disease. Uncertainty is substantially lowered thanks to the availability of OS data for azacitidine from the Swedish registry that is very similar to the OS of aza in Viale-A. This data was used to make sure the the long-term modelling of azacitidine had a good fit to the expected outcome in clinical practice.

- Redegør for de kliniske input til at vælge en weibull funktion for venetoclax + azacitidin?

AbbVie's reply:
The clinician we asked believed the Gompertz, generalized gamma, log-logistic and log-normal were maybe too optimistic.

PFS: EFS

- I tester for proportional hazard mellem venetoclax + azacitidin og azacitidin uden at forholde jer til betydningen af resultatet. Hvorfor vælger I at lave individual fit på data i stedet for joint fit? AbbVie: See reply to the corresponding question for OS.
- Hvad er jeres argumenter for at vælge at ekstrapolere data for venetoclax + azacitidin og azacitidin med to forskellige parametriske funktioner? AbbVie: See reply to the corresponding question for OS.
- Hvad er jeres argumenter for at vælge at ekstrapolere data for venetoclax + azacitidin og azacitidin med to forskellige parametriske funktioner? The question was duplicated.
- Redegør for den kliniske plausibilitet af de valgte ekstrapoleringer

AbbVie's reply: We have very similar average time in the PD/RL state, about three months. Once a patient has progressed or relapsed, as per the expectance of a clinician we spoke to, we would expect the remaining time alive for the patient to be very similar, regardless of whether ven+aza or aza was the treatment chosen. Current choice of parametric functions OS/EFS is in line with this expectation.

ToT:

- I tester for proportional hazard mellem venetoclax + azacitidin og azacitidin uden at forholde jer til betydningen af resultatet. Hvorfor vælger I at lave individual fit på data i stedet for joint fit? AbbVie: See reply to the corresponding question for OS.

- Hvad er jeres argumenter for at vælge at ekstrapolere data for venetoclax + azacitidin og azacitidin med to forskellige parametriske funktioner? AbbVie: See reply to the corresponding question for OS.
- Hvad er jeres argumenter for at vælge at ekstrapolere data for venetoclax + azacitidin og azacitidin med to forskellige parametriske funktioner? The question was duplicated.
- Redegør for den kliniske plausibilitet af de valgte ekstrapoleringer AbbVie: Due to clinical input from Scandinavian haematologists, we added the functionality of a ceiling, a maximum duration. This was also considered realistic by TLV. However, the Danish haematologist we discussed this issue with believed that his colleagues would never consider to end ven+aza treatment if the patient was still in remission and the toxicity was acceptable. Because of this input the dosing ceiling is not applied in the base-case scenario. AbbVie does think it is reasonable to evaluate the ceiling scenario as AbbVie belive this could be a scenario also for Denmark in the future.
- Redegør for de kliniske input til at vælge eksponentiel funktion for venetoclax + azacitidin? Det er den funktion, som fitter data dårligst

AbbVie's reply: The clinician we asked believed the exponential and Weibull seemed to be the most reasonable for both aza and ven+aza. Gompertz, generalized gamma, log-logistic and log-normal were maybe too optimistic

Utility-værdier for stadierne og bivirkninger:

- I bedes præsentere utility-værdierne fra studiet opdelt på armene i studiet inkl. konfidensintervaller

A table has been added to the new appendix J: Model-based estimates of EQ-5D health state utility values by treatment.

- Redegør for andel, der har rapporteret deres livskvalitet, ved alle opfølgninger og for alle patientgrupper. Denne skal inkludere en redegørelse for, og analyse af, manglende besvarelser og forskelle blandt patientgrupperne

The following has been added to the new appendix J.

The table below shows the number of patients who were still on treatment, and how many patients that provided valid questionnaire responses. Some patients were excluded due to unknown health at the time of measurement, ie whether they were in EFS with or without CR / CRi or PD / RL. In this analysis, it was not a requirement to have answered the questionanaire

more than once, so that all information available was included in the analysis. We hope this table answers your questions above, but we are happy to supplement if you see that further information is needed.

- Redegør for hvordan manglende (missing) data er håndteret. Denne skal inkludere en fuld beskrivelse af metoder, der er benyttet

Patients who were included in the analysis have 3.87% missing scheduled visits on average. This analysis did not impute values for missing evaluations and thus a subject who did not have an evaluation on a scheduled visit would be excluded from the analysis for that visit.

The information was added to the application document.

- Redegør for hvorfor nogle af utility-værdierne for bivirkninger er positive. Er anæmi og neutropeni ikke forbundet med en disutility?

AbbVie's reply:

We have added the following text:

None of the disutilities for adverse event were statistically significant. Some of the adverse events are associated with a numerically positive impact on utility. Looking at neutropenia, this was present to a higher degree at baseline for the ven + aza arm (72% vs. 62%), and was more frequently reported as an adverse event in Viale-A (42% vs 29%) keeping in mind that time on therapy was longer in the ven+ aza arm. Hence, neutropenia was common and expected in the experimental arm with the best clinical response to treatment. Looking at an analysis of utilities by treatment arms (Table 57 in Appendix J) there also seem to be a tendency towards higher utility with ven + aza, maybe due to even deeper response, than the current three-state mixed-effects model could take into account. One could speculate that the positive utility estimate of of neutropenia could be a result of it being associated with a better treatment outcome, not completely captured by the three health states.

- Hvad er antagelser bag utility-værdierne for febril neutropeni, sepsis, urinvejsinfektion, atrieflimren, som ikke er listet i tabel 24?

AbbVie's reply:

Atrial fibrillation, sepsis or urinary tract infection were not included in the mixed-effects model because of the low event rates (i.e., less than 10 number of visits with each AE), which would lead to non-convergence issue of the model if included. The impact on incremental QALYs from AEs is small, and we would any particular or significant impact on incremental QALYs if we would have had more EQ-5D observations associated with the missing AEs.

Neutropenia included febrile neutropenia.

This information has been added/clarified in the submission document.

RDI:

- Var der taget højde for reduceret dosis af venetoclax i forbindelse med CYP3Ai i dosisintensiteten på 71 % fra studiet?

AbbVie's reply:

71% was the dose intensity of azacitidine in the ven+aza arm in Viale-A. Inhibiting CYP3A does not affect the level of azacitidine in the blood, so anti-fungal treatment is no reason to adjust the dose of aza.

Dose intensity for venetoclax in the ven+aza arm in Viale-A was 60% when comparing the mg actually taken with the amount that would have been taken if the following dosing schedule would have been followed: the ramp-up of 100 mg day one, 200 mg day to and thereafter 400 mg/day. If a patient would take 100 mg on day 10 either due to concomitant use of the anti-fungal treatment posaconazole, or for whatever reason, this would count as 25% dose intensity for that day in this calculation.

CYP3Ai:

- Redegør for klinikernes input til fordelingen mellem de to typer af CYP3Ai for azacitidin. Forklar herudover gerne hvad CYP3Ai er, og hvordan det anvendes

AbbVie's reply:

Below Table 28 we added " For azacitidine arm, one clinician did typically not use anti-fungals, while one stated that fluconazole is typically used, but that the lowering price of posaconazole might change this, and a third one expected only fluconazole to be used, but to a lesser degree when the patient is not severely neutropenic or not presenting recurrent infection. Our interpretation of this input is presented in the column for azacitidine." and removed "The low price of posaconazole is to some degree also expected to increase the use in the Azacitidine arm."

