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CADTH Reimbursement Review

Venetoclax (Venclexta)

Sponsor: AbbVie Corporation

Therapeutic area: Acute myeloid leukemia

Clinical Review
Pharmacoeconomic Review

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AML	acute myeloid leukemia
ANC	absolute neutrophil count
ATB-MPG	Alberta Tumour Board Myeloid Physicians Group
AZA	azacitidine
BSC	best supportive care
CBC	complete blood count
CI	confidence interval
CLL	chronic lymphocytic leukemia
CLSG	Canadian Leukemia Study Group
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete remission
CRh	complete remission with incomplete hematological recovery
CRi	complete remission with incomplete bone marrow recovery
CrI	credible interval
DB	double-blind
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EFS	event-free survival
EORTC QLQ-30C	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ VAS	EuroQol Visual Analogue Scale
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels questionnaire
FLT3	FMS-like tyrosine kinase 3
GHS/QoL	global health status quality of life scale (EORTC QLQ-30C)
HMA	hypomethylating agent
HRQoL	health-related quality of life
IA1	first interim analysis
IA2	second interim analysis
IDMC	independent data monitoring committee
ITC	indirect treatment comparison
LDAC	low-dose cytarabine
LLSC	Lymphoma Society of Canada
MDS	myelodysplastic syndrome
MID	minimal important difference
MLFS	morphological leukemia-free state
MRD	minimal/measurable disease
NMA	network meta-analysis
OR	odds ratio
OS	overall survival
PROMIS 7a	Patient-Reported Outcomes Measurement System Short Form v1.0–Fatigue 7a
QoL	quality of life
RCT	randomized controlled trial

SAE	serious adverse event
SD	standard deviation
WDAE	withdrawal due to adverse event

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Introduction

Acute myeloid leukemia (AML) is a hematological malignancy defined by WHO as a myeloid neoplasm with greater than 20% blasts in the peripheral blood or bone marrow. Proliferating myeloid precursor cells leads to disruption of normal hematopoiesis and a clinical presentation of symptoms and complications of pancytopenia or leukostasis. Diagnosis is by complete blood count (CBC) and bone marrow biopsy, with identification of characteristic mutations and chromosomal rearrangements for targeted treatment and cytogenetic risk stratification. AML predominately occurs in older adults, with a median age of diagnosis of 67 years in Canada, and increasing incidence with age. Standard treatment for patients who are medically fit is intensive induction therapy with cytarabine and an anthracycline, but a substantial portion of patients with AML are ineligible for induction therapy due to frailty associated with age or comorbidities. Patients ineligible for treatment with induction therapy may be treated with hypomethylating agents (HMAs), such as azacitidine or low-dose cytarabine (LDAC), but rates of complete remission (CR) are low and duration of remission tends to be short. Prognosis for AML in older patients is poor, with 1 study reporting 5-year overall survival (OS) as 6.3% in patients aged 65 years.

Venetoclax is an orally administered highly selective inhibitor of the anti-apoptotic protein B-cell lymphoma 2 (BCL2). Health Canada granted a Notice of Compliance on December 4, 2020 for the following indication: Venclexta, in combination with azacitidine or LDAC, is indicated for the treatment of patients with newly diagnosed AML who are 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy. The recommended dose of venetoclax in combination with azacitidine is 400 mg/day for each day of a 28-day cycle following a 3-day ramp-up; azacitidine should be administered at 75 mg/m^2 for days 1 to 7 of the cycle. Dose adjustments are required in patients treated with strong and moderate inhibitors of CYP3A enzymes. Venetoclax has previously been reviewed by CADTH for its use in chronic lymphocytic leukemia (CLL) as monotherapy for patients with 17p deletion or without a 17p deletion who did not have other available treatment options in combination with obinutuzumab in previously untreated patients, and in combination with

Table 1: Submitted for Review

Item	Description
Drug product	Venetoclax (Venclexta), 10 mg, 50 mg, 100 mg, tablets, oral
Indication	Venclexta, in combination with azacitidine or low-dose cytarabine is indicated for the treatment of patients with newly diagnosed AML who are 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	December 4, 2020
Sponsor	AbbVie Corporation

AML = acute myeloid leukemia; NOC = Notice of Compliance.

rituximab for patients who had received at least 1 prior therapy. A concurrent CADTH review of venetoclax with LDAC is ongoing.

The objective of the systematic review was to review the beneficial and harmful effects of venetoclax in combination with azacitidine for the treatment of patients with newly diagnosed AML who are 75 years or older, or who have comorbidities that preclude use of intensive induction therapy.

Stakeholder Perspectives

The information in this section is a summary of input provided by Canadian patient and clinician groups who responded to CADTH's call for patient input and by clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

One patient advocacy group, the Leukemia and Lymphoma Society of Canada (LLSC), provided input on venetoclax in combination with azacitidine for the treatment of AML. The LLSC used an online survey for its submission, which was conducted between December 7, 2020 and January 24, 2021. Twenty-nine patients responded, all from Canada, 5 of whom had experience with venetoclax in combination with azacitidine.

Many patients did not provide information on specific symptoms but described being diagnosed with AML as a life-changing event that affected not only themselves but their caregivers. Some patients needed to relocate to access treatment. Side effects of treatment, transfusion dependence and hospital admissions had a large impact on patients' quality of life (QoL), as did isolation due to their vulnerability to infection. Patients reported the desired characteristics of treatment options as those that could maintain remission, were targeted with fewer side effects, covered by public plans, and accessible in their geographic region.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The experts indicted that currently available lower-intensity treatments have low rates of CR, and the CRs that are produced are not durable. They indicated that venetoclax plus azacitidine (or other HMAs) would change the current treatment paradigm, becoming the new standard of care for patients with treatment-naive AML who were ineligible for standard induction therapy, and providing an option for patients aged 75 years or older who were eligible for intensive chemotherapy, following discussion about risks and benefits.

The experts indicated that, at this time, there is insufficient information to make treatment decisions based on disease characteristics, and that while certain subgroups had been excluded from clinical trials, such as patients with central nervous system (CNS) involvement, these groups might reasonably be expected to benefit. The experts indicated that current evidence does not fully support the use of venetoclax plus azacitidine in fit patients eligible for standard induction treatment or in patients aged 75 years and older with good cytogenetic risk (core binding factor) AML who are fit for intensive induction chemotherapy, and their opinions differed in its suitability for patients with relapsed or refractory disease.

The experts indicated that response to treatment would be determined by achievement of CR with or without complete hematological recovery, as measured by CBC and bone marrow biopsy and/or transfusion independence or stable disease. OS and hospital visits, transfusion

needs, and QoL were the most important end points. Assessment of response could be carried out after the first or second cycle.

The experts indicated that discontinuation of treatment might be determined by disease progression or intolerable adverse events, but could not comment whether venetoclax could be continued after azacitidine discontinuation. One respondent indicated that a bone marrow biopsy should be performed after the first and second treatment cycles, as response would be expected after a maximum of 2 cycles. Another indicated that response should be assessed at minimum after 4 to 6 cycles, but that most practitioners assess after the first cycle, given cost and to guide dosing of venetoclax for subsequent cycles.

The experts indicated that treatment should be given in a hospital or outpatient setting by a physician with experience looking after acute leukemia patients. Pharmacist involvement would be needed for management of drug interactions (e.g., azoles). Hospitalization might be required for ramping up the dose of venetoclax, with prophylaxis for tumour lysis syndrome, and the need for admission to manage neutropenic fever and other complications during therapy should be anticipated.

Clinician Group Input

Four clinician groups provided input: the Canadian Leukemia Study Group (CLSG), the Ontario Health (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee (OH-CCO Hem-DAC), the Leukemia/Bone Marrow Transplant (L/BMT) Program of British Columbia, and the Alberta Tumour Board Myeloid Physicians Group (ATB-MPG).

There were no substantive differences in opinions between the clinical experts consulted by CADTH and the clinical groups. The groups noted that patients are aware of venetoclax and azacitidine, and some patients have been "self-funding" venetoclax by using CYP3A inhibitors to reduce the dose and, thus, the cost of venetoclax.

Drug Program Input

The drug programs indicated that current treatment options for patients with newly diagnosed AML who are ineligible for intensive chemotherapy include azacitidine, LDAC, and best supportive care (BSC). The reimbursement of venetoclax plus azacitidine would likely replace azacitidine in this treatment setting. Azacitidine is funded in most jurisdictions for patients with AML who are ineligible for intensive chemotherapy, and some jurisdictions fund alternate dosing schedules for azacitidine (i.e., 5 to 2-2 and 6 consecutive days) in addition to the schedule of 7 consecutive days. However, it was noted that some patients 75 years of age and older may be fit to tolerate intensive chemotherapy. The ramp-up dosing schedule for venetoclax with azacitidine differs significantly from the ramp-up dosing schedule already in use for chronic lymphocytic leukemia (CLL) indications and the current packaging for venetoclax is designed for the CLL ramp-up dosing schedule. Venetoclax plus azacitidine includes an oral and an IV and subcutaneous drug and therefore would be reimbursed through different programs in some jurisdictions. The drug programs identified the potential for indication creep for patients with a high risk of myelodysplastic syndrome (MDS), those who have progressed or have had an inadequate response on low-dose chemotherapy for AML, and patients who have relapsed after induction chemotherapy and are not eligible for stem cell transplant and who are then treated with azacitidine. It was noted that treatment combination increases the need for health care resources (i.e., hospital admission and additional pharmacy and nursing resources for the potential management of tumour lysis

syndrome and monitoring for drug interactions). Affordability was also identified as an issue since the combination is expected to replace azacitidine monotherapy.

Clinical experts were consulted by CADTH for questions related to implementing venetoclax plus azacitidine into current provincial drug plans. Overall, most implementation questions related to the dosing schedule and administration and the eligible patient population.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One double-blind, placebo-controlled phase III randomized controlled trial (VIALE-A) contributed evidence to this review. The trial objective was to evaluate the efficacy and safety of venetoclax plus azacitidine compared with placebo plus azacitidine in adults with newly diagnosed AML who were 18 years or older and ineligible for standard induction therapy due to age or comorbidities. The trial was restricted to patients who had not previously been treated with an HMA and who had intermediate or poor risk cytogenetics. The primary outcomes were OS and composite complete remission rate (i.e., CR plus complete remission with incomplete marrow recovery [CR + CRi]). Secondary outcomes were CR, CR plus complete remission with incomplete hematological recovery [CR + CRh], rate of CR + CRi by the initiation of cycle 2, transfusion-independence rate, minimal/measurable disease (MRD) response rate, response rates and OS in molecular subgroups, fatigue, global health status and quality of life (GHS/QoL), and event-free survival (EFS).

A total of 431 patients were randomized in a 2:1 ratio: 286 to venetoclax plus azacitidine and 144 to placebo plus azacitidine. The most common reasons given for patients to be considered ineligible for standard induction therapy were age and Eastern Cooperative Oncology Group Performance Status (ECOG PS). Patients were elderly, with poor performance and markers of severe disease. The mean age was 75.4 years, with 60.6% aged 75 years or older. Almost all patients were White or Asian, and the majority of patients were male (60.1%). Most (75.2%) had de novo rather than secondary AML. Nearly 2-thirds had intermediate risk cytogenetics, 1-third had poor risk, and 1-half had bone marrow blasts of 50% or greater at baseline.

Efficacy Results

Table 2 shows a summary of the key efficacy and safety outcomes. Venetoclax plus azacitidine improved most outcome measures that were identified as being of interest to clinicians and patients. Statistically significant treatment differences were seen for OS, EFS, measures of disease response (CR + CRi, CR + CRh, CR), and post-baseline transfusion independence. Improvements were also seen for OS and CR + CRi in the subgroup of patients with isocitrate dehydrogenase 1 (IDH1) or IDH2 mutation and for CR + CRi among patients with FMS-like tyrosine kinase 3 (FLT3) mutations. No statistically significant difference was detected in OS for patients with FLT3 mutations; however, the subgroup was small, making it difficult to detect a difference. While clinically meaningful differences in patient-reported outcomes of GHS/QoL and fatigue were observed at individual end points, differences between treatment groups could not be interpreted because the sequential testing strategy failed before this level.

Harms Results

Table 2 shows a summary of the key efficacy and safety outcomes. All patients in both groups experienced at least 1 adverse event, and almost all experienced at least 1 grade 3 or greater adverse event. Compared with patients who received placebo plus azacitidine, a greater proportion of patients who received venetoclax plus azacitidine experienced 1 or more serious adverse events (SAEs), 1 or more adverse events leading to discontinuation or dose interruption of venetoclax or placebo or azacitidine, or 1 or more adverse events leading to death. Common harms in all categories are generally predictable from the known mechanism of action for venetoclax and/or azacitidine and the underlying disease. Cytopenias were common, with neutropenia, febrile neutropenia, thrombocytopenia, and anemia represented across all categories, as were gastrointestinal adverse effects. Febrile neutropenia and infections contributed substantially to most common SAEs and were the most frequent adverse events leading to death.

The notable harms identified for the protocol were neutropenia, febrile neutropenia, infections, tumour lysis syndrome, hemorrhage, and secondary malignancies. Neutropenia, febrile neutropenia, infections and infestations, and secondary primary malignancies all occurred in a greater proportion of patients who received venetoclax plus azacitidine than in patients who received placebo plus azacitidine. Hemorrhage and tumour lysis syndrome occurred in similar proportions, and the proportion of patients with tumour lysis syndrome was low (≤ 2.5%). The most common secondary malignancies were basal cell carcinoma and squamous cell carcinoma of the skin.

Critical Appraisal

The study was well conducted, with no clinically meaningful imbalance in baseline characteristics, minimal loss to follow-up, and a collection of end points that were standardized and meaningful to patients. Multiplicity was controlled throughout testing of the primary and secondary efficacy end points, with pre-specified strategies for testing of end points. The overall rate of discontinuations from the study was low and assumptions surrounding missing data were conservative for most end points. Interpretation of patient-reported outcome data is limited due to attrition of numbers over cycles.

The generalizability concerns that were identified included the assumption that patients aged 75 years and older would not be eligible for standard induction therapy, and the need for venetoclax and azacitidine to be limited to settings that could provide monitoring and supportive care. In the Canadian setting, patients aged 75 years and older would be considered for treatment if they were medically fit, especially if they had good or intermediate risk cytogenetics. Patients from rural and remote Canadian settings would have to travel for care or would be limited to other treatment options.

Indirect Comparisons

Description of Studies

A systematic review was conducted of trials comparing venetoclax plus azacitidine, venetoclax plus LDAC, azacitidine alone, LDAC alone, and BSC in adults with AML who were not eligible for standard induction chemotherapy. Three indirect treatment comparison (ITC) analyses were conducted: 1 network meta-analysis (NMA) and 2 propensity score–weighting analyses that compared venetoclax plus azacitidine with LDAC and azacitidine with LDAC. For the NMA, HR data were available for OS for 4 trials in a connected network and for proportions of patients with CR + CRi for 3 trials. For the propensity score–weighting

Table 2: Summary of Key Results From VIALE-A

Results	VEN + AZA N = 286	PBO + AZA N = 145
OS		
Events (deaths), n (%)	161 (56.3)	109 (75.2)
Median OS, months (95% CI)	14.7 (11.9 to 18.7)	9.6 (7.4 to 12.7)
HR (Cox proportional hazards model)[a] (95% CI)	0.662 (0.518 to 0.845)	
P value (stratified log-rank test)[a]	< 0.001[b]	
Event-free survival		
Number of patients with events, n (%)	191 (66.8)	122 (84.1)
Median duration of event-free survival (months; 95% CI)	9.8 (8.4 to 11.8)	7.0 (5.6 to 9.5)
HR (Cox proportional hazards model)[a] (95% CI)	0.632 (0.502 to 0.796)	
P value (stratified log-rank test)[a]	< 0.001[b]	
Best response (CR + CRi) by investigator assessment		
CR + CRi rate at IA1, n (%; 95% CI)[c]		
Number of patients at IA1	147	79
CR + CRi	96 (65.3; 57.0 to 73.0)	20 (25.3; 16.2 to 36.4)
P value (stratified CMH test)[a]	< 0.001	
CR + CRi rate (as best response), n (%; 95% CI)[c]		
CR	105 (36.7; 31.1 to 42.60)	26 (17.9; 12.1 to 25.2)
P value (stratified CMH test)[a]	< 0.001[b]	
CR + CRi	190 (66.4; 60.6 to 71.9)	41 (28.3; 21.1 to 36.3)
CR + CRi rate (as best response) by initiation of cycle 2, n (%; 95% CI)[a]		
CR + CRi	124 (43.4; 37.5 to 49.3)	11 (7.6; 3.8 to 13.2)
P value (stratified CMH test)[a]	< 0.001[b]	
Time to response (CR + CRi) by investigator assessment		
Time to first response, months, mean (SD) median (range)		
CR + CRi	2.1 (1.82) 1.3 (0.6 to 9.9)	3.3 (2.61) 2.8 (0.8 to 13.2)
Time to best response, months, mean (SD) median (range)		
CR + CRi	3.6 (3.66) 2.3 (0.6 to 24.5)	4.2 (2.89) 3.7 (0.8 to 13.2)
Duration of response (CR + CRi and CR) based on investigator assessment		
CR + CRi		
Number of patients with events, n/N (%)	84/190 (44.2)	23/41 (56.1)

Results	VEN + AZA N = 286	PBO + AZA N = 145
DOR (months)[a]		
Median (95% CI)	17.5 (13.6, NE)	13.4 (5.8 to 15.5)
CR		
Number of patients with events, n/N (%)	39/105 (37.1)	13/26 (50.0)
DOR (months)[a]		
Median (95% CI)	17.5 (15.3 to NE)	13.3 (8.5 to 17.6)
Post-baseline transfusion-independence rate		
RBC and platelet, n (%; 95% CI)	166 (58.0; 52.1 to 63.8)	49 (33.8; 26.2 to 42.1)
Treatment difference, % (95% CI)	24.2 (14.7 to 33.8)	
RBC	171 (59.8; 53.9 to 65.5)	51 (35.2; 27.4 to 43.5)
Treatment difference, % (95%)	24.6 (15.0 to 34.2)	
P value (stratified CMH test)[a]	< 0.001[b]	
Platelet	196 (68.5; 62.8 to 73.9)	72 (49.7; 41.3 to 58.1)
Treatment difference, % (95%)	18.9 (9.1 to 28.6)	
P value (stratified CMH test)[a]	< 0.001[b]	
Harms		
Patients with any AE, n (%)	283 (100)	144 (100)
Patients with AE grade ≥ 3, n (%)	279 (98.6)	139 (96.5)
Patients with any SAE, n (%)	235 (83.0)	105 (72.9)
Patients with VEN- or PBO-related AE,[a] n (%)	241 (85.2)	96 (66.7)
Patients with AZA-related AE,[a] n (%)	246 (86.9)	108 (75.0)
Patients with any AE leading to discontinuation of VEN or PBO, n (%)	69 (24.4)	29 (20.1)
Patients with any AE leading to AZA discontinuation, n (%)	68 (24.0)	29 (20.1)
Patients with any AE leading to VEN or PBO dose interruption or reduction, n (%)	204 (72.1)	84 (58.3)
Patients with any AE leading to AZA dose interruption or reduction, n (%)	190 (67.1)	67 (46.5)
Patients with any AE leading to death, n (%)	64 (22.6)	29 (20.1)
Subgroups		
OS		
IDH1 and/or IDH2 mutation		
N	61	28
Median OS, months (95% CI)	NE (12.1 to NE)	6.2 (2.3 to 12.7)

Results	VEN + AZA N = 286	PBO + AZA N = 145
HR (unstratified Cox model) (95% CI)	0.345 (0.199 to 0.598)	
P value (unstratified log-rank test)	< 0.0001[b]	
FLT3 mutation		
N	29	22
Median OS, months (95% CI)	12.7 (7.3 to 23.5)	8.6 (5.9 to 14.7)
HR (unstratified Cox model) (95% CI)	0.664 (0.351 to 1.257)	
P value (unstratified log-rank test)	0.2054	
CR + CRi		
IDH1 and/or IDH2 mutation		
N	61	28
CR, n (%; 95% CI)	26 (42.6; 30.0 to 55.9)	1 (3.6; 0.1 to 18.3)
CR + CRi, n (%; 95% CI)	46 (75.4; 62.7 to 85.5)	3 (10.7; 2.3 to 28.2)
Risk difference % (95% CI)	64.70 (48.9 to 80.4)	
P value (Fisher's exact test)	< 0.001[b]	
FLT3 mutation		
N	29	22
CR, n (%; 95% CI)	10 (34.5; 17.9 to 54.3)	3 (13.6; 2.9 to 34.9)
CR + CRi, n (%; 95% CI)	21 (72.4; 52.8 to 87.3)	8 (36.4; 17.2 to 59.3)
Risk difference (%; 95% CI)	36.05 (10.2 to 61.9)	
P value (Fisher's exact test)	0.021[b]	

AE = adverse event; AML = acute myeloid leukemia; AZA = azacitidine; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete remission; CRh = complete remission with incomplete hematological recovery; CRi = complete remission with incomplete blood count recovery; DOR = duration of response; FLT3 = FMS-like tyrosine kinase 3; HR = hazard ratio; IA1 = first interim analysis; OS = overall survival; PBO = placebo; RBC = red blood cell; SD = standard deviation; VEN = venetoclax.

Note: Data cut-off was January 4, 2020.

[a]Stratified by age (18 to < 75 years, ≥ 75 years) and cytogenetic risk (intermediate risk, poor risk).

[b]Statistically significant under the preplanned testing strategy.

[c]Calculated from the exact binomial distribution.

Source: Clinical Study Report.[1]

analysis, data were available for OS, EFS, and CR + CRi from VIALE-A and the LDAC group from VIALE-C.

Efficacy Results

In the NMA, the results favoured a lower hazard of death for patients assigned to venetoclax plus azacitidine compared with azacitidine (HR = 0.66; 95% credible interval [CrI], 0.52 to 0.85), LDAC (HR = 0.57; 95% CrI, 0.40 to 0.81), and BSC (HR = 0.37; 95% CrI, 0.24 to 0.58), with no treatment favoured between venetoclax plus azacitidine and venetoclax plus LDAC (HR = 0.81; 95% CrI, 0.50 to 1.31). For CR + CRi, venetoclax plus azacitidine was favoured over azacitidine (odds ratio [OR] = 5.05; 95% CrI, 3.30 to 7.87), LDAC (OR = 5.42; 95% CrI, 2.80 to

10.50), and BSC (OR = 61.55; 95% CrI, 8.23 to 1,881.53), with no treatment favoured between venetoclax plus azacitidine and venetoclax plus LDAC (OR = 0.86; 95% CrI, 0.30 to 2.35).

In the first propensity-score analysis, venetoclax plus azacitidine was favoured over LDAC for OS (HR = 0.50; 95% confidence interval [CI], 0.35 to 0.73), EFS (HR = 0.40; 95% CI, 0.28 to 0.58), and CR + CRi (OR = 10.17; 95% CI, 4.55 to 22.73). In the second propensity-score analysis for OS, venetoclax plus azacitidine was favoured over LDAC (HR = 0.52; 95% CrI, 0.36 to 0.77) and azacitidine (HR = 0.64; 95% CrI, 0.50 to 0.82), and no statistically significant difference was seen between azacitidine and LDAC (HR = 0.78; 95% CrI, 0.52 to 1.17). For EFS, venetoclax plus azacitidine was favoured over azacitidine (HR = 0.62; 95% CrI, 0.49 to 0.77) and LDAC (HR = 0.41; 95% CrI, 0.29 to 0.59), and azacitidine was favoured over LDAC (HR = 0.63; 95% CrI, 0.43 to 0.92). For CR + CRi, venetoclax plus azacitidine was favoured over azacitidine (OR = 5.02; 95% CrI, 3.24 to 7.77) and LDAC (OR = 9.69; 95% CrI, 4.30 to 21.85), and no statistically significant difference was seen between azacitidine and LDAC (OR = 1.93; 95% CrI, 0.82 to 4.54).

Harms Results

No analysis of harms was included in the indirect comparisons.

Critical Appraisal

A key limitation of the NMA was the clinical heterogeneity between studies in potential treatment-effect modifiers of blast count at baseline, prior treatment with an HMA, and cytogenetic risk. As the network was sparse, fixed-effects models had to be used, and there was no opportunity for baseline covariate adjustments. Due to these limitations, the comparative efficacy estimates may be biased, and it is not possible to quantify or identify the direction of the bias. Certain estimates, particularly for CR + CRi, were imprecise due to sparse data. In the propensity-score analyses, weighting was generally good, but the relatively small numbers of patients in the LDAC comparator group limited the number of covariates that could be included in the model. The comparisons were not randomized and the results were highly susceptible to bias due to imbalances in unmeasured confounders.

Conclusions

One double-blind, placebo-controlled phase III randomized clinical trial (RCT) (VIALE-A) and 1 ITC provided evidence supporting the efficacy and safety of venetoclax plus azacitidine in adult patients ineligible for standard induction chemotherapy due to age or comorbidities. Compared with azacitidine alone, patients treated with venetoclax (400 mg daily) and azacitidine (75 mg/m^2 on days 1 through 7 of a 28-day cycle) showed benefits in important clinical end points of OS, overall and early composite complete remission (CR + CRi), EFS, CR, and transfusion-independence data (red blood cell or platelet). All study participants reported treatment-emergent adverse events. For most categories of adverse events, there was an overall higher proportion of patients reporting in venetoclax plus azacitidine. The most common adverse events were cytopenias and infections. No firm conclusions can be drawn for differences between groups in GHS/QoL and fatigue, and patient attrition reduced the number of observations over the cycles, which limits the interpretation for these end points. Overall, the study was well conducted.

The VIALE-A study did not include a comparison between venetoclax plus azacitidine and current standards of care of induction therapy (in patients aged ≥ 75 and fit), LDAC, or BSC, or the alternative combination of venetoclax plus LDAC. In an ITC, venetoclax plus azacitidine

was favoured over monotherapies and basic supportive care, but no treatment was favoured for survival or for composite complete remission between venetoclax plus azacitidine and venetoclax plus LDAC. No data are available for the comparison of venetoclax plus azacitidine with induction therapy. Results for 2 propensity-score comparisons between venetoclax plus azacitidine and azacitidine and LDAC were consistent. Small study and patient numbers and the potential for bias limit the reliability of the ITC, and the propensity-score comparisons were not randomized and therefore highly susceptible to bias.

Introduction

Disease Background

AML is a hematological malignancy defined by WHO as a myeloid neoplasm with greater than 20% blasts in the peripheral blood or bone marrow.[2] AML results from malignant transformation of myeloid precursor cells to produce 1 or more clonal populations that can proliferate but do not normally differentiate into their mature forms. This leads to an accumulation of leukemic blasts or immature cells in the bone marrow, peripheral blood, and extramedullary tissues, which disrupt normal hematopoiesis. WHO 2016 guidelines[2] identify 6 distinct groups of AML:

- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related changes
- therapy-related myeloid neoplasms
- AML not otherwise specified
- myeloid sarcoma
- myeloid proliferations related to Down syndrome

AML is the most common form of acute leukemia in adults. According to the Canadian Cancer Society's most recent data, in 2016, 1,090 people were diagnosed with AML, 610 men and 480 women.[3] In 2017, 1,184 people died of AML, 678 men and 506 women.[3] Projections for the Canadian population in 2020 only report figures for all forms of leukemia; according to these projections, 6,900 patients would be diagnosed with leukemia, and 3,000 would die. Assuming that around 24% of leukemia in Canada is AML (data from 1992 to 2008),[4] the subgroup diagnosed with AML would comprise approximately 1,660 patients.

AML occurs predominately in older adults, with a median age at diagnosis of 67 years in Canada.[4] Incidence increases with age. There is an increased incidence in men and non-Hispanic Whites compared with women and other racial or ethnic groups. Certain environmental exposures have been associated with an increased risk of AML (e.g., chemicals, radiation, tobacco, and retroviruses). AML can occur as a secondary malignancy following chemotherapy, or develop out of a pre-existing hematopoietic abnormality such as MDS, other myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria, aplastic anemia, or clonal hematopoiesis of indeterminate prognosis. Rarely, it can be associated with an inherited genetic abnormality or familial predisposition to hematologic disorders.

Patients typically present with the symptoms or complications of disrupted hematopoiesis (bleeding or bruising, infection that can be life-threatening, fatigue or shortness of breath,

headache or focal neurologic complaints) or symptoms of leukostasis resulting from an excess of immature white cells in the peripheral blood. A presumptive diagnosis of leukemia may be made from a CBC and smear, but confirmation is usually by bone marrow biopsy and aspirate. Characterization of specific genetic abnormalities enables stratification by genetic risk into favourable, intermediate, and poor risk categories, which is used to guide treatment decisions or use of therapies targeted against specific mutations.

The overall 5-year survival for AML in adults in Canada is 21%.[5] Older patients have notably poorer survival. In US data, the 5-year survival is 44.8% in patients younger than 65 years and 6.3% in patients aged 65 years and older.[6] In another study, patients aged 60 years and older had 1-year and 5-year survival of 20.1% and 8.4%, respectively.[7] Survival is influenced by cytogenetic and genetic risk.

Standards of Therapy

Standard treatment for patients who are medically fit consists of cytotoxic remission induction therapy with cytarabine, administered by infusion over 7 days, combined with an anthracycline, usually daunorubicin or idarubicin, given daily for the first 3 days. Induction therapy is followed by high-intensity consolidation therapy. This may be accompanied by targeted therapy for specific clinical situations or genetic mutations: midostaurin in patients with FLT3, and gemtuzumab ozogamicin (monoclonal antibody against CD33) in patients with favourable and intermediate risk disease.[8]

Determination of eligibility for intensive chemotherapy is based on patient age, fitness, presence of comorbidities, and patient preferences. In general, intensive therapy is poorly tolerated by older patients. According to the 2017 Canadian Consensus Guidelines for treatment of older patients with AML[8] induction therapy shows a survival benefit for patients up to age 80, with the exception of those with major comorbidities or those with adverse risk cytogenetics who were not candidates for hematopoietic stem cell transplant.[8] Anthracycline and cytarabine are the recommended drugs for induction therapy, with the addition of midostaurin for patients with an FLT3 mutation, and the addition of gemtuzumab ozogamicin for patients with de novo AML and favourable or intermediate risk cytogenetics. For patients who are not eligible for induction therapy, azacitidine is recommended for those with adverse risk cytogenetics or transformed from MDS, while either HMA or LDAC could be used for others. Acute promyelocytic leukemia would be treated with arsenic trioxide plus all-trans retinoic acid (with an anthracycline for those with white blood cell count > 10×10^9/L).

Azacitidine has been approved by Health Canada for patients with low blast count AML (blast counts of 20% to 30%); however, in multiple jurisdictions, it is used and provides clinical benefit in patients with blast counts of 30% or greater. Some jurisdictions fund alternative dosing schedules for azacitidine besides the standard 7-day consecutive regimen. According to input from the clinicians consulted by CADTH for the purpose of this review, in real-world clinical practice in Canada, many eligible patients were unable to receive azacitidine-based therapy, as this drug has to be administered in an oncology clinic setting because of its instability after reconstitution. Many patients who live in rural areas and some in urban settings are unable to travel to these clinics regularly to receive treatment due to the distances involved, their overall frailty, and challenges in obtaining suitable transportation.[9]

Not all patients respond to first-line therapy and all become refractory to current treatment options, with limited life expectancy. There are few effective treatment options following relapse on front-line AML therapy[8]; some patients will receive off-label azacitidine with or

without venetoclax or participate in a clinical trial. A minority of patients with FLT3 mutations receive gilteritinib, but many patients are not well enough to tolerate further therapy; hence, they receive BSC only.[8]

Drug

Venetoclax is an orally administered highly selective inhibitor of the anti-apoptotic protein BCL2. Increased expression of BCL2 has been measured in AML blasts, and a majority of AML stem cells express high levels of BCL2 and are dependent on BCL2 for survival. High levels of expression of BCL-2 have been associated with poorer response to chemotherapy and poorer survival in patients with AML. Azacitidine is also thought to affect the inhibition of the pro-survival proteins MCL1 and BCL-XL, so co-administration of azacitidine should increase the dependence of leukemia cells on the BCL2 pathway for survival, and potentiate the effect of venetoclax.

Venetoclax was granted a Health Canada Notice of Compliance on December 4, 2020. The approved indication was: Venclexta (venetoclax) in combination with azacitidine or LDAC, is indicated for the treatment of patients with newly diagnosed AML who are 75 years or older, or who have comorbidities that preclude use of intensive induction therapy. This is consistent with the reimbursement request. Venetoclax has also been approved for the treatment of CLL, as monotherapy for patients with or without a 17p deletion who do not have other available treatment options, in combination with obinutuzumab in previously untreated patients, and in combination with rituximab for patients who have received at least 1 prior therapy. A concurrent CADTH review of venetoclax with LDAC is ongoing, and previous CADTH reviews were conducted for the indications in CLL.

Table 3 summarizes the characteristics and indications for venetoclax, azacitidine, and cytarabine.

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

About the Patient Group(s) and Information Gathered

One patient advocacy group, the LLSC, provided input on venetoclax in combination with azacitidine for the treatment of AML.

The LLSC's mission is to cure leukemia, lymphoma, Hodgkin's disease, and myeloma, as well as to improve the QoL of all Canadians affected by blood cancers. The LLSC has received funding from AbbVie.

The LLSC used an online survey for its submission, which was conducted between December 7, 2020 and January 24, 2021.

A total of 29 patients responded. All respondents were from Canada: 13 from Ontario, 6 from Quebec, 6 from British Columbia, and 4 from Alberta. Patient ages ranged from 25 to 84 years

old and 2 were 75 years old or older. There were 18 females and 10 males and 1 did not report

Table 3: Key Characteristics of Venetoclax, Azacitidine, and Cytarabine

Characteristic	Venetoclax	Azacitidine	Low-dose cytarabine
Mechanism of action	Selective inhibitor of the anti-apoptotic protein BCL2	Inhibits DNA methyltransferase, blocking methylation of new DNA. Hypomethylation of DNA can reverse hypermethylation leading to gene silencing	Kills cells undergoing DNA synthesis (S-phase). Under certain conditions, blocks progression of cells from G_1 phase to S-phase. Acts through inhibition of DNA polymerase
Indication[a]	In combination with azacitidine or low-dose cytarabine for the treatment of patients with newly diagnosed AML who are 75 years or older, or who have comorbidities that preclude use of intensive induction therapy	AML with 20% to 30% blasts and multi-lineage dysplasia, according to WHO classification	
Route of administration	Oral, tablet	SC	SC
Recommended dose	In combination with azacitidine 400 mg/day following a 3-day ramp-up. In combination with LDAC 600 mg/day following a 4-day ramp-up	75 mg/m^2 daily for 7 consecutive days in a 28-day treatment cycle for a recommended minimum of 6 cycles	20 mg SC twice daily, or 20 mg/m^2 SC daily for 10 consecutive days in a 28-day treatment cycle for a recommended minimum of 4 cycles
Serious adverse effects or safety issues	Serious warnings and precautions[10]: • tumour lysis syndrome (prophylaxis required) • serious infections Warnings and precautions: • secondary primary malignancies • hemorrhage • neutropenia • infections	Serious warnings and precautions[11]: • thrombocytopenia • renal failure Warnings and precautions: • tumour lysis syndrome • anemia, neutropenia, thrombocytopenia	Serious warnings and precautions[12]: • cardiomyopathy with subsequent death • GI toxicity, at times fatal • acute pancreatitis • CNS toxicity, severe neurologic adverse reactions, paraplegia, necrotizing leukoencephalopathy, and spinal cord toxicity • infection • pulmonary toxicity, adult respiratory distress syndrome, pulmonary edema • myelosuppression
Other	Concomitant use of strong CYP3A inhibitors during initiation and ramp-up requires venetoclax dose reduction		Not beneficial in patients with poor risk cytogenetics

AML = acute myeloid leukemia; BCL2 = B-cell leukemia protein 2; CNS = central nervous system; GI = gastrointestinal; LDAC = low-dose cytarabine; SC = subcutaneous.

[a]Health Canada–approved indication.

Source: Product monographs for venetoclax,[10] azacitidine,[11] and cytarabine.[12]

gender. Comorbidities were not reported. All patients had been diagnosed with AML within the past 7 years. Five of the respondents had experience with venetoclax in combination with azacitidine.

Disease Experience

According to the patient respondents to the LLSC survey, the symptoms that patients with AML experience that impact QoL include fatigue, suddenness of symptom development, anxiety, fear of relapse (number of patients unspecified for preceding symptoms), and loss of eyesight (n = 1). One patient experienced a spleen rupture and was in a coma for 8 days. Fatigue was the symptom mentioned most often among patient respondents. Fatigue and other symptoms subsequently affected social and family life along with other symptoms. Patients reported that these symptoms compounded with the changes related to the coronavirus disease 2019 (COVID-19) pandemic, which led to further social isolation. Some patients reported they are unable to work due to their disease and associated symptoms. Many patients did not provide information on the specific symptoms they experienced but described being diagnosed with AML as a life-changing event. Below are comments from patients regarding their experiences with AML:

> "Everything in my life stopped cold turkey-employment, social life, relationships, etc. I made a complete personal 360 degree pivot to focus on my healing and living."

> "Well COVID and my compromised immune system has caused me to be very socially isolated. I haven't seen some very important people in my life for almost 2 years at this point."

When asked if there are any aspects or symptoms of AML that are easier to control, most patients (n = 7) indicated no, and 1 patient commented there was no control with AML. Three patients indicated exercise was helpful in alleviating some symptoms, reporting that exercise and keeping physically active helped, particularly with fatigue.

Two patients reported feeling no impact or back to normal at the time of survey.

AML affects not just those who are diagnosed, but also their caregivers, which may include a spouse, immediate family members, and friends. Patients reported needing assistance for physician visits and daily activities. According to the LLSC survey, patients reported that caregivers seemed to feel multiple emotions about the patient's AML: stress, worry, sadness, insecurity, and fear of dying were all frequently mentioned. Their companion through the disease journey was important for patients.

Experiences With Currently Available Treatments

According to the LLSC survey, the front-line treatments that patients received after diagnosis included chemotherapy (n = 24), stem cell transplant or bone marrow transplant (n = 16), drug therapy (n = 6), radiation therapy (n = 5), and chimeric antigen receptor (CAR) T-cell therapy (n = 1). One patient reported receiving Vyxeos (daunorubicin and cytarabine). Patients reported a wide range of side effects with current treatments, and the ones they considered to have a large impact on their QoL included hair loss (n = 17); weakness (n = 15); extreme fatigue (n = 14); diarrhea (n = 10); infections (n = 8); anemia (n = 8); mouth sores (n = 8); nausea and vomiting (n = 7); fever (n = 6); low blood cell counts (n = 6); tingling sensations (n = 4); constipation (n = 2); graft-versus-host disease (n = 2); lung, heart, kidney, or nerve problems (n = 2); cough (n = 1); rashes (n = 1); shortness of breath (n = 1); and psychological distress

(n = 1). The side effects due to chemotherapy and stem cell transplant had a large impact on patients' QoL, summarized the LLSC survey administrator. These side effects from front-line treatments led to changes in physical activity (n = 15), anxiety (n = 11), problems in mental health and overall happiness (n = 11), eating challenges (n = 12), and social development (n = 6) and educational development (n = 6) challenges. Overall, the side effects from front-line treatments caused significant disturbance to daily living. Patients were isolated from visitors during stem cell transplant. Opportunistic infection could occur. The following are comments from patients regarding their experiences with front-line AML treatments:

> "The main challenge was the nausea and vomiting. I didn't seem to have much control over it and had my wonderful bucket always with me. I could be fast asleep and awake and vomit."