The following is added in the new section 7.1.4:

Venetoclax is largely eliminated through metabolization by cytochrome P450 3A (CYP3A). Co-administration with strong or moderate inhibitors of CYP3A (CYP3Ai) increase the exposure of venetoclax and consequently the dose of venetoclax should be reduced. Most relevant in the context of AML is concomitant prophylactic use of antifungal medication to neutropenic patients or patients otherwise at risk of infections. Several of the most commonly used antifungal drugs (prophylactic and therapeutic use) are moderate or strong inhibitors of CYP3A, most notably posaconazole and other

antifungal therapies belonging to the azol-group. Of note the patient may also be exposed to CYP3Ai in the diet, hence it is recommended to avoid grapefruit products, seville oranges, and starfruit during treatment with venetoclax.

- Redegør for hvordan I kommer frem til en dosisintensitet på 44,5 % pga. CYP3Ai

44.5% is the value in cell F57 in the sheet Drug Cost input and is a number used to calculate the impact of CYP3Ai on total dose intensity.

F55 is calculating the average days per course of anti-fungal treatment. As one physician claimed a course of three cycles (3*28 days) was appropriate, two other said they would use it throghout the whole treatment (dynamic). The average of those three is the result in F55.

The proportion of time on treatment when the dose should be reduced does however include a wash-out period of 2-3 days. This is calculated in the cell F57 for strong CYP3Ai by the part ”F52*(1+IFERROR(1/F55;0)*2,5)”. It can possibly be argued that this string could have been calculated in a cell of its own for increased clarity. IFERROR is there simply to handle an input of 0 in days per course of treatment as that would result in division by zero. Otherwise, it could have been simplified as ”F52*(1+2,5/F55)” which is more clear. We could also have written ”F52*(1+IFERROR(2,5/F55;0))”

So, F57 is using the proportion of patients that should have lower dose due to strong/moderate CYP3Ai, the proportion of time on ven+aza treatment this applies for and if it is a strong (like posaconazole) or moderate one (like fluconazole) reduces the dose with either 75% or 50%.

Selv-administration:

- Redegør for hvorfor 1/3 af patienter kun selv kan administrere azacitidin 3 ud af 5 dage? Hvorfor ikke alle 5 dage? Redegør for de kliniske inputs hertil

AbbVie’s reply: As we have understood it, based on discussions with a clinician, the main reason is that azacitidine has to be prepared and put into syringes by health care staff and once prepared it must be used within a few days. The patient has to come to the hospital anyways in the beginning of the treatment cycle for tests and to see the haematologist. Azacitidine is then administered. If one were to provide the patient with the syringes on the first day to take home, the patient would still have to come back for the last one due to the expiration of the prepared drug. Therefore, the patient is administered the first two doses of aza at the clinic, and then takes three doses home.

Our impression is that this practice is very patient-centered, helping the patient to live a somewhat more normal and convenient life. As far as we know, it is unique for Denmark, and does not take place in Norway or Sweden, but maybe with time it will spread.

Monitorering:

- Ressourceforbruget i forbindelse med sundhedsydelser er opgjort fordelt på stadier i modellen. Antager I, der ikke er forskel i ressourceforbruget mellem venetoclax + azacitidin og azacitidin?

AbbVie's reply: There are differences between treatments in adverse events which has an effect on resource use for adverse events, leading to a small cost difference. There is also a difference in relative dose intensity for azacitidine between the arms, and use of anti-fungals.

For patients that are in-patients at treatment start, we have heard reports of the ven+aza due to quick onset of remission possibly shortening the time at hospital, making them be able to return home sooner, but this is so far anecdotal, and not something we have included in the calculations. In AML, there is also practically no risk of any clinical TLS, meaning that there is no additional cost due to monitoring for TLS or administration of TLS prophylaxis.

Most of the resource use differences that arise are due to different time spent in different health states, where the costs are not dependent on treatment arm. The increased efficacy with ven + aza and thereby longer time on treatment is leading to higher total administration costs regarding the subcutaneous administration of azacitidine compared to what is seen in the aza arm.

- Redegør for i hvilken forbindelse vil der være behov for telefonsamtaler? Det er uklart om det vil være telefonsamtale med egen læge eller læge på hospitalet? I anvender en enhedsomkostning for telefonkonsultation ved egen læge

AbbVie's reply: According to expert opinion, the phone calls would take place in the EFS without CR/CRi – this stage of the disease is the window of opportunity where the health care servise is trying to get the patient into remission, which is our understanding to why the communication is more frequent between the hospital and the patient. Once remission is reached, the close communication is not longer necessary. Phone consulting cost changed to phone call by hospital using DRG-tariff

65TE01 “Telefon- og email konsultation, samt skriftlig kommunikation ved prøvesvar” 129 kr for 2021. The impact in the base case is small. ICERs have been updated.

- Derudover bedes i opdatere enhedsomkostningen for telefonkonsultation og blodprøve til 2021-priser samt inkludere koden for laboratorieundersøgelsen, som I anvender for blodprøve

AbbVie’s reply: Updated based on expert opinion and the current tariffs in the lab portal of Rigshospitalet (https://labportal.rh.dk/Metodeliste.asp). ICERs have been recalculated. The following table was added to the submission document and costs were updated.

Labka code	Name	Price (DKK)
HB	B-hæmoglobin	37 kr.
Lymfomik	B-leukocytter	17 kr.
Neutromik	B-neutrofilocytter	17 kr.
THROMMIK	B-trombocytter	257 kr.
ASAT	P-ASAT	29 kr.
ALAT	P-ALAT	29 kr.
BILI	P-Bilirubiner	29 kr.
GGT	P-gamma-Glutamyltransferase	29 kr.
BASP	P-basisk fosfatase	29 kr.
ALB	P-Albumin	29 kr.
CA	P-calcium	29 kr.
CRP	P-CRP	29 kr.
CREA	P-kreatinin	29 kr.
CARB	P-karbamid	29 kr.
GLU	P-glukose	29 kr.
K	P-kalium	17 kr.
CL	P-klorid	31 kr.
MG	P-magnesium	29 kr.
NA	P-natrium	17 kr.
PHOS	P-phosphat	29 kr.
URAT	P-Urat	29 kr.
APTT	P-koagulation, tid	22 kr.
CREACLEA	Nye-Kreatinin-clearance	95 kr.
Total		684 kr.

Patient- og transportomkostninger:

- Hvorfor er der ingen transportomkostninger til blodprøve?

AbbVie’s reply: These are typically done in connection to haematologist visits, transfusions, in-patient time.

- Hvorfor er der ingen transportomkostninger til transfusion, thrombocytes, allogenic?

AbbVie’s reply: If thrombocytes are administered, it would typically be in connection to a haematologist visit or other blood transfusion.