> "Your whole world changes when you are diagnosed with AML. Suddenly, you confront your mortality. You feel extremely weak, you have to go into hospital for months, and you don't realize you MUST go into remission to have a stem cell transplant."

> "Extremely tired and little desire to be active. Difficulty eating and keeping it down. A few days of low hemoglobin and fluid on the lung that caused shortness of breath."

> "The worst issue is that I have no more job and that the treatments made me lose a lot of concentration and I get exhausted easily."

> "Had to move to Vancouver for treatment for 9 months. 2 or 3 months total in hospitals. Daily outpatient care. Kinda turns your life upside-down."

Patients who responded to the LLSC survey reported a mixture of both positive and negative experiences accessing treatments. Thirteen respondents reported generally positive experiences and some patients attributed their experience to the support from medical staff. Six patients reported negative experiences. Negative experiences were related to challenges with receiving care and treatment plans. Some patients needed to relocate to receive treatments.

Improved Outcomes

The majority of respondents to the LLSC survey indicated that the factors they considered about a new cancer treatment were physician recommendation (n = 19), possible impact on disease (n = 17), QoL (n = 12), closeness of home to the treatment centre (n = 9), and outpatient treatment (n = 8).

The LLSC survey patient respondents also reported the characteristics of new treatment options they hoped to have, particularly those that could maintain remission, have fewer side effects, be covered by public plans, and be accessible in their geographic region. The opportunity to have access to other supportive options, such as meditation, hypnosis, neuro-linguistic programming support, and awareness support (thoughts, emotions, and behaviours), was also mentioned.

Experience With Drug Under Review

Five of the LLSC respondents indicated they took venetoclax in combination with azacitidine. Three respondents received it through compassionate use from the pharmaceutical company and 2 respondents received it through physician prescription. Two respondents reported difficulties in accessing the drug because of the costs and 1 reported a long wait time. The

financial costs reported by 3 patients ranged from $10,000 to $13,000. Three respondents took this treatment because of physicians' recommendation and 2 patients considered side effects to be the main factor for adopting this treatment. One of them also considered the chance of survival the reason to take this treatment.

Patients' responses to this treatment varied greatly, including an overall great experience (n = 1), experiences with side effects (tiredness and loss of appetite, n = 1), no side effects but relapse (n = 1), significant side effects (n = 1), and transition to transplant (n = 1). Serious and very serious side effects reported by patients were fatigue (n = 3), low platelets (n = 2), and anemia (n = 1). Other side effects were minor or manageable, such as diarrhea, nausea, constipation, cough, back pain, and headache. One patient thought multiple visits to the hospital, transfusion, and infection made managing the side effects more challenging.

Two patients strongly agreed that venetoclax in combination with azacitidine improved their QoL compared with other treatments they received. Two patients also agreed and 1 disagreed. Two patients thought this treatment led to remission and thus improved their QoL. Overall, patients' experiences with this treatment varied greatly. Compared with other treatments they received, patients indicated this treatment was significantly more challenging (n = 2), more challenging (n = 1), neutral (n = 1), less challenging (n = 1), and significantly less challenging (n = 1). The 5 patients were willing to tolerate the side effects of this treatment. One patient tolerated the side effects to live and another thought there was no other choice.

Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 3 clinical specialists with expertise in the diagnosis and management of AML in adults.

Unmet Needs

The experts indicated that current lower-intensity treatments have low rates of CR, and CRs that are produced are not durable. Treatments producing higher rates of CR had increased toxicity and are not tolerable in the patient population under study. The Health Canada approval for azacitidine is only for treatment-naive patients with higher-risk MDS and AML (according to the International Prognostic Scoring System) and with up to 30% blasts by WHO classification, although certain local jurisdictions make azacitidine available for patients with 30% or greater blasts.

Place in Therapy

The experts indicated that venetoclax plus azacitidine (or other HMA) would change the current treatment paradigm. It would be the new standard of care for patients with treatment-naive AML aged 18 years or older who are not eligible for intensive chemotherapy, and would replace, for the most part, single-agent HMAs or LDAC. For patients with treatment-naive AML aged 75 years or older who were eligible for intensive chemotherapy, especially those with good or intermediate risk cytogenetics, there would have to be a discussion with the patient about the risks and benefits of the different treatment options. It should be noted there is no consistency as to the upper age limit at which an acute leukemia treatment centre would

administer intensive chemotherapy. As venetoclax plus azacitidine is myelosuppressive, it may not be suitable for a small number of frail patients, or for those who would be unable to travel to the treating hospital for count checks. This, too, would need to be assessed by the treating physician in conjunction with the patient.

Patient Population

The experts indicated that patients must have a diagnosis of AML with greater than 20% blasts, and that making this diagnosis from blood and bone marrow is straightforward. Patients with isolated granulocytic sarcoma were not included in the trial.

The clinicians indicated that selection of patients for treatment would be based on clinician judgment and patient preferences. At this time, there is not enough information to make treatment decisions based on disease characteristics, and the data to predict response have not yet been validated in large studies.

Patients with good risk cytogenetics and patients with myeloproliferative neoplasm in blast crisis have been excluded from studies of venetoclax plus azacitidine or LDAC. Patients who had previously used an HMA were not eligible for the VIALE-A trial, but were eligible for the VIALE-C trial. One respondent indicated that studies suggest response to venetoclax plus HMA following HMA is similar to response to venetoclax plus LDAC; however, there are no direct comparisons of these 2 treatments post HMA. Patients with CNS involvement by AML have been excluded from all AML studies, but this does not mean this group of patients would not benefit from venetoclax plus azacitidine with concomitant intrathecal therapy, similar to the current practice of administering systemic intensive chemotherapy and intrathecal therapy to those patients who have CNS involvement by AML.

One expert suggested venetoclax with azacitidine was preferred over venetoclax plus LDAC in patients who had not received prior HMA. Venetoclax plus HMA was reasonable in patients with prior HMA use, and ivosidenib plus azacitidine would be reasonable in patients with IDH1 mutations, if ivosidenib were available.

The experts indicated that venetoclax plus azacitidine would not be suitable for fit patients (i.e., those eligible for standard induction treatment) with good cytogenetic risk AML, or for patients with acute promyelocytic leukemia. Emerging evidence may support the use of venetoclax plus azacitidine in fit patients as a bridge to allogeneic bone marrow transplant in higher-risk AML. Opinions differed in the use of venetoclax plus azacitidine in patients with relapsed or refractory disease, as venetoclax plus azacitidine has reduced activity in relapsed and refractory disease: 1 respondent did not recommend it, and another thought it was a reasonable option.

Assessing Response to Treatment

The experts indicated that, in clinical practice, response to treatment would be determined by achievement of CR, CRh, or CRi and/or transfusion independence or hematological improvement or stable disease. A clinically meaningful response to treatment would be represented by improved OS, improved EFS, achievement of durable CR, decreased hospitalizations, decreased transfusion requirements, slower progression, stabilization of disease (which would presumably improve or not worsen symptoms), and improved QoL. One clinician noted that the strict definitions of response did not necessarily identify responding patients. One clinician indicated that OS, hospital visits, transfusion dependence, and QoL were likely the most important end points. The clinicians indicated it is difficult to determine

a minimum improvement over standard of care and what a meaningful response represents will vary by physician and patient.

Response would be measured by CBC and bone marrow blasts. One respondent indicated bone marrow biopsy should be performed after the first and second cycles of treatment, as response would be expected after a maximum of 2 cycles. Another indicated that response should be assessed at minimum after 4 to 6 cycles, but that most practitioners assess after the first cycle, given cost and to guide dosing of venetoclax for subsequent cycles. Once a response was obtained, then CBC could be followed for evidence of progression.

Discontinuing Treatment

The experts agreed that disease progression and intolerable adverse events were factors to be considered in the decision to discontinue treatment. Disease progression could be indicated by worsening CBC, increasing blasts in bone marrow, and/or loss of transfusion independence. The clinicians could not comment whether venetoclax could be continued if a patient stopped azacitidine.

Prescribing Conditions

The experts indicated that a hospital or outpatient clinic would be appropriate settings for treatment. As venetoclax plus azacitidine is myelosuppressive, physicians should have experience in looking after acute leukemia patients. Patients might require hospital admission for venetoclax dose ramping up. The proportion depends upon population: 1 respondent indicated the proportion would small, and another that it could be 25% to 50%. Patients would also require pre-treatment and monitoring for tumour lysis syndrome (occurring in 1% to 2% of patients). A not-insignificant proportion of patients will need to be hospitalized for neutropenic fever and other complications during their cycle of therapy. Pharmacists would be involved in reviewing medications, as a significant proportion of patients are on azoles, which interact with venetoclax and require dose modifications.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups.

Four clinician groups provided input on the reimbursement review of venetoclax in combination with an HMA or in combination with LDAC, for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

The ATB-MPG is a group of physicians who treat myeloid malignancies and acute leukemias (myelodysplastic syndromes, myeloproliferative neoplasms, AML, and acute lymphoblastic leukemia) within Alberta and function as a group within the Alberta Hematology Tumour Group. There are Edmonton and Calgary groups that meet regularly and provincially every 3 months as well as annually to update the treatment guidelines on these diseases for Alberta. Information was collected by ATB-MPG for this review through literature review and group discussions. The group reviews written guidelines in a group setting and modifies its opinions based on written and oral discussion among the members. The discussed information is then approved by the full group.

The CLSG is a cross-Canada collective of physicians who treat acute leukemia and who represent all major leukemia centres in all provinces. The purpose of CLSG is "to improve the diagnosis and treatment of leukemia in Canada by identifying diagnostic and management

best practices, promoting Canada-wide standards of care, fostering clinical and basic leukemia research, and improving new drug access." Information for this review was gathered through ongoing group discussions and polling of members, with input requested from other international experts as appropriate. The written opinions were further edited and approved by the full group.

Ontario Health's (Cancer Care Ontario) Hematology Disease Site Drug Advisory Committee (OH-CCO Hem-DAC) provides evidence-based clinical and health system guidance on drug-related issues in support of OH-CCO's mandate, including provincial drug reimbursement programs and the Systemic Treatment Program. The group gathered its information for this review through discussions at the DAC meeting.

The L/BMT Program of British Columbia is a joint program of BC Cancer and Vancouver Coastal Health with a primary mandate for the province to treat acute leukemia, perform stem cell transplantation, and deliver cellular therapies for patients with hematologic malignancies. Members from the acute working group within the program provided input for this review. The group primarily reviewed published data from the phase III trial (DiNardo)[23] as well the data from the phase Ib trial and reviewed National Comprehensive Cancer Network (NCCN) guidelines.

Unmet Needs

All 4 clinician groups agreed that the current treatment paradigm for this disease includes azacitidine, LDAC, and BSC.

In addition, the L/BMT program of British Columbia noted that determination of eligibility for intensive chemotherapy is based on patient age, fitness, presence of comorbidities, and patient preferences. The group added that in British Columbia, azacitidine is given at many BC Cancer sites as well as in other hospital outpatient settings depending on the geographic location and treating physician. The treatment is given as a subcutaneous injection usually in either a 7-day or 5 days plus 2 days schedule. L/BMT members added that response to azacitidine is not evident before cycles 3 to 4 and is usually formally assessed around cycles 6 to 7 with a repeat bone marrow aspirate and biopsy. The group added that treatment with azacitidine continues indefinitely as long as the patient benefits and tolerates the treatment. L/BMT noted that LDAC is also given as a subcutaneous injection of 20 mg twice a day for 10 days every 4 to 6 weeks and can be given by the patient or a caregiver at home and also requires patient education by a chemotherapy-trained nurse before initiation. The group noted that LDAC is given less frequently than azacitidine and is beneficial for patients who live a long distance from a cancer centre that administers azacitidine or who would prefer to receive treatment at home. L/BMT also noted that in the province of British Columbia, LDAC is generally reserved for patients with intermediate risk karyotype. L/BMT added that older patients with AML also receive supportive treatments either with azacitidine or LDAC or alone, and these supportive treatments include transfusion support, hydroxyurea, antibiotic treatment, pain control, and palliative care. The group noted that currently there are no relevant special access programs available and that novel treatments for AML and non-intensive treatments with LDAC and azacitidine can improve symptoms and result in clinical responses, with a small proportion of patients achieving CR. L/BMT added that this treatment (venetoclax plus azacitidine) is associated with an improvement in OS, but it is not considered curative and responding patients will ultimately have disease progression.

The ATB-MPG added that, currently, for AML patients who are ineligible for induction chemotherapy, the common clinical practice for the majority of patients is to use azacitidine 75 mg/m^2 per day for 7 days every 28 days, and some patients receive cytarabine 20 mg twice daily for 10 days. For elderly patients, the group noted there was no survival benefit noted with cytarabine, and azacitidine is preferred. They also added that azacitidine is approved in Canada for patients with low blast count AML (20% to 30%), but is commonly used and provides clinical benefit to patients unfit for induction chemotherapy who have blast counts higher than 30%. In addition, the group noted there is a temporary compassionate access to an oral decitabine and cedazuridine compound that is available to patients with low blast count AML (20% to 30%); however, ongoing access to this drug is not yet established. The ATB-MPG agreed that palliative basic supportive care options include hydroxyurea and blood transfusion support as well as antibiotics, and patients may be offered clinical trials when they are available. The group noted that patients are aware of venetoclax and azacitidine and some have been "self-funding" venetoclax by using CYP3A inhibitors to reduce the dose, and thereby the cost, of venetoclax.

CLSG agreed with the other clinician groups that approximately 40% to 50% of newly diagnosed AML patients are judged to be unfit for intensive induction chemotherapy and this includes patients aged 75 and older as well as younger patients with severe comorbidities. For these patients, CLSG noted that the treatment options include azacitidine, LDAC, or BSC alone. The group added that for patients with poor risk cytogenetics or AML transformed from MDS, azacitidine is the current treatment of choice, while for patients with AML arising de novo with standard risk cytogenetics, azacitidine or LDAC can be used. The group noted that in the real-world clinical setting, many patients in Canada are not able to receive azacitidine-based therapy, as this drug needs to be given in an oncology clinic setting due to its instability after reconstitution. As a result, many patients who live in rural areas and some in urban settings are unable to travel to these clinics regularly to receive treatment because of the distances, overall frailty, and challenges in obtaining suitable transportation.

All 4 clinician groups agreed with most important treatment goals. These included improvement in survival, improvement in QoL, improvement in hematopoiesis, and transfusion independence. The L/BMT program of British Columbia added that prevention of infection, time to remission, and minimization of toxicity and adverse events associated with treatment are also important treatment goals. In addition to these objectives, the ATB-MPG noted that the reduction of burden on caregivers is also an important treatment goal. All 4 clinician groups also agreed that the currently available treatments offer short survival advantage and short transfusion independence. The short remissions often require several monthly cycles of the therapy, up to 6 cycles, to achieve maximal effect, and translate to an extended period of transfusion dependence, as noted by CLSG. CLSG also added that once a maximally achieved response is lost, disease progression is quite rapid, typically followed quickly by death due to poor salvage therapies. The ATB-MPG added that time to remission for azacitidine is around 4 months and maximal response can take more than 6 months; during this time, patients are transfusion-dependent and have significant burden of disease. The treatment under review was noted by the ATB-MPG as having a median time to response of 1.2 months (faster time to response and clinical improvement). The L/BMT program of British Columbia added that the primary unmet goals for this population are low response rates and short OS.

All 4 clinician groups also agreed that patients with AML who are not eligible for standard 7 plus 3 induction therapy (older or with comorbidities) have the greatest unmet need.

Place in Therapy

All 4 clinician groups agreed that the combination of venetoclax and azacitidine would replace current front-line therapies, including azacitidine alone in a population that has an unmet medical need. The ATB-MPG noted that some patients who received induction chemotherapy and relapsed but are no longer eligible for transplantation, or who relapsed after transplantation and had never received an HMA such as azacitidine before, would commonly use azacitidine and the combination of azacitidine and venetoclax would be expected to be more effective; however, this population was not included in the current reimbursement request.

All 4 clinician groups also agreed it would not be appropriate to recommend that patients try other treatments before initiating treatment with venetoclax and azacitidine, as this therapy is for first-line use and there is no evidence to support sequencing this combination after other treatments. The groups added that the clinical trial was also for newly diagnosed patients.

With respect to sequencing, all 4 clinician groups agreed that the combination of venetoclax and azacitidine would replace current first-line treatment. CLSG also added that after failure of the combination of venetoclax and azacitidine, possible therapeutic options would include therapy targeted to a specific molecular lesion, if present and available, an early phase clinical trial, LDAC, BSC, or palliation. L/BMT agreed with CLSG on this approach and noted that, currently, there is no standard of care practice for patients who fail first-line treatment. The ATB-MPG noted that in second-line treatment, if patients have FLT3-positive AML, they can receive gilteritinib and, if they have FLT3-negative AML, they can receive cytarabine if they are being treated with azacitidine, or with azacitidine if they are being treated with cytarabine. In third-line treatment, the ATB-MPG noted that hydroxyurea and transfusions as well as basic supportive care can be used.

Patient Population

All 4 clinician groups agreed that patients with newly diagnosed AML who are unfit for intensive chemotherapy (due to age, comorbidities, or patient decision not to undergo intensive treatment that is potentially curative) are best suited for treatment with venetoclax and azacitidine, as these patients need more effective therapy options. The L/BMT program of British Columbia noted that the age cut-off of 75 years or greater, as per the Health Canada indication, is based on the clinical trial; however, they expect that, in most centres in Canada, only a small number of patients older than 70 years of age are treated with intensive chemotherapy. The group also added there is some evidence that AML patients with mutations in genes 1DH1 or 1DH2 have a particularly good response to azacitidine and venetoclax, but patients with other genetic subsets of AML as well as de novo and secondary AML also appear to benefit.

All 4 clinician groups also agreed there is a standard diagnosis of AML (i.e., the presence of greater than 20% myeloid blasts in the bone marrow or peripheral blood). Through clinical examination and judgment, as well as bone marrow results, patients can be objectively diagnosed. The groups added that testing is widely available and that patients should be treated at the time of diagnosis, as they would be expected to decline rapidly and develop serious infections or other complications that preclude effective treatment if they are not treated at diagnosis.

It was noted that patients who are least suitable for the venetoclax and azacitidine treatment are those who are younger and fit, without significant comorbidities, or very frail older adults.

The clinician groups also noted that patients who are unable to travel to outpatient clinicians to receive azacitidine would be least suitable for treatment. Also, the L/BMT program of British Columbia noted that patients who are not able to have regular blood work monitoring for tumour lysis syndrome during the initial ramp-up and regular monitoring of blood work later on are also not good candidates.

With respect to identifying patients who are most likely to exhibit a response to treatment with venetoclax and azacitidine, the clinician groups noted that some patients with specific molecular mutations (IDH1 or IDH2) on next-generation sequencing may be expected to respond better; however, this is based on subgroup analysis and there is no patient group that would not be expected to benefit within the group of patients this reimbursement request is for. The groups also noted that at this point, there is no specific test or biomarker to indicate who will or will not respond or benefit from treatment.

Assessing Response to Treatment

All 4 clinician groups agreed that important outcomes in clinical practice are remission status following treatment, tolerance of treatment, QoL, and transfusion requirements. The groups added that bone marrow biopsy to assess disease response is an important outcome; however, it was done more frequently in the clinical trial than in practice.

All 4 groups agreed that a clinically meaningful response to treatment would be remission status on bone marrow biopsy, reduced or eliminated transfusion requirements for red blood cells and platelets, and improvement in symptoms (i.e., infections, bleeding, improved functional status due to improved hemoglobin and fewer hospital admissions or outpatient visits for transfusion support). Additionally, the groups added that in patients without CR or CRi (incomplete count recovery), a partial remission or improvement in blood counts may also be a meaningful improvement for some patients.

CLSG, L/BMT program of British Columbia, and the ATB-MPG noted that response should be assessed with a bone marrow biopsy as well as evaluation of blood counts following 1 to 2 cycles (4 to 8 weeks) of azacitidine and venetoclax. The L/BMT program of British Columbia noted that in patients achieving CR or CRi, they would suggest repeating the bone marrow aspirate biopsy as clinically indicated (e.g., repeated if there is concern that a patient is losing response due to worsening blood counts or the appearance of circulating blasts). The group added that in patients with less than CR or CRi after 1 to 2 cycles who continue on treatment, they would generally repeat bone marrow biopsies every 3 to 4 months to evaluate a response. The ATB-MPG added that once remission or maximal response is obtained, repeat bone marrow biopsy would be indicated if there is clinical deterioration or significant cytopenias requiring reassessment of disease status. The OH-CCO's Hem-DAC noted that treatment should be assessed frequently with regular CBC and bone marrow assessments, as per clinician judgment.

Discontinuing Treatment

All 4 clinician groups agreed that adverse events such as severe nausea, neutropenic infections, and severe infections may lead to a decline in patients' ability to safely administer the treatment. The groups also agreed that failure of response or disease progression (significant increase in bone marrow blasts), treatment-related toxicities, and patient preference would be the primary reasons for treatment discontinuation.

Prescribing Conditions

All 4 clinician groups agreed that the most appropriate setting for treatment administration can be in the community setting and outpatient clinic. Inpatient hospital treatment may also be required due to tumour lysis syndrome or AML complications while continuing on the treatment. CLSG noted there should be expertise in the outpatient clinic with chemotherapy preparation and administration. The L/BMT program of British Columbia noted that treatment with venetoclax and azacitidine requires monitoring of blood counts, renal function, and electrolytes more frequently early on during the first week of administration due to the risk of tumour lysis syndrome. CLSG was of the opinion that the treatment should be given in a setting where there is blood-bank support; physician, nursing, and pharmacy expertise in chemotherapy; an ability to deliver IV fluids and antibiotics; and an ability to admit patients to hospital for complications of treatment.

Additional Considerations

OH-CCO's Hem-DAC noted that venetoclax dose adjustment with co-administration of azole is sometimes required. In addition, the group added that in patients presenting with hyperleukocytosis, a longer ramp-up phase should be considered when initiating venetoclax.

The group added that the additional toxicities of the combination are largely related to increased myelosuppression and increased rates of febrile neutropenia early on during treatment, but this is manageable and does not offset the benefit of the treatment combination. The group also strongly supported the reimbursement of this treatment for older and unfit patients with AML due to the large, anticipated benefit for this group of patents, where there currently exists an unmet need for more effective treatment options.

CLSG noted that patients are already treated in many jurisdictions with azacitidine alone and adding an oral medication, like venetoclax, which is well tolerated with a straightforward administration schedule, does not increase the complexity of the treatment regimen. The group also added that the benefits obtained with this combination are seen much quicker than with azacitidine alone.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation.

The drug programs indicated that current treatment options for patients with newly diagnosed AML who are ineligible for intensive chemotherapy include azacitidine, LDAC, and BSC. The reimbursement of venetoclax plus azacitidine would likely replace single-agent azacitidine in this treatment setting. Azacitidine is funded in most jurisdictions for patients with AML who are ineligible for intensive chemotherapy, and some jurisdictions fund alternate dosing schedules for azacitidine (i.e., 5 to 2-2, and 6 consecutive days) in addition to the schedule of 7 consecutive days. However, it was noted that some patients 75 years of age and older may be fit to tolerate intensive chemotherapy. The ramp-up dosing schedule for venetoclax with azacitidine differs significantly from the ramp-up dosing schedule already in use for CLL indications, and the current packaging for venetoclax is designed for the CLL ramp-up dosing schedule. Venetoclax plus azacitidine includes an oral and an IV and subcutaneous drug and, therefore, would be reimbursed through different programs in some jurisdictions. The drug programs identified the potential for indication creep for patients with

a high risk of MDS, those who have progressed or have had an inadequate response on low-dose chemotherapy for AML, and patients who have relapsed after induction chemotherapy and are not eligible for stem cell transplant and who are then treated with azacitidine. It was noted that treatment combination may require the need for increased health care resources (i.e., hospital admission and additional pharmacy and nursing resources for the potential management of tumour lysis syndrome and monitoring for drug interactions). Affordability was also identified as an issue since the combination is expected to replace azacitidine monotherapy.

The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 4.

Clinical Evidence

The clinical evidence included in the review of venetoclax (Venclexta) in combination with azacitidine is presented in 3 sections. The first section, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence from the sponsor and indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of venetoclax in combination with azacitidine for the treatment of patients with newly diagnosed AML who are 75 years or older, or who have comorbidities that preclude use of intensive induction therapy.

Methods

Studies selected for inclusion in the systematic review will include pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 5. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[21]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid and Embase (1974–) through Ovid. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Venclexta (venetoclax) and AML. Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

Table 4: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Are all patients with newly diagnosed AML who are ineligible for treatment with intensive induction chemotherapy, regardless of cytogenetic risk, eligible for treatment with venetoclax plus azacitidine?	Although the VIALE-A trial excluded patients with favourable cytogenetic risk (defined according to NCCN guidelines for AML), all patients who are considered ineligible for treatment with intensive induction chemotherapy should be eligible for treatment with venetoclax plus azacitidine.
AML patients who previously received azacitidine for treatment of MDS were not eligible for treatment with venetoclax plus azacitidine in the VIALE-A trial but were included in the VIALE-C trial and eligible for treatment with venetoclax plus LDAC. Would these patients not be eligible for treatment with venetoclax plus azacitidine?	The VIALE-A trial excluded patients who had received previous treatment with an HMA for MDS; therefore, there is no evidence from the pivotal trial on the efficacy of venetoclax plus azacitidine in this group of patients. However, there is non-comparative clinical trial evidence[13] demonstrating that patients previously treated with azacitidine for MDS benefit from venetoclax plus azacitidine; the response rate, although lower than what has been observed in patients without prior exposure to azacitidine, is comparable to the response rate observed in the VIALE-C trial among patients with prior exposure to an HMA treated with venetoclax plus LDAC.[14] Based on these data, it would be reasonable to consider the use of venetoclax plus azacitidine in this subgroup of patients.
Can venetoclax be used with alternate azacitidine dosing schedules (e.g., 5-2-2 for 6 consecutive days)?	In clinical practice, azacitidine is usually administered on a 5-2-2 dosing schedule. There is evidence[15] demonstrating there is no difference in clinical outcome based on the dosing schedule used (i.e., 5-2-2, 6 and 7 consecutive days); therefore, venetoclax can be used with alternative azacitidine dosing schedules.
The highest strength of venetoclax available is a 100 mg tablet. At full dose, patients will need to take 4 × 100 mg tablets to make up the dose, which is a high pill burden. Is there a plan to manufacture a higher-strength tablet? Is any supportive care required during ramp-up (i.e., for TLS prophylaxis)?	During the ramp-up period of venetoclax, patients need to be treated in a setting where they can be monitored daily and would be treated with allopurinol as prophylaxis for TLS. Hydroxyurea should be administered to patients with a high WBC count to lower the WBC to less than 25 × 10^9/L before administering venetoclax to reduce the risk of developing TLS (same as on study).
There are differences in the eligibility criteria of the trials, VIALE-A and VIALE-C. Should the eligibility criteria for venetoclax plus azacitidine be consistent with the criteria for venetoclax plus LDAC? Should the following patients be considered for treatment with venetoclax plus azacitidine: • patients who have received prior HMA (azacitidine) or chemotherapy for the treatment of MDS (these patients were excluded from the VIALE-A trial) • patients with favourable cytogenic risk (these patients were excluded from the VIALE-A trial) • patients ≥ 75 years of age with an ECOG Performance Status greater than 2 (these patients were excluded from VIALE-A trial).	Although there were some differences in the patient eligibility requirements for each trial, criteria for reimbursement should be consistent for both venetoclax-based regimens. Regarding the eligibility of the following patient groups: • As noted earlier, patients who have received prior HMA or chemotherapy for the treatment of MDS and patients with favourable cytogenetic risk should be eligible for venetoclax plus azacitidine.[16] • Patients ≥ 75 years of age with an ECOG Performance Status greater than 2 may be eligible for venetoclax plus azacitidine, depending on whether their performance status is judged to be related to their AML; therefore, eligibility for venetoclax plus azacitidine should be determined for these patients on an individual basis. • Only 4 patients (2%) in the VIALE-C trial had favourable risk cytogenetics (3 patients in the placebo + LDAC arm and 1 patient in the venetoclax + LDAC arm); this is not a significant difference between the 2 studies.

Drug program implementation questions	Clinical expert response
Can venetoclax plus azacitidine be given to improve response as a bridge to allogeneic SCT in patients with AML who have a contraindication to chemotherapy, but are otherwise candidates for an allogeneic SCT?	It is uncommon to have a patient with a contraindication to chemotherapy proceed to allogeneic SCT, but it may happen in some circumstances (e.g., for patients who have an ejection fraction of less than 50% and hence have a comorbidity that renders them ineligible for intensive chemotherapy). These patients may achieve a response to venetoclax plus azacitidine and a (reduced intensity conditioning) allogeneic SCT could be considered. Evidence is emerging on the use of venetoclax plus azacitidine as a bridge to allogeneic SCT, especially in patients with treatment-naive, poor-risk AML who are fit for intensive chemotherapy (due to high response rates, low early deaths or induction deaths, and/or infections) and, as such, the combination is being used for this indication in other countries.[17-20] Hence, it would be reasonable to use venetoclax plus azacitidine as a bridge to allogeneic SCT in this small group of patients. However, long-term outcomes are limited.
There is a time-limited need to allow patients currently on azacitidine whose disease has not yet progressed to add venetoclax who otherwise meet the eligibility criteria. What is the appropriate time frame of treatment on azacitidine to consider the addition of venetoclax?	There is no evidence to inform the appropriate time frame to consider adding venetoclax for patients who are receiving azacitidine alone. In general, clinicians typically give up to 6 cycles (i.e., 6 months) of azacitidine alone to determine a patient's response to therapy. Therefore, it would be reasonable to add venetoclax to azacitidine if patients were within the 6-month time frame of initiating azacitidine and had not progressed. The value of adding venetoclax for a patient who has achieved a response or remission on azacitidine alone is unknown.
Inpatient administration may be required during the ramp-up portion for venetoclax. Are there specific groups or an estimated percentage of patients who would require hospital admission for the ramp-up portion of venetoclax?	Hospital administration will be required for some patients and this is not necessarily limited to the ramp-up portion of venetoclax. This is an older patient population of whom some may be frail; and patients may develop febrile neutropenia or infection any time during the treatment window. It is difficult to estimate, but up to 30% of patients may require hospitalization during the ramp-up portion of venetoclax, and this may vary depending on the treatment setting (i.e., treatment centre vs. community where they may not have the appropriate resources to monitor for TLS daily during the ramp-up period). However, this percentage is expected to decrease over time as clinicians become more experienced with administering venetoclax. Special groups of patients who may be an increased risk of hospitalization during the ramp-up period include those who have an elevated WBC count, high tumour burden, or underlying renal insufficiency.
Are patients with a good risk prognosis eligible for venetoclax plus azacitidine? Please confirm that all cytogenetic risks are eligible for treatment with venetoclax plus azacitidine.	As previously noted, all patients considered ineligible for intensive induction chemotherapy, regardless of prognostic or cytogenetic risk, should be eligible for venetoclax plus azacitidine.
If a patient stops treatment with the azacitidine component for reasons other than disease progression, can the venetoclax be continued until disease progression?	The VIALE-A clinical trial did not have a provision for patients to stop azacitidine and continue on venetoclax or placebo.

AML = acute myeloid leukemia; ECOG = Eastern Cooperative Oncology Group; HMA = hypomethylating agent; LDAC = low-dose cytarabine; MDS = myelodysplastic syndrome; NCCN = National Comprehensive Cancer Network; SCT = stem cell transplant; TLS = tumour lysis syndrome; WBC = white blood cell.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

Table 5: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Patients newly diagnosed with AML who are 75 years or older or who have comorbidities that preclude use of intensive induction therapy Subgroups: • age (75 years or older) or comorbidities • Eastern Cooperative Oncology Group Performance Status • prior myelodysplastic syndrome or myeloproliferative neoplasm • prior exposure to chemotherapy or radiation due to other malignancies • primary or secondary malignancy (secondary or therapy-related AML) • cytogenetic risk • blast count • mutations (IDH1 and IDH2, FLT3, NPM1, TP53)
Intervention	Venetoclax oral 400 mg per day (every day) and azacitidine 75 mg/m^2 per day, IV or SC (days 1 through 7 of 28-day cycle)
Comparators	Azacitidine monotherapy Low-dose cytarabine monotherapy Venetoclax + low-dose cytarabine Induction chemotherapy (for patients aged 75 years or older)[a] Best supportive care
Outcomes	Overall survival[b] Event-free survival[b] Complete remission rate with and without hematological recovery Partial remission or hematological improvement Time to remission Duration of remission Need for transfusion, transfusion independence Hospital admission Patient quality of life Symptom severity **Harms outcomes:** • AEs, SAEs, TEAEs, WDAEs, mortality Notable harms and harms of special interest: • neutropenia • febrile neutropenia • infections • tumour lysis syndrome • hemorrhage • secondary malignancies

Criteria	Description
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; AML = acute myeloid leukemia; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; HRQoL = quality of life; LDAC = low-dose cytarabine; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

[a]Induction chemotherapy was added as a comparator based on feedback from the clinical experts consulted by CADTH on this review, as it is considered a potential option for approximately 10% of patients who are aged 75 years or older.

[b]These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The initial search was completed on February 11, 2021. Regular alerts updated the search until the meeting of the CADTH pan-Canadian Oncology Drug Review Expert Committee (pERC) on June 10, 2021.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[22] Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

One study[23] was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 6. A list of excluded studies is presented in Appendix 2.

Description of Studies

VIALE-A

VIALE-A is a phase III, randomized, double-blind, placebo-controlled, multi-centre study comparing venetoclax plus azacitidine with placebo plus azacitidine in adults with newly diagnosed AML aged 18 years or older and ineligible for standard induction therapy due to age or comorbidities. The trial was conducted at 134 sites in Europe, Asia, South America, Canada, and the US. Trial characteristics are summarized in Table 6.

The primary objective was to evaluate whether venetoclax plus azacitidine would improve OS and composite complete remission rate (CR + CRi) compared with placebo plus azacitidine.

The secondary objectives were to evaluate whether, compared with placebo plus azacitidine, venetoclax plus azacitidine would improve the CR rate, CR + CRh rate, CR + CRi rate by the initiation of cycle 2, transfusion-independence rate, MRD response rate, response rates and OS in molecular subgroups, fatigue, GHS/QoL, and EFS. Improvement of fatigue and GHS/QoL were measured using patient-reported outcome assessments (Patient-Reported

Outcomes Measurement Information System Short Form v1.0–Fatigue 7a [PROMIS 7a] and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30]). Definitions and further details of outcomes are given in Table 8.

Exploratory objectives included the study of biomarkers predictive of venetoclax plus azacitidine activity and the evaluation of additional subscales and items from the EORTC QLQ-C30 and EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L) scales.

A total of 579 patients were screened and 433 patients were randomized in a 2:1 ratio to venetoclax plus azacitidine (287 patients), or placebo plus azacitidine (146 patients). Randomization was stratified for age (18 years to < 75 years, ≥ 75 years) and cytogenetic risk (intermediate, poor) for protocol amendment 1 and subsequent amendments. Prior to amendment 1, stratification was by age and region; the 2 patients (1 in each group)

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

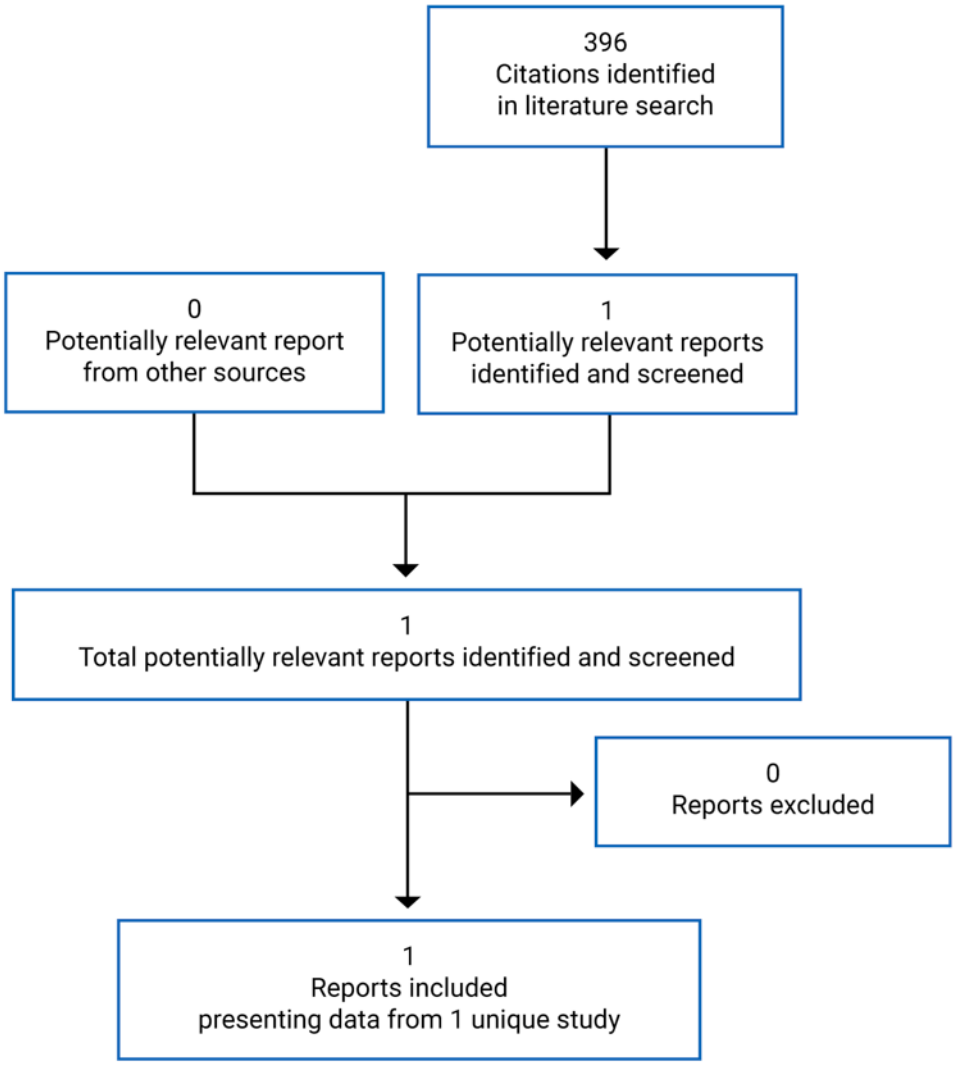


Table 6: Details of Included Studies

Detail	VIALE-A
Designs and populations	
Study design	Phase III, multi-centre, double-blind, placebo-controlled RCT
Locations	134 sites Canada, Europe, Russia, Asia, US, and South Africa
Patient enrolment dates	February 6, 2017 to May 31, 2019
Randomized (N)	433 (2 randomized under stratification criteria of original protocol)
Inclusion criteria	AML by WHO criteria, previously untreated and ineligible for treatment with standard cytarabine and anthracycline due to age or comorbidities Ineligible for induction therapy defined by the following: • age ≥ 75 years, or • age 18 to 74 years with at least 1 of: ◦ ECOG PS 2 or 3 ◦ history of CHF requiring treatment, EF ≤ 50%, or chronic stable angina ◦ DLCO ≤ 65% or FEV_1 ≤ 65% ◦ creatinine clearance ≥ 30 mL/min to 45 mL/min ◦ moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 ULN ◦ other comorbidity considered incompatible with intensive chemotherapy, as reviewed and approved by sponsor ECOG PS 0 to 2 (≥ 75 years), 0 to 3 (18 to 74 years) Adequate renal function as demonstrated by creatinine clearance ≥ 30 mL/min calculated by Cockcroft Gault formula or measured by 24 hours of urine collection Adequate liver function as demonstrated by: • aspartate aminotransferase (AST) ≤ 3.0 × ULN[a] • alanine aminotransferase (ALT) ≤ 3.0 × ULN[a] • bilirubin ≤ 1.5 × ULN[a] (patients < 75 years could have bilirubin ≤ 3.0 × ULN)

Detail	VIALE-A
Exclusion criteria	Has received treatment with the following: • HMA and/or any chemotherapeutic drug for MDS • CAR T-cell therapy • experimental therapy for MDS or AML • current participation in another research or experimental study History of myeloproliferative neoplasm, including myelofibrosis, essential thrombocythemia, polycythemia vera, chronic myeloid leukemia with or without BCR-ABL1 translocation, and AML with BCR-ABL1 translocation Acute promyelocytic leukemia Known active CNS involvement with AML Known HIV infection Known hepatitis B or C infection, with the exception of those with undetectable viral load within 3 months of screening Received strong and/or moderate CYP3A inducers within 7 days before initiation of study treatment Consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit within 3 days before the initiation of study treatment Cardiovascular disability status of NYHA class 2 Chronic respiratory disease requiring continuous oxygen; significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, or hepatic disease; cardiovascular disease; any other medication condition, or known hypersensitivity to any of the study medications, including excipients of azacitidine that in the opinion of the investigator would adversely affect the patient's participation in the study History of other malignancies within 2 years before study entry, with the exception of: • adequately treated in situ carcinoma of the cervix uteri or carcinoma in situ of breast • basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin • previous malignancy confined and surgically resected (or treatment with other modalities) with curative intent (required discussion with sponsor) White blood cell count > 25 × 10^9/L (hydroxyurea or leukapheresis were permitted to meet this criterion)
Drugs	
Intervention	Venetoclax 400 mg per day after dose titration plus azacitidine 75 mg/m^2 (days 1 to 7 of 28-day cycle), SC or IV. Venetoclax dose titration, cycle 1: day 1 = 100 mg, day 2 = 200 mg, day 3 and thereafter = 400 mg per day.
Comparator(s)	Azacitidine 75 mg/m^2 (days 1 to 7, 28-day cycle) SC or IV

Detail	VIALE-A
Duration	
Phase	
Double-blind	Until disease progression per investigator assessment, unacceptable toxicity, withdrawal of consent, or patient met other protocol criteria for discrimination
Follow-up	Survival information and post-treatment follow-up for approximately 2 years after enrolment of last patient. For patients discontinuing for a reason other than disease progression, hematological and disease assessment until approximately 1 year after last patient.
Outcomes	
Primary end point	OS CR + CRi
Secondary and exploratory end points	Secondary: • CR • CR + CRh • CR + CRi by initiation of cycle 2 • EFS • transfusion independence • MRD response • fatigue • HRQoL • OS and CR + CRi in molecular subgroups Exploratory: • biomarkers predictive of venetoclax activity and DOR • HRQoL (additional measures) • health utility
Notes	
Publications	Di Nardo (2020)[23]

AML = acute myeloid leukemia; CAR T-cell therapy = chimeric antigen receptor T-cell therapy; CHF = congestive heart failure; CNS = central nervous system; CR = complete remission; CRh = complete remission with partial hematological recovery; CRi = complete remission with incomplete hematological recovery; DB = double-blind; DLCO = diffusing capacity of the lungs for carbon monoxide; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EF = ejection fraction; EFS = event-free survival; FEV_1 = forced expiratory volume in 1 second; HMA = hypomethylating agent; HRQoL = health-related quality of life; MDS

= myelodysplastic syndrome; MRD = minimal/measurable residual disease; NYHA = New York Heart Association; OS = overall survival; RCT = randomized controlled trial; SC = subcutaneous; ULN = upper limit of normal.
Note: Additional VIALE-A reports included a Clinical Study Report[1] and patient-reported outcome report.[1]
[a]Unless considered due to leukemic organ involvement.
Source: Clinical Study Report.[1]

randomized under the original protocol were not included in the efficacy analysis. An additional open-label cohort of up to 12 patients was recruited to receive venetoclax plus azacitidine so as to provide pharmacokinetic and safety data required by the Chinese regulatory authorities before the recruitment of Chinese patients into the double-blind randomized portion of the study. These patients were not included in the efficacy or safety analyses for the main study and will not be described further in this report.

The first patient was randomized on February 6, 2017 and the last on May 31, 2019. Analysis of the co-primary efficacy end point of CR + CRi was planned for 6 months after the first 225 patients were randomized (first interim analysis [IA1]), at which time an interim analysis of survival was conducted. Interim data were reviewed by an independent data monitoring committee (IDMC) and the trial proceeded blinded. A second interim analysis (IA2) was planned when approximately 270 OS events accrued, before the final analysis at approximately 360 OS events. Review of the results against preplanned stopping criteria led to a recommendation by the IDMC to stop the trial on March 16, 2020. Data cut-off for IA1 was October 1, 2018 and January 4, 2020 for IA2.

Populations

Inclusion and Exclusion Criteria

Eligible patients had to be 18 years or older with confirmed AML according to WHO criteria and be considered ineligible for induction therapy on account of age (≥ 75 years) or significant cardiac, pulmonary, renal, hepatic, or other comorbidity. Patients aged 75 years and older had to have an ECOG PS of 0 to 2, and those aged 18 to 74 years could have an ECOG 0 to 3.

Patients were ineligible if they had acute promyelocytic leukemia, AML with favourable risk cytogenetics such as t(8;21), inv(16), t(16;16) or t(15;17) (as per NCCN Guidelines Version 2, 2016 for AML), AML with known active CNS involvement, a history of myeloproliferative neoplasm, or if they had previously received an HMA and/or any chemotherapeutic agent for MDS, or CAR T-cell therapy or any other experimental therapy.

Baseline Characteristics

Table 7 shows the baseline characteristics for the efficacy population. The mean age overall was 75.4 (SD = 5.95) years, and 60.6% of patients were aged 75 years or older. The majority were male (60.1%) and White (75.6%), followed by Asian (23.0%). Most had an ECOG PS of 1 (41.5%) or 2 (29.9%). The most common reasons patients were ineligible for standard induction therapy were because they were aged 75 years or older (56.8%) and had an ECOG PS of 2 or 3 (43.2%). Most patients (75.2%) had de novo AML; of those with secondary AML, 67.3% had prior MDS or chronic myelomonocytic leukemia. Cytogenetics were intermediate risk in 62.9% and poor in 37.1%. Of individual mutations, 23.9% of patients with known mutation status had mutations detected in IDH1 and/or IDH2, 16.2% had FLT3-ITD mutations and/or tyrosine kinase domain (TKD) mutations, 17.7% had nucleophosmin 1 (NPM1) mutations, and 20.9% had tumour protein p53 (TP53) mutations. Half (49.9%) had a bone marrow blast count of 50% or greater, 21.8% had a blast count between 30% and less than 50%, and 29.2% had a blast count of less than 30%. More than half (54.8%) had required a red blood cell or platelet transfusion within 8 weeks of first study treatment.

The demographic and baseline characteristics were well balanced. A greater proportion of patients receiving placebo plus azacitidine had mutations in FLT3 (20.4%) compared with those receiving venetoclax plus azacitidine (14.1%); conversely, a greater proportion of patients receiving venetoclax plus azacitidine had mutations in TP53 (23.3%) compared with

placebo plus azacitidine (16.3%). Overall cytogenetic risk was a stratification variable and was well balanced.

Interventions

Venetoclax in the venetoclax plus azacitidine group was dosed at 400 mg oral per day after the initial dose titration of 100 mg at cycle 1 day 1, 200 mg at day 2, and 400 mg at day 3 and thereafter. Dosing was based on a phase Ib dose-escalation study of venetoclax in combination with HMAs (azacitidine and decitabine) in treatment-naive patients with AML who were aged 65 years or older and ineligible for the standard induction regime (Study M14 to 358).

Azacitidine in the venetoclax plus azacitidine and azacitidine groups was dosed at 75 mg/m^2 subcutaneous or IV (depending on local practice) on days 1 to 7 of a 28-day cycle. The dose is as specified for the treatment of adult patients with AML in the EU Summary of Product Characteristics and for MDS in the US dose prescribing information.

Treatment was planned for a minimum of 6 cycles. Treatment could continue as long as the patient derived clinical benefit and did not have documented disease progression or develop unacceptable toxicity.

To allow for hematologic recovery from cytopenias, the dosing of venetoclax or placebo could be interrupted, the start of the next cycle delayed, or the duration reduced according to preplanned criteria. If the recovery did not reach a certain threshold, then the administered dose of azacitidine could be reduced by preplanned steps.

- If a patient achieved CRi or a morphologic leukemia-free state (MLFS) after cycle 1, they could interrupt venetoclax or placebo dosing from day 29 until an absolute neutrophil count (ANC) of 500/μL or greater, or for up to 14 days. Cycle 2 administration would be delayed until ANC was 500/μL or greater.
- If a patient experienced a new onset grade 4 neutropenia for more than 1 week during subsequent cycles that was not thought to be due to the underlying disease, venetoclax or placebo dosing could be interrupted until ANC was 500/μL or greater.
- After cycle 3, a patient in CR/CRi who needed interruption or delay of study drug for cytopenia could receive venetoclax plus azacitidine for 21 out of 28 days of each cycle.
- If a patient showed hematological recovery (ANC or platelets) within 14 days after completion of a cycle, the duration of venetoclax was reduced to 21 days of the cycle. During subsequent cycles, if hematologic recovery with more than a 25% increase above the nadir was not seen within 21 days after cycle completion, the azacitidine dose was reduced to 50% in patients with bone marrow cellularity of 15% to 50%, and to 33% in patients with bone marrow cellularity of less than 15%.

Protocol-specified dose adjustments were also made to adjust for drug interactions with systemic anti-fungal agents and other drugs that produced moderate or strong inhibition of CYP3A. Venetoclax or placebo was to be reduced at least twofold in patients receiving moderate CYP3A inhibitors and at least eightfold in those receiving strong CYP3A inhibitors. Moderate CYP3A inducers were excluded during the ramp-up phase and used with caution and after discussion with the sponsor.

All patients received prophylaxis against tumour lysis syndrome with oral and/or IV hydration and uric acid reducer and were admitted for monitoring during ramp-up of venetoclax plus

Table 7: Demographic and Baseline Characteristics — Efficacy Population

Characteristic	VEN + AZA (N = 286)	PBO + AZA (N = 145)
Age (years)		
Mean (SD)	75.6 (6.08)	75.1 (5.70)
Median	76	76
Minimum, maximum	49.0, 91.0	60.0, 90.0
Age category, n (%)		
< 75 years	121 (42.3)	64(44.1)
≥ 75 years	165 (57.5)	81 (55.5)
Sex or gender, n (%)		
Male	172 (60.1)	87 (60.0)
Female	114 (39.9)	59 (40.0)
Race, n (%)		
White	217 (75.9)	109 (75.2)
Asian	66 (23.1)	33 (22.8)
Black or African American	3 (1.4)	2 (1.0)
American Indian or Alaska Native	0	1 (0.7)
Region, n (%)		
US	50 (17.5)	24 (16.6)
EU	116 (40.6)	59 (40.7)
China	24 (8.4)	13 (9.0)
Japan	24 (8.4)	13 (9.0)
Rest of world	72 (25.5)	36 (24.8)
ECOG Performance Status, n (%)		
0	37 (12.9)	23 (15.9)
1	120 (42.0)	58 (40.0)
2	113 (39.5)	59 (40.7)
3	16 (5.6)	5 (3.4)
Cytogenetic risk, n (%)		
Intermediate	182 (63.6)	89 (61.4)
Poor	104 (36.4)	56 (38.6)
AML disease type, n (%)		
Primary or de novo	214 (74.8)	110 (75.9)

Characteristic	VEN + AZA (N = 286)	PBO + AZA (N = 145)
Secondary (prior MDS and therapy-related AML), n (%)	72 (25.2)	35 (24.1)
Type of secondary AML, n (%, of those with secondary AML)		
Therapy-related	26 (36.1)	9 (25.7)
Post MDS or CMML	46 (63.9)	26 (74.3)
Antecedent history of MDS, n (%)		
Yes	49 (17.1)	27 (18.6)
No	237 (82.9)	118 (81.4)
RBC or platelet transfusion,[b] n (%)		
Yes	155 (54.2)	81 (55.9)
No	131 (45.8)	64 (44.1)
RBC transfusion,[b] n (%)		
Yes	144 (50.3)	76 (52.4)
No	142 (49.7)	69 (47.6)
Platelet transfusion,[b] n (%)		
Yes	68 (23.8)	32 (22.1)
No	218 (76.2)	113 (77.9)
Bone marrow blast, n (%)		
< 30%	85 (29.7)	41 (28.3)
≥ 30% to < 50%	61 (21.3)	33 (22.8)
≥ 50%	140 (49.0)	71 (49.0)
IDH1 or IDH2 mutation, n[c,d] (%)		
IDH1	23 (9.4)	11 (8.7)
IDH2	40 (16.3)	18 (14.2)
IDH1 and/or IDH2	61 (24.9)	28 (22.0)
No mutation detected	184 (75.1)	99 (78.0)
Undetermined or missing	41	18
FLT3 mutation, n[c,e] (%)		
ITD	23 (11.2)	13 (12.0)
TKD	7 (3.4)	10 (9.3)
ITD and/or TKD	29 (14.1)	22 (20.4)
Not detected	177 (85.9)	86 (79.6)

Characteristic	VEN + AZA (N = 286)	PBO + AZA (N = 145)
Undermined or missing	80	37
NPM1 mutation, n[c] (%)		
Detected	27 (16.6)	17 (19.8)
Not detected	136 (83.4)	69 (80.2)
Undetermined or missing	123	59
TP53 mutation, n[c] (%)		
Detected	38 (23.3)	14 (16.3)
Not detected	125 (76.7)	72 (83.7)
Undetermined or missing	123	59
Reasons for being ineligible for standard induction therapy,[a] n (%)		
≥ 75 years of age	165 (57.7)	80 (55.2)
≥ 18 to 74 years of age	121 (42.3)	65 (44.8)
ECOG Performance Status of 2 or 3	95 (33.2)	50 (34.5)
History of congestive heart failure requiring treatment	2 (0.7)	3 (2.1)
Ejection fraction ≤ 50%	5 (1.7)	3 (2.1)
Chronic stable angina	5 (1.7)	1 (0.7)
DLCO ≤ 65%	11 (3.8)	12 (8.3)
FEV_1 ≤ 65%	12 (4.2)	7 (4.8)
Creatinine clearance ≥ 30 mL/min to < 45 mL/min	11 (3.8)	5 (3.4)
Moderate hepatic impairment with total bilirubin > 1.5 to ≤ 3.0 × ULN	3 (1.0)	2 (1.4)
Other	12 (4.2)	6 (4.1)
CTC grade: Neutropenia		
0	53 (18.5)	29 (20.0)
1	7 (2.4)	11 (7.6)
2	20 (7.0)	14 (9.7)
3	48 (16.7)	30 (20.8)
4	159 (55.4)	60 (41.4)
Missing	0	1
CTC grade: Anemia		
0	2 (0.7)	2 (1.4)

Characteristic	VEN + AZA (N = 286)	PBO + AZA (N = 145)
1	39 (13.6)	17 (11.7)
2	157 (54.9)	74 (50.7)
3	88 (30.8)	52 (35.9)
CTC grade: Thrombocytopenia		
0	36 (12.6)	19 (13.1)
1	61 (21.3)	28 (19.3)
2	44 (15.4)	25 (17.2)
3	78 (27.3)	42 (29.0)
4	67 (23.4)	31 (21.4)

AML = acute myeloid leukemia; AZA = azacitidine; CMML = chronic myelomonocytic leukemia; CTC = circulating tumour cell; DLCO = diffusing capacity of the lungs for carbon monoxide; ECOG = Eastern Cooperative Oncology Group; FEV_1 = forced expiratory volume in 1 second; FLT3 = FMS-like tyrosine kinase 3; IDH = isocitrate dehydrogenase; ITD = internal tandem duplication; MDS = myelodysplastic syndrome; MRC = myelodysplasia-related changes; NPM1 = nucleophosmin 1; PBO = placebo; SD = standard deviation; TKD = tyrosine kinase domain; TP53 = tumour protein p53; ULN = upper limit of normal; VEN = venetoclax.

[a]Patients could have more than 1 reason for ineligibility.

[b]Transfusion within 8 weeks of start of PBO or VEN.

[c]Percentages exclude patients with undetermined or missing mutation status.

[d]A patient could have both the IDH1 and IDH2 mutations.

[e]A patient could have both FLT3-ITD and FLT3-TKD mutations.

Source: Clinical Study Report.[1]

placebo dosing. Patients with a white blood cell count greater than 25×10^9/L received cytoreduction before dosing.

Outcomes

Table 8 provides definitions of the efficacy end points that were assessed in the clinical trials included in this review and identified in the CADTH review protocol. Response measures (CR, CRi), partial remission, MLFS, resistant disease, and morphologic relapse were based on the revised guidelines for the International Working Group (IWG) for AML. Progressive disease was defined according to European LeukemiaNet recommendations. CRh is a derived end point based on bone marrow and hematological measurements. These end points are further summarized in Table 8. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

EORTC QLQ-C30 (Version 3.0) is a cancer-specific measure of health-related quality of life (HRQoL).[24] It comprises 30 individual questions organized into 5 functional scales (physical, role, cognitive, emotional, and social function), 3 symptom scales (fatigue, pain, and nausea and vomiting), 6 single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial impact), and a global QoL scale (GHS/QoL). Function and symptoms are assessed over a 1-week recall period. Most questions have 4 response options ("not at all," "a little," "quite a bit," "very much"), with scores on these items ranging from 1 to 4.[25] For the 2 items that form the GHS/QoL scale, the response format is a 7-point Likert-type scale, with anchors between 1 (very poor) and 7 (excellent).[25] Each raw scale score is converted to a standardized score ranging from 0 to 100, with a higher score reflecting better function on the function scales, higher symptoms on the symptom scales, and better QoL on the QoL scales.

Table 8: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome	VIALE-A definition
OS	Number of days from date of randomization to the date of death.
EFS	Number of days from randomization to the date of progressive disease, relapse from CR or CRi, treatment failure (failure to achieve CR, CRi, or MLFS after at least 6 cycles of study treatment), or death from any cause.
CR	Absolute neutrophil counts > 10^9/L, platelets > 100 × 10^9/L, RBC transfusion independence, and bone marrow with < 5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.
CRi	All criteria as CR except for residual neutropenia ≤ 10^9/L (1,000/μL), thrombocytopenia ≤ 100 × 10^9/L (100,000/μL), or RBC dependence.
CRh	Peripheral blood neutrophil count > 0.5 × 10^9/L, peripheral blood platelet count > 50 × 10^9/L, bone marrow < 5% blasts.
PR	All hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.
MLFS	Less than 5% blasts in aspirate sample with marrow spicules and with a count of at least 200 nucleated cells. Absence of circulating blasts and extramedullary disease without peripheral blood cell recovery that meets thresholds for either CR or CRi.
RD	Failure to achieve CR, CRi, PR, or MLFS; only for patients surviving at least 7 days following completion of cycle 1 treatment with evidence of persistent leukemia by blood or bone marrow examination.
MR	Reappearance of ≥ 5% blasts after CR/CRi in peripheral blood or bone marrow or development of extramedullary disease.
PD[a]	50% increase in marrow blasts over baseline (minimum 15% increase 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 of ANC to an absolute level (> 0.5 × 10^9/L [500/μL], and/or platelet count to > 50 × 10^9/L [50,000/μL]); or 50% increase in peripheral blasts (WBC × % blasts) to > 25 × 10^9/L [25,000/μL]); or New extramedullary disease.
DOR	The number of days from the date of first response (CR, CRi, or CRh) to the earliest evidence of confirmed MR, PD, or death due to disease progression.
Transfusion independence	≥ 56 days with no transfusion between the first dose of the study drug and the last dose of the study drug + 30 days. Applies to both RBC and platelets.
EORTC QLQ-C30	Consists of 30 items assessing quality of life in cancer patients. Includes 15 questions to assess HRQoL domains, including 5 multi-item functional scales (physical, emotional, cognitive, social, and role functioning), 3 multi-item symptom scales (fatigue, nausea and vomiting, pain), 6 single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) and a global health status and quality of life scale (MCT = 10).
PROMIS 7a	Consists of 7 items assessing impact of fatigue over past 7 days in patients with cancer. Each response is on a 5-item scale ranging from 1 = never to 5 = always (MCT = 5).
EQ VAS	Visual analogue scale ranging from 100 (best imaginable health) to 0 (worst imaginable health) (MCT = 7).

ANC = absolute neutrophil count; CR = complete remission; CRh = complete remission with partial hematological recovery; CRi = complete remission with incomplete blood count recovery; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L VAS = EuroQol 5-Dimensions 5-Levels questionnaire Visual Analogue Scale; EFS = event-free survival; MCT = meaningful change threshold; MLFS = morphological leukemia-free state; MR = morphologic relapse; OS = overall survival; PD = progressive disease; PR = partial remission; PROMIS 7a = Patient-Reported Outcomes Measurement Information System Short Form v1.0–Fatigue 7a; RBC = red blood cell; RD = resistant disease; WBC = white blood cell.

[a]PR defined by European LeukemiaNet criteria.

Source: Clinical Study Report.[1]

Construct validity and internal consistency reliability were assessed by 2 separate studies using convenience samples of cancer patients in Singapore[26] and Kenya,[27] most of whom had breast or colon cancer. No relevant studies of responsiveness were found. Two studies estimated the minimal important difference (MID), 1 in patients with breast and small-cell lung cancer, using an anchor-based approach using change as measured by the subjective significance questionnaire,[28] and the other in Canadian patients newly diagnosed with breast and colorectal cancer.[29] Both estimated an MID of 10 points. A third study in Canadian patients[30] used the EORTC (the GHS/QoL questions) to estimate MIDs for the overall EORTC QLQ C30 scales, but the method did not allow estimation of the MID for the GHS/QoL subscale itself.

The **PROMIS 7a** is a 7-item, patient-reported, tool that measures both the experience of fatigue and the interference of fatigue on daily activities over the past week. Responses are measured on a 5-point Likert scales from 1 = never to 5 = always, with total scores ranging from 7 to 35, with higher scores indicating greater fatigue.

There were no published validation studies of PROMIS 7a in cancer. Concurrent and discriminant validity were assessed in a mixed group of non-cancer patients and healthy controls. Known-groups validity was assessed by comparing PROMIS 7a scores in the clinical samples with healthy controls.[31]

The researchers who conducted the VIALE-A trial assessed the MID using anchor- and distribution-based approaches in a group of AML patients from the VIALE-C study.[1] A 3-point difference that fell within the range of 3 to 5 proposed in the literature was considered an appropriate MID for patients with AML.

The **EQ-5D-5L** is a generic HRQoL instrument applicable to a wide range of health conditions.[32,33] The first of 2 parts of the EuroQol 5-Dimensions questionnaire (EQ-5D) is a descriptive system that classifies respondents (aged ≥ 12 years) in 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D-5L has 5 possible domains, representing "no problems," "slight problems," "moderate problems," "severe problems" and "extreme problems." Respondents are asked to choose the level that reflects their health state for each of the 5 dimensions, corresponding with 3,125 different health states. The second part is a visual analogue scale in which patients are asked to appraise their overall QoL on a scale of 0 to 100. There are 3 outputs: a 5-digit profile indicating the health states on the 5 dimensions, a population preference-weighted health index score based on the descriptive system, and a self-reported assessment of health status based on the EuroQol Visual Analogue Scale (EQ VAS).

Validity was assessed in 184 Canadian cancer patients with breast, colorectal, or lung cancer.[34] The EQ-5D was able to discriminate between groups based on self-reported health status (excellent/good versus fair/very poor), somewhat based on ECOG PS (0 versus 1 to 3), but not for stage of cancer.[34] Internal consistency reliability was calculated for the same study, and all 5 functioning scales along with GHS showed acceptable consistency (alpha > 0.70). Responsiveness was not reported. No relevant studies reported the MID.

Statistical Analysis

The analysis of the co-primary efficacy end point of CR + CRi was planned for 6 months after the first 225 patients were randomized. Three analyses were planned for the co-primary efficacy end point of OS:

- at the same time as the CR + CRi analysis
- when approximately 270 OS events (75%) had occurred of a planned total 360 events (IA2)
- when approximately 360 events had occurred (final analysis)

There was a formal interim analysis for safety after approximately 20 patients received study medication and had been followed for at least 3 months. Subsequently, safety reviews were conducted every 3 months.

Interim data were reviewed by an IDMC that could make recommendations for the ongoing conduct of the trial. The trial design allowed for early regulatory submission in the EU following IA1, if desired. Following review of the results of IA, the IDMC recommended no modification and the trial continued without unblinding. Review of the results of IA2 led to an IDMC recommendation to stop the trial on March 16, 2020.

Table 9 summarizes the methods used for statistical analysis of the efficacy end points. Time-to-event end points were analyzed with stratified Kaplan–Meier estimates and stratified log-rank comparisons. Proportions were compared by calculation of stratified ORs with statistical comparison by stratified Cochrane-Mantel-Haenszel tests. Stratification was by age and cytogenetic risk categories. Patient-reported outcomes were compared by linear mixed-effects regression models fitted to longitudinal data with covariance structure.

The sample size calculation assumed that patients would be randomized 2:1 to venetoclax plus azacitidine to placebo plus azacitidine. Other assumptions were:

- A 2-sided alpha of 0.05 would be divided between co-primary end points to allocate 0.01 alpha to CR + CRi and 0.04 alpha to OS.
- The rate of CR + CRi was projected to be 28% for placebo plus azacitidine and 55% for venetoclax plus azacitidine.
- A median OS of 10.4 months was projected for placebo plus azacitidine and 14.9 months (HR = 0.7) for venetoclax plus azacitidine.
- An interim OS 75% calculation with O'Brien-Fleming boundary, with an interim data cut-off at 270 deaths.

Based on these assumptions, 225 patients (150 venetoclax plus azacitidine, 75 placebo plus azacitidine) would give 88% power to detect difference at a 2-sided alpha of 0.01, and 360 death events would have 86.7% power to detect a difference in OS with a 2-sided alpha of 0.04. Approximately 400 patients would be randomized: 267 to venetoclax plus azacitidine, and 133 to placebo plus azacitidine.

A hierarchical testing strategy was used for the control of multiplicity. The co-primary analysis of CR + CRi was performed on the first 225 patients (IA1). Two interim analyses of OS were planned, the first at IA1, with an administrative significance level of 0.0001. IA2 was performed after approximately 270 deaths (75% of predetermined deaths), using a Lan-DeMets alpha-spending function with O'Brien-Fleming boundary to control the 1-sided false-positive rate. Based on this analysis and pre-specified stopping rules, the IDMC made a recommendation to stop for success at IA2 rather than proceed to the final analysis. For the CR + CRi rate, CR + CRh rate, CR + CRi rate by the initiation of cycle 2, CR + CRh rate by the initiation of cycle 2, CR rate, and transfusion independence rate outcomes, the information fraction to be used at IA2 was calculated based on the proportion of the planned number of patients who had reached the desired amount of follow-up (e.g., for CR + CRi, at least 6 months of follow-up).

Table 9: Statistical Analysis of Efficacy End Points

End point	Statistical model	Stratification and adjustment factors	Sensitivity analyses
VIALE-A			
OS	HR estimated from stratified Kaplan–Meier model Stratified log-rank test For IDH1/IHD2 and FLT3 subgroups, unstratified log-rank test	Stratified by age (18 to < 75 years, ≥ 75 years), cytogenetics (intermediate risk, poor risk)	All data in extracted database Censoring of patients who received post-study treatment before experiencing event at start of post-study treatment
EFS	HR estimated from stratified Kaplan–Meier model Stratified log-rank test	Stratified by age (18 to < 75 years, ≥ 75 years), cytogenetics (intermediate risk, poor risk)	Censoring of patients who received post-study treatment before experiencing event at start of post-study treatment
CR + CRi (investigator assessment)	Proportions with CR + CRi Comparisons by OR Comparisons by CMH stratified by age, cytogenetics For IDH1/IHD2 and FLT3 subgroups, Fisher's Exact Test	Stratified by age (18 to < 75 years, ≥ 75 years), cytogenetics (intermediate risk, poor risk)	
CR + CRh (investigator assessment)	Proportions with CR + CRh Comparisons by OR Comparisons by CMH stratified by age, cytogenetics For IDH1/IHD2 and FLT3 subgroups, Fisher's Exact Test	Stratified by age (18 to < 75 years, ≥ 75 years), cytogenetics (intermediate risk, poor risk)	
Duration of CR + CRi	HR estimated from stratified Kaplan–Meier model	Stratified by age (18 to < 75 years, ≥ 75 years), cytogenetics (intermediate risk, poor risk)	Censoring of patients who received post-study treatment before experiencing event at start of post-study treatment
Transfusion independence	Proportions with transfusion independence Comparisons by stratified CMH	Stratified by age (18 to < 75 years, ≥ 75 years), cytogenetics (intermediate risk, poor risk)	
Fatigue (PROMIS 7a)	Comparisons by linear mixed effects regression model fitted to longitudinal data with covariance structure Exploratory TTD HR estimated from stratified Kaplan–Meier model (MCT = 5)	Models includes baseline score, stratification factors (age and cytogenetics), treatment arm, visit, and treatment arm by visit interaction	

End point	Statistical model	Stratification and adjustment factors	Sensitivity analyses
QoL (EORTC QLQ-C30, GHS/QoL)	Comparisons by linear mixed effects regression model fitted to longitudinal data with covariance structure Exploratory TTD HR estimated from stratified Kaplan–Meier model (MCT = 10)	Models includes baseline score, stratification factors (age and cytogenetics), treatment arm, visit, and treatment arm by visit interaction	Cochrane regression models including treatment arm and prognostic variables (age, baseline ECOG store, AML type, cytogenetic risk, baseline PRO)

AML = acute myeloid leukemia; CMH = Cochran-Mantel-Haenszel; CR = complete remission; CRh = complete remission with incomplete hematological recovery; CRi = complete remission with incomplete blood count recovery; EFS = event-free survival; EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FLT3 = FMS-like tyrosine kinase 3; GHS/QoL = global health status quality of life scale; HR = hazard ratio; IDH = isocitrate dehydrogenase; MCT = meaningful change threshold; PROMIS 7a = Patient-Reported Outcomes Measurement Information System Short Form v1.0–Fatigue 7a; OS = overall survival; PRO = patient-reported outcome; TTD = time to deterioration.

Source: Clinical Study Report.[1]

An overall 2-sided significance level of 0.05 was initially allocated between the co-primary end points: 0.01 to the analysis of CR + CRi and 0.04 to the analysis of OS. If the results of statistical testing for CR + CRi at IA1 were significant, then the 0.01 allocated to CR + CRi would be recycled to the OS analysis. If the results of statistical testing for OS were significant, then the fixed testing procedure would be performed at a 2-sided significance level of 0.05 for each of the selected secondary efficacy end points in sequence. If the results of statistical testing for OS were not significant, then statistical significance would not be declared for any of the end points.

Table 10 shows the actual alpha-spending boundary and information fraction for the end points tested under the hierarchical testing strategy, in order of testing.

Drop-outs or missing data were handled using the following rules:

- Patients who had not died were censored at the last known dates they were known to be alive on or before the cut-off date for the analysis of OS.
- Patients who were randomized but did not have an IWG disease assessment were considered nonresponders in the calculation of CR, CR + CRi.
- Patients who did not receive the study drug were considered post-baseline transfusion-dependent in the analysis of post-baseline transfusion-independent rates.
- Patients who did not experience relapse or death after response were censored at the date of last disease assessment (bone marrow or hematology laboratory measurement).
- Patients who did not experience an EFS event and did not start on post-treatment therapy were censored at the time of the last disease assessment date on or before the data cut-off date. Patients who did not experience an EFS event and started on post-treatment therapy were censored at the time of initiation of post-treatment therapy.
- There was no imputation of PROMIS 7a scores at a time point if scores were missing entirely; the summary was of available data. The scoring of missing individual items was according to the manual.
- There was no imputation of EORTC QLQ-C30 and subscales data at a time point if scores were missing entirely; the summary was of available data. If there were missing items for a scale (i.e., the participant did not provide a response), the score for the scale could still be computed if there were responses for at least 1-half of the items. In calculating the scale

score, the missing items were simply ignored — an approach that assumed the missing items had values equal to the average of those items that the respondent completed.[25]

Analysis Populations

Two analysis populations were identified:

- The efficacy population included all patients randomized under protocol amendment 1 and subsequent amendments. It excluded the 2 patients randomized under the original protocol and the open-label China cohort of 10 patients (n = 431).
- The safety population included all patients under the study protocol who received at least 1 dose of the study drug, but not the open-label China cohort (n = 427).

The longitudinal analysis population in the supplementary analysis of patient-reported outcomes included all patients in the efficacy population who survived up to a given time point and had available data for at least 1 patient-reported outcome measurement at baseline and at that time point.

Table 10: Actual Alpha-Spending Boundary and Information Fraction for End Points in Hierarchical Testing Strategy at IA2 (EU and EU Reference Countries)

End point	Information fraction	Interim boundary P value (2-sided)	Included in CADTH review
Primary			
1. CR + CRi	First 226 patients	0.01	Yes
2. OS	75% (270 events)	0.02	Yes
Secondary			
3. CR + CRi by cycle 2	100%	0.05	Yes
4. Post-baseline RBC transfusion independence	98%	0.047	Yes
5. CR + CRi rate IDH1/IDH2 subgroup	100%	0.05	Yes
6. CR rate	98%	0.047	Yes
7. CR + CRi rate FLT3 subgroup	100%	0.05	Yes
8. Post-baseline platelet transfusion independence	98%	0.047	Yes
9. EFS	87% (313 of 360 events)	0.032	Yes
10. CR + CRi MRD response rate	100%	0.05	No
11. OS in IDH1/2 subgroup	NA	0.0002	Yes
12. OS in FLT3 subgroup	NA	0.0002	Yes
13. EORTC QLQ-C30 GHS/QoL	NA	0.0002	Yes
14. PROMIS Short Form v1.0–Fatigue 7a	NA	0.0002	Yes

CR = complete remission; CRi = complete remission with incomplete blood count recovery; EFS = event-free survival; EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FLT3 = FMS-like tyrosine kinase 3; IA2 = second interim analysis; IDH = isocitrate dehydrogenase; GHS/QoL = global health status quality of life scale; MRD = minimal/measurable residual disease; NA = not applicable; OS = overall survival; PROMIS = Patient-Reported Outcomes Measurement Information System; RBC = red blood cell.

Source: Clinical Study Report.[1]

Results

Patient Disposition

Table 11 shows the patient disposition. Of the 579 patients screened, 2 patients were randomized under the original protocol (group 1) and 431 patients were randomized under protocol amendment 1 and subsequent amendments (group 2). As the stratification variables changed under amendment 1, only patients in group 2 were included in the efficacy population. All eligible patients were included in the safety population.

A total of 579 patients was screened, with 146 excluded on screening, primarily because they did not meet the inclusion or exclusion criteria. Of the 431 patients randomized under amendment 1 and subsequent amendments, 286 were randomized to venetoclax plus azacitidine and 144 to placebo plus azacitidine. The primary reason for study discontinuation was death, in 56.7% of patients randomized to venetoclax plus azacitidine, and 75.2% of patients randomized to placebo plus azacitidine. Both loss to follow-up and withdrawal of consent were very low: less than 2% were lost to follow-up in both arms, and less than 2.5% withdrew consent. Three patients randomized to venetoclax plus azacitidine and 1 randomized to placebo plus azacitidine did not receive their assigned treatment and were excluded from the safety population.

Exposure to Study Treatments

Table 12 shows a summary of exposure for the safety population. Patients randomized to venetoclax plus azacitidine had longer exposure on average than those randomized to placebo plus azacitidine. The median duration of exposure for patients randomized to venetoclax plus azacitidine was 7.6 months (range, 0.0 to 30.7) and the median number of cycles was 7 (range, 1 to 30), compared with 4.3 months (range, 0.1 to 24.0) and 4.5 cycles (range, 1 to 26), respectively, for placebo plus azacitidine. A total of 106 patients (37.4%) who received venetoclax plus azacitidine and 42 (29.1%) patients who received placebo plus azacitidine received 10 or more cycles.

More patients who received venetoclax plus azacitidine had a dose reduction and/or dose interruption than those who received placebo plus azacitidine, either drug in each combination, venetoclax or placebo alone, and azacitidine alone. Of the patients who received venetoclax plus azacitidine, 21.6% had 1 dose reduction, 4.6% had 2 dose reductions, and 2.5% had more than 2 dose reductions, compared with 18.1%, 2.1%, and 2.1%, respectively, for patients who received placebo plus azacitidine. Of the patients who received venetoclax plus azacitidine, 94.3% had at least 1 dose interruption for any reason and 66.1% had at least 1 dose interruption for count recovery, compared with 77.8% and 20.1%, respectively, for patients who received placebo plus azacitidine. Of the patients who received venetoclax plus azacitidine, 52.8% had a dose interruption of venetoclax or placebo and 65.3% had a dose interruption of azacitidine, compared with 27.7% and 25.5%, respectively, for patients who received placebo plus azacitidine.

Efficacy

Table 13 shows an overall summary of the efficacy outcomes and the subgroup analyses for the efficacy population at the time of the second interim analysis. Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported subsequently. Between-treatment differences that were statistically significant with controlled multiplicity (co-primary end points and sequential testing protocol) are indicated with a footnote.

At the time of the second interim analysis, the median duration of follow-up for patients randomized to venetoclax plus azacitidine was 20.7 months (95% CI, 20.1 to 22.0), and for those randomized to placebo plus azacitidine, it was 20.2 months (95% CI, 19.6 to 22.4).

Overall Survival

Table 13 summarizes the OS results for the efficacy population at IA2 (data cut-off: January 4, 2020) and Figure 2 shows the Kaplan–Meier survival curves.