AbbVie replies to questions submitted in the e-mail of February 22, 2022

I refererer til en del kliniske eksperter. Indsend venligst navne på de klinikere, som I refererer til i ansøgningen. Vi vil behandle oplysningerne fortroligt og ikke navngive klinikere i vores materiale.

We have updated section 11. List of experts.

I bedes uddybe de kliniske argumenter for at vælge at ekstrapolere data (EFS, OS og ToT) for ventetoclax + azacitidin og azacitidin med to forskellige parametriske funktioner. Forklar hvordan behandlingerne varierer fra hinanden i form af mode of action samt timingen af effekt. Og redegør for hvordan det passer med de underliggende hazardfunktioner for de ekstrapoleringer, som I vælger for intervention og komparator for både EFS, OS og ToT.

We have updated section 8.3.2. and the corresponding section in the appendix in the same way.

Redegør for om der taget højde for reduceret dosis af venetoclax i forbindelse med CYP3Ai i dosisintensiteten fra studiet?

Indeed, we have adjusted the dose intensity from the study due to the CYP3Ai that was prescribed there before calculating dose intensity due to the expected Danish use of CYP3Ai. Please see updated section 8.5.1.

Medicinrådet skal sikre størst mulig åbenhed i vurderingen af nye lægemidler. Der skal være åbenhed i processer, metoder og kriterier og det materiale, der ligger til grund for og udarbejdes i forbindelse med vurderingen af lægemidler. Det er derfor vigtigt at alt materiale, som ikke er fortroligt, bliver offentliggjort.

- Er det rigtigt forstået, at information om kontaktpersonerne for ansøgningen skal markeres fortroligt?
- Redegør venligst for, hvorfor patientantallet i tabel 2 anses som fortrolige? Patientantallet er ikke markeret fortroligt de øvrige steder i ansøgningen, hvor det er nævnt.
- Redegør venligst for, hvorfor markedsoptaget for venetoclax + azacitidin anses som fortroligt i tabel X? Markedsoptaget er ikke markeret fortroligt de øvrige steder i teksten, hvor det er nævnt.
- Der er flere resultater i tabel 43 og 49, som ikke er markeret fortrolig øvrige steder i ansøgningen, hvor det er nævnt.
- Er det en fejl, at I ikke har markeret figur 24 og 25 som fortrolig?

We ask you to keep the phone numbers and e-mail addresses confidential, if possible.

Patient numbers in table 2 as well as market uptake, budget calculations and dose intensity are information regarding how AbbVie looks at the size of the market, and this information is sensitive. These must be classified as they contain information about AbbVie's own estimated use and sales value. This is company-sensitive information for the company's financial forecasts and AbbVie may suffer damage if it comes to the attention of the public and competitors.

Market uptake has now been marked as sensitive information throughout the document.

We have revised what results that should be regarded as sensitive information, in the tables and thoughout the document.

Figures 24 (Scatterplot) and 25 (CEAC) should be classified.

AbbVie replies to questions submitted in the e-mail of March 30, 2022

1. Sammenligning af venetoclax og azacitidin med lavdosis cytarabin

Fagudvalget har gjort opmærksom på, at patienter med blasttal >30% i dansk klinisk praksis behandles med lavdosis cytarabin og ikke azacitidin monoterapi. Vi beder jer derfor redegøre for, hvorfor de indsendte analyser er baseret på den samlede population fra VIALE-A, uanset blasttal, samt anvendeligheden af resultaterne af azacitidin som komparator for hele gruppen.

Redegørelsen bør både være en tekst der beskriver problemstillingen samt argumenterer for at de indsendte analyser er anvendelige og i form af subgruppeanalyser, som det er beskrevet i NICEs vurdering af venetoclax og azacitidin (venetoclax + azacitidin vs. azacitidin til ptt med <30% blaster; venetoclax + azacitidin vs. lavdosis cytarabin til ptt med >30 % blaster (VIALE-C)).

Summary of reply to question one

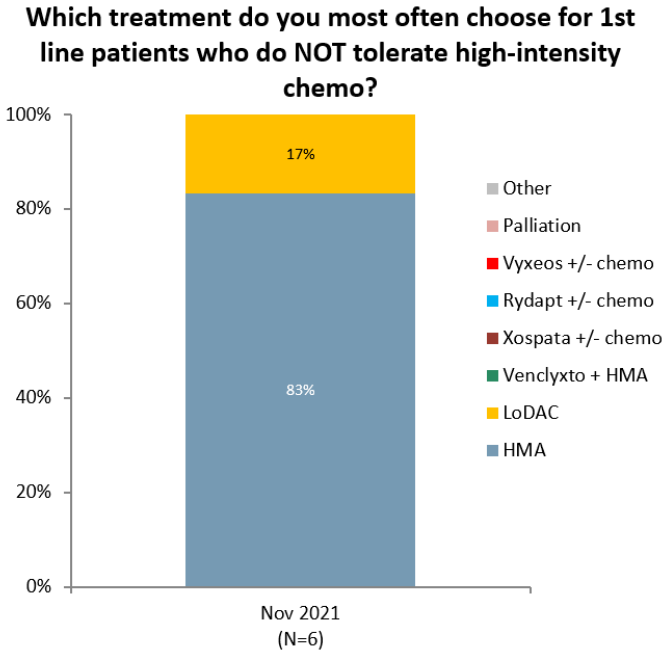
- Both azacitadine and LDAC seem to be used for patients with >30% blasts in Denmark. That azacitadine is used for this subgroup in Denmark makes it a relevant comparator in this subgroup. In addition, the input AbbVie has received from the Danish market demonstrate that azacitadine is what is mainly used.
- According to the Danish guidelines, azacitidine can be used for patients with more than 30% blasts, and LDAC is not recommended for patients with high-risk cytogenetics. Hence, the Danish guidelines is not advocating the use of LDAC for all patients with >30% blasts.
- According to a phase III trial, azacitidin has at least as good efficacy as LDAC in the subgroup, probably better.
- Looking at the costs connected to treatment of azacitadine and LDAC, the cost of treating with azacitidine is lower than treating with LDAC, especially if one can assume a well-functioning generic competition in Denmark.
- That azacitidine is at least as good and probably better than LDAC in terms of efficacy but also costs makes the current use of LDAC in this subgroup seem out of date.
- There are fewer subcutaneous administrations with azacitadine than with LDAC, making its administration procedures less cumbersome for the patient
- Due to the reasons presented, azacitidine is a better option than LDAC for the patient, the health care services and the tax payers.
- Since azacitadine due to reasons presented is the relevant comparator for both subgroups, and the indication for both azacitadine and Venclyxto combined with azacitadine allows for the treatment of these patients regardless of the percentage of blasts, there is no valid reason to analyse cost-effectiveness for subgroups. To split the analysis into several subgroups with different comparators would significantly increase the complexity of the submission and increase the time to when a decision can be made with many months, without adding any value. We believe there are plenty of reasons that make it possible for Medicinrådet to make a decision for the whole patient population comparing with azacitidine without going into cost-effectiveness analysis for subgroups. Generally speaking, a more detailed analysis does not necessarily mean a better analysis, and in this case it does not.