Venetoclax plus azacitidine improved survival over placebo plus azacitidine (P value [stratified log-rank test] < 0.001; P value boundary = 0.02), with median survival in patients randomized to venetoclax plus azacitidine of 14.7 months (95% CI, 11.9 to 18.7) compared with 9.6 months (59% CI, 7.4 to 12.7) in patients randomized to placebo plus azacitidine (HR for mortality = 0.662; 95% CI, 0.518 to 0.845). The estimated survival at 12 months for venetoclax plus azacitidine was 55.8% (95% CI, 49.7% to 61.5%); for placebo plus azacitidine it was 43.8% (95% CI, 35.5% to 51.8%).

Table 11: Patient Disposition for VIALE-A

Patient disposition	VIALE-A	
	VEN + AZA	PBO + AZA
Screened, N	579	
Excluded on screening	146	
Did not meet inclusion or exclusion criteria	98	
Withdrew consent	21	
Other	27	
Randomized to both groups 1a and 2b; N (%)	287	146
Randomized and in group 2b; N (%)	286	145
Randomized, in group 2b; and received treatment, N (%)	283	144
Primary reason for study discontinuation, group 1 N (%)		
Death	1 (100)	1 (100)
Primary reason for study discontinuation, group 2, N (%)		
Death	161 (56.4)	109 (75.2)
Lost to follow-up	5 (1.7)	2 (1.4)
Withdrew consent	7 (2.4)	1 (0.7)
Efficacy population, N (group 2 only)	286	145
Safety population, N (all patients enrolled and treated)	283	144

PBO + AZA = placebo plus azacitidine; VEN + AZA = venetoclax plus azacitidine.

Note: Data cut-off was January 4, 2020.

[a]Group 1 comprised the patients randomized under the original protocol.

[b]Group 2 comprised the patients randomized under protocol amendment 1 and subsequent amendments.

Source: Clinical Study Report.[1]

Table 12: Summary of Exposure to Treatment, Safety Population

Characteristic	VEN + AZA N = 283	PBO + AZA N = 144
Duration of exposure, months		
Mean (SD)	9.9 (8.25)	6.7 (6.55)
Median	7.6	4.3
Minimum to maximum	0.0 to 30.7	0.1 –to 24.0
Duration interval, months		
0 to 1	45 (15.9)	31 (21.5)
> 1 to 2	22 (7.8)	18 (12.5)
> 2 to 4	29 (10.2)	18 (12.5)
> 4 to 6	20 (7.1)	23 (16.0)
> 6 to 8	27 (9.5)	5 (3.5)
> 8 to 10	24 (8.5)	11 (7.6)
> 10 to 12 months	10 (3.5)	8 (5.6)
> 12	106 (37.5)	30 (20.8)
Number of cycles		
Mean (SD)	8.8 (7.32)	6.9 (6.53)
Median	7	4.5
Minimum to maximum	1.0 to 30.0	1.0 to 26.0
Number of cycles, n		
1	45 (15.9)	33 (22.9)
2	32 (11.3)	16 (11.1)
3	16 (5.7)	12 (8.3)
4	15 (5.3)	11 (7.6)
5	13 (4.6)	11 (7.6)
6	19 (6.7)	8 (5.6)
7	20 (7.1)	3 (2.1)
8	9 (3.2)	4 (2.8)
9	8 (2.8)	4 (2.8)
≥ 10	106 (37.4)	42 (29.1)
Dose reduction, n (%)		
No reduction	202 (71.4)	112 (77.8)
1 reduction	61 (21.6)	26 (18.1)
2 reductions	13 (4.6)	3 (2.1)

Characteristic	VEN + AZA N = 283	PBO + AZA N = 144
≥ 2 reductions	7 (2.5)	3 (2.1)
Dose interruption, n (%)		
No interruption	16 (5.7)	32 (22.2)
All reasons	267 (94.3)	112 (77.8)
1 interruption	50 (17.7)	34 (23.6)
2 interruptions	33 (11.7)	29 (20.1)
> 2 interruptions	184 (65.0)	49 (34.0)
Due to count recovery	187 (66.1)	29 (20.1)
1 interruption	28 (9.9)	15 (10.4)
2 interruptions	22 (7.8)	4 (2.8)
> 2 interruptions	137 (48.4)	10 (6.9)
Venetoclax or placebo dose interruption, n (%)		
Due to count recovery	114 (52.8)	13 (27.7)
1 interruption	49 (22.7)	7 (14.9)
2 interruptions	32 (14.8)	5 (10.6)
> 2 interruptions	33 (15.3)	1 (2.1)
AZA dose interruption, n (%)		
Due to count recovery	141 (65.3)	12 (25.5)
1 interruption	34 (15.7)	6 (12.8)
2 interruptions	21 (9.7)	3 (6.4)
> 2 interruptions	86 (39.8)	3 (6.4)

AZA = azacitidine; PBO = placebo; SD = standard deviation; VEN = venetoclax.

Note: Data cut-off was January 4, 2020.

Source: Clinical Study Report.[1]

A sensitivity analysis that included all of the data in the extracted database showed similar results, with an HR for mortality of 0.653 (95% CI, 0.513 to 0.832), and an estimated survival rate at 12 months of 56% for venetoclax plus azacitidine (95% CI, 49.9% to 61.6%) and 43.9% for placebo plus azacitidine (95% CI, 35.6% to 51.9%).

Event-Free Survival and Duration of Event-Free Survival

Table 13 summarizes the results for EFS for the efficacy population at IA2 (data cut-off: January 4, 2020) and Figure 3 shows the Kaplan–Meier survival curves.

Venetoclax plus azacitidine improved EFS over placebo plus azacitidine (P value [stratified log-rank test] < 0.001; P value boundary of 0.032), with a median EFS duration of 9.8 months (95% CI, 8.4 to 11.8) for patients randomized to venetoclax plus azacitidine compared with 7.0 months (95% CI, 5.6 to 9.5) for patients randomized to placebo plus azacitidine (HR for EFS = 0.632; 95% CI, 0.502 to 0.796). At 12 months, 43.5% of the patients randomized

Table 13: Summary of Efficacy Outcomes and Subgroup Analyses, Efficacy Population, IA2

Outcomes and analyses	VEN + AZA N = 286	PBO + AZA N = 145
OS		
Events (deaths), n (%)	161 (56.3)	109 (75.2)
Median OS, months (95% CI)	14.7 (11.9 to 18.7)	9.6 (7.4 to 12.7)
HR (Cox proportional hazards model)[a] (95% CI)	0.662 (0.518 to 0.845)	
P value (stratified log-rank test)[a]	< 0.001[b]	
6-month OS estimate, % (95% CI)	71.9 (66.3 to 76.8)	63.9 (55.5 to 71.2)
12-month OS estimate, % (95% CI)	55.8 (49.7 to 61.5)	43.8 (35.5 to 51.8)
24-month OS estimate, % (95% CI)	36.5 (29.7 to 43.3)	18.3 (11.1 to 27.0)
Event-free survival		
Number of patients with events, n (%)	191 (66.8)	122 (84.1)
Confirmed morphologic relapse or disease progression	83 (43.5)	35 (28.7)
Treatment failure	4 (2.1)	12 (9.8)
Death	104 (54.5)	75 (61.5)
Number of patients without an event	95 (33.2)	23 (15.9)
Treatment comparison		
HR (Cox proportional hazards model)[a] (95% CI)	0.632 (0.502 to 0.796)	
P value (stratified log-rank test)[a]	< 0.001[b]	
Median duration of event-free survival (months; 95% CI)	9.8 (8.4 to 11.8)	7.0 (5.6 to 9.5)
No event rate at month 6, % (95% CI)	67.7 (61.8 to 72.8)	56.2 (47.6 to 63.9)
No event rate at month 12, % (95% CI)	43.5 (37.4, 49.3)	31.3 (23.6, 39.2)
No event rate at month 24, % (95% CI)	23.8 (17.9 to 30.2)	NA
Best response (CR + CRi) by investigator assessment		
CR + CRi rate at IA1, n (%; 95% CI)[c]		
Number of patients at IA1	147	79
CR	44 (29.9; 22.7 to 36.0)	12 (15.2; 8.1 to 25.0)
CRi	52 (35.4; 27.7 to 43.7)	8 (10.1; 4.5 to 19.0)
CR + CRi	96 (65.3; 57.0 to 73.0)	20 (25.3; 16.2 to 36.4)
P value (stratified CMH test)[a]	< 0.001	
CR + CRi rate (as best response), n (%; 95% CI)[c]		
CR	105 (36.7; 31.1 to 42.60)	26 (17.9; 12.1 to 25.2)
P value (stratified CMH test)[a]	< 0.001[b]	
CRi	85 (29.7; 24.5 to 35.4)	15 (10.3; 5.9 to 16.5)

Outcomes and analyses	VEN + AZA N = 286	PBO + AZA N = 145
CR + CRi	190 (66.4; 60.6 to 71.9)	41 (28.3; 21.1 to 36.3)
Best IWG response, n (%)		
CR	105 (36.7)	26 (17.9)
CRi	85 (29.7)	15 (10.3)
PR	3 (1.0)	3 (2.1)
MLFS	24 (8.4)	6 (4.1)
RD	36 (12.6)	69 (47.6)
MR	0	0
PD	3 (1.0)	6 (4.1)
Discontinued with no response data	30 (10.5)	20 (13.8)
No response data but still active	0	0
CR + CRi rate (as best response) by initiation of cycle 2, n (%; 95% CI)[a]		
CR	37 (12.9; 9.3 to 17.4)	3 (2.1; 0.4 to 5.9)
CRi	87 (30.4; 25.1 to 36.1)	8 (5.5; 2.4 to 10.6)
CR + CRi	124 (43.4; 37.5 to 49.3)	11 (7.6; 3.8 to 13.2)
P value (stratified CMH test)[a]	< 0.001[b]	
Time to response (CR + CRi) by investigator assessment		
Time to first response, months, mean (SD) median (range)		
CR + CRi	2.1 (1.82) 1.3 (0.6 to 9.9)	3.3 (2.61) 2.8 (0.8 to 13.2)
Time to best response, months, mean (SD) median (range)		
CR	4.5 (4.38) 3.2 (0.9 to 24.5)	4.5 (2.95) 4.0 (1.0 to 13.2)
CRi	2.4 (2.03) 1.3 (0.6 to 8.8)	3.5 (2.77) 3.4 (0.8 to 11.2)
CR + CRi	3.6 (3.66) 2.3 (0.6 to 24.5)	4.2 (2.89) 3.7 (0.8 to 13.2)
Best response (CR + CRh) by investigator assessment		
CR + CRh rate (as best response), n (%; 95% CI)[a]		
CR	105 (36.7; 31.1 to 42.6)	26 (17.9; 12.1 to 25.2)
CRh	80 (28.0; 22.8 to 33.6)	7 (4.8; 2.0 to 9.7)
CR + CRh	185 (64.7; 58.8 to 70.2)	33 (22.8; 16.2 to 30.5)
Patients with best response to CR + CRh		

Outcomes and analyses	VEN + AZA N = 286	PBO + AZA N = 145
CR + CRh rate (as best response) by initiation of cycle 2, n (%; 95% CI)[a]		
CR	37 (12.9; 9.3 to 17.4)	3 (2.1; 0.4 to 5.9)
CRh	77 (26.9; 21.9 to 32.5)	5 (3.4; 1.1 to 7.9)
CR + CRh	114 (39.9; 34.1 to 45.8)	8 (5.5; 2.4 to 10.6)
Time to response (CR + CRh) by investigator assessment		
Time to first response (months) mean (SD) median (range)		
CR + CRh	2.2 (2.23) 1.0 (0.6 to 14.3)	3.0 (2.35) 2.6 (0.8 to 13.2)
Time to best response (months) mean (SD) median (range)		
CR	4.5 (4.38) 3.2 (0.9 to 24.5)	4.5 (2.95) 4.0 (1.0 to 13.2)
CRh	2.6 (2.66) 1.0 (0.6 to 14.3)	2.7 (1.52) 2.8 (1.1 to 5.5)
CR + CRh	3.6 (3.84) 2.3 (0.6 to 24.5)	4.1 (2.79) 3.6 (1.0 to 13.2)
Duration of response (CR + CRi and CR) based on investigator assessment		
CR + CRi		
Number of patients with events, n/N (%)	84/190 (44.2)	23/41 (56.1)
DOR (months)[a]		
Median (95% CI)	17.5 (13.6 to NE)	13.4 (5.8 to 15.5)
No event rate, month 6, % (95% CI)	80.6 (73.8 to 85.8)	65.6 (47.2 to 78.9)
No event rate, month 12, % (95% CI)	60.6 (52.6 to 67.7)	51.0 (32.3 to 66.9)
No event rate, month 18, % (95% CI)	48.0 (39.4 to 56.0)	20.4 (6.8 to 39.1)
CR		
Number of patients with events, n/N (%)	39/105 (37.1)	13/26 (50.0)
DOR (months)[a]		
Median (95% CI)	17.5 (15.3 to NE)	13.3 (8.5 to 17.6)
No event rate, month 6, % (95% CI)	83.3 (74.1 to 89.4)	84.4 (63.7 to 93.9)
No event rate, month 12, % (95% CI)	72.6 (62.1 to 80.6)	59.4 (33.2 to 78.2)
No event rate, month 18, % (95% CI)	47.5 (34.2 to 59.7)	13.0 (1.0 to 40.6)
Post-baseline transfusion independence		
Post-baseline transfusion-independence rate		

Outcomes and analyses	VEN + AZA N = 286	PBO + AZA N = 145
RBC and platelet, n (%; 95% CI)	166 (58.0; 52.1 to 63.8)	49 (33.8; 26.2 to 42.1)
Treatment difference, % (95% CI)	24.2 (14.7 to 33.8)	
RBC	171 (59.8; 53.9 to 65.5)	51 (35.2; 27.4 to 43.5)
Treatment difference, % (95% CI)	24.6 (15.0 to 34.2)	
P value (stratified CMH test)[a]	< 0.001[b]	
Platelet	196 (68.5; 62.8 to 73.9)	72 (49.7; 41.3 to 58.1)
Treatment difference, % (95%)	18.9 (9.1 to 28.6)	
P value (stratified CMH test)[a]	< 0.001[b]	
Duration of post-baseline transfusion independence (days)		
RBC and platelet		
N	166	49
Mean (SD)	256.7 (204.49)	245.1 (182.48)
Median (minimum to maximum)	179.5 (57 to 33)	188 (56 to 727)
RBC		
N	171	51
Mean (SD)	262.5 (202.35)	241.6 (181.94)
Median (minimum to maximum)	199 (57 to 933)	193 (56 to 727)
Platelet		
N	196	72
Mean (SD)	282.8 (223.24)	276.7 (191.52)
Median (minimum to maximum)	210 (56 to 933)	227.5 (58 to 730)
Post-baseline transfusion-independence rate by baseline transfusion status, n/N (%; 95% CI)		
RBC or platelet transfusion within 8 weeks before first dose of study drug	76/155 (49.0; 40.9 to 57.2)	22/81 (27.2; 17.9 to 38.2)
No transfusion within 8 weeks before first dose of study drug	90/131 (68.7; 60.0 to 76.5)	27/64 (42.2; 29.9 to 55.2)
Post-baseline RBC transfusion-independence rate by baseline transfusion status, n/N (%; 95% CI)		
RBC transfusion within 8 weeks before first dose of study drug	71/144 (49.3; 40.9 to 57.8)	21/76 (27.6; 18.0 to 39.1)
No RBC transfusion within 8 weeks before first dose of study drug	100/142 (70.4; 62.2 to 77.8)	30/69 (43.5; 31.6 to 56.0)
Post-baseline platelet transfusion-independence rate by baseline transfusion status, n/N (%; 95% CI)		

Outcomes and analyses	VEN + AZA N = 286	PBO + AZA N = 145
Platelet transfusion within 8 weeks before first dose of study drug	34/68 (50.0; 37.6 to 62.4)	12/32 (37.5; 21.1 to 56.3)
No platelet transfusion within 8 weeks before first dose of study drug	162/218 (74.3; 68.0 to 80.0)	60/113 (53.1; 43.5 to 62.5)

AML = acute myeloid leukemia; AZA = azacitidine; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete remission; CRh = complete remission with incomplete hematological recovery; CRi = complete remission with incomplete blood count recovery; DOR = duration of response; HR = hazard ratio; IA2 = second interim analysis; IWG = International Working Group; MLFS = morphologic leukemia-free state; MR = morphologic relapse; NA = not applicable; NE = not estimable; NPM1 = nucleophosmin 1; OS = overall survival; PBO = placebo; PD = progressive disease; PR = partial remission; RBC = red blood cell; RD = resistant disease; SD = standard deviation; VEN = venetoclax.

Note: Data cut-off was January 4, 2020.

[a]Stratified by age (18 to < 75 years; ≥ 75 years) and cytogenetic risk (intermediate, poor risk).

[b]Statistically significant under preplanned testing strategy.

[c]Calculated from the exact binomial distribution.

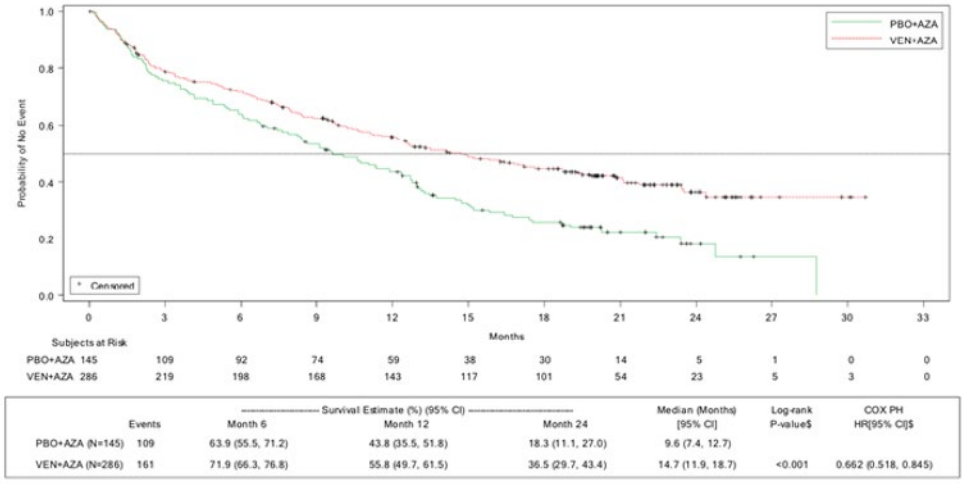
Source: Clinical Study Report.[1]

to venetoclax plus azacitidine were free of confirmed morphologic relapse or disease progression, treatment failure, or death, compared with 31.3% of patients randomized to placebo plus azacitidine. A higher proportion of patients in the venetoclax plus azacitidine group (43.5%) had a confirmed morphologic relapse or disease progression event than in the placebo plus azacitidine group (28.7%); conversely, a higher proportion of patients had death as an event in the placebo plus azacitidine group (61.5%) than in the venetoclax plus azacitidine group (54.5%).

Response: CR + CRi, CR, CR + CRh

Table 13 summarizes the results for composite complete remission (CR + CRi) for the efficacy population at the second interim assessment. The table also summarizes the results for CR + CRh, which has required minimum values for neutrophils and platelet counts.

Figure 2: Overall Survival, Efficacy Population, IA2



CI = confidence interval; COX PH = Cox proportional hazards model; IA2 = second interim analysis; PBO + AZA = placebo plus azacitidine; VEN + AZA = venetoclax plus azacitidine.

Note: Data cut-off was January 4, 2020.

Source: Clinical Study Report.[1]

CR + CRi at IA1 was a co-primary efficacy end point, as assessed for the first 226 patients (data cut-off: October 1, 2018). Venetoclax plus azacitidine improved CR + CRi (P value for stratified Cochran-Mantel-Haenszel [CMH] test < 0.001; P value boundary = 0.01) with 65.3% (95% CI, 57.0 to 73.0%) of patients meeting the end point compared with 25.3% (95% CI, 16.2% to 36.4%) of those who received placebo plus azacitidine.

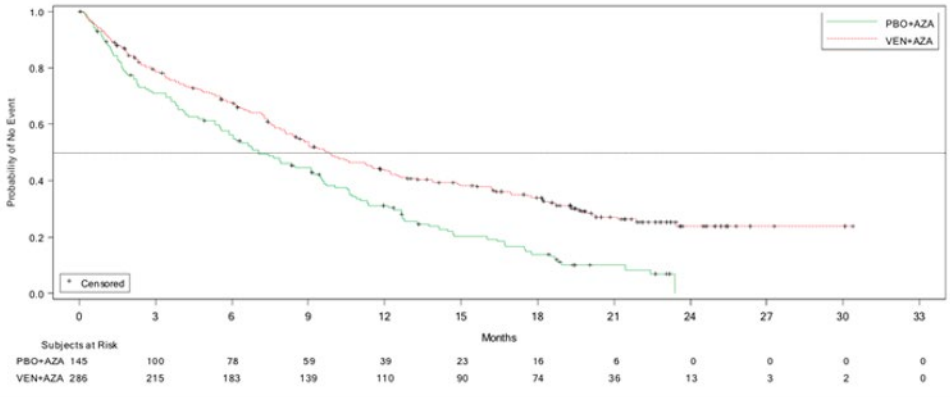
Similar results were seen for conventional care regimen at IA2, with 66.4% (95% CI, 60.6 to 71.9%) of patients randomized to venetoclax plus azacitidine reaching the end point of CR + CRi compared with 28.3% (95% CI, 21.1% to 36.3%) of patients randomized to placebo plus azacitidine. This end point was not tested. Venetoclax plus azacitidine improved CR (P value [stratified CMH test] < 0.001; P value boundary = 0.047), with 36.7% (95% CI, 31.1% to 42.6%) of patients meeting the criteria for CR compared with 17.9% (95% CI, 12.1% to 25.2) of patients randomized to placebo plus azacitidine.

Among patients who had a partial response, 1.0% of those randomized to venetoclax plus azacitidine and 2.1% of those randomized to placebo plus azacitidine met the criteria for partial remission, while 8.4% of those randomized to venetoclax plus azacitidine and 4.1% of those randomized to placebo plus azacitidine met the criteria for MLFS.

Venetoclax plus azacitidine also improved early composite complete remission (P value [stratified CMH test] < 0.001; P value boundary = 0.05), with 43.4% (95% CI, 37.5% to 49.3%) of patients reaching the end point of CR + CRi by the beginning of cycle 2, compared with 7.6% (95% CI, 3.8 to 13.2) of patients randomized to placebo plus azacitidine. Results for time to first response (next section) were consistent.

Results for CR + CRh were consistent with those for composite complete remission, with 64.7% (95% CI, 58.8% to 70.2%) of patients randomized to venetoclax plus azacitidine reaching the end point of CR + CRh compared with 22.8% (95% CI, 16.2% to 30.5%) of patients

Figure 3: Event-Free Survival, Efficacy Population, IA2



	Events	No Event Rate Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median Months [95% CI]	Log-rank P-value$	COX PH HR[95% CI]$
PBO+AZA (N=145)	122	56.2 (47.6, 63.9)	31.3 (23.6, 39.2)	NA	7.0 (5.6, 9.5)		
VEN+AZA (N=286)	191	67.7 (61.8, 72.8)	43.5 (37.4, 49.3)	23.8 (17.9, 30.2)	9.8 (8.4, 11.8)	<0.001	0.632 (0.502, 0.796)

CI = confidence interval, COX PH = Cox proportional hazards model, IA2 = second interim analysis; PBO + AZA = placebo plus azacitidine, VEN + AZA = venetoclax plus azacitidine.

Note: Data cut-off was January 4, 2020.

Source: Clinical Study Report.[1]

randomized to placebo plus azacitidine, and similar results for time to first and time to best response.

Time to Response

Table 13 shows time to first and time to best response for CR + CRi and CR + CRh. Time to first response was 1.3 months (95% CI, 0.6 to 9.9) for patients randomized to venetoclax plus azacitidine and 2.8 months (95% CI, 0.8 to 13.2) for those randomized to placebo plus azacitidine. Median times to best CR or CRi were 2.3 (95% CI, 0.6 to 24.5) months and 3.7 (0.8 to 13.2) months for patients randomized to venetoclax plus azacitidine and placebo plus azacitidine, respectively. Very similar results were seen for CR + CRh.

Duration of Response

Table 13 shows the duration of response for CR + CRi and CR for the efficacy population at IA2 (data cut-off: January 4, 2020). The duration of response for patients who reached CR or CRi was 17.5 months (95% CI, 13.6 to not estimable) for patients randomized to venetoclax plus azacitidine and 13.4 (95% CI, 8.5 to 17.6) months for patients randomized to placebo plus azacitidine. At 12 months, 60.6% of responding patients randomized to venetoclax plus azacitidine still met the response criteria compared with 51.0% of responding patients randomized to placebo plus azacitidine.

Post-Baseline Transfusion Independence

Table 13 summarizes independence and duration of independence from red blood cell and platelet transfusions and from both combined for the efficacy population at IA2 (January 4, 2020). The table also shows results for patients who were and were not transfusion-independent at baseline.

Venetoclax plus azacitidine improved post-baseline transfusion independence for red blood cells (P value [stratified CMH test] < 0.001; P value boundary = 0.047). For red blood cells, 59.8% (95% CI, 53.9% to 65.5%) of patients randomized to venetoclax plus azacitidine were transfusion-independent compared with 35.2% (95% CI, 27.4% to 43.5%) of patients randomized to placebo plus azacitidine, a treatment difference of 24.6% (95% CI, 15.0 to 34.2). The median duration of red blood cells transfusion independence was 199 days (range of 57 to 933 days) for patients randomized to venetoclax plus azacitidine and 193 days (range of 56 to 727 days) for patients randomized to placebo plus azacitidine. For both groups, a greater proportion of patients who were transfusion-independent at baseline were transfusion-independent post baseline compared with patients who were not transfusion-dependent at baseline.

Venetoclax plus azacitidine improved post-baseline transfusion independence for platelets (P value [stratified CMH test] < 0.001; P value boundary = 0.047). For platelets, 68.5% (95% CI, 62.8% to 73.9%) of patients randomized to venetoclax plus azacitidine were transfusion-independent compared with 49.7% (95% CI, 41.3% to 58.1%), a treatment difference of 18.9% (95% CI, 9.1% to 28.6%). The median duration of platelet transfusion independence was 210 days (range of 56 to 933 days) for patients randomized to venetoclax plus azacitidine, and 227.5 days (range of 58 to 730 days) for patients randomized to placebo plus azacitidine. For both groups, a greater proportion of patients who were transfusion-independent at baseline were still transfusion-independent post baseline compared with patients who were not transfusion-independent at baseline.

Hospitalization

Overall rates of hospitalization were not reported. A higher percentage of patients who received venetoclax plus azacitidine experienced adverse events leading to hospitalization than those who received placebo plus azacitidine (80.6% versus 66.7%). The most common adverse events leading to hospitalization involved cytopenias or were infectious: febrile neutropenia (29.3% for venetoclax plus azacitidine versus 10.4% for placebo plus azacitidine), pneumonia (14.8% versus 20.1%), anemia (4.9% versus 4.2%), neutropenia (4.6% versus 2.1%), sepsis (4.6% versus 6.9%), and thrombocytopenia (3.9% versus 0.7%).

Overall Survival and CR + CRi in Subgroups

Table 38 (Appendix 3) shows the results for the comparison of the molecular subgroups in the efficacy population, as of IA2, for OS and CR + CRi. Data were available for the subgroups of age (age < 75 years, age ≥ 75 years), ECOG PS (ECOG < 2, ECOG ≥ 2), cytogenetic risk (intermediate versus poor), de novo versus secondary AML, AML with and without myelodysplastic syndrome, blast count at baseline (< 30%, 30% to < 50%, and 50%), and mutations (IDH1 and/or IDH2, FLT3, NPM1, and TP53).

OS in patients with IDH1 and/or IDH2 and in patients with FLT3, and CR + CRi with IDH1 and/or IDH2 and in patients with FLT3 were included as end points in the sequential testing strategy.

Venetoclax plus azacitidine improved OS in patients with an IDH1 and/or IDH2 mutation compared with placebo plus azacitidine (P value unstratified log-rank test < 0.0001; P value boundary = 0.0002). Median survival for patients randomized to venetoclax plus azacitidine was not estimable, compared with 6.2 months (95% CI, 2.3 to 12.7) for patients randomized to placebo plus azacitidine (HR = 0.345; 95% CI, 0.199 to 0.598).

No statistically significant difference was identified for OS in patients with FLT3 mutation between patients randomized to venetoclax plus azacitidine and those randomized to placebo plus azacitidine (P value [unstratified log-rank test] < 0.2054; P value boundary = 0.0002). Median survival for patients randomized to venetoclax plus azacitidine was 12.7 months (95% CI, 7.3 to 23.5) compared with 8.9 months (95% CI, 5.9 to 14.7) for patients randomized to placebo plus azacitidine (HR = 0.664; 95% CI, 0.351 to 1.257).

Venetoclax plus azacitidine improved CR + CRi in patients with IDH1 and/or IDH2 mutation compared with placebo plus azacitidine (P value [Fisher's exact test] < 0.001; P value boundary = 0.05). The composite remission rate for patients randomized to venetoclax plus azacitidine was 75.4% (95% CI, 52.9% to 87.3%), compared with 10.7% (95% CI, 2.3% to 28.2%) for patients randomized to placebo plus azacitidine.

Venetoclax plus azacitidine improved CR + CRi in patients with FLT3 mutation, compared with placebo plus azacitidine (P value [Fisher's exact test] < 0.021; P value = 0.05). Median survival for patients randomized to venetoclax plus azacitidine was 72.4% (95% CI, 52.8% and 87.3%) compared with 36.4% (95% CI, 17.2% to 59.3%) for patients randomized to placebo plus azacitidine.

For the other subgroups, the greatest difference in point estimates for OS and CR + CRi was observed for age and cytogenetic risk. In patients aged less than 75 years, the HR for OS for the comparison of venetoclax plus azacitidine to placebo plus azacitidine was 0.888 (95% CI, 0.591 to 1.33), compared with an HR of 0.535 (95% CI, 0.394 to 0.727) in patients aged 75 years and older. In patients aged less than 75 years, the risk difference in CR + CRi

for the comparison of venetoclax plus azacitidine to placebo plus azacitidine was 21.12% (95% CI, 5.6% to 36.6%), compared with 49.43% (95% CI, 38.6% to 60.2%) in patients aged 75 years and older.

In patients with intermediate cytogenetic risk, HR for OS for the comparison of venetoclax plus azacitidine versus placebo plus azacitidine was 0.566 (95% CI, 0.407 to 0.786), compared with an HR of 0.775 (95% CI, 0.538 to 1.117) in patients with poor cytogenetic risk. In patients with intermediate risk, the risk difference in CR + CRi for the comparison of venetoclax plus azacitidine versus placebo plus azacitidine was 42.72% (95% CI, 31.2% to 54.3%), compared with 29.67% (95% CI, 15.0% to 44.3%) in patients with poor cytogenetic risk.

Differences in point estimates were minimal for the other identified subgroups.

Patient-Reported Outcomes

Overall QoL was captured by the EORTC QLQ-C30 GHS/QoL and health utility was captured by the EQ-5D. Fatigue was reported in the PROMIS 7a scale and the fatigue subscale in the EORTC QLQ-C30. Nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea were all reported as part of the EORTC.

The EORTC QLQ-30 GHS/QoL and PROMIS 7a were secondary end points and included in the statistical testing strategy. EQ-5D was reported as an exploratory end point. Exploratory analyses were conducted of the time to deterioration of individual scores and subgroups.

EORTC QLQ-C30 GHS/QoL

Table 38 shows the mean scores at baseline and day 1 of subsequent treatment cycles, the least squares (LS) mean change from baseline, and the LS mean difference between venetoclax plus azacitidine and placebo plus azacitidine, for EORTC QLQ-C30 GHS/QoL. Data are shown up to cycle 13, after which the attrition of patients due to death and discontinuation due to disease progression had reduced the study cohorts to a small number.

Figure 4 shows the time to deterioration on the EORTC QLQ-C30 GHS/QoL. At baseline, compliance in responding to the questionnaire was 92.9% and 90.9% in the venetoclax plus azacitidine and placebo plus azacitidine groups, respectively. In subsequent cycles (up to cycle 13), compliance in individual treatment groups ranged from 72.4% to 83.9%.

The mean EORTC QLQ-C30 GHS/QoL at baseline was similar in patients in the venetoclax plus azacitidine group and placebo plus azacitidine group: 52.61 (n = 262) and 55.96 (n = 130), respectively. There was a greater change from baseline in the venetoclax plus azacitidine group than in the placebo plus azacitidine group at all points except cycle 19. The difference met or exceeded the MID of 5 points at cycles 5 and 21. There were no clinically meaningful differences in mean change from baseline between treatment groups. This end point was part of the statistical testing hierarchy, but testing failed for an end point before this. Thus, conclusions cannot be drawn based on the results of this outcome without risk of increased type I error.

The median time to deterioration for patients randomized to venetoclax plus azacitidine was 16.5 months, compared with 9.3 months for patients randomized to placebo plus azacitidine. The adjusted HR was 0.81 (95% CI, 0.553 to 1.183). The meaningful change threshold was 10 points.

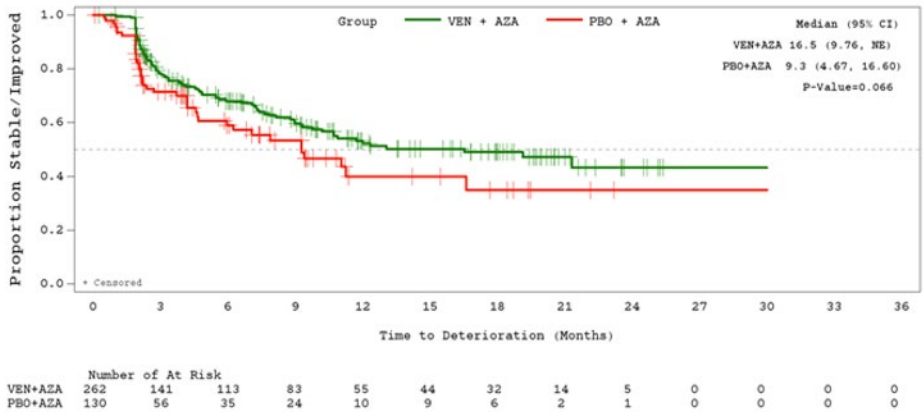
PROMIS 7a

Fatigue was assessed using the patient-reported PROMIS 7a scale, which assessed the experience and impact of fatigue over the previous 7 days. Table 38 shows the mean scores at baseline and on day 1 of subsequent treatment cycles, the LS mean change from baseline, and the LS mean difference between venetoclax plus azacitidine and placebo plus azacitidine, for PROMIS 7a. Figure 5 shows the time to deterioration on the EORTC QLQ-C30 GHS/QoL. Values run from 0 to 100, with higher values indicating greater fatigue. At baseline, compliance in completing the PROMIS 7a was 93.6% and 92.3% in the venetoclax plus azacitidine and the placebo plus azacitidine groups, respectively. In subsequent cycles (up to cycle 13), compliance in individual treatment groups ranged from 72.4% to 84.9%.

The mean PROMIS 7a score at baseline was similar among patients in the venetoclax plus azacitidine group and the placebo plus azacitidine group: 53.86 (n = 264) and 54.97 (n = 132), respectively. There was a greater change from baseline in PROMIS 7a scores among patients in the venetoclax plus azacitidine group versus the placebo plus azacitidine group on day 1 of cycles 5, 7, 9, 11, and 13, but no clinically meaningful differences in mean change from baseline between treatment groups. This end point was part of the statistical testing hierarchy, but testing failed for an end point before this. Thus, conclusions cannot be drawn based on the results of this outcome without risk of increased type I error.

The median time to deterioration for patients randomized to venetoclax plus azacitidine was 9.3 months compared with 8.6 months for patients randomized to placebo plus azacitidine. The adjusted HR was 0.72 (95% CI, 0.509 to 1.011). The meaningful change threshold was 5 points.

Figure 4: Time to Deterioration on the EORTC QLQ-C30 GHS/QoL, Longitudinal Analysis Population



Abbreviations: LAP = Longitudinal Analysis Population; PRO = Patient Reported Outcome; AZA = Azacitidine; PBO = Placebo; VEN = Venetoclax.
[1] The EORTC QLQ-C30 measures the HRQoL of cancer patients. It is composed of 30 items addressing 15 Health Related Quality of Life (HRQoL) domains, including five multi-item functional scales (physical, emotional, cognitive, social, and role functioning), three multi-item symptom scales (fatigue, nausea and vomiting, pain), six single-item symptom scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) and a global health status/Quality of Life (QoL) scale. The higher score indicates the improvement in GHS/QOL domain & Functional domains. The lower score indicates the improvement for symptom scales.
[2] The LAP includes all randomized subjects who have survived up to a given assessment and have available data on at least one PRO measure at baseline.
[3] P-value for Log Rank test of Venetoclax in Combination with Azacitidine versus placebo in combination with azacitidine.
[4] Deterioration is defined using the first event of PRO score worsening of at least 10.

AZA = azacitidine; CI = confidence interval; GHS/QoL = global health status quality of life scale; HRQoL = health-related quality of life; LAP = longitudinal analysis population; EORTC QLQ-30C = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; PBO = placebo; PRO = patient-reported outcome; VEN = venetoclax.

Source: Patient-reported outcome report.[1]

EORTC QLQ-C30 Symptom Scales

The mean baseline EORTC QLQ-C30 fatigue subscale score for venetoclax plus azacitidine was 47.67 (n = 262) and for placebo plus azacitidine it was 49.83 (n = 130). Change from baseline showed improvement in subsequent cycles for both treatments, but the observed differences in LS means between the treatments were small at each time point. At baseline, compliance in responding to the questionnaire was 92.2% and 90.9% in the venetoclax plus azacitidine and the placebo plus azacitidine groups, respectively. In subsequent cycles (up to cycle 13), compliance in individual treatment groups ranged from 72.4% to 82.9%.

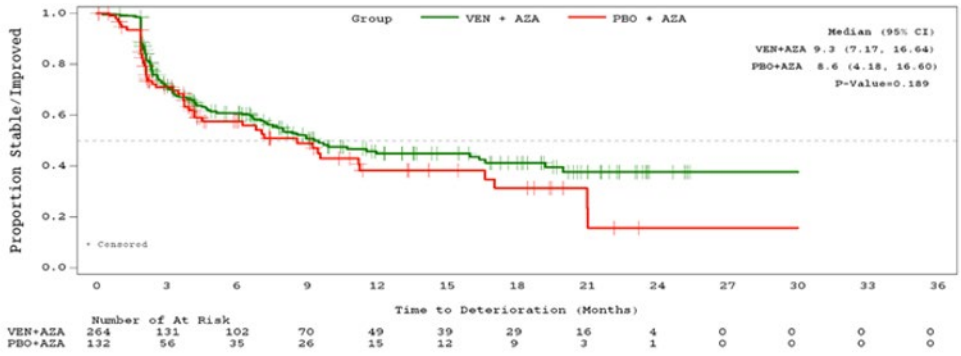
The mean baseline EORTC QLQ-30 nausea and vomiting subscale score for venetoclax plus azacitidine was 7.95 (n = 262) and for placebo plus azacitidine it was 7.63 (n = 130). Change from baseline showed improvement in subsequent cycles for both treatments, but the observed differences in LS means between the treatments were small at each time point.

The mean baseline EORTC QLQ-30 pain subscale score for venetoclax plus azacitidine was 21.95 (n = 262) and for placebo plus azacitidine it was 25.90 (n = 130). There was a numerically greater improvement for venetoclax plus azacitidine at most time points, but the observed differences in LS means between the treatments were small at each time point.

The mean baseline EORTC QLQ-30 appetite loss subscale score for venetoclax plus azacitidine was 31.42 (n = 262) and for placebo plus azacitidine it was 30.77 (n = 130). There was a greater improvement for venetoclax plus azacitidine from cycle 5 to cycle 13, but the observed differences in LS means between the treatments were small at each time point.

The mean baseline EORTC QLQ-30 constipation subscale score for venetoclax plus azacitidine was 20.23 (n = 262) and for placebo plus azacitidine it was 15.8 (n = 130). There

Figure 5: Time to Deterioration on the PROMIS Fatigue 7a, Longitudinal Analysis Population



Abbreviations: LAP = Longitudinal Analysis Population; PRO = Patient Reported Outcome; AZA = Azacitidine; PBO = Placebo; VEN = Venetoclax.
[1] PROMIS Fatigue 7A is a seven item questionnaire that assesses the impact and experience of fatigue over the past 7 days. All questions employ the following five response options: 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Often, and 5 = Always. The lower score indicates the improvement in PROMIS Fatigue 7A scale.
[2] The LAP includes all randomized subjects who have survived up to a given assessment and have available data on at least one PRO measure at baseline.
[3] P-value for Log Rank test of Venetoclax in Combination with Azacitidine versus placebo in combination with azacitidine.
[4] Deterioration is defined using the first event of PRO score worsening of at least 5.

AZA = azacitidine; CI = confidence interval; GHS/QoL = global health status quality of life scale; HRQoL = health-related quality of life; LAP = longitudinal analysis population; EORTC QLQ-30C = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; PBO = placebo; PRO = patient-reported outcome; PROMIS Fatigue 7a = Patient-Reported Outcomes Measurement Information System Short Form v1.0–Fatigue 7a; VEN = venetoclax.

Source: Patient-reported outcome report.[1]

was a greater improvement in subsequent cycles for venetoclax plus azacitidine, but the observed differences in LS means between the treatments were small at each time point.

The mean baseline EORTC QLQ-30 diarrhea subscale score for venetoclax plus azacitidine was 10.56 (n = 262) and for placebo plus azacitidine it was 9.74 (n = 130). There was improvement in subsequent cycles for venetoclax plus azacitidine for both treatments, but the observed differences in LS means between the treatments were small at each time point.

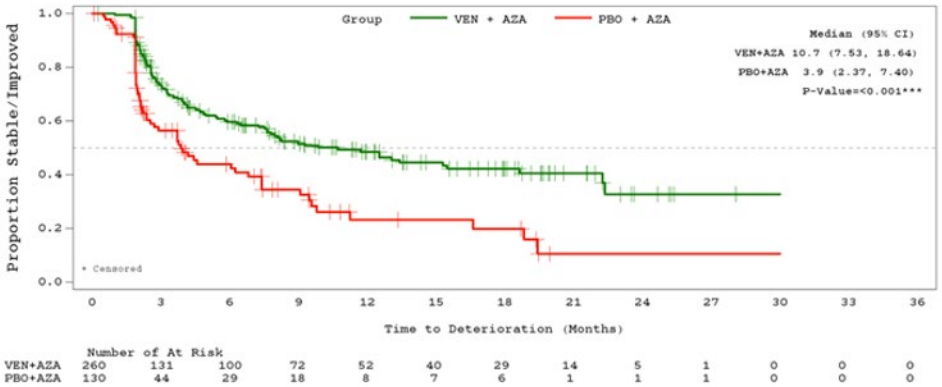
EuroQol Visual Analogue Scale

Table 38 shows the mean scores at baseline and day 1 of subsequent treatment cycles, the LS mean change from baseline, and the LS mean difference between venetoclax plus azacitidine and placebo plus azacitidine, for the EQ VAS. Figure 6 shows the time to deterioration on the EQ VAS.

The mean baseline EQ-5D-5L index score for venetoclax plus azacitidine was 0.76 (n = 260) and for placebo plus azacitidine it was 0.74 (n = 130). There was improvement (increase) in subsequent cycles for venetoclax plus azacitidine for both treatments, but the observed differences in LS means between the treatments were small at each time point. The mean baseline EQ VAS for venetoclax plus azacitidine was 60.29 (n = 260) and for placebo plus azacitidine it was 64.27 (n = 130). There was improvement (increase) in subsequent cycles for venetoclax plus azacitidine for both treatments, but the observed differences in LS means between the treatments were small at each time point.

The median time to deterioration for patients randomized to venetoclax plus azacitidine was 10.7 months, compared with 3.9 months for patients randomized to placebo plus azacitidine. The adjusted HR was 0.55 (95% CI, 0.394 to 0.768). The meaningful change threshold was 7 points.

Figure 6: Time to Deterioration on the EQ VAS, Longitudinal Analysis Population



Abbreviations: LAP = Longitudinal Analysis Population; PRO = Patient Reported Outcome; AZA = Azacitidine; PBO = Placebo; VEN = Venetoclax.
[1] In the assessment of EuroQol 5 Dimensions Visual Analog Scale (EQ VAS), subjects are asked to indicate their overall health status on a 0 to 100 visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. This information is used as a quantitative measure of health as judged by the individual respondents. The higher score indicates the improvement in EQ5D-VAS scale.
[2] The LAP includes all randomized subjects who have survived up to a given assessment and have available data on at least one PRO measure at baseline.
[3] P-value for Log Rank test of Venetoclax in Combination with Azacitidine versus placebo in combination with azacitidine.
[4] Deterioration is defined using the first event of PRO score worsening of at least 7.

AZA = azacitidine; LAP = longitudinal analysis population; EQ-5D = EuroQol 5-Dimensions questionnaire; EQ VAS = EuroQol Visual Analogue Scale; PBO = placebo; PRO = patient-reported outcome; VEN = venetoclax.

Source: PRO report.[1]

Harms

Only those harms identified in the review protocol are reported subsequently. Table 14 shows an overall summary of the treatment-emergent adverse events, most common treatment-emergent adverse events, grade 3 or greater treatment-emergent adverse events, SAEs, adverse events leading to death, adverse events leading to discontinuation of venetoclax or placebo and azacitidine, and notable harms (January 4, 2020). Individual adverse events are in descending order of frequency for patients receiving venetoclax plus azacitidine.

All patients in both groups experienced at least 1 adverse event, and almost all experienced at least 1 grade 3 or greater adverse event. Compared with patients who received placebo plus azacitidine, a greater proportion of patients who received venetoclax plus azacitidine experienced 1 or more SAEs, 1 or more adverse events leading discontinuation or dose interruption for venetoclax or placebo or azacitidine, or 1 or more adverse events leading to death. Of the patients who received venetoclax plus azacitidine, 279 (98.6%) had grade 3 or greater adverse events, 235 (83.0%) had SAEs, 69 (24.4%) had adverse events leading to discontinuation of venetoclax or placebo, 68 (24.0%) had adverse events leading to discontinuation of azacitidine, and 64 (22.6%) had adverse events leading to death. Of the patients who received placebo plus azacitidine, 139 (96.5%) had grade 3 or greater adverse events, 105 (72.9%) had SAEs, 29 (20.1%) had adverse events leading to discontinuation of venetoclax or placebo, 29 (20.1%) had adverse events leading to discontinuation of azacitidine, and 29 (20.1%) had adverse events leading to death.

Treatment-Emergent Adverse Events

Table 14 shows treatment-emergent adverse events that were reported in 10% or more of patients and treatment-emergent adverse events reported in 5% or more of patients in the safety population at the time of IA2 (January 4, 2020). The most common adverse events were thrombocytopenia, nausea, constipation, neutropenia, febrile neutropenia, diarrhea, vomiting, hypokalemia, and anemia. The most common grade 3 or greater treatment-emergent adverse events were thrombocytopenia, neutropenia, febrile neutropenia, anemia, leukopenia, pneumonia, and hypokalemia.

The treatment-emergent adverse events reported with a frequency of 5% or greater in patients receiving venetoclax plus azacitidine compared with those receiving placebo plus azacitidine were thrombocytopenia, neutropenia, febrile neutropenia, anemia, leukopenia, nausea, diarrhea, vomiting, stomatitis, hemorrhoids, peripheral edema, asthenia; decreased appetite, arthralgia; dizziness, syncope, presyncope, vertigo; dyspnea; pruritus; and rash maculopapular.

Serious Adverse Events

Table 14 shows SAEs reported in 2% or more patients in the safety population at IA2 (January 4, 2020). The most common SAEs were febrile neutropenia, pneumonia, sepsis, anemia, and neutropenia. Febrile neutropenia, anemia, neutropenia, and thrombocytopenia were more frequent in patients who received venetoclax plus azacitidine, and pneumonia and sepsis were more frequent in patients who received placebo plus azacitidine.

Mortality

Table 14 shows adverse events leading to death for the safety population. A total of 64 (22.6%) patients who received venetoclax plus azacitidine and 29 (20.1%) who received placebo plus azacitidine had adverse events leading to death. The most frequent adverse events leading to death were pneumonia, sepsis, cardiac arrest, and an event recorded

Table 14: Treatment-Emergent Adverse Events, Serious Adverse Events, and Adverse Events Leading to Discontinuation, Safety Population, IA2

Adverse events	VEN + AZA (N = 283) n (%)	PBO + AZA (N = 144) n (%)
Patients with any AE	283 (100)	144 (100)
Patients with AE grade ≥ 3	279 (98.6)	139 (96.5)
Patients with any SAE	235 (83.0)	105 (72.9)
Patients with VEN- or PBO-related AE[a]	241 (85.2)	96 (66.7)
Patients with AZA-related AE[a]	246 (86.9)	108 (75.0)
Patients with any AE leading to VEN or PBO discontinuation	69 (24.4)	29 (20.1)
Patients with any AE leading to AZA discontinuation	68 (24.0)	29 (20.1)
Patients with any AE leading to VEN or PBO dose interruption or reduction	204 (72.1)	84 (58.3)
Patients with any AE leading to AZA dose interruption or reduction	190 (67.1)	67 (46.5)
Patients with any AE leading to death	64 (22.6)	29 (20.1)
Treatment-emergent adverse events reported in ≥ 10% of patients in either arm		
Thrombocytopenia	130 (45.9)	58 (40.3)
Nausea	124 (43.8)	50 (34.7)
Constipation	121 (42.8)	56 (38.9)
Neutropenia	119 (42.0)	42 (29.2)
Febrile neutropenia	118 (41.7)	27 (18.8)
Diarrhea	117 (41.3)	48 (33.3)
Vomiting	84 (29.7)	33 (22.9)
Hypokalemia	81 (28.6)	41 (28.5)
Anemia	78 (27.6)	30 (20.8)
Decreased appetite	72 (25.4)	25 (17.4)
Edema peripheral	69 (24.4)	26 (18.1)
Pyrexia	66 (23.3)	32 (22.2)
Pneumonia	65 (23.0)	39 (27.1)
Fatigue	59 (20.8)	24 (16.7)
Leukopenia	58 (20.5)	20 (13.9)
Asthenia	44 (15.5)	12 (8.3)
Dizziness	37 (13.1)	10 (6.9)
Dyspnea	37 (13.1)	11 (7.6)

Adverse events	VEN + AZA (N = 283) n (%)	PBO + AZA (N = 144) n (%)
Weight decreased	37 (13.1)	14 (9.7)
Cough	35 (12.5)	20 (13.9)
Hypophosphatemia	35 (12.4)	17 (11.8)
Insomnia	35 (12.4)	15 (10.4)
Stomatitis	33 (11.7)	8 (5.6)
Arthralgia	33 (11.7)	7 (4.9)
Abdominal pain	31 (11.0)	12 (8.3)
Headache	30 (10.6)	10 (6.9)
Treatment-emergent adverse events of grade ≥ 3 reported for ≥ 5% of the patients in either arm		
Thrombocytopenia	126 (44.5)	55 (38.2)
Neutropenia	119 (42.0)	41 (28.5)
Febrile neutropenia	118 (41.7)	27 (18.8)
Anemia	74 (26.1)	29 (20.1)
Leukopenia	58 (20.5)	17 (11.8)
Pneumonia	56 (19.8)	36 (25.0)
Hypokalemia	30 (10.6)	15 (10.4)
Hypophosphatemia	21 (7.4)	11 (7.6)
Atrial fibrillation	17 (6.0)	3 (2.1)
Sepsis	17 (6.0)	13 (9.0)
Hypertension	17 (6.0)	6 (4.2)
Urinary tract infection	11 (3.9)	8 (5.6)
Serious adverse events reported in ≥ 2% of the patients in either arm		
Febrile neutropenia	84 (29.7)	15 (10.4)
Pneumonia	47 (16.6)	32 (22.2)
Sepsis	16 (5.7)	12 (8.3)
Anemia	14 (4.9)	6 (4.2)
Neutropenia	13 (4.9)	3 (2.1)
Thrombocytopenia	12 (4.2)	2 (1.4)
Atrial fibrillation	13 (4.6)	2 (1.4)
Escherichia sepsis	8 (2.8)	2 (1.4)
Influenza	8 (2.8)	2 (1.4)
Lung infection	8 (2.8)	3 (2.1)
Pyrexia	7 (2.5)	3 (2.1)
Septic shock	7 (2.5)	1 (0.7)

Adverse events	VEN + AZA (N = 283) n (%)	PBO + AZA (N = 144) n (%)
Urinary tract infection	7 (2.5)	3 (2.1)
Diarrhea	6 (2.1)	2 (1.4)
Acute kidney injury	5 (1.8)	5 (3.5)
Respiratory failure	5 (1.8)	1 (0.7)
General physical health deterioration	3 (1.1)	4 (2.8)
Malignant neoplasm progression	2 (0.7)	5 (3.5)
Acute myocardial infarction	2 (0.7)	3 (2.1)
Pleural effusion	2 (0.7)	3 (2.1)
Fall	1 (0.4)	3 (2.1)
AEs leading to death for > 1 patient		
Pneumonia	11 (3.9)	3 (2.1)
Sepsis	6 (2.1)	5 (3.5)
Death	4 (1.4)	2 (1.4)
Cardiac arrest	3 (1.1)	2 (1.4)
Hemorrhage intracranial	3 (1.1)	0
Respiratory failure	3 (1.1)	1 (0.7)
Septic shock	3 (1.1)	1 (0.7)
Atrial fibrillation	2 (0.7)	0
Multiple organ dysfunction syndrome	2 (0.7)	1 (0.7)
Systemic inflammatory response syndrome	2 (0.7)	1 (0.7)
General physical health deterioration	1 (0.4)	1 (0.7)
Klebsiella infection	1 (0.4)	1 (0.7)
Cerebral hemorrhage	1 (0.4)	1 (0.7)
AEs leading to PBO/VEN discontinuation for ≥ 2 patients in either group		
Acute kidney injury	4 (1.4)	2 (1.4)
Atrial fibrillation	4 (1.4)	0
Febrile neutropenia	4 (1.4)	1 (0.7)
Neutropenia	4 (1.4)	2 (1.4)
Pneumonia	4 (1.4)	4 (2.8)
Sepsis	4 (1.4)	5 (3.5)
Thrombocytopenia	3 (1.1)	3 (2.1)
Malignant neoplasm progression	3 (1.1)	3 (2.1)
Respiratory failure	3 (1.1)	1 (0.7)
Cardiac failure	2 (0.7)	0

Adverse events	VEN + AZA (N = 283) n (%)	PBO + AZA (N = 144) n (%)
Death	2 (0.7)	0
Systemic inflammatory response syndrome	2 (0.7)	1 (0.7)
Fatigue	2 (0.7)	1 (0.7)
Klebsiella infection	2 (0.7)	0
Septic shock	2 (0.7)	0
AEs leading to AZA discontinuation for ≥ 2 patients in either group		
Acute kidney injury	4 (1.4)	2 (1.4)
Atrial fibrillation	4 (1.4)	0
Neutropenia	4 (1.4)	1 (0.7)
Pneumonia	4 (1.4)	4 (2.8)
Sepsis	4 (1.4)	5 (3.5)
Febrile neutropenia	3 (1.1)	1 (0.7)
Malignant neoplasm progression	3 (1.1)	3 (2.1)
Thrombocytopenia	3 (1.1)	3 (2.1)
Cardiac failure	2 (0.7)	0
Death	2 (0.7)	0
Systemic inflammatory response syndrome	2 (0.7)	1 (0.7)
Fatigue	2 (0.7)	1 (0.7)
Klebsiella infection	2 (0.7)	0
Septic shock	2 (0.7)	0
Summary of notable harms for VEN + AZA and PBO + AZA		
Neutropenia search[b]	201 (71.0)	64 (44.4)
Febrile neutropenia	118 (41.7)	27 (18.8)
Infections and infestations, all	239 (84.5)	97 (67.4)
Most common[c]		
Pneumonia	65 (23.0)	39 (27.1)
Upper respiratory tract infection	26 (9.2)	13 (9.0)
Urinary tract infection	26 (9.2)	11 (7.6)
Lung infection	19 (6.7)	4 (2.8)
Sepsis	18 (6.4)	13 (9.0)
Oral herpes	17 (6.0)	6 (4.2)
Cellulitis	16 (5.7)	8 (5.6)
Oral candidiasis	16 (5.7)	5 (3.5)

Adverse events	VEN + AZA (N = 283) n (%)	PBO + AZA (N = 144) n (%)
Bronchitis	15 (5.3)	4 (2.8)
Hemorrhage	107 (37.8)	53 (36.8)
Tumour lysis syndrome[d]		
Met Howard criteria	7 (2.5)	3 (2.1)
Reported AE of tumour lysis syndrome	3 (1.1)	0
Secondary primary malignancy	11 (3.9)	2 (0.7)

AE = adverse event; AZA = azacitidine; IA2 = second interim analysis; PBO = placebo; VEN = venetoclax.

[a]Reported as "any reasonable possibility" of being a treatment-related AE, as assessed by investigator.

[b]Includes terms: neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis.

[c]Individual AEs reported for ≥ 5% of patients in either group.

[d]Evaluated between the first dose of the study drug and 7 days after the first dose of the study drug.

Note: Data cut-off was January 4, 2020.

Source: Clinical Study Report.[1]

as death. Pneumonia, death, and cardiac arrest occurred more frequently in patients who received venetoclax plus azacitidine.

Treatment Discontinuations Due to Adverse Events

Table 14 shows adverse events leading to discontinuation of placebo or venetoclax for 2 or more patients in either group in the safety population by adverse event and system organ class.

The most frequent adverse events leading to venetoclax or placebo treatment discontinuation in the venetoclax plus azacitidine group were acute kidney injury, atrial fibrillation, febrile neutropenia, neutropenia, pneumonia, sepsis, thrombocytopenia, malignant neoplasm progression, and respiratory failure. In patients who received venetoclax plus azacitidine, atrial fibrillation, febrile neutropenia, cardiac failure, *Klebsiella* infection, and septic shock were more frequent, and in patients who received placebo plus azacitidine, pneumonia, sepsis, thrombocytopenia, and malignant neoplasm progression were more frequent.

The most frequent adverse events leading to azacitidine treatment discontinuation in the venetoclax plus azacitidine group were acute kidney injury, atrial fibrillation, neutropenia, pneumonia, sepsis, febrile neutropenia, and malignant neoplasm progression. In patients who received venetoclax plus azacitidine, atrial fibrillation, neutropenia, febrile neutropenia, cardiac failure, *Klebsiella* infection, and septic shock were more frequent, and in patients who received placebo plus azacitidine, pneumonia, sepsis, malignant neoplasm progression, and thrombocytopenia were more frequent.

Notable Harms

The notable harms identified for the protocol were neutropenia, febrile neutropenia, infections, tumour lysis syndrome, hemorrhage, and secondary malignancies. The search for adverse events of neutropenia included terms for neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis. Tumour lysis syndrome was a known risk and all patients received prophylaxis with oral and/or IV hydration and uric acid reducer, and were admitted for monitoring during ramp-up of venetoclax.

Patients with a white blood cell count greater than 25 × 10^9/L required cytoreduction before treatment.

Neutropenia, febrile neutropenia, infections and infestations, and secondary primary malignancies all occurred in a greater proportion of patients who received venetoclax plus azacitidine than in patients who received placebo plus azacitidine. Hemorrhage and tumour lysis syndrome occurred in similar proportions, and the proportion of patients with tumour lysis syndrome was low (≤ 2.5%).

The most common secondary malignancies were basal cell carcinoma and squamous cell carcinoma of the skin: 3 (1.1%) and 2 (0.7%) instances, respectively, in patients receiving venetoclax plus azacitidine, and none in patients receiving placebo plus azacitidine. Other malignancies reported for patients who received venetoclax plus azacitidine were gastric adenocarcinoma (recurrence), adenocarcinoma of colon, chloroma (manifestation of AML), erythroleukemia (AML), neuroendocrine carcinoma of the skin, and plasma cell myeloma. Other malignancies reported for patients receiving placebo plus azacitidine were malignant melanoma and renal cancer.

Critical Appraisal

Internal Validity

Randomization was conducted by an independent statistician, allocation was through an interactive voice recognition system (IVRS), and the study was double blinded, with identical-appearing oral venetoclax and placebo. Venetoclax does not appear to have any adverse events that are so specific as to unblind patients or physicians; therefore, the blinding was likely to remain intact. Blinding was not assessed.

There was no clinically meaningful imbalance in the baseline characteristics that might favour 1 group or the other, and there was minimal loss to follow-up (1.7% for venetoclax plus azacitidine and 1.4% for placebo plus azacitidine). The number of patients who withdrew consent after randomization was small (approximately 2%).

The duration of exposure and number of treatment cycles received was longer in the venetoclax plus azacitidine group, which is probably reflective of the difference in survival: patients receiving venetoclax plus azacitidine survived longer and received more cycles. A similar proportion of patients discontinued treatment due to adverse events. Procedures for assessing compliance with treatment (i.e., counting of returned doses) were described in the protocol but the results were not reported.

OS is a standard outcome in oncology drug investigation, with robust methods for ascertainment. Collection was likely to be complete and the timing of events was likely to be accurately determined. Standard methods for survival analysis were used, with surviving patients censored at the date they were known to be alive on or before the cut-off date. There was minimal loss to follow-up or withdrawal and good balance at baseline, so censoring is unlikely to be related to prognosis. The prognosis of the patients recruited is unlikely to have changed with time, as there were no changes to the inclusion and exclusion criteria that would be likely to affect prognosis, and recruitment took place over a relatively short time period.

EFS is a composite end point consisting of death from any cause, confirmed morphologic relapse from CR + CRi, confirmed disease progression, and treatment failure. Treatment failure was defined as failure to reach CR, CRi, or MLFS after at least 6 cycles. No protocol-

specific support for the validity of the end point was offered in the protocol or statistical analysis plan. EFS is an accepted end point in the development of treatments for leukemia,[25] although empirical data show inconsistent correlation between EFS and OS.[35] However, it provides a more direct measurement of the ability of the treatment to achieve a response and the durability of the response achieved than OS, since EFS is affected by trial treatment alone, while OS is affected by trial treatment, post-trial treatment, and supportive or palliative care.[35] A time-to-event analysis of all individual end points making up the composite was not reported, making it difficult to fully assess for violations of the assumptions underlying the composite end points (i.e., the events were of equal importance to patients, occur with similar frequency, and have a similar sensitivity to the treatment). Death was reported for the greatest proportion of patients (54.5% and 61.5% for venetoclax plus azacitidine and placebo plus azacitidine, respectively), followed by confirmed morphologic relapse or confirmed disease progression (43.5% and 28.7% for venetoclax plus azacitidine and placebo plus azacitidine, respectively), and then by treatment failure (2.1% and 9.8% for venetoclax plus azacitidine and placebo plus azacitidine, respectively). The proportion of patients with each end point was reported, and the distribution for each treatment was consistent with the observed results for survival and CR + CRi, which were higher in the venetoclax plus azacitidine group than in the placebo plus azacitidine group. Results for individual analyses of OS, duration of response, and CR + CRi show similar directions of effect, but this does not adjust for competing events. Standard methods for survival analysis were used, with surviving patients censored at the date they were known to be alive on or before the cut-off date. There was minimal loss to follow-up or to withdrawal and a good balance at baseline, so censoring is unlikely to be related to prognosis. The prognosis of the patients recruited is unlikely to have changed with time, as there were no changes to the inclusion and exclusion criteria that would be likely to affect prognosis, and recruitment took place over a relatively short time period.

Composite complete remission (CR + CRi) and CR were investigator-assessed based on laboratory and clinical findings, with independent review. No protocol-specific support for the validity of the end point was offered in the protocol or statistical analysis plan. CR + CRi is an accepted end point in the development of treatments for leukemia,[25] although empirical data suggest the strength of the correlation between CR + CRi and OS may be population- and treatment-dependent.[35] The results were cross tabulated, and the differences minimal between investigator and independent review results. Treatment effect was not calculated for the end point and its 2 components, and statistical testing for CR + CRi and CR was performed at different interim analyses. CR and CRi both reflect bone marrow and peripheral blood improvement, with different thresholds, and the direction of effect was the same for both. Randomized patients without a post-baseline disease assessment were considered nonresponders. This is a conservative assumption, biasing the individual estimates of response downward, but accounts for a competing risk of death in an aged population.

Transfusion-independence rate was a pre-specified end point that was included in the sequential testing strategy. It is not clear how data on transfusion were collected, or whether these data might be susceptible to survivor bias, i.e., whether patients had to survive until the next transfusion visit for the previous visit to be captured. This risks undercounting transfusions in seriously ill patients. Patients who did not receive the study drug were considered transfusion-dependent, a conservative assumption affecting only a small number of patients.

Overall QoL was measured using the EOTRC QLQ-C30 GHS/QoL scale, cancer-related fatigue was measured using the PROMIS 7a, fatigue and other symptoms of interest were measured using EORTC QLQ-30C subscales, and health utility was measured using the EQ-5D-5L. The

EOTRC QLQ-C30 GHS/QoL scale had previously been validated in mixed groups of cancer patients and an MID established. The PROMIS 7a has been validated in published studies of chronic illness, and the sponsor reported steps to validate the measure using the data from the VIALE-C study of venetoclax plus LDAC. Mean change from baseline was calculated using available data without imputation, and the level of compliance with the tool was not reported. Compliance post baseline was around 80%, meaning about 20% of available patients were not represented, and attrition due to death and disease progression was pronounced, meaning that later time points in particular represent a small survivor subgroup.

There were 2 preplanned interim analyses with preplanned stopping boundaries, with recommendations to stop or proceed made by an independent monitoring committee. Multiplicity due to interim analyses and the testing of multiple end points was controlled by a preplanned alpha-spending strategy and pre-specified hierarchy of testing with gatekeeping. Testing boundaries for selected end points representing proportions were adjusted by an information fraction to accommodate incomplete accrual at the interim analysis. Planned methods were reported on and adhered to.

Protocol violations included violations of inclusion and exclusion criteria, where patients were included although their bone marrow blast count did not meet the threshold at the time of testing for the study or the data were missing. A review provided evidence that they had previously met the criteria. Protocol violations in dosing included the use of strong and moderate CYP3A inhibitors without modifying the dose of venetoclax or placebo. These cases were reviewed for safety concerns. No violations were reported that substantially affected the internal validity of the study.

Subgroups of interest were pre-specified. Age (18 to < 75 years and ≥ 75 years) and cytogenetic risk (intermediate, poor) were used as stratification variables; other subgroups were not stratified. The aseline balance of all covariates was not reported for subgroups. Some subgroups were small, which was reflected in the high uncertainty of treatment estimates. This particularly affected estimates of CR + CRi, where both the number of specific events and total number of events could be small. Subgroup analyses of patients with IHD1, IHD2, and FLT3 mutations were included in the sequential testing strategy. Other subgroup analyses, including those on patients negative for mutations, were not adjusted for multiplicity.

There were 7 protocol amendments with corresponding changes in the statistical analysis plan. An early change to stratification factors meant that 2 patients randomized under the original protocol were not included in the efficacy analysis. Minor changes were made to inclusion criteria for safety reasons, there were clarifications on the dosing of concomitant medications, and the sample size was adjusted to allow for longer follow-up. Changes were made to the definition of EFS to align it with VIALE-C and to CR and CRi. All changes were made before the stopping and unblinding of the study following IA2 and are unlikely to have affected the internal validity of the study.

External Validity

The inclusion criteria for VIALE-A assumed that patients aged 75 years and older would not be eligible for standard induction chemotherapy, and age was the most common reason given for randomized patients being considered ineligible for standard induction chemotherapy. In Canadian practice, there is no consistency in defining an upper age limit for intensive chemotherapy. Chemotherapy may be considered for patients with treatment-naive AML aged 75 years and older, especially those with good or intermediate risk cytogenetics. The

myelosuppressive nature of venetoclax plus azacitidine means it may not be suitable for frail patients or those who cannot travel for frequent lab visits, regardless of age.

Patients with CNS involvement were excluded, but clinical experts indicated that patients with CNS involvement might benefit from venetoclax plus azacitidine with concomitant intrathecal therapy. Patients with secondary AML (arising from prior myeloproliferative neoplasm including myelofibrosis, essential thrombocythemia, and polycythemia vera) were excluded from enrolling onto the study. However, there is data that shows activity of venetoclax plus azacitidine in this group of patients.[36,37] Patients with isolated granulocytic sarcoma were not included in the study.

Venetoclax dosing in the trial was aligned with the Health Canada–approved dosing. Up-titration and monitoring would be expected to be the same in clinical practice. Dosing of azacitidine was also aligned with Health Canada–indicated dosing; however, the current Health Canada approval for azacitidine is for patients with AML with less than 30% blasts. In practice, experts and clinician groups noted that jurisdictions are funding azacitidine and centres are already using it in patients with a blast count of 30% or greater. There is no maximum blast restriction in the Health Canada–approved indication for venetoclax plus azacitidine for patients with AML who are aged 75 years and older or ineligible for standard induction therapy, and the indication aligns with the submission. In the study, azacitidine was dosed for 7 consecutive days while, in practice, alternative dosing regimens are used to reduce the hematological toxicity, e.g., 5 to 2-2 and 6 consecutive days.

The outcome measures were relevant to patients and clinicians. They captured clinically important end points such as OS, clinically important surrogate end points of response and remission, overall QoL, and factors identified as influencing QoL (e.g., transfusion dependence). Disease remission, avoidance of relapse, symptoms, QoL, independence from transfusion and avoidance of hospitalization, and OS were all identified as important to patients and physicians. In clinical practice, strict responder definitions may not capture responding patients; patients may not reach strict response categories but may still derive clinical benefit.

The settings for the study were predominately urban hospitals and clinics. It therefore does not necessarily address the rural or remote Canadian context, where patients would not have access to frequent laboratory testing to monitor the ramp-up of venetoclax and cytopenias, nor access to outpatient or inpatient treatment for side effects and complications. Patients would be required to travel for treatment or to receive an alternative.

Duration of follow-up was around 20 months, with a median OS for venetoclax plus azacitidine of 14.7 months. Five-year follow-up is standard in oncology trials.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

An ITC was required because of a lack of studies directly comparing venetoclax plus azacitidine and venetoclax plus LDAC with other treatments currently in use in the Canadian setting.

Search Methods

A focused literature search for NMAs dealing with Venclexta (venetoclax) and AML was run in MEDLINE All (1946–) on February 11, 2021. No limits were applied.

Description of Indirect Treatment Comparison

One report that included ITCs was supplied by the sponsor. It included a systematic review with an NMA comparing venetoclax plus azacitidine and venetoclax plus LDAC with azacitidine, LDAC and BSC, and 2 propensity-score analyses comparing venetoclax plus azacitidine with LDAC (2-way comparison), and venetoclax plus azacitidine with azacitidine with LDAC (3-way comparison).

Table 15 shows the study selection criteria and key aspects of the methods for the systematic review. The patient population of interest included treatment-naive adult patients with AML who were ineligible for intensive chemotherapy, but the search allowed flexible wording to ensure retrieval of studies. Treatment naive was considered interchangeable with "previously untreated" or "newly diagnosed," and "ineligible for chemotherapy" included patients described as old or elderly, unfit for intensive chemotherapy, unfit for standard chemotherapy, or unfit for high-dose chemotherapy. The initial search for articles included a broader set of comparators and included controlled clinical trials as a study design. More restricted selection criteria that were developed for a planned EUnetHTA submission were applied at the full-text review stage; the table reflects these criteria. The reasons for selection of comparators were not given, but the overall declared intention was to select high-quality studies that might enable ITCs.

Methods of the ITC

Objectives

The objective of this study was to compare the efficacy of venetoclax combination therapies with alternative treatments in treatment-naive patients with AML who were ineligible for intensive chemotherapy, including:

- Objective 1: Comparison of venetoclax plus azacitidine and venetoclax plus LDAC with azacitidine, LDAC, and BSC using NMA.
- Objective 2: Comparison of venetoclax plus azacitidine versus LDAC using propensity score–weighting analysis.
- Objective 3: Comparison of venetoclax plus azacitidine versus azacitidine versus LDAC using 3-way propensity score–weighting analysis.

Study Selection Methods

To be included in the NMAs, trials retrieved by the systematic review had to meet the following criteria:

- Study design: phase III RCTs
- Population: Treatment-naive adult patients with AML who were ineligible for intensive chemotherapy
- Interventions: Venetoclax plus azacitidine, venetoclax plus LDAC, LDAC, azacitidine, and BSC (including blood transfusion, etoposide, mercaptopurine, and hydroxyurea)
- Outcomes of interest: OS, EFS, CR, CRi, CR + CRi

Table 15: Study Selection Criteria and Methods for the Systematic Review

Criteria	ITC
Population	Treatment-naive adult patients (age ≥ 18 years) with AML who were ineligible for intensive chemotherapy: • Patients who had not received any prior treatment for AML with the exception of hydroxyurea (allowed through the first cycle of treatment). Prior treatment for MDS was allowed, except for cytarabine. • Patients with secondary AML with or without prior treatment with an HMA for MDS were included. Studies were excluded if they were not on humans; not on adults; not on treatment-naive AML; specifically recruited patients with HIV, HBV, or HCV infection; or included patients with APL.
Intervention or comparator	Studies with at least 1 of the following regimens: • venetoclax + azacitidine • venetoclax + low-dose cytarabine • venetoclax + decitabine • azacitidine • low-dose cytarabine • decitabine • glasdegib + low-dose cytarabine • best supportive care, including blood transfusion, etoposide, mercaptopurine, or hydroxyurea
Outcome	Studies reporting at least 1 of the following outcomes: • overall survival • event-free survival • progression-free survival • relapse-free survival • complete remission (CR) • CR with incomplete blood count recovery (CRi) • composite complete remission (CR + CRi) • CR with partial hematologic recovery (CRh) • objective response • partial remission • duration of remission • minimal/measurable residual disease • grade 3 or 4 adverse events • discontinuation due to adverse events
Study design	Included designs: • RCTs
Other selection criteria	• Inclusion restricted to English-language studies • Inclusion limited to studies with ≥ 20 patients per arm • Exclusion of studies with mixed MDS and AML populations, unless outcomes were reported for the AML subgroup • Bibliographies of systematic reviews and meta-analyses identified in the search were screened for studies before exclusion

Criteria	ITC
Databases searched	Searched through Ovid: • MEDLINE and Epub Ahead-of-Print, In-Process and Other Non-Indexed Citations, Daily and Versions • EMBASE • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews • Database of Abstracts of Reviews of Effects Abstract search (2017 onward) through Ovid Northern Light Life Sciences Conference Abstracts (http://www.ovid.com/site/catalog/databases/13207.jsp) or through the conference website if the latest conference abstracts were not indexed in Northern Light database: • European Hematology Association (https://ehaweb.org/) • American Society of Clinical Oncology (https://www.asco.org/) • British Society for Haematology (https://b-s-h.org.uk/) • American Society of Hematology (https://www.hematology.org/) • European Society for Medical Oncology (https://www.esmo.org/) Also searched: • ClinicalTrials.gov (https://clinicaltrials.gov/) to identify unpublished trial results • National Institute for Health and Care Excellence (https://www.nice.org.uk/) • Scottish Medicines Consortium (https://www.scottishmedicines.org.uk/) • Validated filters (Scottish Intercollegiate Guidelines Network) were used to retrieve RCTs
Selection process	Level 1 screening was by title and abstract. Potentially relevant studies were passed on to level 2, where the full text was screened. Each level of screening was conducted by 2 independent reviewers. Discrepancies were reconciled by a third reviewer.
Data extraction process	Data were extracted independently by 2 reviewers into a predefined extraction table. Discrepancies were reconciled by a third reviewer.
Quality assessment	The quality assessment was done according to the Centre for Reviews and Dissemination Risk of Bias Assessment checklist for RCTs: • Was the method used to generate random allocations adequate? • Was the concealment of treatment allocation adequate? • Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease? • Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)? • Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for? • Were there any evidence to suggest that the authors measured more outcomes than they reported? • Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

AML = acute myeloid leukemia; APL = acute promyelocytic leukemia; CR = complete remission; CRh = complete remission with incomplete hematological recovery; CRi = complete remission with incomplete bone marrow recovery; HBV = hepatitis B virus; HCV = hepatitis C virus; HMA = hypomethylating agent; ITC = indirect treatment comparison; MDS = myelodysplastic syndrome; RCT = randomized controlled trial.

Source: Systematic review report.[38]

The decision to restrict selection to phase III RCTs for reasons of quality led to the exclusion of trials containing glasdegib, as there was no phase III trial connected to the network

containing venetoclax plus azacitidine and venetoclax plus LDAC.

ITC Analysis Methods

Three analyses were conducted: 1 NMA and 2 propensity score–weighted comparisons.

The NMA compared venetoclax plus azacitidine and venetoclax plus LDAC with comparators for the available end points of OS and CR + CRi. The feasibility of pooling to create a network for analysis was pre-assessed on the basis of study and patient characteristics. The main analysis excluded patients from the VIALE-C LDAC group who would not have been eligible to enter VIALE-A because they had previously been treated with an HMA or had good cytogenetic risk. For OS, the proportional hazards assumption was assessed using log-log cumulative hazard plots, which led to the decision to model OS using proportional hazards.

The model was a Bayesian mixed-treatment comparison using a generalized linear model framework, with OS modelled using the identity link and dichotomous outcomes modelled using the logit link. Due to limited data, only fixed-effects models were estimated. Prior distributions were non-informative and selected according to a process that was not detailed. Posterior probabilities were modelled using Markov chain Monte Carlo methods, with 50,000 iterations on 3 chains and a burn-in period of 50,000 iterations. Convergence was assessed using trace and density plots and Gelman-Rubin plots and diagnostics. Selection between models was made by the difference information criterion (DIC). The chosen definition of a meaningful difference in DIC was not given.

Two propensity score–weighting analyses were conducted. No specific rationale was provided for these additional analyses. The comparisons were:

- Two-way propensity-score weighting of individual patient data was used to compare to compare venetoclax plus azacitidine with LDAC, using the venetoclax plus azacitidine group from VIALE-A and the LDAC group from VIALE-C. Data were available for outcomes of OS, EFS, and CR + CRi. Individual patient data were available for both trials, with a data cut-off for VIALE-A of January 4, 2020 and for VIALE-C of August 15, 2019.
- Three-way propensity-score weighting of individual patient data was used to compare venetoclax plus azacitidine with azacitidine and with LDAC, using the venetoclax plus azacitidine and azacitidine groups from VIALE-A (which were randomized) and the LDAC group from VIALE-C. Data were available for outcomes of OS, EFS, and CR + CRi. Data cut-offs were the same as stated previously.