As per the request from fagudvalget, AbbVie has also included subgroup analyses, including those of Ven+aza vs aza and LDAC that were submitted to NICE, although it follows from the above that AbbVie considers them superfluous. These analyses show that ven+aza is superior to azacitidine and LDAC regardless of subgroup.

Azacitadine is used in first line in Denmark for patients with >30% blasts

In AbbVie's experience, after talking to a number of Danish haematologists, azacitadine as a monotherapy is used in patients with blasts >30%.

In a market research study performed for AbbVie, only one of six Danish haematologists were chosing LDAC more often than HMA for patients ineligible for high-intensity chemo. Had LDAC been the treatment used for all patients in the subgroup, it would have come out as the preferred treatment for the full population, as patients with more than 30% blasts constitutes about 70% of the of the full ineligible population (based on that in Viale-A this subgroup constituted 70% of the full population, and that the study baseline population has been confirmed to us, by Danish haematologists, to correspond well to the Danish ineligible population).



According to the Danish guidelines, azacitidine can be used for patients with more than 30% blasts, and LDAC is not recommended for patients with high-risk cytogenetics. Hence, the Danish guidelines is not advocating the use LDAC for all patients with >30% blasts.

Azacitidine is EMA approved and recommended by international guidelines (ESMO, ELN, and NCCN) as a first line treatment for all AML patients ineligible for intensive chemotherapy, including patients with >30% bone marrow blasts. The input from the market reasearch indicates that Danish haematologists treat in accordance to international guidelines.

Heuser, M., Ofran, Y., Boissel, N., Brunet Mauri, S., Craddock, C., Janssen, J., Wierzbowska, A. and Buske, C., 2020. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, 31(6), pp.697-712. (page 705, column 1, paragraph 2)

Döhner, H., Estey, E., Grimwade, D., Amadori, S., Appelbaum, F., Büchner, T., Dombret, H., Ebert, B., Fenaux, P., Larson, R., Levine, R., Lo-Coco, F., Naoe, T., Niederwieser, D., Ossenkoppele, G., Sanz, M., Sierra, J., Tallman, M., Tien, H., Wei, A., Löwenberg, B. and Bloomfield, C., 2017. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood, 129(4), pp.424-447. (page 434, table 8; page 436, column 1, paragraph 5)

Nccn.org. 2020. Acute Myeloid Leukemia Version 1.2021 – October 14, 2020. [online] Available at: <https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf> [Accessed 16 September 2020]. (page 34, AML-6)

Better outcomes with azacitidine than LDAC for patients with >30% blasts in a phase III trial

The international phase 3 AZA-AML-001 study was a randomized clinical study to evaluate the efficacy and safety of azacitidine compared with CCR (doctor's choice of BSC only, LDAC, or standard IC) in patients age 65 years or older with newly diagnosed AML and >30% BM blasts. (Dombret et al., article is attached)

> "Before randomization, CCR (standard induction chemotherapy, low-dose ara-c, or supportive care only) was preselected for each patient. Patients then were assigned 1:1 to azacitidine (n = 241) or CCR (n = 247). Patients assigned to CCR received their preselected treatment. Median overall survival (OS) was increased with azacitidine vs CCR: 10.4 months (95% confidence interval [CI], 8.0-12.7 months) vs 6.5 months (95% CI, 5.0-8.6 months), respectively (hazard ratio [HR] was 0.85; 95% CI, 0.69-1.03; stratified log-rank P = .1009). One-year survival rates with azacitidine and CCR were 46.5% and 34.2%, respectively (difference, 12.3%; 95%CI, 3.5%-21.0%). A prespecified analysis censoring patients who received AML treatment after discontinuing study drug showed median OS with azacitidine vs CCR was 12.1 months (95% CI, 9.2-14.2 months) vs 6.9 months (95% CI, 5.1-9.6 months; HR, 0.76; 95% CI, 0.60-0.96; stratified log-rank P = .0190). Univariate analysis showed favorable trends for azacitidine compared with CCR across all subgroups defined by baseline demographic and disease features."

There were also exploratory analyses performed, comparing azacitidine with individual CCRs within treatment preselection groups (IC, LDAC, or BSC). They were however not powered to detect statistical differences between treatments. Despite this, the difference in OS between aza and LDAC for those patients preselected for LDAC (4.8 months) had a 95% confidence interval higher than zero (1.7-7.9 months). The one year survival was also higher for aza, 48.5% compared to 34% for LDAC, a difference of 14.5 percentage points and with a 95% confidence interval of 3.5-25.5 percentage points (redacted version of table 3 from the article below).

Table 3. Kaplan-Meier estimated median OS and 1-y survival comparisons within preselected treatment subgroups

		OS										
		Median		Difference					1-y survival			
	No. of patients	Months	95% CI	Months	95% CI	HR	95% CI	*P*	%	95% CI	Difference	95% CI
Preselected for LDAC	312											
Azacitidine	154	11.2	8.8-13.4	4.8	1.7-7.9	0.90	0.70-1.16	.4270	48.5	40.3-56.2	14.5	3.5-25.5
LDAC	158	6.4	4.8-9.1						34.0	26.6-41.6		

Cost comparison of Azacitidine vs. LDAC

AbbVie has prepared a back-of-the-envelope cost analysis of the cost per treatment cycle of LDAC vs. azacitidine, that is of a very conservative nature as the cost of azacitidine used is not reflecting the

true cost of the drug under effective generic competition (using list AIP without the unknown discount) and thereby an overestimation.

Assumptions:

- Drug cost of LDAC is zero (underestimation)
- Drug cost of azacitidine is AIP of 2140 DKK per vial (overestimation as it is fails to capture current and future price competition for the drug)
- Two scenarios for LDAC: 7 or 10 days of administrations per treatment cycle. According to an AbbVie market research report from 2020, based on interviews with five Danish haematologists, the 10-day routine is considered the most common.
- The guidelines recommend using an additional 7 days of LDAC in the first cycle if needed to control the number of leukocytes. This cost was not included in the analysis (underestimation).
- As in our submission, for 1/3 of patients, 3/5 administrations of azacitidine can be carried out by the patients themselves, corresponding to 20% of administrations in total. The corresponding factor for LDAC is unknown to us, but we have used the same assumption for LDAC.

	LDAC		**Azacitidine**
Dosis	20 mg		100 mg/m^2
Administration	Subcutaneous		Subcutaneous
Cost per admin	3203		3203
Cost per vial	0		2140
Vials used per admin			2
Cost of drug per administration	0		4280
Number of days of administrations	7	10	5
Admins per day	2	2	1
Number of admins per cycle	14	20	5
Admins that can be done by the patient (not incurring cost)	*20%*	*20%*	20%
Admin cost	35873,6	51248	12812
Drug cost	0	0	21400
Total cost	**35873,6**	**51248**	**34212**

In this comparison, azacitidine has lower total cost per treatment cycle than both scenarios of LDAC. If patient cost were to be included, this would be beneficial to azacitidine, as there are fewer administrations and therefore less time spent on them.

As there are generics of azacitidine available, the competition should lead to lower prices. We do not know what the current discounted price for azacitadine is, and could therefore not include it in the analysis, and the calculation is therefore overestimating the cost for azacitidin. We know that the price in Sweden is between 333-466 SEK, corresponding to 264-336 DKK (1 SEK ≈ 0.72 DKK) for a vial for most Swedish regions, so if the price is not as low in Denmark yet, there should be room for improvement, especially if quantities used are growing.

Based on this simplified and conservative analysis, the cost per treatment cycle is in favour of azacitadine, especially for the time ahead. As azacitadine seem to provide similar or better outcome than LDAC for the subgroup, it is a more appropriate treatment option for these patients than LDAC.

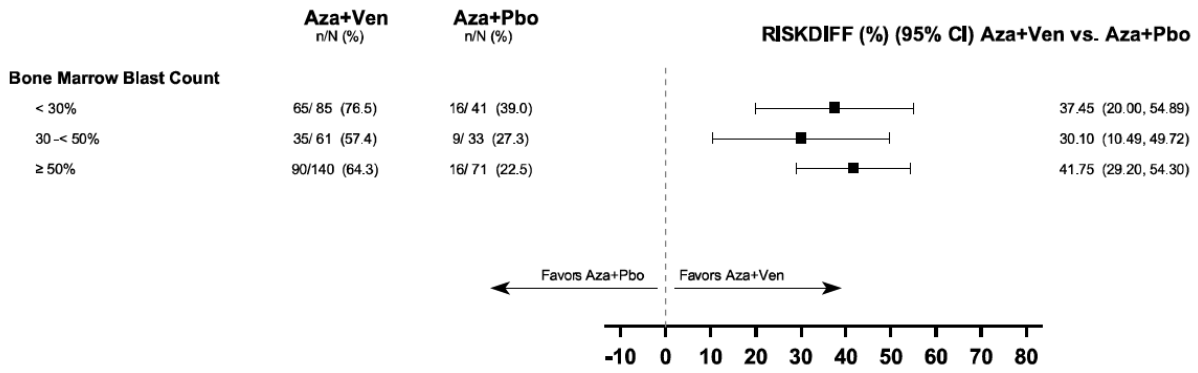
Subgroup analyses

As per the request from fagudvalget, AbbVie has also included subgroup analyses, including those of Ven+aza vs aza and LDAC that were submitted to NICE (attached as a separate document), although it follows from the above that AbbVie considers them superfluous. These analyses show that ven+aza is superior to azacitidine and LDAC regardless of subgroup.

Viale-A:

	VIALE-A median OS outcomes			
	All patients[1]	20-30% blasts[2]	>30–50% blasts[3]	>50% blasts[4]
VEN+AZA	14.7 months HR=0.66 *(p<0.001)*			
PBO+AZA	9.6 months			

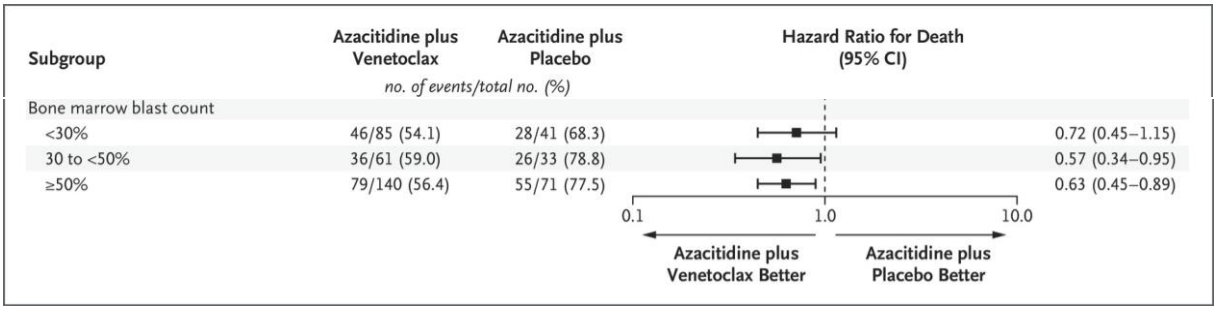
1. DiNardo, C., Jonas, B., Pullarkat, V., Thirman, M., Garcia, J., Wei, A., Konopleva, M., Döhner, H., Letai, A., Fenaux, P., Koller, E., Havelange, V., Leber, B., Esteve, J., Wang, J., Pejsa, V., Hájek, R., Porkka, K., Illés, Á., Lavie, D., Lemoli, R., Yamamoto, K., Yoon, S., Jang, J., Yeh, S., Turgut, M., Hong, W., Zhou, Y., Potluri, J. and Pratz, K., 2020. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *New England Journal of Medicine*, 383(7), pp.617-629. (page 617, under Results)
2. AbbVie Data on File: m15656-ossub2.sas-R&D-18-1190 (page 1, Figure 14.2__5)
3. AbbVie Data on File: m15656-ossub2.sas-R&D-18-1190 (page 2, Figure 14.2__6)
4. AbbVie Data on File: m15656-ossub2.sas-R&D-18-1190 (page 3, Figure 14.2__7)



Excerpt from Figure S1. Subgroup Analysis of Composite Complete Remission (CR+CRi)

Data included are subject to a cutoff date of 04 January 2020.

From: Supplement to DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med 2020;383:617-29. DOI: 10.1056/NEJMoa2012971



Excerpt from Figure 3. Subgroup Analysis of Overall Survival.

The hazard ratio for death was estimated with the unstratified Cox proportional-hazards model. Data included are subject to a cutoff date of January 4, 2020. The dashed vertical line represents a hazard ratio of 1.0. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability. TP53 and NPM1 data are from the central laboratory and were determined with the use of the MyAML assay. IDH1 or IDH2 and FLT3 data were determined with the use of the CDx assay.

From: DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med 2020;383:617-29. DOI: 10.1056/NEJMoa2012971

2. Livskvalitet

Fagudvalget ønsker livskvalitet opgjort som gennemsnitlige ændringer fra baseline på de tilgængelige skalaer i stedet for som "tid til forværring", som det er angivet i ansøgningen nu.

Please see the attachement where we present the quality of life for EQ-5D-5L index using Danish value set per the timepoints available. The responses were collected the first day of treatment in every other treatment cycle. The actual cycle info does not correspond to strict 28-day cycles. Treatment cycles could be delayed allowing for the patient to recover blood values before starting the next treatment cycle. This means that the timepoint in terms of days from baseline when the EQ-5D-5L was administered could be different between patients, and furthermore, this means that there is a difference between the arms here, as treatment more oftenly was postponed in the ven+aza arm. There was also a window allowed of +/- 10 days around the first day on the treatment cycles for the EQ-5D-5L to be analysed for that cycle. This is why we belive that the time to deterioration analyses are valuable as they can correct for the different timing.

3. Bivirkninger

Fagudvalget efterspørger mere information om den samlede byrde af bivirkninger, som belyser følgende:

- Aftager bivirkninger over tid?
- Information om indlæggelsesdage?
- Hvor mange bivirkninger er der samlet set og samlet set per patient?
- Hvor mange gange får hver enkelt patient de forskellige bivirkninger, fx febril neutropeni (fx per år)?
- Hvor mange patienter blev henholdsvis pauseret og seponeret i studiet pga. bivirkninger og hvilke bivirkninger var årsag til dette?