For both analyses, the propensity score for treatment was calculated for each patient using a logistic regression model with treatment with venetoclax plus azacitidine versus LDAC as the outcome and the baseline demographic and clinical characteristics as covariates. Analyses of OS, EFS, and CR + CRi were then conducted using data weighted by the inverse of the probability score. The covariates were:

- Demographic characteristics: Age (< 75 years, ≥ 75 years), sex (male, female), race (White, non-White).
- Clinical characteristics: AML type (primary and secondary), AML with myelodysplasia-related changes (yes, no), prior MDS (yes, no), bone marrow blasts (< 30%, ≥ 30%), cytogenetic risk (poor, intermediate), and ECOG PS (< 2, ≥ 2). Patients with missing values for any of these were excluded from the analysis.

For comparability, the propensity score–weighting analyses excluded patients from the VIALE-C LDAC group who would not have been eligible to enter VIALE-A: those who had been previously treated with an HMA and those who had good cytogenetic risk. For the 2-way propensity-score analysis, a subgroup analysis was conducted that was restricted to those patients in the main analysis who had greater than 30% bone marrow blasts at the baseline assessment, with a corresponding sensitivity analysis of all patients who had 30% bone marrow blasts. For the 3-way propensity-score analysis, a planned subgroup analysis of patients with 20% to 30% bone marrow blasts was not conducted, as the number of patients meeting these criteria in the LDAC arm was small.

Standard mean differences, t-tests (continuous variables), and chi-square tests (categorical variables) were used to assess balance before weighting, and weighted standard mean differences, weighted t-tests, and weighted chi-square tests were used to assess balance after weighting. An effective sample size was calculated and distributions of weights inspected to identify potential sensitivity to extreme weights. Time-to-event comparisons (OS and EFS) were made using weighted Cox proportional hazards models. Standard errors, 95% CIs, and P values were based on robust estimates of variances accounting for variability in propensity-score weights.

Results of ITC

Summary of Included Studies

Following removal of duplicates, 7,319 records were screened by title and abstract; of these, 225 were screened in full text. With the addition of the VIALE-A and VIALE-C study reports, the final selection was 7 RCTs with at least 2 arms of interest.

With the additional restriction of the comparators for the NMA inclusion criteria, removing decitabine from the comparators, 4 trials were included in the NMA: VIALE-A, VIALE-C, AZA-001, and AZA-AML-001. Table 16 shows a summary of the study characteristics for these 4 trials.

Table 17 shows a summary of patient baseline characteristics for the 4 studies included in the NMA. Only the arms used in the NMA are included. The table is in 2 panels, the first showing demographic and clinical characteristics and the second showing the cytogenetic and mutation data. Table 19 shows an assessment of heterogeneity based on the study and patient characteristics. The most important source of heterogeneity was in indicators of disease severity, bone marrow blast counts, proportion of patients with poor cytogenetic risk, and baseline ECOG PS.

Table 20 shows the results of the risk-of-bias assessment for the 4 trials included in the ITC. The quality assessment questions appear in Table 15. Risk of bias was low for all trials for treatment randomization, allocation concealment, and baseline balance. Trials AZA-001 and AZA-AML-001 were open-label, so the risk of bias was high, whereas VIALE-A and VIALE-C were double-blind, with a low risk of bias. AZA-001 was at high risk of bias for imbalance in drop-outs, as more patients appear to have dropped out of the conventional care arm, and there was selective reporting, as overall adverse events were not available. All were at unclear risk of bias for the inclusion of intention-to-treat analyses. Where a reason was given, the concern was with lack of detail on methods for handling missing data.

Table 16: Study Characteristics of Trials Included in the Systematic Review

Study	Design	N	Intervention vs. comparator	Key inclusion criteria	Key exclusion criteria
VIALE-A (M15-656)	Phase III, double-blind, RCT Randomized 2:1, VEN + AZA:PBO + AZA	VEN + AZA: 286 PBO + AZA: 145	VEN + AZA vs. PBO + AZA VEN 400 mg orally once a day (1 to 28 days) AZA 75 mg/m^2 SC or IV daily (1 to 7 days)	Aged ≥ 18 years, with AML, ineligible for standard induction due to age or comorbidities Treatment-naive ECOG: • aged 75 years: 0 to 2 • aged 18 to 74 years: 0 to 3	Prior treatment for AML, except hydroxyurea; prior HMA or VEN chemotherapy for MDS; prior CAR T-cell therapy; received strong or moderate CYP3A inducers within 7 days Prior myeloproliferative neoplasm, acute promyelocytic leukemia, active CNS involvement Cytogenetic risk: Good
VAILE-C (M16-043)	Phase III, double-blind Randomized 2:1, VEN + AZA:PBO + AZA	VEN + LDAC: 143 LDAC: 68	VEN + LDAC vs. LDAC VEN 600 mg orally once a day (1 to 28 days) LDAC 20 mg/m^2 SC (1 to 10 days)	≥ 18 years, with AML, ineligible for intensive induction therapy, (aged ≥ 75 years, or ≥ 18 to 74 years and met at least 1 of criteria for lack of fitness for intensive induction therapy) Treated for MDS (except cytarabine) ECOG 75 years: 0 to 2 ECOG 18 to 74 years: 0 to 3	Prior treatment for AML, except hydroxyurea Prior myeloproliferative neoplasm, acute PML, active CNS involvement
AZA-001	Phase III, open-label	AZA: 55 LDAC: 20 BSC: 27	AZA vs. LDAC AZA vs. BSC AZA 75 mg/m^2 SC daily (1 to 7 days) BSC (blood product infusion, antibiotics, GSF) LDAC 20 mg/m^2 SC (1 to 14 days)	AML patients ≥ 20% bone marrow or peripheral blasts	Therapy-related disease

Study	Design	N	Intervention vs. comparator	Key inclusion criteria	Key exclusion criteria
AZA-AML-001	Phase III, open-label	AZA: 241 LDAC: 158 BSC: 45	AZA vs. BSC AZA vs. LDAC AZA 75 mg/m^2 SC daily (1 to 7 days) BSC (blood product infusion, antibiotics, GSF) LDAC 20 mg/m^2 SC (1 to 10 days)	Aged ≥ 65 years, newly diagnosed AML, > 30% blasts Intermediate or poor risk cytogenetics	Acute AML with t(15;17)(q22;q12) and AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22), t(8;21)(q22;q22), or t(9;22)(q34;q11.2). Not FAB M3 AML

AML = acute myeloid leukemia; AZA = azacitidine; BSC = best supportive care; CAR T-cell therapy = chimeric antigen receptor T-cell therapy; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; GSF = granulocyte stimulating factor; HMA = hypomethylating agent; LDAC = low-dose cytarabine; MDS = myelodysplastic syndrome; PBO = placebo; PML = promyelocytic leukemia; RCT = randomized controlled trial; SC = subcutaneous; VEN = venetoclax.

Source: Indirect treatment comparison report.[39]

Trial Networks

Figure 7 shows the network for the NMA for OS. Four trials reported this end point and were included in the NMA. The network was linear with a single branch and included 5 treatments. There were no closed loops. Azacitidine was the best-represented treatments with 3 trials contributing data, followed by LDAC with 2.

Figure 8 shows the network for the NMA for CR + CRi. Three trials reported this end point and were included in the NMA; the fourth trial, AZA-001, did not report data on CRi. The network was linear with a single branch and included 5 treatments. There were no closed loops. Azacitidine and LDAC were the best-represented treatments, with 2 contributing trials each.

Table 21 shows the data included in the NMAs for the 2 end points of OS and CR + CRi. In the 2 trials comparing azacitidine with BSC, the HRs for OS were 0.60 (95% CI, 0.38 to 0.95) and 0.48 (95% CI, 0.24 to 0.94) for AZA-001 and AZA-AML-001, respectively. In the 2 trials comparing azacitidine with LDAC, the HRs for OS were 0.37 (95% CI, 0.12 to 1.13) and 0.90 (95% CI, 0.70 to 1.16) for AZA-001 and AZA-AML-001, respectively.

Results

Results of the NMA

OS: Table 22 shows the results for the NMA for OS. Venetoclax plus azacitidine was favoured over comparators azacitidine (HR = 0.66; 95% CrI, 0.52 to 0.85), LDAC (HR = 0.57; 95% CrI,

Table 17: Summary of Patient Baseline Characteristics

Study	Treatment	N	Age (years), median (range)	Gender (male) n (%)	ECOG/ WHO PS 0 or 1, n (%)	ECOG/ WHO PS 2, n (%)	Primary/de novo AML, n (%)	Secondary AML, n (%)
VIALE-A	VEN + AZA	286	76.0 (49 to 91)	172 (60.1)	157 (54.9)	113 (39.5)	214 (74.8)	72 (25.2)
	PBO + AZA	145	76.0 (60 to 90)	87 (60.0)	81 (55.9)	59 (40.7)	110 (75.9)	35 (24.1)
VIALE-C	VEN + LDAC	143	76.0 (36 to 93)	78 (54.5)	74 (51.7)	63 (44.1)	85 (59.4)	58 (40.6)
	Placebo + LDAC	68	76.0 (41 to 88)	39 (57.4)	34 (50.0)	25 (36.8)	45 (66.2)	23 (33.8)
	CCR + preselected LDAC	20	71.0 (56 to 83)	15 (75.0)	19 (95.0)	0 (0.0)	NR	NR
	CCR + preselected BSC	45	78.0 (67 to 89)	29 (64.4)	30 (66.7)	15 (33.3)	NR	NR
	CCR + preselected LDAC	158	75.0 (65 to 88)	94 (59.5)	123 (77.8)	35 (22.2)	NR	NR

AML = acute myeloid leukemia; AZA = azacitidine; BSC = best supportive care; CCR = conventional care regimen; ECOG = Eastern Cooperative Oncology Group; LDAC = low-dose cytarabine; NR = not reported; PS = Performance Status; VEN = venetoclax.

Source: Systematic review report.[38]

0.40 to 0.81), and BSC (HR = 0.37; 95% CrI, 0.24 to 0.58), with no treatment favoured between venetoclax plus azacitidine, and venetoclax plus LDAC (HR = 0.81; 95% CrI, 0.50 to 1.31).

CR + CRi: Table 23 shows the results for the NMA for OS. Venetoclax plus azacitidine was favoured over comparators azacitidine (OR 5.05; 95% CrI, 3.30 to 7.87), LDAC (OR = 5.42; 95% CrI, 2.80 to 10.50), and BSC (OR = 61.55; 95% CrI, 8.23 to 1,881.53), with no treatment favoured between venetoclax plus azacitidine and venetoclax plus LDAC (OR = 0.86; 95% CrI, 0.30 to 0.35).

Results of Propensity-Score Analyses: Venetoclax Plus Azacitidine Versus Low-Dose Cytarabine

Table 24 shows the baseline characteristics for the comparison between venetoclax plus azacitidine and LDAC for the analysis of the whole population, before and after weighting. Patients in the LDAC group with favourable cytogenetic risk or prior HMA use were excluded. The largest baseline imbalances in terms of standardized mean difference were in ECOG PS, secondary AML, and race, all of which were reduced by adjustment. This weighting was used for all efficacy analyses for this comparison in this population.

OS, overall population: Table 25 shows the results of the weighted and unweighted comparisons for OS for the comparison of venetoclax plus azacitidine and LDAC. Figure 9 shows the survival curves for both unweighted and weighted comparisons. Venetoclax plus azacitidine was favoured over LDAC in both the unweighted (HR = 0.47; 95% CI, 0.33 to 0.67) and weighted comparisons (HR = 0.50; 95% CI, 0.35 to 0.73). Median OS in the weighted

Table 18: Summary of Patient Baseline Characteristics

Trial	Treatment	Cytogenetic risk		WBC (95% CI)	Platelets	Bone marrow blasts			
		Intermediate, n (%)	Poor, n (%)	n (%)	n (%)	% (95% CI)	< 30% n (%)	30 to < 50% n (%)	≥ 50% n (%)
VIALE-A	VEN + AZA	182 (63.6%)	104 (36.4%)	NR	NR	47.0 (4.4 to 100.0)	85 (29.7%)	61 (21.3%)	140 (49.0%)
	PBO + AZA	89 (61.4%)	56 (38.6%)	NR	NR	47.0 (11.0 to 99.0)	41 (28.3%)	33 (22.8%)	71 (49.0%)
VIALE-C	VEN + LDAC	91 (63.6%)	47 (32.9%)	NR	NR	NR	42 (29.4%)	36 (25.2%)	65 (45.5%)
	PBO + LDAC	46 (67.6%)	20 (29.4%)	NR	NR	NR	18 (26.5%)	22 (32.4%)	28 (41.2%)
	CCR + preselected LDAC	18 (90.0%)	1 (5.0%)	NR	NR	22.0 (20.0 to 28.0)	NR	NR	NR
	CCR + preselected LDAC	104 (65.8%)	54 (34.2%)	2.3 (0.0 to 73.0)	54 (6, 327)	74.0 (4.0 to 100.0)	NR	NR	128 (81.0%)

AML = acute myeloid leukemia; AZA = azacitidine; BSC = best supportive care; CCR = conventional care regimen; LDAC = low-dose cytarabine; NR = not reported; PBO = placebo; VEN = venetoclax.

Source: Systematic review report.[38]

comparison was 14.69 months (95% CI, 12.12 to 19.25) for venetoclax plus azacitidine compared with 7.43 months (95% CI, 3.15 to 10.18) for LDAC.

Event-free survival, overall population: Table 26 shows the results of the weighted and unweighted comparison for EFS between venetoclax plus azacitidine and LDAC. Figure 10 shows the survival curves for both weighted and weighted comparisons. Venetoclax plus azacitidine was favoured over LDAC in both the unweighted (HR = 0.40; 95% CI, 0.28 to 0.56) and the weighted comparisons (HR = 0.40; 95% CI, 0.28 to 0.58). Median EFS in the

Table 19: Assessment of Heterogeneity for NMA

Detail	Description and handling of potential effect modifiers
Disease severity	Patient groups varied in bone marrow blast counts. Where available, median bone marrow blasts ranged from 23.0% to 76%, and 42.1% to 81% of patients had ≥ 50% blasts. Where available, the proportion of patients with poor cytogenetic risk ranged from 29.6% to 38.6%, with the exception of 1 arm with a single patient (0.5%). The proportion of patients with poorer ECOG PS (= 2) varied from 0% to 44.1% across trial arms.
Treatment history	All studies included treatment-naive or newly diagnosed patients with AML.
Clinical trial eligibility criteria	Three studies selected older adults and/or treatment-ineligible patients. One did not specify. Two studies did not specify threshold for bone marrow blasts, 1 specified ≥ 20% blasts, and 1 specified > 30% blasts. Three studies prohibited prior treatment with HMAs; 1 study (VIALE-C) permitted it.
Comparators	Dosing was largely consistent across studies: • AZA was administered at a dose of 75 mg/m^2 SC per day for 7 consecutive days of a 28-day cycle, whether given alone or in combination. • LDAC when given alone was administered at a dose of 20 mg/m^2 twice a day, and when given in combination with VEN was administered at a dose of 20 mg/m^2 once a day. Dosing was for 10 days of a 28-day cycle, except for AZA-001, where it was 14 days. • VEN in combination with AZA was administered at a dose of 400 mg once a day for a continuous 28-day cycle, following ramp-up over 3 days (100 mg, 200 mg, 400 mg). • VEN in combination with LDAC was administered at a dose of 600 mg once a day for a continuous 28-day cycle, following ramp-up over 4 days (100 mg, 200 mg, 400 mg, 600 mg).
Definitions of end points	Details of end points were not extracted in the report. Variability in end point definitions or assessments was not identified as a source of heterogeneity.
Timing of end point evaluation or trial duration	Median length of study follow-up ranged from 17.5 (VIALE-C) to 24 months (AZA-AML-001).
Withdrawal frequency	Not reported in data extraction. Quality appraisal rated risk of bias due to unexpected imbalances in drop-outs between groups as high for AZA-001 and low for other studies.
Clinical trial setting	Details of setting were not extracted in the report.
Study design	All were parallel group randomized controlled trials. VIALE-A and VIALE-C were double-blind, and AZA-001 and AZA-AML-001 were open-label. AZA-001 and AZA-AML-001 included stratified randomization according to investigator's pre-selection of comparator to LDAC, AZA, and intensive chemotherapy. (Data from the intensive chemotherapy was not used in the ITC.)

AML = acute myeloid leukemia; AZA = azacitidine; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HMA = hypomethylating agent; LDAC = low-dose cytarabine; NMA = network meta-analysis; SC = subcutaneous; VEN = venetoclax.

Source: Systematic review report,[38] indirect treatment comparison report.[39]

weighted comparison was 9.79 months (95% CI, 8.41 to 11.99) for venetoclax plus azacitidine compared with 3.06 months (95% CI, 1.71 to 5.82) for LDAC.

CR + CRi, overall population: Table 27 shows the results for the comparison between venetoclax plus azacitidine and LDAC for CR, CRi, and CR + CRi before and after weighting. Venetoclax plus azacitidine was favoured over LDAC for CR + CRi in both the unweighted (OR = 10.32; 95% CI, 4.67 to 22.89) and weighted comparison (OR = 10.17; 95% CI, 4.55 to 22.73). After weighting, the proportion of patients with CR + CRi was 0.66 (95% CI, 0.61 to 0.72) for venetoclax plus azacitidine and 0.16 (95% CI, 0.08 to 0.29) for LDAC.

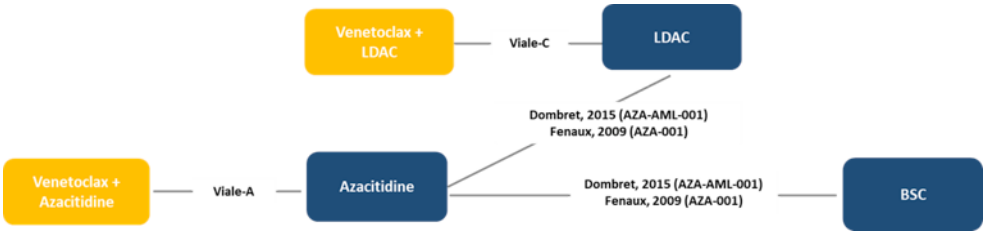
Table 20: Summary of Risk-of-Bias Assessment

Trial	Randomization	Allocation concealment	Baseline balance	Blinding	Imbalance in drop-outs	Selective reporting	Inclusion of ITT analysis
	Risk of bias (high/low/ unclear)	Risk of bias (high/low/ unclear)	Risk of bias (high/low/ unclear)	Risk of bias (high/low/ unclear)	Risk of bias (high/low/ unclear)	Risk of bias (high/low/ unclear)	Risk of bias (high/low/ unclear)
VIALE-A	Low	Low	Low	Low	Low	Unclear	Unclear
VIALE-C	Low	Low	Low	Low	Low	Unclear	Unclear
AZA-001	Low	Low	Low	High	High	High	Unclear
AZA-AML-001	Low	Low	Low	High	Low	Unclear	Unclear

ITT = intention to treat.

Source: Systematic review report.[38]

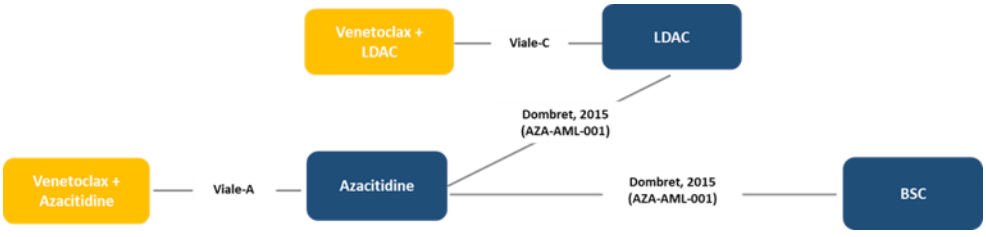
Figure 7: Network Diagram for the NMA for OS



BSC = best supportive care; LDAC = low-dose cytarabine; NMA = network meta-analysis; OS = overall survival.

Source: Indirect treatment comparison report.[39]

Figure 8: Network Diagram for the NMA for CR + CRi



BSC = best supportive care; CR = complete remission; CRi = complete remission with incomplete hematological recovery; LDAC = low-dose cytarabine; NMA = network meta-analysis.

Source: Indirect treatment comparison report.[39]

Sensitivity analysis, overall population: The sensitivity analysis included all patients enrolled in the LDAC arm in VIALE-C (n = 66), regardless of prior HMA use or good cytogenetic risk. The results for the comparison of venetoclax plus azacitidine versus LDAC were consistent with the results from the main analysis, with an after-weighting OS HR of 0.47 (95% CI, 0.34 to 0.66), an EFS HR of 0.38 (95% CI, 0.28 to 0.43), and an OR for CR + CRi of 10.52 (95% CI, 4.90 to 22.58).

OS, subgroup with baseline bone marrow blast count of 30% or greater: Table 28 shows the baseline characteristics for the comparison between venetoclax plus azacitidine and LDAC for the analysis of the subpopulation of patients with 30% or greater blasts, before and after weighting. Patients in VIALE-C with favourable cytogenetic risk or prior HMA use were excluded. The largest baseline imbalances in terms of standard mean difference were in ECOG PS, secondary AML, and race, all of which were reduced by adjustment. This weighting was used for all efficacy analyses for this comparison in this subgroup.

OS, subgroup with baseline bone marrow blast count of 30% or greater: Table 29 shows the results of the weighted and unweighted comparison for OS for the comparison of venetoclax plus azacitidine versus LDAC in patients with a baseline bone marrow blast count of 30% or greater. Venetoclax plus azacitidine was favoured over LDAC in both the unweighted (HR = 0.47; 95% CI, 0.33 to 0.67) and the weighted comparisons (HR = 0.47; 95% CI, 0.32 to

Table 21: Data Included in NMAs of OS and CR + CRi, Whole Population

Trial	Treatment arm	OS		CR + CRi		
		N	HR (95% CI)	N	n	%
VIALE-A	VEN + AZA	286	0.66 (0.52 to 0.85)	286	190	66.43
	AZA[d]	145		145	41	28.28
VIALE-C	VEN-LDAC	143	0.70 (0.50 to 0.99)	143	69	48.25
	LDAC[d]	68		68	9	13.24
AZA-001[b]	AZA	36	0.48 (0.24 to 0.94)	NR	NR	NR
	BSC[d]	27		NR	NR	NR
AZA-001[b]	AZA	14	0.37 (0.12 to 1.13)	NR	NR	NR
	LDAC[d]	20		NR	NR	NR
AZA-AML-001[a,c]	AZA	44	0.60 (0.38 to 0.95)	44	7	15.91
	BSC[d]	45		47	1	2.13
AZA-AML-001[a]	AZA	154	0.90 (0.70 to 1.16)	154	42	27.27
	LDAC[d]	158		158	41	25.95

AZA = azacitidine; BSC = best supportive care; CR = complete remission; CRi = complete remission with incomplete hematological recovery; LDAC = low-dose cytarabine; NR = not reported; NMA = network meta-analysis; OS = overall survival; VEN = venetoclax.

[a]AZA-AML-001 (Dombret, 2015) included patients > 30% bone marrow blasts. Patients were randomly assigned on the basis of local pathology assessment of baseline bone marrow blast count; which was subsequently reviewed by the central pathologist; in a small number of cases; baseline blast count was < 30% upon central review.

[b]AZA-001 (Fenaux, 2009) included patients with 20% to 30% bone marrow blasts. One patient in the BSC group had a bone marrow blast count of 13% but was included based on a peripheral blast count of 20%. In addition; 1 patient in the LDAC arm had blast count of 34%.

[c]A CR + CRi rate of 0 was reported. In accordance with National Institute for Health and Care Excellence guidance; the numerator and denominator were increased by 1 and 2 respectively to allow estimation of treatment effect.

[d]Comparator treatment.

Source: Indirect treatment comparison report.[39]

0.69). Median OS in the weighted comparison was 14.06 months (95% CI, 10.61 to 17.15) for venetoclax plus azacitidine compared with 3.61 months (95% CI, 3.12 to 10.18) for LDAC.

EFS, subgroup with baseline bone marrow blast count of 30% or greater: Table 30 shows the results of the weighted and unweighted comparison for EFS between venetoclax plus

Table 22: Pairwise Treatment Comparisons for OS

Treatment, HR (95% CrI)	LDAC	VEN + AZA	AZA	BSC	VEN + LDAC
LDAC	–	0.57[a] (0.40 to 0.81)	0.86 (0.67 to 1.10)	1.54 (0.98 to 2.43)	0.70[a] (0.50 to 0.99)
VEN + AZA	1.75 [a] (1.24 to 2.49)	–	1.51[a] (1.18 to 1.94)	2.70[a] (1.72 to 4.25)	1.23 (0.76 to 2.01)
AZA	1.16 (0.91 to 1.49)	0.66[a] (0.52 to 0.85)	–	1.78[a] (1.22 to 2.62)	0.82 (0.54 to 1.24)
BSC	0.65 (0.41 to 1.03)	0.37[a] (0.24 to 0.58)	0.56[a] (0.38 to 0.82)	–	0.46[a] (0.26 to 0.81)
VEN + LDAC	1.42[a] (1.01 to 1.99)	0.81 (0.50 to 1.31)	1.23 (0.80 to 1.86)	2.19[a] (1.23 to 3.85)	–

AZA = azacitidine; BSC = best supportive care; HR = hazard ratio; LDAC = low-dose cytarabine; OS = overall survival; VEN = venetoclax.

Comparisons should be read as HR for the treatment specified in the column vs. that specified in the row. An HR < 1 favours the treatment specified in the column.

[a]The 95% credible interval does not contain 1 (indicating what what be interpreted as representing a treatment difference).

Source: Indirect treatment comparison report.[39]

Table 23: Pairwise Treatment Comparisons for CR + CRi

Treatment, OR (95% CrI)	LDAC	VEN + AZA	AZA	BSC	VEN + LDAC
LDAC	–	5.42[a] (2.80 to 10.50)	1.07 (0.64 to 1.78)	0.09[a] (0.00 to 0.68)	6.24[a] (2.98 to 14.42)
VEN + AZA	0.18[a] (0.10 to 0.36)	–	0.20[a] (0.13 to 0.30)	0.02[a] (0.00 to 0.12)	1.16 (0.43 to 3.33)
AZA	0.94 (0.56 to 1.56)	5.05[a] (3.30 to 7.87)	–	0.08[a] (0.00 to 0.59)	5.84[a] (2.39 to 15.22)
BSC	11.38[a] (1.47 to 344.71)	61.55a (8.23 to 1,881.53)	12.07[a] (1.70 to 356.61)	–	73.35[a] (8.05 to 2,370.88)
VEN + LDAC	0.16[a] (0.07 to 0.34)	0.86 (0.30 to 2.35)	0.17[a] (0.07 to 0.42)	0.01[a] (0.00 to 0.12)	–

AZA = azacitidine; BSC = best supportive care; CR = complete remission; CRi = complete remission with incomplete blood count recovery; LDAC = low-dose cytarabine; OR = odds ratio; OS = overall survival; VEN = venetoclax.

Comparisons should be read as OR for the treatment specified in the column vs. that specified in the row. An OR < 1 favours the treatment specified in the row.

[a]The 95% credible interval does not contain 1 (indicating what what be interpreted as representing a treatment difference).

Source: Indirect treatment comparison report.[39]

azacitidine and LDAC in patients with a baseline bone marrow blast count of 30% or greater. Venetoclax plus azacitidine was favoured over LDAC in both the unweighted (HR = 0.41; 95% CI, 0.28 to 0.61) and the weighted comparisons (HR = 0.42; 95% CI, 0.28 to 0.61). Median EFS in the weighted comparison was 9.00 (95% CI, 7.69 to 11.53) months for venetoclax plus azacitidine compared with 3.06 (95% CI, 1.71 to 5.82) months for LDAC.

CR + CRi, subgroup with baseline bone marrow blast count of 30% or greater: Table 31 shows the results for the comparison between venetoclax plus azacitidine and LDAC for CR,

Table 24: Baseline Characteristics for Venetoclax Plus Azacitidine and LDAC Before and After Weighting

	Before weighting				After weighting			
Baseline characteristics	VEN + AZA[a] N = 285	LDAC[a] N = 50	SMD	P value[b]	VEN + AZA[a] N = 285	LDAC[a] N = 50	SMD	P value[b]
Age < 75	38.95%	40.00%	0.022	1.000	39.10%	38.67%	0.009	0.955
Female	40.00%	44.00%	0.081	0.708	40.62%	42.05%	0.029	0.853
Race: White	75.79%	68.00%	0.174	0.322	74.62%	74.52%	0.002	0.987
Secondary AML	25.26%	18.00%	0.177	0.354	24.19%	24.97%	0.018	0.917
AML with MRC	32.28%	28.00%	0.093	0.663	31.68%	33.71%	0.043	0.792
Antecedent history of MDS	17.19%	12.00%	0.147	0.479	16.46%	18.47%	0.053	0.765
ECOG Performance Status < 2	55.09%	46.00%	0.183	0.301	53.73%	53.97%	0.005	0.976
IVRS cytogenetic risk: poor	34.74%	32.00%	0.058	0.830	34.29%	33.51%	0.017	0.918
Bone marrow blast count, mean ± SD	52.04 ± 24.26	54.13 ± 24.21	0.086	0.573	52.39 ± 24.32	53.49 ± 24.33	0.045	0.773

AML = acute myeloid leukemia; ECOG = Eastern Cooperative Oncology Group; IVRS = interactive voice recognition system; LDAC = low-dose cytarabine; MDS = myelodysplastic syndrome; MRC = myelodysplasia-related changes; OS = overall survival; SMD = standard mean difference; VEN + AZA = venetoclax plus azacitidine; VEN + LDAC = venetoclax plus low-dose cytarabine.

[a]Two patients were excluded from the analysis due to missing data. One had missing data for cytogenetic risk in the LDAC group and 1 had missing bone marrow data in the VEN + AZA arm.

[b]Before weighting, categorical variables were compared using chi-square tests and continuous outcomes with analyses of variance (ANOVAs). After weighting, categorical variables were compared using weighted chi-square tests and continuous outcomes with weighted ANOVAs.

Source: Indirect treatment comparison report.[39]

Table 25: Comparison of OS for Overall Population, Before and After Weighting

			Before weighting		After weighting	
Treatment	N	Events	Median OS, months (95% CI)	HR (95% CI)	Median OS, months (95% CI)	HR (95% CI)
VEN + AZA	285	161	14.69 (11.53 to 18.69)	0.47 (0.33 to 0.67)	14.69 (12.12 to 19.25)	0.50 (0.35 to 0.73)
LDAC[a]	50	40	6.13 (2.23 to 8.90)		7.43 (3.15 to 10.18)	

AZA = azacitidine; CI = confidence interval; HR = hazard ratio; LDAC = low-dose cytarabine; OS = overall survival; VEN = venetoclax.

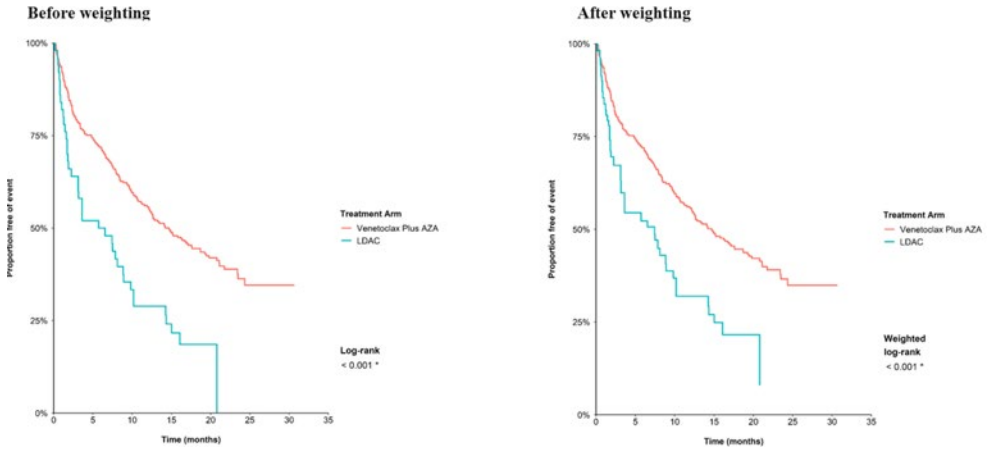
[a]Reference treatment.

Source: Indirect treatment comparison report.[39]

CRi, and CR + CRi before and after weighting, for patients with a bone marrow blast count of 30% or greater. Venetoclax plus azacitidine was favoured over LDAC for CR + CRi in both the unweighted (OR = 10.39; 95% CI, 3.88 to 27.84) and weighted comparison (OR = 10.80; 95% CI, 3.89 to 29.94). After weighting, the proportion of patients with CR + CRi was 0.62 (95% CI, 0.55 to 0.69) for venetoclax plus azacitidine and 0.13 (95% CI, 0.05 to 0.29) for LDAC.

Sensitivity analysis, subgroup with baseline bone marrow blast count of 30% or greater: The sensitivity analysis included all patients enrolled in the LDAC arm in VIALE-C (n = 66), regardless of prior HMA use or good cytogenetic risk. The results for the comparison of venetoclax plus azacitidine versus LDAC were consistent with the results from the main analysis, with an after-weighting OS HR of 0.47 (95% CI, 0.34 to 0.66), an EFS HR of 0.38 (95% CI, 0.28 to 0.43), and an OR for CR + CRi of 9.99 (95% CI, 3.85 to 25.94).

Figure 9: OS for Venetoclax Plus Azacitidine Versus LDAC for the Overall Population, Before and After Weighting



AZA = azacitidine; LDAC = low-dose cytarabine; VEN = venetoclax.
Source: Indirect treatment comparison report.[39]

Table 26: Comparison of EFS for Overall Population, Before and After Weighting

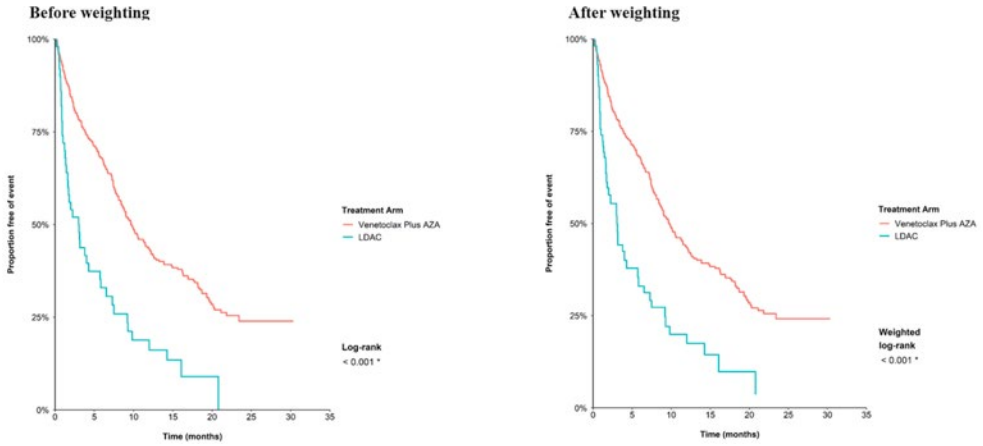
Treatment	N	Events	Before weighting		After weighting	
			Median OS, months (95% CI)	HR (95% CI)	Median, months OS (95% CI)	HR (95% CI)
VEN + AZA	285	190	9.66 (8.41 to 11.53)	0.40 (0.28 to 0.56)	9.79 (8.41 to 11.99)	0.40 (0.28 to 0.58)
LDAC[a]	50	43	3.02 (1.45 to 5.72)		3.06 (1.71 to 5.82)	

AZA = azacitidine; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; LDAC = low-dose cytarabine; OS = overall survival; VEN = venetoclax.
[a]Reference treatment.
Source: Indirect treatment comparison report.[39]

Results of 3-Way Propensity-Score Analyses: Venetoclax Plus Azacitidine Versus LDAC Versus Azacitidine

Table 32 shows the baseline characteristics for the 3-way comparison for venetoclax plus azacitidine versus LDAC versus azacitidine for the analysis of the whole population, before and after weighting. Patients in the LDAC group with favourable cytogenetic risk or prior HMA use were excluded. The largest baseline imbalances in terms of standard mean difference were in ECOG PS, secondary AML, and race, all of which were reduced by adjustment. This weighting was used for all efficacy analyses for this comparison in this population.

Figure 10: EFS for Venetoclax Plus Azacitidine Versus LDAC for the Overall Population, Before and After Weighting



AZA = azacitidine; EFS = event-free survival; LDAC = low-dose cytarabine.

Source: Indirect treatment report.[39]

Table 27: Comparison of CR, CRi, and CR + CRi for VEN Plus AZA Versus LDAC for the Overall Population, Before and After Weighting

Outcome	Before weighting			After weighting		
	VEN + AZA % (95% CI)	LDAC % (95% CI)	OR for VEN + AZA vs. LDAC (95% CI)	VEN + AZA % (95% CI)	LDAC % (95% CI)	OR for VEN + AZA vs. LDAC (95% CI)
CR	0.37 (0.31 to 0.43)	0.10 (0.04 to 0.22)	5.25 (2.02 to 13.64)	0.37 (0.31 to 0.43)	0.10 (0.04 to 0.22)	5.17 (1.97 to 13.56)
CRi	0.29 (0.24 to 0.35)	0.06 (0.02 to 0.17)	6.55 (1.98 to 21.62)	0.29 (0.24 to 0.35)	0.06 (0.02 to 0.17)	6.46 (1.94 to 21.52)
CR + CRi	0.66 (0.61 to 0.72)	0.16 (0.08 to 0.29)	10.34 (4.67 to 22.89)	0.66 (0.61 to 0.72)	0.16 (0.08 to 0.29)	10.17 (4.55 to 22.73)

AZA = azacitidine; CR = complete remission; CRi = complete remission with incomplete hematological recovery; OR = odds ratio; LDAC = low-dose cytarabine; VEN = venetoclax; vs. = versus.

Source: Indirect treatment comparison report.[39]

OS, overall population: Table 33 shows the median OS for venetoclax plus azacitidine, LDAC, and azacitidine before and after weighting. Table 34 shows the weighted and weighted results for the comparisons, and Figure 11 shows the survival curves.