Please find the reply to each of the questions below.

- Aftager bivirkninger over tid?

The occurrence of TLS was only identified in three subjects during the ramp-up period (day 1-3) and not thereafter. Only one of these patients had symptoms of TLS. The other two were found by lab values. All were transient biochemical changes that resolved with uricosuric agents and calcium supplements without treatment interruption (Data cutoff date: January 4, 2020. DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29)

Specific information related to side effects decreasing over time is not available from Viale-A. In a study by Davids et al. for venetoclax monotherapy for R/R patients in CLL the prevalence of cytopenias decreased over time.

Davids et al.: https://aacrjournals.org/clincancerres/article/24/18/4371/80977/Comprehensive-Safety-Analysis-of-Venetoclax

- Information om indlæggelsesdage?
  This analysis was not performed for Viale-A.

  In an american study, during ramp-up of Ven, <10% of pts required hospitalization for any reason.

  https://ashpublications.org/blood/article/138/Supplement%201/1265/481178/Treatment-Initiation-of-Venetoclax-in-Combination

- Hvor mange bivirkninger er der samlet set og samlet set per patient?
  Unfortunately, we do not have that analysis for Viale-A.

  All patients in the VIALE-A trial had at least one adverse event.

- Hvor mange gange får hver enkelt patient de forskellige bivirkninger, fx febril neutropeni (fx per år)?
  87% of VEN+AZA treated patients with best response of CR/CRh had a post remission Grade 4 cytopenia lasting ≥7 days. 13% 0 events, 19% 1 event, 68% ≥2 events

  45% of PBO+AZA treated patients with best response of CR/CRh had a post remission Grade 4 cytopenia lasting ≥7 days. 55% 0 events, 24% 1 event, 21% ≥2 events

  Pratz K, et al. Cytopenia Management in Patients With Newly Diagnosed Acute Myeloid Leukemia Treated With Venetoclax Plus Azacitidine in the VIALE-A Study. Poster #1944. 62nd ASH Annual Meeting; Dec 5-8, 2020; Virtual

- Hvor mange patienter blev henholdsvis pauseret og seponeret i studiet pga. bivirkninger og hvilke bivirkninger var årsag til dette?

The interruption of VEN + AZA or PBO + AZA between cycles due to AEs (AZA+VEN / AZA+PBO) occurred in 72% / 57%.

The percentages of patients who discontinued due to AEs were similar between the VEN + AZA vs PBO + AZA arms (24% vs 20%). The most common AEs leading to dose interruption or reduction were neutropenia (19%), Febrile Neutropenia (20%) and thrombocytopenia (10%).

(Data cutoff date: January 4, 2020. 1. DiNardo CD, et al. N Engl J Med. 2020;383(7):617-29 [suppl]. 2. DiNardo CD, et al. Oral LB2601. 25th EHA Congress. June 11-21, 2020.)

4. Opgørelse af utility-værdier

Hvor mange besvarelser på EQ-5D-5 er utility-værdierne for de forskellige stadier baseret på?

The EQ-5D-5L utilities are based on the following number of observations.

EFS without CR/CRi	377
EFS with CR/CRi	674
PD/RL	122

AbbVie replies to questions submitted in the e-mails of April 26 and 27, 2022

Mht. punkt 2 om livskvalitet, vil vi gerne bede om også at få livskvalitet opgjort som gennemsnitlige ændringer fra baseline på de andre skalaer, I har anvendt i første version af ansøgningen, og også meget gerne illustreret grafisk (som kurver), hvis det er muligt?

We would like to further describe the issues with the analyses requested. We did not previously describe the issues of not capturing the impact of progression and the bias developing over time. The issues are the same for the table for EQ-5D-5L data your received in response to the previous set of questions.

Survival bias over time and impact of progression not captured
The data analysis requested would only use data for baseline and visits referring to specific treatment cycles, as well as only looking at patients on treatment. Final visits (post progression) are not included as they are not attributed to a specific cycle. The tables requested cannot capture the effect of progression on quality of life (and obviously not death either). As only patients on treatment are included, patients in the placebo + azacitidine arm disappears from the data in a quicker way than in the active arm. This has the consequence of a selection bias (survival bias) forming and increasing over time, where patients corresponding to those that are included in the ven + aza arm are not present in the placebo + aza arm. We believe these patients to a higher degree are patients with higher risk and in poorer starting condition.

Uneven length of treatment cycles between patients and systematic difference between the arms
As described in reply to a previous question, the treatment cycles are not corresponding to strict 28-day cycles as in the model. Treatment cycles could be postponed allowing for the patient to regain blood values before starting the next treatment cycle. This means that the timepoint in terms of days from baseline that the EQ-5D-5L was administered differed between patients, and that we can assume that there was a difference between the arms on number of days from baseline that the EQ-5D-5L was filled in, where the ven + aza arm day 1 for a cycle on average would take place at a later point in time. Also, EQ-5D-5L was not always administered on day 1 per treatment cycle. There was a window allowed of +/- 10 days before the first day on the treatment cycle for the EQ-5D-5L to be answered.

Not answering to the reason behind your request
In fact, we are unsure whether the data requested is corresponding to the reason you had this request. We believe that the Kaplan-Meier plots of PRO time to deterioration are more informative as it can take timing of the scoring into account in a better way, as well as including final visit. There are also other results in the article "Venetoclax combinations delay the time to deterioration of HRQoL in unfit patients with acute myeloid leukemia", that could be of interest.

Vi er blevet opmærksomme på, at jeres ansøgning ikke indeholder en analyse mod placebo, som det står beskrevet i metodehåndbogen, når komparator ikke tidligere er vurderet af Medicinrådet. Se afsnit 2.4.2 i Medicinrådets metodehåndbog for vurdering af nye lægemidler: Medicinrådets metodevejledning for vurdering af nye lægemidler version 1.2 (medicinraadet.dk)
Redegør derfor venligst for, hvorfor en analyse mod placebo ikke er relevant i denne sag.

Azacitadine, although not previously evaluated by Medicinrådet, is a well-established AML treatment with documented efficacy for patients with AML that are not eligible for high-dose chemotherapy. It is a recommended treatment for these patients in both international and Danish guidelines. In

Denmark, it is also subject to generic competition which has pushed down the cost of treating with azacitidine. For these reasons, and referring to the the DMC methods guide, a comparison versus best supportive care or placebo is not relevant for the Danish setting.

AbbVie replies to question submitted in the e-mails of June 8, 2022

Vi mangler en mere præcis definition af 'eventfri overlevelse' (event-free survival (EFS)). Det står pt som følgende:

Event-free survival (EFS) er defineret som tid fra behandlingsstart til første dokumenterede progression (målt ved antal blaster i knoglemarv), relaps efter CR/CRi eller treatment failure (ingen opnåelse af CR eller < 5 % knoglemarvsblaster efter mindst 6 serier af behandling) eller død af alle årsager.

Vi mangler en nærmere definition af "disease progression" - det er målt ved antal blaster, men hvad er antallet eller ændringen i blasttal, som skal til?
Og hvad er forskellen mellem "treatment failure" og "disease progression"?