Venetoclax plus azacitidine was favoured over LDAC in both the unweighted (HR = 0.47; 95% CI, 0.33 to 0.66) and weighted (HR = 0.52; 95% CI, 0.36 to 0.77) comparisons. Before

Table 28: Baseline Characteristics for VEN Plus AZA and LDAC Before and after Weighting, Patients With Baseline Bone Marrow Blast Count of 30% or Greater

	Before weighting				After weighting			
Baseline characteristics	VEN + AZA[a] N = 206	LDAC[a] N = 36	SMD	P value[b]	VEN + AZA[a] N = 206	LDAC[a] N = 36	SMD	P value[b]
Age < 75	37.86%	47.22%	0.190	0.381	39.33%	41.50%	0.044	0.813
Female	39.32%	36.11%	0.066	0.858	38.88%	40.06%	0.024	0.900
Race: White	74.27%	63.89%	0.226	0.277	72.71%	72.40%	0.007	0.968
Secondary AML	23.79%	16.67%	0.178	0.468	22.72%	22.76%	0.001	0.996
AML with MRC	26.70%	25.00%	0.039	0.993	26.47%	28.65%	0.049	0.805
Antecedent history of MDS	16.99%	11.11%	0.170	0.468	16.16%	17.23%	0.029	0.892
ECOG Performance Status < 2	55.34%	41.67%	0.276	0.182	53.23%	49.83%	0.068	0.721
IVRS cytogenetic risk: poor	32.04%	38.89%	0.144	0.539	32.97%	32.60%	0.008	0.967
Bone marrow blast count, mean ± SD	62.78 ± 19.75	65.75 ± 17.90	0.157	0.400	63.24 ± 19.77	64.91 ± 16.67	0.091	0.580

AML = acute myeloid leukemia; ANOVA = analysis of variance; AZA = azacitidine; ECOG = Eastern Cooperative Oncology Group; IVRS = interactive voice recognition system; LDAC = low-dose cytarabine; MDS = myelodysplastic syndrome; MRC = myelodysplasia-related changes; OS = overall survival; SD = standard deviation; SMD = standard mean difference; VEN = venetoclax.

[a]One patient was excluded from the analysis due to missing data for cytogenetic risk in the LDAC group and 1 had missing bone marrow data in the VEN + AZA arm.

[b]Before weighting, categorical variables were compared using chi-square tests and continuous outcomes with ANOVAs. After weighting, categorical variables were compared using weighted chi-square tests and continuous outcomes with weighted ANOVAs.

Source: Indirect treatment comparison report.[39]

Table 29: Comparison of OS for Patients With a Bone Marrow Blast Count of 30% or Greater Before and After Weighting

			Before weighting		After weighting	
Treatment	N	Events	Median OS, months (95% CI)	HR (95% CI)	Median OS, months (95% CI)	HR (95% CI)
VEN + AZA	206	121	14.06 (10.41 to 16.95)	0.47 (0.31 to 0.70)	14.06 (10.61 to 17.15)	0.47 (0.32 to 0.69)
LDAC[a]	36	30	3.61 (1.87 to 7.85)		3.61 (3.12 to 10.18)	

AZA = azacitidine; CI = confidence interval; HR = hazard ratio; LDAC = low-dose cytarabine; OS = overall survival; VEN = venetoclax.

[a]Reference treatment.

Source: Indirect treatment comparison report.[39]

weighting, azacitidine was favoured over LDAC (HR = 0.69; 95% CI, 0.48 to 0.99) but, after weighting, there was no statistically significant difference (HR = 0.78; 95% CI, 0.52 to 1.17). With weighting, the median OS for LDAC increased from 6.1 months (95% CI, 2.2 to 8.9) to 7.4 months (95% CI, 3.2 to 14.3), compared with 14.7 months (95% CI, 11.9 to 18.7) for venetoclax plus azacitidine and 9.6 months (95% CI, 7.4 to 12.7) for azacitidine alone.

EFS: Table 35 shows the EFS for venetoclax plus azacitidine, LDAC, and azacitidine before and after weighting. Table 35 shows the unweighted and weighted results for the comparisons, and Figure 12 shows the survival curves.

Venetoclax plus azacitidine was favoured over LDAC in both the unweighted (HR = 0.40; 95% CI, 0.28 to 0.56) and weighted comparisons (HR = 0.41; 95% CI, 0.29 to 0.59). Azacitidine was also favoured over LDAC in both weighted (HR = 0.61; 95% CI, 0.43 to 0.86) and unweighted (HR = 0.63; 95% CI, 0.43 to 0.92) comparisons. With weighting, the median EFS for LDAC increased from 3.0 months (95% CI, 1.5 to 5.7) to 3.1 months (95% CI, 1.8 to 5.8), compared

Table 30: Comparison of EFS for Patients With Bone a Marrow Blast Count of 30% or Greater Before and After Weighting

Treatment	N	Events	Before weighting		After weighting	
			Median OS, months (95% CI)	HR (95% CI)	Median, months OS (95% CI)	HR (95% CI)
VEN + AZA	206	136	9.00 (7.59 to 11.50)	0.41 (0.28 to 0.61)	9.00 (7.69 to 11.53)	0.42 (0.28 to 0.61)
LDAC[a]	36	32	3.02 (1.45 to 5.72)		3.06 (1.71 to 5.82)	

AZA = azacitidine; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; LDAC = low-dose cytarabine; OS = overall survival; VEN = venetoclax.

[a]Reference treatment.

Source: Indirect treatment comparison report.[39]

Table 31: Comparison of CR, CRi, and CR + CRi for Patients With a Bone Marrow Blast Count of 30% or Greater Before and After Weighting

Outcome	Before weighting			After weighting		
	VEN + AZA % (95% CI)	LDAC % (95% CI)	OR for VEN + AZA vs. LDAC (95% CI)	VEN + AZA % (95% CI)	LDAC % (95% CI)	OR for VEN + AZA vs. LDAC (95% CI)
CR	0.34 (0.28 to 0.41)	0.08 (0.03 to 0.23)	5.79 (1.72 to 19.51)	0.34 (0.28 to 0.41)	0.08 (0.03 to 0.24)	5.75 (1.62 to 20.48)
CRi	0.28 (0.22 to 0.35)	0.06 (0.01 to 0.20)	6.66 (1.55 to 28.63)	0.28 (0.22 to 0.35)	0.05 (0.01 to 0.18)	7.49 (1.73 to 32.52)
CR + CRi	0.63 (0.56 to 0.69)	0.14 (0.06 to 0.29)	10.39 (3.88 to 27.84)	0.62 (0.5 to 0.69)	0.13 (0.05 to 0.29)	10.80 (3.89 to 29.94)

AZA = azacitidine; CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete hematological recovery; OR = odds ratio; LDAC = low-dose cytarabine; VEN = venetoclax; vs. = versus.

Source: Indirect treatment comparison report.[39]

with 9.8 months (95% CI, 8.4 to 11.8) for venetoclax plus azacitidine and 7.0 months (95% CI, 5.6 to 9.5) for azacitidine.

CR + CRi, overall population: Table 37 shows the results for the comparison between venetoclax plus azacitidine and LDAC for CR, CRi, and CR + CRi, before and after weighting, for patients with a bone marrow blast count of 30% or greater. Venetoclax plus azacitidine

Table 32: Baseline Characteristics for VEN Plus AZA, LDAC, and AZA Before and After Weighting

Baseline characteristics	VEN + AZA N = 286	LDAC[a] N = 50	AZA N = 145	VEN + AZA vs. LDAC		AZA vs. LDAC		VEN + AZA vs. AZA	
				SMD	P value[2]	SMD	P value[b]	SMD	P value[b]
Before weighting									
Age < 75	39.16%	40.00%	40.00%	0.017	1.000	0.000	1.000	0.017	0.949
Female	39.86%	44.00%	40.00%	0.084	0.694	0.081	0.742	0.003	1.000
Race: White	75.87%	68.00%	75.17%	0.176	0.315	0.160	0.422	0.016	0.967
Secondary AML	25.17%	18.00%	24.14%	0.175	0.360	0.151	0.484	0.024	0.907
AML with MRC	32.17%	28.00%	33.79%	0.091	0.674	0.126	0.562	0.035	0.817
History of MDS	17.13%	12.00%	18.62%	0.146	0.485	0.185	0.391	0.039	0.803
ECOG Performance Status < 2	54.90%	46.00%	55.86%	0.179	0.313	0.198	0.298	0.019	0.930
IVRS cytogenetic risk: Poor	34.97%	32.00%	36.55%	0.063	0.806	0.096	0.683	0.033	0.827
Bone marrow blast count, mean ± SD[c]	52.04 ± 24.26	54.13 ± 24.21	53.46 ± 24.52	0.086	0.573	0.028	0.867	0.058	0.567
After weighting									
Age < 75	39.16%	39.79%	40.00%	0.013	0.937	0.004	0.980	0.017	0.949
Female	39.86%	40.08%	40.00%	0.005	0.977	0.002	0.992	0.003	1.000
Race: White	75.87%	74.97%	75.17%	0.021	0.888	0.005	0.977	0.016	0.967
Secondary AML	25.17%	25.41%	24.14%	0.005	0.976	0.029	0.876	0.024	0.907
AML with MRC	32.17%	35.65%	33.79%	0.074	0.663	0.039	0.828	0.035	0.817
History of MDS	17.13%	20.76%	18.62%	0.093	0.615	0.054	0.784	0.039	0.803
ECOG Performance Status < 2	54.90%	56.86%	55.86%	0.040	0.802	0.020	0.905	0.019	0.930
IVRS cytogenetic risk: Poor	34.97%	36.73%	36.55%	0.037	0.824	0.004	0.983	0.033	0.827
Bone marrow blast count, mean ± SD[c]	52.04 ± 24.26	55.51 ± 24.31	53.46 ± 24.52	0.143	0.366	0.084	0.617	0.058	0.567

AML = acute myeloid leukemia; ANOVA = analysis of variance; AZA = azacitidine; ECOG = Eastern Cooperative Oncology Group; IVRS = interactive voice recognition system; LDAC = low-dose cytarabine; MDS = myelodysplastic syndrome; MRC = myelodysplasia-related changes; OS = overall survival; SMD = standard mean difference; VEN = venetoclax; vs. = versus.

[a]One patient from the LDAC arm was removed from the analysis due to missing cytogenetic risk.

[b]Categorical outcomes were compared using chi-square tests and continuous outcomes with ANOVAs.

[c]Bone marrow blast count for the VEN + AZA arm of VIALE-A was calculated among 285 patients with non-missing data for that variable.

Source: Indirect treatment comparison report.[39]

was favoured over LDAC for CR + CRi in both the unweighted (OR = 10.39; 95% CI, 4.69 to 23.01) and weighted comparisons (OR = 9.69; 95% CI, 4.30 to 21.85). No statistically significant difference was seen between azacitidine and LDAC in either the unweighted (OR = 2.07; 95% CI, 0.90 to 4.78) or weighted comparison (OR = 1.93; 95% CI, 0.82 to 4.54). After weighting, the proportion of patients with CR + CRi was 0.62 (95% CI, 0.55 to 0.69) for

Table 33: OS for Venetoclax Plus Azacitidine, LDAC, and Azacitidine Before and After Weighting

Treatment	N	Events	Median OS (95% CI)	
			Before weighting	After weighting
VEN + AZA	286	161	14.7 (11.9 to 18.7)	14.7 (11.9 to 18.7)
LDAC	50	40	6.1 (2.2 to 8.9)	7.4 (3.2 to 14.3)
AZA	145	109	9.6 (7.4 to 12.7)	9.6 (7.4 to 12.7)

AZA = azacitidine; LDAC = low-dose cytarabine; OS = overall survival; VEN = venetoclax.

Source: Indirect treatment comparison report.[39]

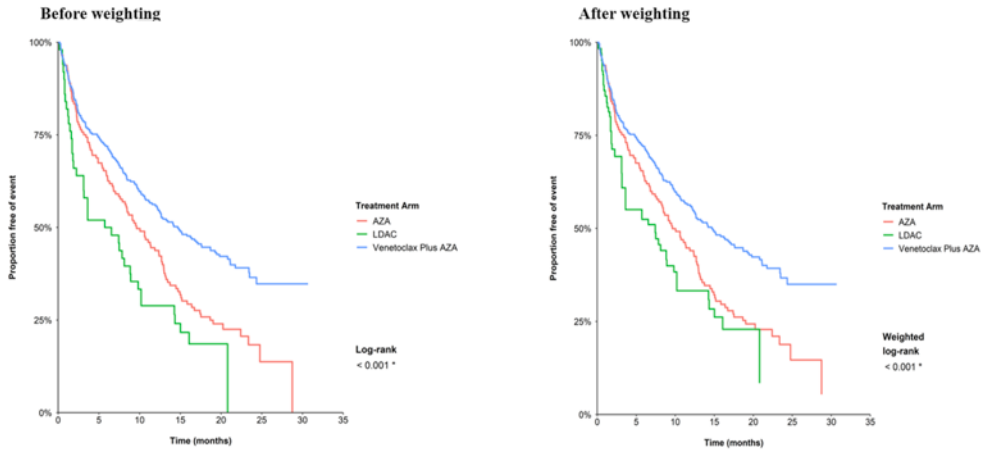
Table 34: Comparison of OS for Venetoclax Plus Azacitidine, LDAC, and Azacitidine Before and After Weighting

Comparison	HR (95% CI)	
	Before weighting	After weighting
VEN + AZA vs. LDAC	0.47 (0.33 to 0.66)	0.52 (0.36 to 0.77)
VEN + AZA vs. AZA	0.64 (0.50 to 0.82)	0.64 (0.50 to 0.82)
AZA vs. LDAC	0.69 (0.48 to 0.99)	0.78 (0.52 to 1.17)

AZA = azacitidine; CI = confidence interval; HR = hazard ratio; LDAC = low-dose cytarabine; OS = overall survival; VEN = venetoclax; vs. = versus.

Source: Indirect treatment comparison report.[39]

Figure 11: OS for Venetoclax Plus Azacitidine, LDAC, and Azacitidine Before and After Weighting



AZA = azacitidine, LDAC = low-dose cytarabine; OS = overall survival.

Source: Indirect treatment report.[39]

venetoclax plus azacitidine, 0.28 (95% CI, 0.21 to 0.36) for azacitidine, and 0.13 (95% CI, 0.05 to 0.29) for LDAC.

Critical Appraisal of Indirect Treatment Comparisons

NMA and propensity-score analyses are considered separately in this section.

Table 35: EFS for Venetoclax Plus Azacitidine, LDAC, and Azacitidine Before and After Weighting

Treatment	N	Events	Median EFS (95% CI)	
			Before Weighting	After Weighting
VEN + AZA	286	191	9.8 (8.4 to 11.8)	9.8 (8.4 to 11.8)
LDAC	50	43	3.0 (1.5 to 5.7)	3.1 (1.8 to 5.8)
AZA	145	122	7.0 (5.6 to 9.5)	7.0 (5.6 to 9.5)

AZA = azacitidine; CI = confidence interval; EFS = event-free survival; LDAC = low-dose cytarabine; VEN = venetoclax.

Source: Indirect treatment comparison report.[39]

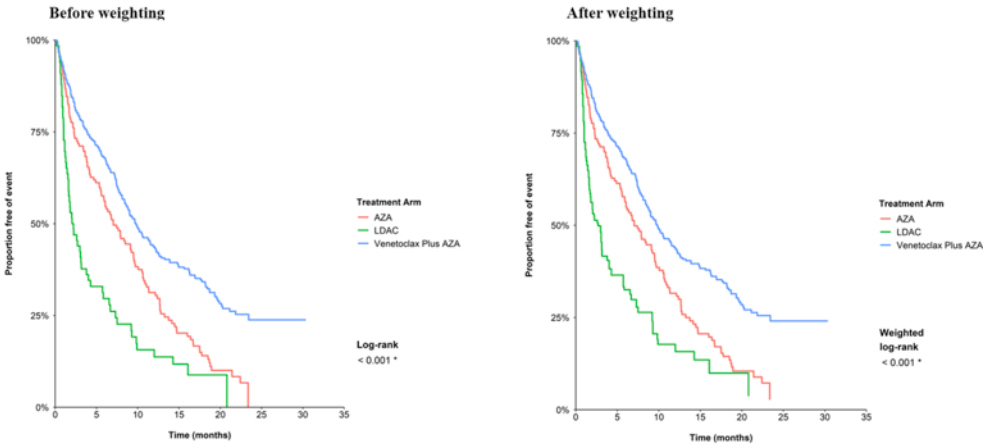
Table 36: EFS for Comparisons of Venetoclax Plus Azacitidine With LDAC, Venetoclax Plus Azacitidine With Azacitidine, and Azacitidine With LDAC

Treatment	HR (95% CI)	
	Before weighting	After weighting
VEN + AZA vs. LDAC	0.40 (0.28 to 0.56)	0.41 (0.29 to 0.59)
VEN + AZA vs. AZA	0.62 (0.49 to 0.77)	0.62 (0.49 to 0.77)
AZA vs. LDAC	0.61 (0.43 to 0.86)	0.63 (0.43 to 0.92)

AZA = azacitidine; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; LDAC = low-dose cytarabine; VEN = venetoclax.

Source: Indirect treatment comparison report.[39]

Figure 12: EFS for Venetoclax Plus Azacitidine, LDAC, and Azacitidine Before and After Weighting



AZA = azacitidine, EFS = event-free survival; LDAC = low-dose cytarabine.

Source: Indirect treatment comparison report.[39]

The key limitations of the NMA include the small size and structure of the network, which had no closed loops, potential sources of heterogeneity across the trials related to differences in study design, and patient characteristics. These limitations resulted in imprecise estimates and the potential for bias.

The key limitations of the propensity-score analyses include the intrinsic high susceptibility to bias of the method due to the lack of an anchor for comparison and the possibility for unmeasured covariates and residual confounding. Relatively small numbers were involved, with the potential for unstable estimates susceptible to the influence of high weights.

Critical Appraisal of Systematic Review

The ITC (NMA) was based on a systematic literature review that identified studies according to pre-specified inclusion criteria. These included a broad selection of comparators and outcomes. The literature search was last conducted in October 2020 and appeared comprehensive in terms of the databases searched and the search strategy. Two sets of selection criteria were applied: an initial broader set of criteria and, at the full-text review step, a narrowed set of criteria intended to create a high-quality dataset for meta-analysis. The selection of comparators was not justified, but those meaningful to the Canadian context were included. Lists of studies excluded at the full-text state for both sets of criteria were provided. Screening and selection was done by 2 independent reviewers, with a third involved

Table 37: Comparison of CR, CRi, and CR + CRi for VEN Plus AZA, LDAC, and AZA Before and After Weighting

Outcome	VEN + AZA % (95% CI)	LDAC % (95% CI)	AZA % (95% CI)	VEN + AZA vs. LDAC OR (95% CI)	AZA vs. LDAC OR (95% CI)	VEN + AZA vs. AZA OR (95% CI)
Before weighting						
CR	0.37 (0.31 to 0.43)	0.10 (0.04 to 0.22)	0.18 (0.12 to 0.25)	5.22 (2.01 to 13.56)	1.97 (0.71 to 5.43)	2.66 (1.63 to 4.32)
CRi	0.30 (0.25 to 0.35)	0.06 (0.02 to 0.17)	0.10 (0.06 to 0.17)	6.63 (2.01 to 21.87)	1.81 (0.50 to 6.53)	3.67 (2.03 to 6.62)
CR + CRi	0.66 (0.61 to 0.72)	0.16 (0.08 to 0.29)	0.28 (0.21 to 0.36)	10.39 (4.69 to 23.01)	2.07 (0.90 to 4.78)	5.02 (3.24 to 7.77)
After weighting						
CR	0.37 (0.31 to 0.43)	0.11 (0.04 to 0.23)	0.18 (0.12 to 0.25)	4.93 (1.88 to 12.98)	1.86 (0.66 to 5.20)	2.66 (1.63 to 4.33)
CRi	0.30 (0.25 to 0.35)	0.06 (0.02 to 0.19)	0.10 (0.06 to 0.17)	6.15 (1.80 to 21.00)	1.68 (0.45 to 6.26)	3.67 (2.03 to 6.63)
CR + CRi	0.66 (0.61 to 0.72)	0.17 (0.09 to 0.31)	0.28 (0.21 to 0.36)	9.69 (4.30 to 21.85)	1.93 (0.82 to 4.54)	5.02 (3.24 to 7.77)

AZA = azacitidine; CR = complete remission; CRi = complete remission with incomplete hematological recovery; OR = odds ratio; LDAC = low-dose cytarabine; VEN = venetoclax.

Source: Indirect treatment comparison report.[39]

to reconcile differences. Data extraction was also done by 2 independent reviewers. The data were extracted to pre-designed data sheets, with differences reconciled by a third reviewer.

Critical Appraisal of the NMA

Studies included in the NMA were selected from those identified by the systematic literature review. The criteria for the inclusion of studies for the NMA were provided and are consistent with the objective. The eligible interventions were restricted further to those used in Canada for the treatment of the population of interest, which was defined as treatment-naive adult patients with AML who are ineligible for intensive chemotherapy. Only clinical efficacy outcomes were pre-specified for the NMA. Available data limited the end points further to OS and CR + CRi for the NMA and OS, EFS, and CR + CRi for the propensity-score analysis. Patient-reported QoL and safety end points were not represented.

Heterogeneity in study and patient baseline characteristics was reported and reviewed by the authors as part of the assessment of feasibility for the meta-analysis. Baseline differences were noted in the prognostic variables and potential treatment-effect modifiers of blast count at baseline, prior treatment with an HMA, and cytogenetic risk. The proportion of patients with 50% or greater bone marrow blasts at baseline ranged from 0% (AZA-001 trial) to 100% (AZA-AML-001) in the network for OS and 70.8% (VIALE-A) to 100% (AZA-AML-001) in the network for CR + CRi. Patients with prior HMA treatment were excluded from VIALE-A, AZA-001, and AZA-AML-001, but not from VIALE-C, in which 19.9% had been treated with an HMA. This might represent a group more refractory to treatment with azacitidine, affecting both OS and CR + CRi end points. Patients with poor cytogenetic risk were more represented in the azacitidine arm of VIALE-A compared with the azacitidine arm of AZA-001 (39% versus 26%). This difference potentially affects the NMA network for OS. The median length of study follow-up ranged from 17.5 (VIALE-C) to 24 months (AZA-AML-001). The variability was unlikely to affect CR + CRi, as response tended to occur early, but may affect OS, as patients may be censored before OS events in studies with short follow-up.

Four studies formed a mainly linear connected network for OS and 3 studies for CR + CRi. The end point of CR + CRi was not reported for AZA-001. There were no closed loops in the network, meaning that inconsistency within the network could not be statistically assessed. The dose and duration for azacitidine and the dose (but not duration) for LDAC was the same across trials, and BSC included the same constituents, limiting heterogeneity in dosing. In AZA-001 and AZA-AML-001, patients were preselected for the comparator therapy, so the comparison of azacitidine against LDAC was made in patients preselected for LDAC, and the comparison of azacitidine against BSC was made in patients preselected for BSC. These were treated as 2 separate contrasts, not as a 3-arm trial.

A standard Bayesian generalized linear model was used for the meta-analysis and the diagnostics and model selection were sufficiently described. The reviewers checked the proportional hazards assumption for OS for the contributing plots using log-log plots. The risk of violation of the proportional hazards assumption was low for VIALE-A and VIALE-C and low to moderate for AZA-AML-001, where the survival curves were largely overlapping and intermittently crossing. The model in the NMA used assumed constant hazards, which was an appropriate choice, given the low-to-moderate risk of violation of the proportional hazards assumption and the small number of studies available.

The networks for all analyses were small. Thus, the decision was made a priori to limit the analysis to fixed-effects models. This entailed the assumption that between-study heterogeneity was zero, which was unlikely to be the case. The small number of studies led

to imprecise estimates, with the risk of not detecting a difference. In the analysis of CR + CRi, low response counts (including 0, requiring a zero-cell adjustment) led to highly uncertain estimates with wide CrIs. The small number of studies meant there was no opportunity to use statistical methods (such as meta-regression) to adjust for variability in baseline treatment-effect modifiers and correct for potential bias. Finally, non-informative prior distributions were used in the models, as is usual practice, under the assumption that the final estimates will reflect only the data. However, with a low information dataset, the prior distributions may add to the imprecision. Consideration of alternative priors was mentioned but not detailed.

Critical Appraisal of Propensity-Score Analyses

Comparisons of venetoclax plus azacitidine with azacitidine (2-way propensity score) and venetoclax plus azacitidine with azacitidine and with LDAC (3-way propensity score) were conducted by propensity-score weighting on the individual patient data from both arms of VIALE-A and the LDAC arm of VIALE-C.

VIALE-A restricted recruitment to patients with a cytogenetic risk of intermediate or poor and excluded those who previously been treated with an HMA, whereas those patients were eligible for VIALE-C. For the purposes of the analysis, only patients who met the eligibility criteria for VIALE-A were included in the LDAC comparator arm for the main analysis. A sensitivity analysis included all patients in both studies.

Three efficacy outcomes were available for the propensity score–weighting analysis, OS, EFS, and CR + CRi. Weights were generated from a logistic regression model that included pre-specified demographic and clinical covariates anticipated to affect prognosis. The demographic characteristics were age, sex, race. The clinical characteristics were AML type, AML with myelodysplasia-related changes, prior MDS, bone marrow blasts, cytogenetic risk, and ECOG PS. All were dichotomized. These represented the important covariates and the dichotomization thresholds were the same as those accepted as meaningful in clinical practice. It is possible there is residual heterogeneity within the categories and residual confounding following adjustment, although the analysis was carried out on data from 2 closely related trials from the same sponsor on a similar population. There was no reported estimate of the potential risk of bias due to unmeasured confounders.

The comparisons were not randomized and the results were highly susceptible to bias due to imbalances in unmeasured confounders. Baseline comparisons were reported for dichotomized baseline covariates before and after adjustment for each end point. Weighting was generally good, with observed reduction of standardized differences. The weights themselves were not reported, and it was not indicated which methods were needed or applied to stabilize overly large or overly small weights. Effective sample size was calculated but not reported, also limiting appraisal of the weighting process. Relatively small numbers of patients were involved, particularly in the LDAC group, limiting the number of covariates that could be included in the model. Weighted statistical tests were used appropriately for the comparison of baseline covariates after adjustment; weighted Cox models were used for the calculation of time-to-event outcomes for OS and EFS. Log-log plots suggested a low risk of bias for the proportional hazards assumption. A subgroup analysis was conducted for the 2-way propensity-score analysis for both end points that was limited to patients with blast counts of 30% or greater.

The primary analysis used the subset of patients from VIALE-C who had no previous exposure to HMA as a comparison arm for the LDAC treatment arm (n = 50, compared with n = 285 for

venetoclax plus azacitidine). The LDAC group had relatively few CR + CRi events, resulting in imprecise estimates for this outcome.

Summary

Seven trials met the systematic review inclusion criteria. With the additional restriction of the comparators for the NMA inclusion criteria, removing decitabine from the comparators, 4 trials were included in the ITC. Three analysis were conducted: 1 NMA and 2 propensity score–weighting analyses. One propensity score–weighting analysis compared venetoclax plus azacitidine (VIALE-A) with LDAC (VIALE-C), and the second compared venetoclax plus azacitidine and azacitidine alone (VIALE-A) with LDAC (VIALE-C). For the NMA, data were available for OS for 4 trials in a connected network and for CR + CRi for 3 trials. For the propensity score–weighting analysis, data were available for OS, EFS, and CR + CRi.

In the NMA, venetoclax plus azacitidine had a lower hazard of death compared with azacitidine, LDAC, and BSC, with no difference seen between venetoclax plus azacitidine and venetoclax plus LDAC. For CR + CRi, venetoclax plus azacitidine was favoured over azacitidine, LDAC, and BSC, with no treatment favoured between venetoclax plus azacitidine and venetoclax plus LDAC.

In both propensity score–weighting analyses, venetoclax plus azacitidine was favoured over LDAC for OS, EFS, and CR + CRi.

The systematic review was well conducted and documented. The search was limited to efficacy end points, and data were available only for OS and CR + CRi for the NMA, and OS, CR + CRi, and EFS for the propensity score–matched comparisons; no comparisons were conducted for transfusion independence, hospitalization, QoL end points, or safety. The NMA used appropriate methods to model survival, having assessed the risk of violation of the proportional hazards assumption. There was clinical heterogeneity in potential treatment-effect modifiers of blast count at baseline, prior treatment with an HMA, and cytogenetic risk. As the network was sparse, fixed-effects models had to be used, and there was no opportunity for baseline covariate adjustments. Due to the previously mentioned limitations, the comparative efficacy estimates may be biased, and it is not possible to quantify or identify the direction of the bias. In the propensity-score analyses, weighting was generally good, but the relatively small numbers of patients in the LDAC comparator group limited the number of covariates that could be included in the model. The comparisons were not randomized and the results were highly susceptible to bias due to imbalances in unmeasured confounders. Results of these ITCs must be interpreted with caution.

Discussion

Summary of Available Evidence

One double-blind, placebo-controlled phase III RCT and 1 ITC contributed evidence to this review. The objective of the RCT was to evaluate the efficacy and safety of venetoclax plus azacitidine in adults with newly diagnosed AML who were 18 years or older and ineligible for standard induction therapy due to age or comorbidities. The trial was restricted to patients who had not previously been treated with an HMA and who had intermediate or poor risk cytogenetics. Primary outcomes were OS and composite complete remission rate (CR

+ CRi). Secondary outcomes were CR, CR + CRh, rate of CR + CRi by the initiation of cycle 2, transfusion-independence rate, MRD response rate, response rates and OS in molecular subgroups, fatigue and GHS/QoL, and EFS.

A total of 431 patients were randomized in a 2:1 ratio, 286 to venetoclax plus azacitidine and 144 to placebo plus azacitidine, and included in the efficacy analysis. The most common reasons given for patients to be considered ineligible for standard induction therapy were age and ECOG PS. Patients were elderly, with poor performance, and markers of severe disease. The mean age was 75.4 years, with 60.6% aged 75 years or older. The majority were male (60.1%), and almost all were White or Asian. Most (75.2%) had de novo rather than secondary AML. Nearly 2-thirds had intermediate risk cytogenetics, 1-third had poor risk, and 1-half had 50% or greater bone marrow blasts at baseline.

The study was well conducted, with no clinically meaningful imbalance in baseline characteristics, minimal loss to follow-up, and the collection of end points were standardized and meaningful to patients. Multiplicity was controlled, with pre-specified strategies for testing of end points. The rate of study discontinuation was low and the assumptions surrounding missing data were conservative for most end points.

As RCTs were not available for all comparisons of interest, the sponsor supplied an ITC that included an NMA comparing venetoclax plus azacitidine and venetoclax plus LDAC with alternative treatments, and 2 propensity score–weighting comparisons of venetoclax plus azacitidine versus LDAC. Among the studies, 4 contributed to the NMA for OS, 3 contributed to the NMA for CR + CRi, and 2 contributed to the propensity score–weighting comparisons of OS, CR + CRi, and EFS. Safety end points were not included in the search, and data for other end points were not found.

Interpretation of Results

Efficacy

Venetoclax plus azacitidine improved most of the outcome measures that were identified as being of interest to clinicians and patients. Statistically significant treatment differences were seen for OS, EFS, measures of disease response (CR + CRi, CR + CRh, CR), and post-baseline transfusion independence. Statistically significant improvements were seen for OS and CR + CRi in the subgroup of patients with IDH1 or IDH2 mutations, and for CR + CRi for patients with FLT3 mutations. No statistically significant difference was detected in OS for patients with FLT3 mutations.

At a median duration of follow-up of 20.7 months for patients randomized to venetoclax plus azacitidine (versus 20.2 months for those randomized to placebo plus azacitidine), median OS for patients randomized to venetoclax plus azacitidine was 14.7 months compared with 9.6 months for azacitidine alone. The HR for mortality was 0.662 (95% CI, 0.518 to 0.845), and the stratified log-rank P value was less than 0.001. A similar magnitude of effect was seen for EFS. A greater proportion of patients randomized to venetoclax plus azacitidine had CR + CRi (65.3%) compared with those randomized to placebo plus azacitidine (25.3%), with a stratified P value of less than 0.001. Consistent results were seen for CR and early CR + CRi (after 2 cycles). For transfusion with red blood cells, 59.8% of patients randomized to venetoclax plus azacitidine were transfusion-independent compared with 35.2% of those randomized to placebo plus azacitidine, a treatment difference of 24.6% (95% CI, 15.0 to 34.2; stratified CMH P value < 0.001). For platelets, 68.5% of patients randomized to venetoclax plus azacitidine were transfusion-independent compared with 49.7% of those randomized to

placebo plus azacitidine, a treatment difference of 18.9% (95% CI, 9.1% to 28.6%; stratified CMH P value < 0.001).

In the subgroup of patients with IDH1 or IDH2 mutation, the HR for mortality was 0.345 (95% CI, 0.199 to 0.598) and the risk difference for CR + CRi was 64.70% (95% CI, 48.9% to 80.4%); both differences were statistically significant. In the subgroup of patients with FLT3 mutation, the HR for mortality was 0.664 (95% CI, 0.351 to 1.257), and the risk difference for CR + CRi was 36.05% (95% CI, 10.2 to 61.9); only the risk difference was statistically significant, but the subgroup was small. Although other subgroup comparisons were not tested, the spread between estimates for OS and CR + CRi was widest for age (< 75 years and ≥ 75 years) and cytogenetic risk (intermediate versus poor; patients with good cytogenetic risk were excluded from the study).

Change from baseline in GHS/QoL as measured by the EORTC QLQ-C30 scale and fatigue as measured by the PROMIS 7a scale were secondary end points. While clinically meaningful differences were observed at individual end points, differences between treatment groups cannot be interpreted because the sequential testing strategy failed before this level. Interpretation of patient-reported outcome data is limited due to attrition over cycles.

In the NMA, the results favoured a lower hazard of death for patients assigned to venetoclax plus azacitidine compared with azacitidine alone (HR = 0.66; 95% CrI, 0.52 to 0.85), LDAC (HR = 0.57; 95% CrI, 0.40 to 0.81), and BSC (HR = 0.37; 95% CrI, 0.24 to 0.58), with no treatment favoured between venetoclax plus azacitidine and venetoclax plus LDAC (HR = 0.81; 95% CrI, 0.50 to 1.31). For CR + CRi, venetoclax plus azacitidine was favoured over azacitidine alone (OR = 5.05; 95% CrI, 3.30 to 7.87), LDAC (OR = 5.42; 95% CrI, 2.80 to 10.50), and BSC (OR = 61.55; 95% CrI, 8.23 to 1,881.53), with no treatment favoured between venetoclax plus azacitidine and venetoclax plus LDAC (OR = 0.86; 95% CrI, 0.30 to 2.35).

In the first propensity-score analysis, venetoclax plus azacitidine was favoured over LDAC for OS, EFS, and CR + CRi. In the second propensity-score analysis for OS, venetoclax plus azacitidine was favoured over LDAC and azacitidine alone. For EFS, venetoclax plus azacitidine was favoured over both azacitidine and LDAC, and azacitidine was favoured over LDAC. For CR + CRi, venetoclax plus azacitidine was favoured over both azacitidine and LDAC.

The search for the ITCs was limited to efficacy end points, and data were available only for OS and CR + CRi for the NMA, and OS, CR + CRi, and EFS for the propensity score–matched comparisons; no comparisons were conducted for transfusion independence, hospitalization, QoL end points, or safety. In the NMA, there were important differences in variables that were potentially treatment-effect modifiers between included studies. The small number of studies limited models to fixed effects and did not allow for meta-regression to adjust for baseline differences. Estimates are imprecise and at risk of bias. Estimates from propensity-score adjustment are at high risk of bias, and the small number of available patients limited the number of covariates that could be entered in the model for weighting. The comparisons were not randomized and the results were highly susceptible to bias due to imbalances in unmeasured confounders.

Harms

All patients in both groups experienced at least 1 adverse event, and almost all experienced at least 1 adverse event of grade 3 or greater. Compared with patients who received placebo plus azacitidine, a greater proportion of patients who received venetoclax plus azacitidine experienced 1 or more SAEs, 1 or more adverse events leading to dose discontinuation or

interruption for venetoclax or placebo or azacitidine, or 1 or more adverse events leading to death. Common harms in all categories are generally predictable from the known mechanism of action for venetoclax and/or azacitidine and the underlying disease. Cytopenias were common, with neutropenia, febrile neutropenia, thrombocytopenia, and anemia represented across all categories, as were gastrointestinal adverse effects. Febrile neutropenia and infections contributed substantially to the most common SAEs and were the most frequent adverse events leading to death. The product monograph for venetoclax identifies the risk of serious infections leading to hospitalization or death in its section on serious warnings and precautions.

The same section specifies the need for dose ramp-up and prophylaxis for tumour lysis syndrome, and for dose reduction of the concurrent use of strong CYP3A inhibitors during dose ramp-up. Prophylaxis for tumour lysis syndrome was included in the study, and tumour lysis syndrome was uncommon, occurring in 2.5% of patients or less.

The ITC study did not include harms.

Conclusions

One double-blind, placebo-controlled phase III RCT (VIALE-A) and 1 ITC provided evidence supporting the efficacy and safety of venetoclax plus azacitidine in adult patients ineligible for standard induction chemotherapy due to age or comorbidities. Compared with azacitidine alone, patients treated with venetoclax (400 mg daily) and azacitidine (75 mg/m^2 on days 1 through 7 of a 28-day cycle) showed benefits in the important clinical end points of OS, overall and early composite complete remission (CR and CRi), EFS, CR, and transfusion independence (red blood cell or platelet transfusions). All study participants reported treatment-emergent adverse events. For most categories of adverse events, there was an overall higher proportion of patients reporting these in the venetoclax plus azacitidine group. The most common adverse events were cytopenias and infections. No firm conclusion can be drawn between groups in GHS/QoL and fatigue, and patient attrition reduced the number of observation over the cycles, which limits the interpretation for these end points. Overall, the study was well conducted.

The VIALE-A study did not include a comparison between venetoclax plus azacitidine and current standards of care of induction therapy (in patients aged 75 years and older and fit), azacitidine monotherapy, LDAC, or BSC, or the alternative combination of venetoclax plus LDAC. In an ITC, venetoclax plus azacitidine was favoured over monotherapies and BSC, but no treatment was favoured for survival and composite complete remission between venetoclax plus azacitidine and venetoclax plus LDAC. No data are available for the comparison of venetoclax plus azacitidine with induction therapy. Results for 2 propensity-score comparisons between venetoclax plus azacitidine and azacitidine and LDAC were consistent. Small study and patient numbers and the potential for bias limit the reliability of the ITC, and the propensity-score comparisons were not randomized and therefore highly susceptible to bias.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946 to present)
- Embase (1974 to present)
- **Note:** Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: February 11, 2021

Alerts: Weekly search updates until project completion

Study types: No filters were applied to limit the retrieval by study type

Limits:

- Publication date limit: None
- Language limit: None
- Conference abstracts: Excluded

Table 38: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for 1 character
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.dq	Candidate term word (Embase)

Syntax	Description
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

Search Strategy

1. (venetoclax* or Venclexta* or Venclyxto* or ABT199 or ABT-199 or GDC0199 or GDC-0199 or RG7601 or RG-7601 or N54AIC43PW).ti,ab,kf,ot,hw,nm,rn.
2. exp Leukemia, Myeloid, Acute/
3. (AML or ANLL).ti,ab,kf.
4. (Acute adj5 (granulocytic* or myeloblastic* or myelocytic* or myelogenous* or myeloid* or nonlymphoblastic* or non-lymphoblastic* or nonlymphocytic* or non-lymphocytic* or basophilic* or eosinophilic* or erythroblastic* or megakaryoblastic* or monocytic* or megakaryocytic* or myelomonocytic*) adj5 (leukemia* or leukemia*)).ti,ab,kf.
5. (erythroleukemia* or erythroleukemia*).ti,ab,kf.
6. ((mast-cell or promyelocytic*) adj3 (leukemia* or leukemia*)).ti,ab,kf.
7. or/2-6
8. 1 and 7
9. 8 use medall
10. *venetoclax/ or (venetoclax* or Venclexta* or Venclyxto* or ABT199 or ABT-199 or GDC0199 or GDC-0199 or RG7601 or RG-7601).ti,ab,kw,dq.
11. exp Acute myeloid leukemia/
12. (AML or ANLL).ti,ab,kw,dq.
13. (Acute adj5 (granulocytic* or myeloblastic* or myelocytic* or myelogenous* or myeloid* or nonlymphoblastic* or non-lymphoblastic* or nonlymphocytic* or non-lymphocytic* or basophilic* or eosinophilic* or erythroblastic* or megakaryoblastic* or monocytic* or megakaryocytic* or myelomonocytic*) adj5 (leukemia* or leukemia*)).ti,ab,kw,dq.
14. (erythroleukemia* or erythroleukemia*).ti,ab,kw,dq.
15. ((mast-cell or promyelocytic*) adj3 (leukemia* or leukemia*)).ti,ab,kw,dq.
16. or/11-15
17. 10 and 16
18. 17 use oemezd
19. 18 not (conference review or conference abstract).pt.
20. 9 or 19
21. remove duplicates from 20

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search terms – Venclexta (venetoclax), acute myeloid leukemia]

WHO ICTRP

International Clinical Trials Registry Platform, produced by WHO. Targeted search used to capture registered clinical trials.