Reply:

Event-free survival (EFS) was defined as the number of days from randomization to the date of progressive disease, relapse from CR or CRi, treatment failure (failure to achieve complete remission or <5% bone marrow blasts after at least six cycles of treatment) or death from any cause.

Progressive disease was defined per European LeukemiaNet (ELN) recommendations:

- 50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with < 30% blasts at baseline; or persistent marrow blast percentage of > 70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (> 0.5 × 109/L [500/µL], and/or platelet count to > 50 × 109/L [50 000/µL] non-transfused); or
- 50% increase in peripheral blasts (WBC × % blasts) to > 25 × 109/L (> 25 000/µL); or
- New extramedullary disease

AbbVie's comment to the DMC draft appraisal report

Secondary endpoint of transfusion independence
This endpoint of Viale-A is not at all mentioned in the draft report, although the high need for transfusions for AML patients was underlined. The endpoint is an important one, for the patients, but also for the understanding of how venetoclax works and how it can create more time for the patient outside the hospital. AbbVie insists that this endpoint is included in the final report.

Transfusion independence was defined as the absence of a red-cell or platelet transfusion for at least 56 days between the first and last day of treatment. Rates of post-baseline transfusion independence were significantly improved with venetoclax plus azacitidine compared with azacitidine plus placebo. The red blood cells independence rate improved by about 25 percentage points (59.8% vs 35.2%; p<0.001) and platelet transfusion independence improved with about 19 percentage points (68.5% vs 49,7%; p<0.001).

The need and relevance for cure modelling as a tool to estimate long-term survival in AML
Cure modelling is a technical tool to estimate long-term survival. It is not necessary to assume a cure to use cure modelling, as it can also be used as a method to achieve the modelling of survival patterns seen in a population. As presented in our submission, we are not including the assumption of a cure for venetoclax in combination with azacitadine. We are simply using the tool to estimate survival in a treated AML population, still assuming a higher death rate in the modelled population than in the general population after the time point the function is applied. DMC has itself used cure modelling in the appraisal of gilteritinib for AML. DMC assumed patients to be long-term survivors after two years in EFS but with the lower standardised mortality rate of 1.3 compared to 2 in our base-case for venetoclax + azacitidine. It is not explained in the draft report why DMC model AML differently in the case of venetoclax + azacitadine case compared to the gilteritinib case. DMC has referred to venetoclax + azacitidine not being a time-restricted chemotherapy, but the reason to that venetoclax + azacitidine is not time-restricted in the same way is because of much less toxicity and being better tolerated.

Other HTA agencies have recognised the usefulness and relevance of cure modelling as a way to estimate long-term survival in their appraisal of venetoclax + azacitadine for AML. TLV accepted the use of cure modelling and applied it at the time point of three years (as they did in their gilteritinib evaluation), and NICE explored the possibility of a proportion of patients being cured at three years. It was concluded in NICE final appraisal that "*The evidence for including a cure state in the model is uncertain, but it is plausible that some people may be cured*".

Use of anti-fungal azoles and corresponding dose intensity
DMC has in its draft report assumed a dose intensity of 60% for venetoclax based on an average use of four months of posaconazole. The discussions we have had with clinicians indicates that the use of concomitant pozaconazole in Denmark would be higher than this, as two out of three of the clinicians were expecting to use posaconazole throughout the whole treatment with venetoclax, as reflected in our base-case. The future generic pricing of posaconazole will likely also increase the probability of prescriptions (to more than 2/3 using pozoconazole through the whole treatment), which would lower the dose of venetoclax even more.

Scenario analysis with reduced health state utilities for ven+aza should be rejected and replaced
EQ-5D-5L data (and other quality of life data) was collected at baseline and, starting from treatment cycle 3 every other treatment cycle, in the time window of the first ten days of those cycles.

Since non-treatment specific utilities were estimated (i.e., pooled data from venetoclax + azacitidine and azacitidine arms), the impact of AEs on utility estimates were adjusted in the regression model. The grade 3 or 4 AEs that occurred in ≥ 5% in the Viale-A trial were included as covariates and coded as dummy variables to indicate the presence of specific AEs (1= presence, 0= not presence). Presence here means that the adverse event (of grade 3 or 4) was experienced at the time of the utility measurement. As can be seen in the table below, there are adequate numbers of observations to be able to observe the effect of the most common grade 3 or 4 adverse events.

Table 1: Observations of EQ-5D-5L with presence of a specific adverse events in Viale-A

AEs*	Number of observations with presence of AE
Neutropenia*	347
Thrombocytopenia	285
Anaemia	155
Leukopenia	135
Hypokalemia, hyponatraemia and hypophosphataemia	44
Pneumonia	18
Hypertension	18

* Grade 3/4 AEs that occurred in ≥ 5% patients were selected based on the incidence rates observed in Viale-A. Neutropenia included neutropenia and febrile neutropenia.

However, none of the disutilities for adverse event were statistically significant. Some of the adverse events are even associated with a numerically positive impact on utility. Looking at neutropenia, this was present to a higher degree at baseline for the ven + aza arm (72% vs. 62%), and was more frequently reported as an adverse event in Viale-A (42% vs 29%) keeping in mind that time on therapy was longer in the ven+ aza arm. Hence, neutropenia was common and expected in the experimental arm with the best clinical response to treatment. Looking at a regression analysis of utilities by treatment arms there is a tendency towards higher utility with ven + aza, maybe due to even deeper response, than the current three-state mixed-effects model could take into account.

It is plausible that the positive utility estimate of neutropenia when specifying non-treatment specific utilities, could be a result of it being associated with a better treatment outcome in Viale-A, not completely captured by the three health states.

Claiming that Viale-A utilities does not capture the impact of adverse events and then adjusting for this (with an arbitrary number) in only one of the treatment arms is not reasonable. The placebo + azacitidine arm also had a considerable rate of neutropenia and a higher rate of sepsis than the venetoclax arm.

[1] Analysis not available with the Danish value set. EQ-5D utility scores were estimated from data of the Viale-A trial (data cut 2020-01-04) based on individual dimension scores and using UK preference-weights. The EQ-5D 5L score in the trial data was transferred to EQ-5D 3L score using the UK cross-walk value set based on Van Hout et al. (2012). EQ-5D utility values for health states were estimated using a linear mixed-effects model to account for correlation within patients' repeated assessments.

Medicinrådet

Notat

Opklarende spørgsmål til fagudvalget for akut leukæmi vedr. anbefalingen af venetoclax i kombination med azacitidin

4. september 2022

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Rådet har efterspurgt yderlige oplysninger fra fagudvalget for akut leukæmi vedr. vurderingen af venetoclax til AML. Spørgsmålene kan ses herunder:

1. Kan anbefalingen indskrænkes ud fra patienternes performance status, alder og/eller cytogenetisk profil?
2. Hvilke kriterier for monitorering og seponering af behandlingen er gældende ved manglende effekt (efter ca. 2-3 måneders behandling)?

Spørgsmål 1 omhandler behandlingens forholdsvis tunge bivirkningsprofil sat over for den mulige begrænsede effekt, man ser, hos bestemte undergrupper af patienter i studiet (der alle hører under patientgruppen, som ikke tåler højdosis kemoterapi).

Spørgsmål 2 drejer sig om fagudvalgets vurdering af, at man allerede efter 2 kure vil have en indikation for, om behandlingen virker eller ej, og derudfra vil man kunne beslutte, om behandlingen skal fortsætte eller stoppes.

1. Kan anbefalingen indskrænkes ud fra alder, performance status og/eller cytogenetisk profil?

Svar: Fagudvalget har noteret sig, at Rådet er bekymret for bivirkningsbyrden ved kombinationsbehandlingen. Fagudvalget ønsker at pointere, at der inden valg af behandling sker en grundig gennemgang af fordele og ulemper sammen med den enkelte patient med udgangspunkt i patientens risikoprofil, livssituation m.m. Klinikerne laver i forvejen denne type vurdering, når de skal vurdere, om en patient er egnet til kurativ behandling med højdosis kemoterapi. Fagudvalget har kendskab til de beskrevne hæmatologiske bivirkninger ved venetoclax og håndterer dem rutinemæssigt i klinisk praksis. Selvom bivirkninger som f.eks. febril neutropeni er ubehagelige, er de sjældent livstruende og kan behandles ved indlæggelse. Patienter med AML er neutropene allerede forud for behandling, og tilføjelse af en virksom behandling som venetoclax forventes som beskrevet at give yderligere neutropeni og andre hæmatologiske bivirkninger. Som beskrevet i produktresuméet håndteres bivirkningerne ved venetoclax via pausering og dosisreduktion, og i tillæg til kombinationsbehandlingen gives forebyggende anti-mikrobiel behandling. Det er fagudvalgets forventning, at der vil være en stor andel af patienterne, som dosisreduceres og pauseres, ligesom det var tilfældet i det kliniske studie, dog uden at det medfører, at en større andel af patienterne stopper behandlingen med venetoclax. Fagudvalget vurderer også, at når patientens sygdom er kommet under kontrol, og dosis for venetoclax er tilpasset et tolerabelt niveau, vil niveauet af bivirkninger aftage.

Fagudvalget vurderer, at en mulig effekt af den størrelsesorden, som er observeret i det kliniske studie, vil betyde, at de fleste patienter vil være villige til at acceptere en periode med betydelige bivirkninger, hvis behandlingen kan give en efterfølgende periode med længerevarende remission, hvor patienten har det godt.

Vedr. alder:

I VIALE-A-studiet var patienterne opdelt ud fra alder baseret på inklusionskriterierne. For at deltage i studiet skulle patienterne enten være over 75 år eller under 75 år med samtidig komorbiditet: *"at least one of the following coexisting conditions precluding intensive chemotherapy: a history of congestive heart failure for which treatment was warranted or an ejection fraction of 50% or less or chronic stable angina, a diffusing capacity of the lung for carbon monoxide of 65% or less or a forced expiratory volume in 1 second of 65% or less, and an Eastern Cooperative Oncology Group performance-status score of 2 or 3"*.
En subgruppeanalyse i VIALE-A indikerer, at patienter under 75 år har mindre gavn af behandlingen end den ældre patientgruppe. Fagudvalget vurderer, at det er vanskeligt at fortolke subgruppedata, da det lavere antal patienter medfører usikkerhed om effektstørrelsen, hvilket illustreres af de bredere konfidensintervaller. Fagudvalget mener ikke, at alder alene er et klinisk relevant parameter at træffe behandlingsvalg ud fra. Fagudvalget vurderer, at den reducerede effekt hos patienter under 75 år ikke er relateret til lavere alder, men vurderer, at data indikerer, at patienter med betydende komorbiditeter kan have mindre effekt af lægemidlet.
På baggrund af data for effekten af behandlingen for subgruppen med komorbiditet (< 75 år) sammenholdt med den tunge bivirkningsbyrde vurderer fagudvalget, at man som udgangspunkt ikke bør opstarte behandling med venetoclax i patienter med betydelig komorbiditet. Fagudvalget mener ikke, at der bør være specifikke aldersafgrænsninger.

Vedr. performance status:

I en subgruppeanalyse opdelt efter patienternes ECOG performance status (< 2 vs. >= 2) blev der ikke observeret en forskel i effekten af venetoclax. Fagudvalget vurderer, at jo dårligere performance status patienten har, jo mindre sandsynligt vil det være, at den forventede positive effekt opvejer den tunge bivirkningsbyrde. Patienter over 75 år kunne have en ECOG performance status på 0-2, mens patienter under 75 år kunne have en ECOG performance status mellem 2 og 3. I studiet indgik få (~5 %) patienter med en performance status på 3. Fagudvalget vurderer, at anvendelsen af venetoclax som udgangspunkt bør være for patienter med en ECOG performance status mellem 0 og 2.

Vedr. cytogenetik:

I VIALE-A indgik patienter med henholdsvis intermediær og dårlig cytogenetisk risikoprofil. Subgruppeanalyser opdelt efter cytogenetisk risikoprofil viste ikke en tydelig forskel, idet konfidensintervallerne for effektestimaterne for de to grupper overlappede med punktestimatet for den modsatte gruppe. Punkestimatet for patientgruppen med dårlig cytogenetik var dog lavere end for patientgruppen med intermediær cytogenetik. Fagudvalget vurderer, at cytogenetisk risiko i klinisk praksis ikke er afgørende for, om patienten bør tilbydes behandling med venetoclax. Cytogenetisk risiko vurderes på linje med andre genmutationer, og fagudvalget vurderer ikke, at man som udgangspunkt bør forbeholde behandlingen til bestemte cytogenetiske risikogrupper. Fagudvalget mener også, at en del patienter med favorabel cytogenetisk risiko (indgår ikke i studiet), kan have gavn af venetoclax, hvis de har andre genmutationer, som giver en risiko svarende til den cytogenetiske komponent. Fagudvalget pointerer, at vurderingen af den optimale behandling for hver enkelt patient med AML er kompleks og bør foretages af den behandlende hæmatolog, og at der derfor ikke bør tilføjes nogen specifikke kriterier vedr. cytogenetik for venetoclax.

2. Hvilke kriterier for monitorering og seponering er gældende ved manglende effekt (efter ca. 2-3 måneders behandling)?

Svar: Effekten af venetoclax forventes at indsætte hurtige end ved nuværende standardbehandling med azacitidin monoterapi. Fagudvalget vurderer, at klinisk praksis bør være, at effekten af behandling med venetoclax skal monitoreres efter 2 behandlingscyklusser ved knoglemarvsprøve. Hvis patienten ikke har opnået CR eller CRi, bør behandlingen som udgangspunkt seponeres.

Forslag til tilføjelse til anbefalingstekst:
Behandling med venetoclax er bivirkningstung, og opstart af behandling bør overvejes nøje, hvis patienten har betydelig organpåvirkning såsom hjertesvigt, betydelig nedsat lungefunktion (< 65 %) og/eller ECOG performance status over 2.
Hvis patienten ikke har opnået komplet remission (CR) eller komplet remission med ufuldstændig normalisering af blodtal (CRi) efter 2 behandlingscyklusser, bør behandling med venetoclax seponeres.