[Search terms – Venclexta (venetoclax), acute myeloid leukemia]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms – Venclexta (venetoclax), acute myeloid leukemia]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms – Venclexta (venetoclax), acute myeloid leukemia]

Grey Literature

Search dates: February 8-22, 2021

Keywords: Venclexta (venetoclax), acute myeloid leukemia

Limits:

Updated: Publication years: none

Search updated before the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search
- Open Access Journals.

Appendix 2: Excluded Studies

No studies were excluded on full-text review.

Appendix 3: Detailed Outcome Data

Note that this appendix has not been copy-edited.

Table 39: Results for OS and Composite Complete Remission (CR + CRi) in Subgroups, IA2

Result	VEN + AZA	PBO + AZA
OS in subgroups		
IDH1 and/or IDH2 mutation		
N	61	28
Median OS, months (95% CI)	NE (12.1 to NE)	6.2 (2.3 to 12.7)
HR (unstratified Cox model) (95% CI)	0.345 (0.199 to 0.598)	
P value (unstratified log-rank test)	< 0.0001*	
FLT3 mutation		
N	29	22
Median OS, months (95% CI)	12.7 (7.3 to 23.5)	8.6 (5.9 to 14.7)
HR (unstratified Cox model) (95% CI)	0.664 (0.351 to 1.257)	
P value (unstratified log-rank test)	0.2054	
NPM1 mutation		
N	27	17
Median OS, months (95% CI)	15.0 (3.4 to NE)	13.0 (4.2 to 20.3)
HR (unstratified Cox model) (95% CI)	0.734 (0.357 to 1.505)	
TP53 mutation		
N	38	14
Median OS, months (95% CI)	5.8 (2.6 to 8.3)	5.4 (1.3 to 9.3)
HR (unstratified Cox model) (95% CI)	0.760 (0.398 to 1.450)	
Age		
< 75 years		
N	112	58
HR (unstratified Cox model) (95% CI)	0.888 (0.591 to 1.333)	
≥ 75 years,		
N	174	87
HR (unstratified Cox model) (95% CI)	0.535 (0.394 to 0.727)	
ECOG at baseline		
ECOG < 2		
N	157	81

Result	VEN + AZA	PBO + AZA
HR (unstratified Cox model) (95% CI)	0.607 (0.440 to 0.838)	
ECOG ≥ 2		
N	129	64
HR (unstratified Cox model) (95% CI)	0.704 (0.483 to 1.027)	
Cytogenetic risk		
Intermediate	182	89
N	0.566 (0.407 to 0.786)	
HR (unstratified Cox model) (95% CI)		
Poor	104	56
N	0.775 (0.538 to 1.117)	
HR (unstratified Cox model) (95% CI)		
Type of AML		
De novo		
N	214	110
HR (unstratified Cox model) (95% CI)	0.674 (0.508 to 0.895)	
Secondary		
N	72	35
HR (unstratified Cox model) (95% CI)	0.561 (0.346 to 0.910)	
AML with myelodysplasia-related changes		
Yes		
N	92	49
HR (unstratified Cox model) (95% CI)	0.732 (0.484 to 1.107)	
No		
N	194	96
HR (unstratified Cox model) (95% CI)	0.616 (0.455 to 0.834)	
Bone marrow blast count		
< 30%		
N	85	41
HR (unstratified Cox model) (95% CI)	0.716 (0.447 to 1.148)	
≥ 30% to < 50%		
N	61	33
HR (unstratified Cox model) (95% CI)	0.567 (0.339 to 0.949)	
≥ 50%		

Result	VEN + AZA	PBO + AZA
N	140	71
HR (unstratified Cox model) (95% CI)	0.633 (0.448 to 0.893)	
CR + CRi in subgroups		
IDH1 and/or IDH2 mutation		
N	61	28
CR, n (%; 95% CI)	26 (42.6; 30.0 to 55.9)	1 (3.6; 0.1 to 18.3)
CR + CRi, n (%; 95% CI)	46 (75.4; 62.7 to 85.5)	3 (10.7; 2.3 to 28.2)
Risk difference % (95% CI)	64.70 (48.9 to 80.4)	
P value (Fisher's exact test)	< 0.001*	
FLT3 mutation		
N	29	22
CR, n (%; 95% CI)	10 (34.5; 17.9 to 54.3)	3 (13.6; 2.9 to 34.9)
CR + CRi, n (%; 95% CI)	21 (72.4; 52.8 to 87.3)	8 (36.4; 17.2 to 59.3)
Risk difference (%; 95% CI)	36.05 (10.2 to 61.9)	
P value (Fisher's exact test)	0.021*	
NPM1 mutation		
N	27	17
CR, n (%; 95% CI)	12 (44.4; 25.5 to 64.7)	3 (17.6; 3.8 to 43.4)
CR + CRi, n (%; 95% CI)	18 (66.7; 46.0 to 83.5)	4 (23.5; 6.8 to 49.9)
Risk difference (%; 95% CI)		
TP53 mutation		
N	38	14
CR, n (%; 95% CI)	9 (23.7; 11.4 to 40.2)	0
CR + CRi, n (%; 95% CI)	21 (55.3; 38.3 to 71.4)	0
Risk difference (%; 95% CI)		
Age		
< 75 years		
n/N (%)	70/112 (62.5)	24/58 (41.1)
Risk difference (95% CI)	21.12 (5.6 to 36.6)	
≥ 75 years,		
n/N (%)	120/174	17/87
Risk difference (95% CI)	49.43 (38.6 to 60.2)	
ECOG at baseline		

Result	VEN + AZA	PBO + AZA
ECOG < 2		
n/N (%)	108/157 (68.8)	20/81 (24.7)
Risk difference (95% CI)	44.10 (32.2 to 56.0)	
ECOG ≥ 2		
n/N (%)	82/129 (63.6)	21/64 (32.8)
Risk difference (95% CI)	30.75 (16.6 to 44.9)	
Cytogenetic risk		
Intermediate		
n/N (%)	135/182 (74.2)	28/89 (31.5)
Risk difference (95% CI)	42.72 (31.2 to 54.3)	
Poor		
n/N (%)	55/104 (52.9)	13/56 (23.2)
Risk difference (95% CI)	29.67 (15.0 to 44.3)	
Type of AML		
De novo		
n/N (%)	142/214 (66.4)	33/110 (30.0)
Risk difference (95% CI)	36.36 (25.7 to 47.0)	
Secondary		
n/N (%)	48/72 (66.7)	8/35 (22.9)
Risk difference (95% CI)	43.81 (26.1 to 61.5)	
AML with myelodysplasia-related changes		
Yes		
n/N (%)	56/92 (60.9)	11/49 (22.4)
Risk difference (95% CI)	38.42 (23.1 to 53.8)	
No		
n/N (%)	134/194 (69.1)	30/96 (31.3)
Risk difference (95% CI)	37.82 (26.5 to 49.1)	
Bone marrow blast count		
< 30%		
n/N (%)	65/85 (76.5)	16/41 (39.0)
Risk difference (95% CI)	37.45 (20.0 to 54.9)	
≥ 30% to < 50%		
n/N (%)	35/61 (57.4)	9/33 (27.3)

Result	VEN + AZA	PBO + AZA
Risk difference (95% CI)	30.10 (10.5 to 49.7)	
≥ 50%		
n/N (%)	90/140 (64.3)	16/71 (22.5)
Risk difference (95% CI)	41.75 (29.2 to 54.3)	

AML = acute myeloid leukemia; CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete blood count recovery; FLT3 = FMS-like tyrosine kinase 3; HR = hazard ratio; IA2 = second interim analysis; IDH = isocitrate dehydrogenase; NPM1 = nucleophosmin 1; OS = overall survival; PBO + AZA = placebo plus azacitidine; SD = standard deviation; TP53 = tumour protein p53; VEN + AZA = venetoclax plus azacitidine.

*Statistically significant under the preplanned testing strategy.

Note: Data cut-off was January 4, 2020.

Source: Clinical Study Report.[1]

Table 40: Patient-Reported Outcomes, Efficacy Population, to Cycle 13

Visit Treatment	N	Mean	Change from baseline LS Mean (95% CI)	Between groups LS mean diff (95% CI)	P value
PROMIS 7a					
PROMIS SF 7a treatment effect					0.758†
PROMS SF 7a treatment by visit interaction					0.264†
Baseline					–
VEN + AZA	264	53.86	–	–	–
PBO + AZA	132	54.97	–	–	–
Cycle 3 day 1		–	–	–	–
VEN + AZA	174	52.61	−0.167 (−1.55 to 1.21)	0.294 (−2.09 to 2.67)	–
PBO + AZA	79	54.43	−0.461 (−2.47 to 1.55)	–	–
Cycle 5 day 1		–	–	–	–
VEN + AZA	143	51.97	−3.036 (−4.51 to −1.56)	−2.24 (−4.89 to 0.41)	–
PBO + AZA	54	53.59	−0.796 (−3.06 to 1.47)	–	–
Cycle 7 day 1		–	–	–	–
VEN + AZA	110	51.92	−2.263 (−3.86 to −0.67)	−0.286 (−3.17 to 2.59)	–
PBO + AZA	43	53.55	−1.976 (−4.43 to 0.48)	–	–
Cycle 9 day 1		–	–	–	
VEN + AZA	91	51.59	−3.377 (−5.07, −1.68)	−2.387 (−5.43 to 0.65)	–
PBO + AZA	37	54.8	−0.99 (−3.57 to 1.59)	–	–
Cycle 11 day 1		–	–	–	–
VEN + AZA	77	52.15	−2.209 (−3.99 to −0.43)	−0.464 (−3.84 to 2.91)	–
PBO + AZA	26	54.98	−1.745 (−4.66 to 1.17)	–	–
Cycle 13 day 1		–	–	–	–
VEN + AZA	72	52.6	−1.644 (−3.46 to 0.18)	−0.191 (−3.79 to 3.41)	–

Visit Treatment	N	Mean	Change from baseline LS Mean (95% CI)	Between groups LS mean diff (95% CI)	P value
PBO + AZA	21	55.04	−1.453 (−4.60 to 1.69)	–	–
EORTC QLQ-C30 GHS					
EORTC QLQ-C30 GHS/ QoL Treatment effect	–	–	–	–	0.246†
EORTC QLQ-C30 GHS/ QoL Treatment by visit interaction	–	–	–	–	0.397†
Baseline	–	–	–	–	–
VEN + AZA	262	52.61	–	–	–
PBO + AZA	130	55.96	–	–	–
Cycle 3 day 1		–	–	–	–
VEN + AZA	172	56.83	7.073 (4.09 to 10.05)	1.413 (−3.74 to 6.57)	–
PBO + AZA	77	58.98	5.66 (1.32 to 10.00)	–	–
Cycle 5 day 1		–	–	–	–
VEN + AZA	141	58.04	10.011 (6.82 to 13.20)	5.092 (−0.72 to 10.90)	
PBO + AZA	53	61.95	4.918 (−0.06 to 9.90)	–	–
Cycle 7 day 1		–	–	–	–
VEN + AZA	109	57.03	7.843 (4.36 to 11.33)	2.059 (−4.27 to 8.38)	–
PBO + AZA	43	61.24	5.785 (0.40 to 11.17)	–	–
Cycle 9 day 1		–	–	–	–
VEN + AZA	90	57.13	12.26 (8.53 to 15.99)	4.87 (−1.84 to 11.58)	–
PBO + AZA	37	61.49	7.39 (1.71 to 13.07)	–	–
Cycle 11 day 1		–	–	–	–
VEN + AZA	77	58.23	10.034 (6.10 to 13.96)	4.121 (−3.37 to 11.61)	–
PBO + AZA	26	60.58	5.912 (−0.56 to 12.38)	–	–
Cycle 13, day 1		–	–	–	–
VEN + AZA	72	55.09	8.833 (4.81 to 12.85)	0.76 (−7.26 to 8.78)	–
PBO + AZA	21	59.52	8.073 (1.05 to 15.10)	–	–
EQ-5D Health Index Score					
Baseline	–	–	–	–	–
VEN + AZA	260	0.76	–	–	–
PBO + AZA	130	0.74	–	–	–
Cycle 3, day 1	–	–	–	–	–
VEN + AZA	170	0.78	0.017 (−0.01 to 0.04)	−0.006 (−0.05 to 0.03)	–

Visit Treatment	N	Mean	Change from baseline LS Mean (95% CI)	Between groups LS mean diff (95% CI)	P value
PBO + AZA	77	0.76	0.023 (−0.01 to 0.06)	–	–
Cycle 5, day 1	–	–	–	–	–
VEN + AZA	139	0.79	0.052 (0.03 to 0.08)	0.024 (−0.02 to 0.07)	–
PBO + AZA	53	0.77	0.028 (−0.01 to 0.07)	–	–
Cycle 7, day 1	–	–	–	–	–
VEN + AZA	106	0.79	0.035 (0.01 to 0.06)	0.019 (−0.03 to 0.07)	–
PBO + AZA	43	0.75	0.017 (−0.03 to 0.06)	–	–
Cycle 9, day 1	–	–	–	–	–
VEN + AZA	89	0.78	0.049 (0.02 to 0.08)	0.031 (−0.02 to 0.08)	–
PBO + AZA	37	0.75	0.018 (−0.03 to 0.06)	–	–
Cycle 11, day 1	–	–	–	–	–
VEN + AZA	77	0.77	0.031 (0.00 to 0.06)	−0.009 (−0.07 to 0.05)	–
PBO + AZA	26	0.75	0.039 (−0.01 to 0.09)	–	–
Cycle 13, day 1	–	–	–	–	–
VEN + AZA	72	0.76	0.016 (−0.02 to 0.05)	−0.026 (−0.09 to 0.04)	–
PBO + AZA	21	0.70	0.042 (−0.01 to 0.09)	–	–
EQ-5D VAS Score					
Baseline	–	–	–	–	–
VEN + AZA	260	64.27	–	–	–
PBO + AZA	130	60.29	–	–	–
Cycle 3, day 1	–	–	–	–	–
VEN + AZA	170	0.78	3.363 (0.54 to 6.19)	2.539 (−2.33 to 7.41)	–
PBO + AZA	77	0.76	0.825 (−3.27 to 4.92)	–	–
Cycle 5, day 1	–	–	–	–	–
VEN + AZA	139	0.79	6.392 (3.38 to 9.40)	3.085 (−2.33 to 8.50)	–
PBO + AZA	53	0.77	3.308 (−1.32 to 7.93)	–	–
Cycle 7, day 1	–	–	–	–	–
VEN + AZA	106	0.79	4.933 (1.67 to 8.19)	0.779 (−5.07 to 6.63)	–
PBO + AZA	43	0.75	4.154 (−0.82 to 9.12)	–	–
Cycle 9, day 1	–	–	–	–	–
VEN + AZA	89	0.78	9.027 (5.58 to 12.48)	5.218 (−0.94 to 11.38)	–
PBO + AZA	37	0.75	3.810 (−1.40 to 9.02)	–	–
Cycle 11, day 1	–	–	–	–	–
VEN + AZA	77	0.77	5.688 (2.08 to 9.29)	3.283 (−3.52 to 10.09)	–

Visit Treatment	N	Mean	Change from baseline LS Mean (95% CI)	Between groups LS mean diff (95% CI)	P value
PBO + AZA	26	0.75	2.405 (−3.46 to 8.27)	–	–
Cycle 13, day 1	–	–	–	–	–
VEN + AZA	72	0.76	5.308 (1.63 to 8.99)	−4.860 (−12.11 to 2.39)	–
PBO + AZA	21	0.70	10.168 (3.83 to 16.50)	–	–

CI = confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire in Cancer; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels Health State Instrument; LS = least squares; PBO + AZA = placebo plus azacitidine; PROMIS 7a = Patient-Reported Outcomes Measurement System Cancer Fatigue SF 7a; VEN + AZA = venetoclax plus azacitidine.

†Nominal P values. Sequential testing failed at prior end point on the sequence and there is a risk increased type I error if conclusions were drawn from those results.

Data cut-off: January 4; 2020.

Source: Clinical Study Report[1].

Appendix 4: Description and Appraisal of Outcome Measures

Note that this appendix has not been copy-edited.

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

Findings

Table 41: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[40]	Cancer-specific measure of HRQoL 30-item questionnaire, consisting of 4 scales; 4-item response scale: Function Scale, Symptoms Scale, Single-Item Symptom Scale, 7-item Likert scale: Global QoL Scale/GHS	**Validity:** Construct validity assessed through convergent and discriminative approach **Reliability:** Internal consistency assessed using Cronbach alpha **Responsiveness:** No relevant studies found	10 points change for the individual items and scale scores.[28,29]
EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L)[32,33]	Patient-reported, generic quality of life instrument	**Validity:** Less responsive than disease-specific measures. Moderate to poor ability to distinguish between cancer severity by 3 scales: • self-reported health status (effect size 0.90) • ECOG PS (effect size = 0.31) • stage of cancer (effect size = 0.06) **Reliability:** Five functioning scales and global health status demonstrated acceptable consistency with Cronbach alpha ranging from 0.77 to 0.82. • r = 0.43 between EORTC QLQ-C30 and EQ-5D • r = 0.73 between EORTC QLQ-C30 and EQ VAS • r = 0.43 between EQ-5D and EQ VAS **Responsiveness:** Uncertain in populations with colorectal cancer.	No relevant studies found for patients with AML.

Outcome measure	Type	Conclusions about measurement properties	MID
Patient-Reported Outcome Measurement Information System (PROMIS) Cancer Fatigue Short Form v1.0 Fatigue 7a (PROMIS F-SF)[31]	7-item, patient-reported, tool that measure both the experience of fatigue and the interference of fatigue on daily activities over the past week, using 5-point Likert scales from 1 = never to 5 = always	**Validity:** • **Concurrent validity** exanimated through Pearson's correlations between scores from the PROMIS F-SF, the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), and the Brief Fatigue Inventory (BFI). • **Discriminant validity** evaluated by examining Pearson's correlations between scores on the PROMIS F-SF and measures of stress and depressive symptoms. • **Known-groups validity** assessed by comparing PROMIS F-SH scores in the clinical samples to healthy controls.[31] **Reliability:** Internal consistency assessed using Cronbach alpha.[31] **Responsiveness:** No relevant studies found.	No relevant studies found. 3 points validated and reported in the VIALE-A and VIALE-C trials (AML patients).[41]

ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS = global health status; HRQoL = health-related quality of life; EQ-5D-5L = European Quality of Life 5-Five Dimensions 5-Levels; MID = minimal important difference; PedsQL-Core = Pediatric Quality of Life-Core Module; PROMIS = Patient-Reported Outcome Measurement Information System.

EORTC QLQ-C30

Description

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), is 1 of the most commonly used patient-reported outcome measures in oncology clinical trials.[24] It is a multidimensional, cancer-specific, evaluative measure of HRQoL. It was designed specifically for the purpose of assessing changes in participants' HRQoL in clinical trials, in response to treatment.[42] The core questionnaire of the EORTC QLQ-C30 consists of 30 questions that are scored to create 5 multi-item functional scales, 3 multi-item symptom scales, 6 single-item symptom scales, and a 2-item QoL scale, as outlined in Table 42. Version 3.0 of the questionnaire, used in the included trials in this report, is the most current version and has been in use since December of 1997.[25] It is available in 90 different languages and is intended for use in adult populations only. Notably, the global QoL scale is also known as the GHS, which was reported in the trial mentioned previously.[27]

Table 42: Scales of EORTC QLQ-C30

Functional scales (15 questions)	Symptom scales (7 questions)	Single-item symptom scales (6 questions)	Global quality of life (2 questions)
Physical function (5)	Fatigue (3)	Dyspnea (1)	Global Quality of Life (2)
Role function (2)	Pain (2)	Insomnia (1)	–
Cognitive function (2)	Nausea and vomiting (2)	Appetite loss (1)	–
Emotional function (4)	–	Constipation (1)	–
Social function (2)	–	Diarrhea (1)	–
	–	Financial impact (1)	–

Scoring

The EORTC QLQ-C30 uses a 1-week recall period in assessing function and symptoms. Most questions have 4 response options ("not at all," "a little," "quite a bit," "very much"), with scores on these items ranging from 1 to 4.[25] For the 2 items that form the global QoL scale, however, the response format is a 7-point Likert-type scale, with anchors between 1 (very poor) and 7 (excellent).[25]

Raw scores for each scale are computed as the average of the items that contribute to a particular scale. This scaling approach is based upon the assumption that it is appropriate to provide equal weighting to each item that comprises a scale. There is also an assumption that, for each item, the interval between response options is equal (for example, the difference in score between "not at all" and "a little" is the same as "a little" and "quite a bit," at a value of 1 unit). Each raw scale score is converted to a standardized score that ranges from 0 to 100 using a linear transformation, with a higher score reflecting better function on the function scales, higher symptoms on the symptom scales, and better QoL (i.e., higher scores simply reflect higher levels of response on that scale). Thus, a decline in score on the symptom scale would reflect an improvement, whereas an increase in score on the function and QoL scale would reflect an improvement. According to the EORTC QLQ-C30s scoring algorithm, if there are missing items for a scale (i.e., the participant did not provide a response), the score for the scale can still be computed if there are responses for at least 1-half of the items. In calculating the scale score, the missing items are simply ignored — an approach that assumes that the missing items have values equal to the average of those items for what the respondent completed.[25]

Psychometric Properties

Validity: One cross-sectional study aimed to validate the EORTC QLQ-30 in a convenience sample of 57 cancer patients in Singapore.[26] Most patients had breast and colorectal cancer, but leukemia, lung cancer, lymphoma, germ cell tumour, and other cancers were also reported. Construct validity was assessed by cross-sectional correlational evidence and discriminative evidence. First, convergent validity was assessed using spearman's correlations between QLQ-30 and Short Form-36 (SF-36) scales, hypothesizing moderate to strong correlation (defined as correlation coefficient of 0.35 to 0.5, and > 0.5, respectively) between scales of these 2 instruments measuring similar dimensions of HRQoL. Results showed moderate to strong correlations between QLC-30 and SF-36 scales, ranging from 0.35 to 0.67 across the assessed scales. Next, the known-groups approach was used to compare 6 QLQ-30 scale scores between patients reporting mild and severe symptoms, as well as by stage of disease and presence of comorbid conditions. With the exception of emotional functioning, the remaining 5 scales showed better scores in patients with mild symptoms than those with severe symptoms ($P < 0.05$ for all other comparisons). Patients in early stages of cancer (or with no comorbid conditions) generally had better QLQ-30 scores than those in advanced disease stages (or with comorbid conditions); however, none of these differences was statistically significant.[26]

A recent cross-sectional study in Kenya was conducted to evaluate the psychometric properties of the EORTC QLQ-C30, using the English or Kiswahili version in 100 patients with cancer.[27] Most patients had breast cancer, followed by prostate, Kaposi sarcoma, lung, and other cancers. Construct validity was assessed by examining the inter-scale correlations among the subscales of EORTC QLQ-C 30. The inter-scale correlations were weak to strong; absolute magnitude ranged from 0.07 to 0.73. Notably, with the exception of the cognitive functioning, emotional functioning, nausea and vomiting, dyspnea, appetite loss, constipation, and diarrhea domains, the GHS correlated moderately with the remaining subscales ($r \geq 0.30$). Cross-cultural validity was evaluated but not reported here as not relevant.[27]

Reliability: The Singaporean cross-sectional study above also assessed internal consistency reliability by calculating Cronbach alpha for all QLQ-C30 scales. Cronbach alpha was 0.70 or greater for 6 of the 9 assessed QLQ-30 scales; cognitive functioning, physical functioning, and nausea and vomiting had a Cronbach alpha ranging from 0.19 to 0.68.[26]

The Kenyan study described above assessed the internal consistency of each scale of the questionnaire using Cronbach alpha coefficients. With the exception of the cognitive function scale, all of the scales had a Cronbach alpha of 0.70 or greater.[27]

Studies evaluating the responsiveness of the instrument was not found.

Minimal Important Difference

For use in clinical trials, scores on the EORTC QLQ-C30 can be compared between different groups of patients or within a group of patients over time. One study conducted in breast cancer and small-cell lung cancer patients in 1998 estimated a clinically relevant change in score on any scale of the EORTC QLQ-C30 to be 10 points.[28] The estimate was based on a study that used an anchor-based approach to estimating the MID in which patients who reported "a little" change (for better or worse) on the subjective significance questionnaire had corresponding changes on a function or symptom scale of the EORTC QLQ-C30 of approximately 5 to 10 points. Participants who reported a "moderate" change had corresponding changes in the EORTC QLQ-C30 of about 10 to 20, and those who reported being "very much" changed had corresponding changes of more than 20.[28]

More recently in 2015, a Canadian study estimated the MIDs of EORTC QLQ-C30 scales using data from 193 newly diagnosed breast and colorectal cancer patients.[29] The Supportive Care Needs Survey-Short Form-34 (SCNS-SF34) was used as an anchor; mean changes in EORTC QLQ-C30 scales associated with improvement, worsening, and no-change in supportive care based on the SCNS-SF34 was then calculated. MIDs were assessed for the following scales: Physical function, role function, emotional function, global health/QoL (i.e., GHS), pain, and fatigue. For improvement, MIDs associated with a statistically significantly improved supportive care needs ranged from 10 to 32 points. For worsening, MIDs associated with a statistically significantly worsening of supportive care needs ranged from 9 to 21 points. The range for unchanged supportive care needs was from 1-point worsening to 16-point improvement in EORTC QLQ-C30 score.[29] Based on this, the authors suggested a 10-point change in EORTC QLQ-C30 score represented changes in supportive care needs, and therefore should be considered for clinical use.[29]

In 2014, another Canadian study estimated the MID for EORTC QLQ-C30 in 369 patients with advanced cancer, who completed the questionnaire at baseline and 1 month post radiation.[30] Most common cancer type was breast cancer, followed by lung, prostate, gastrointestinal, renal cell, and others. MID was estimated using both anchor and distribution-based methods for improvement and deterioration. Two anchors of overall health and overall QoL were used, both taken directly from the EORTC QLQ-C30 (questions 29 and 30) where patients rated their overall health and QoL themselves. Improvement and deterioration were categorized as an increase or decrease by 2 units to account for the natural fluctuation of patient scoring. With these 2 anchors, the estimated MIDs across all EORTC QLQ-C30 scales ranged from 9.1 units to 23.5 units for improvement, and from 7.2 units to 13.5 units for deterioration. Distribution-based estimates were closest to 0.5 SD.[30] Notably, this study used the global score as an anchor, without providing an MID for this scale, which was the scale used in the NAVIGATE trial, thereby the MIDs from this study are not applicable to this review.

EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) Health State Instrument

Description

The EQ-5D is a generic HRQoL instrument that may be applied to a wide range of health conditions and treatments.[32,33] The first of 2 parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) based on the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L has 5 possible levels for each domain representing "no problems," "slight problems," "moderate problems," "severe problems," and "extreme problems." Respondents are asked to choose the level that reflects their health state for each of the 5 dimensions, corresponding with 3,125 different health states.

Scoring

A scoring function can be used to assign a value (EQ-5D-5L index score) to self-reported health states from a set of population-based preference weights.[32,33] The second part is a 20 cm visual analogue scale (EQ VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ VAS which best represents their health on that day. Hence, the EQ-5D produces 3 types of data for each respondent:

1. A profile indicating the extent of problems on each of the 5 dimensions represented by a 5-digit descriptor, such as 11121, 33211
2. A population preference-weighted health index score based on the descriptive system
3. A self-reported assessment of health status based on the EQ VAS

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score for the 3L version (corresponding to severe problems on all 5 attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported MIDs for the 3L version of the scale have ranged from 0.033 to 0.074.[43]

Psychometric Properties

Reliability: Teckle et al. conducted a study at the Vancouver Cancer Clinic of patients (N = 184) who had either breast (36%), colorectal (31%), or lung (33%) cancer to investigate whether disease severity could be distinguished by cancer-specific and generic preference-based instruments.[34] Internal consistency was calculated using Cronbach alpha and all 5 functioning scales along with global health status showed acceptable consistency (alpha > 0.7), with values ranging from 0.77 to 0.82.

Validity: Validity was assessed using Pearson's correlation coefficient (r) where r between 0 and 0.3 demonstrated weak correlation, between 0.3 and 0.49 was moderate, and greater than 0.5 was considered strong. Teckle et al. found the following, between the EORTC QLQ-C30 and EQ-5D, r = 0.43; comparing the EORTC QLQ-C30 and EQ VAS, r = 0.73; and between EQ-5D and EQ VAS, r = 0.43. External validity was estimated between cancer severity (self-reported health status, Eastern Cooperative Oncology Group Performance Status [ECOG PS], and cancer stage). An effect size (ES) between 0.2 and 0.5 was considered small, between 0.5 and 0.8 was medium, and greater than 0.8 was large.[34] The EQ-5D was able to discriminate populations based on self-reported health status (excellent/good versus fair/very poor; ES = 0.90), and somewhat based on ECOG PS (0 versus 1 to 3; ES = 0.31), but not for stage of cancer (stages I and II versus stages III and IV; ES = 0.06). The EORTC QLQ-C30 performed better in all 3 areas: self-reported health status (ES = 1.39), ECOG PS (ES = 0.65), and stage of cancer (ES = 0.49). It is worth noting that the EQ-5D was based on a non-Canadian population and the comparison with EORTC QLQ-C30 was based solely on the 2 questions asking about overall health and QoL rather than the questionnaire as a whole. Furthermore, there was no information on what type of treatment the patients were receiving when completing the questionnaires.

Responsiveness: Responsiveness was not reported.

Minimal Important Difference

There were no relevant studies reporting the MID among patients with AML.

Patient-Reported Outcome Measurement Information System Fatigue Short Form v1.0–Fatigue 7a (PROMIS F-SF)

Description

PROMIS is a set of standardized tools funded by the National Institutes of Health for measuring patient-reported outcomes.[31] The PROMIS has 2 major frameworks—Adult Self-Reported Health and Pediatric Self- and Proxy-Reported Health.[31] Each framework has their own physical, mental, and social health domains. Item banks and subsequent PROMIS measures were developed within each framework to assess patient-reported outcomes, such as fatigue and disease conditions.[31] Fatigue is part of the PROMIS physical health domain.[31] The PROMIS F-SF has 7 items to measure both the experience of fatigue and the interference of fatigue on daily activities over the past week.[31]

Scoring

For the 7 items, the response options are measured on a 5-point Likert scale, from 1 = never to 5 = always. One item, "How often did you have enough energy to exercise strenuously," is reverse scored.[31] The total score is the sum of the keyed scores of all items. Total scores can range from 7 to 35, with higher scores indicating greater fatigue.[31]

Psychometric Properties

Reliability: In a secondary analysis that compared fatigue measures in the PROMIS F-SF, the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), and the Brief Fatigue Inventory (BFI) in patients with fibromyalgia (n = 72), patient with sickle cell disease (n = 60), individuals with cardiometabolic risks (n = 63), pregnant women (n = 72), and healthy controls (n = 40) in 4 studies.[31] Reliability of PROMIS F-SF scores was adequate across samples, ranging from 0.72 in pregnant women to 0.88 in healthy controls.[31]

Validity: Concurrent validity was strong based on the correlations between the PROMIS F-SF and the MFSI-SF (r = 0.70 to 0.85) and those between the PROMIS F-SF and the BFI (r = 0.60 to 0.85).[31] Discriminant correlations between the PROMIS F-SF and the Perceived Stress Scale (PSS) were from r = 0.37 to 0.62, and between the PROMIS F-SF and the CES-D ranged from r = 0.45 to 0.64.[31] For known-groups validity, the samples in the 4 study had significantly higher levels of fatigue on the PROMIS F-SF than the healthy controls.[31]

Responsiveness: Responsiveness was not reported.[31]

Minimal Important Difference

The researchers that conducted the VIALE-A trial assessed the MID using anchor- and distribution-based approaches in a group of AML patients.[1] A 3-point difference that fell within the range of 3 to 5 proposed in the literature was considered an appropriate MID for patients with AML.[41] The 3-point difference was also applied for the patients with AML in another related trial, the VIALE-C trial.[41]

Appendix 5: Summary of Protocol Changes for VIALE-A

Note that this appendix has not been copy-edited.

The original protocol (dated October 25, 2016, with 2 patients enrolled globally under the amendment) had several global amendments, and 1 amendment that was specific to China, and allowed enrolment of an open-label cohort. The global amendments are summarized below:

- **Amendment 1**, December 21, 2016 (2 patients enrolled). The eligibility age limit was lowered from ≥ 60 years to ≥ 18 years, to allow for the enrolment of patients younger than 60 years who were ineligible for standard induction therapies on account of comorbidities. The addition of cytogenetic risk to the randomization factors, although formally added in amendment 2, was implemented in the interactive response technology for the 2 patients recruited under this amendment.
- **Amendment 2**, February 20, 2016 (47 patients enrolled). Cytogenetic risk was added to the factors for stratification of randomization. Definitions for progression of disease and EFS were clarified.
- **Amendment 3**, May 10, 2017 (295 patients). Exclusion critieria now included patients hypersensitive to active substances of the study drug. Eligibility of patients with and without BCR-ABL mutation was clarified. Guidance added for use of anti-emetics, to align with the azacitidine prescribing information.
- **Amendment 4**, March 1, 2018 (48 patients). CRh was added as an end point.
- **Amendment 5**, August 8, 2018 (30 patients). Protocol and SAP were aligned for CR + CRi rate analysis. Protocol clarified that OS and CR + CRi dual primary end points would be used for Japan, the EU, and EU reference countries, and OS alone for US and US reference countries. Secondary end points were updated to include MRD evaluation, CRh, transfusion independence, molecular markers. Criteria for RLFS, CRi, and resistant disease were defined in more detail.
- **Amendment 6**, May 15, 2019 (0 patients). The total number of OS events was updated as the enrolment in the study was expected to continue at the anticipated time of survival event accrual for interim survival analysis, to increase the follow-up of patients after enrolment, and to increase the statistical power.
- **Amendment 7**, August 21, 2019 (0 patients). The amendment revised the definition of CR as neutrophil count greater than 1,000/μL and platelets > 100,000/μL according to the IWG criteria and to clarify the version of NCCN guidelines for AML used to stratify cytogenetic risk stratification criteria.

The SAP had 7 versions with amendments to align the SAP with the protocol changes. Version 1 (March 27, 2018) described the initial efficacy and safety analysis methods. Significant amendments, involving changes to end points of interest to this review, follow:

- **Version 2** (September 12, 2018). Followed protocol amendment 5. The sample size was increased to approximately 412 patients. The dual primary end points of OS and CR + CRi rate were clarified for Japan, the EU, and EU reference countries and the single primary end point of OS for the US and US reference countries.
- **Version 4** (May 30, 2019). Following protocol amendment 6. The total number of OS events was increased from 302 to 360, and the number of events at the 75% OS interim analysis was increased from 227 to 270. Confirmed and unconfirmed PD were added as end points.
- **Version 5** (August 28, 2019). Followed protocol amendment 7. Outlined the criteria to be used for stopping the trial early due to a possible detrimental effect of the interventional therapy, with clarification of language in SAP Version 7 (August 21, 2019). Updated the censoring rule for duration of response to use the last adequate assessment before post-treatment therapy rather than the start of post-treatment therapy. Updated the ranking strategy for OS subgroups by FLT3 and IDH/IDH2.

CADTH

Pharmacoeconomic Review

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Abbreviations

AIC	Akaike information criteria
AML	acute myeloid leukemia
BIC	Bayesian information criteria
BSC	best supportive care
CR	complete remission
CRh	complete remission with incomplete hematological recovery
CRi	complete remission with incomplete bone marrow recovery
EFS	event-free survival
HMA	hypomethylating agent
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
LDAC	low-dose cytarabine
NMA	network meta-analysis
OS	overall survival
PD/RL	progressive/relapsed disease
QALY	quality-adjusted life-year
WTP	willingness to pay

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Venetoclax (Venclexta), 10 mg, 50 mg, 100 mg, tablets, oral
Submitted price	Venetoclax, 100 mg tablet: $70
Indication	In combination with azacitidine or low-dose cytarabine, is indicated for the treatment of patients with newly diagnosed acute myeloid leukemia (AML) who are 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	December 4, 2020
Reimbursement request	In combination with azacitidine for the treatment of patients with newly diagnosed AML who are 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
Sponsor	AbbVie Corporation
Submission history	Previously reviewed: Yes Indication: For the treatment of patients with CLL who have received at least 1 prior therapy and have a 17p deletion Recommendation date: December 1, 2016 Recommendation: Not recommended[1] Indication: As monotherapy for the treatment of patients with CLL who have received at least 1 prior therapy and who have failed a B-cell receptor inhibitor Recommendation date: November 30, 2017 Recommendation: Recommended on the condition of cost-effectiveness being improved to an acceptable level[2] Indication: In combination with rituximab for the treatment of adult patients with CLL who have received at least 1 prior therapy, irrespective of their 17p deletion status Recommendation date: May 31, 2019 Recommendation: Recommended on the condition of cost-effectiveness being improved to an acceptable level[3] Indication: In combination with obinutuzumab for the treatment of adult patients with previously untreated CLL who are fludarabine ineligible Recommendation date: November 17, 2020 Recommendation: Recommended on the condition of cost-effectiveness being improved to an acceptable level[4]

AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Patients with newly diagnosed AML for whom IC is unsuitable or who are aged 75 years or older
Treatment	Venetoclax plus azacitidine
Comparators	Azacitidine alone LDAC BSC
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime horizon (90 years)
Key data source	VIALE-C and VIALE-A trials and a network meta-analysis
Submitted results	• Based on the sequential analyses, the optimal treatments (i.e., on the cost-effectiveness frontier) are BSC, LDAC, and venetoclax plus azacitidine. • ICER for venetoclax plus azacitidine when compared with LDAC was $105,286 per QALY gained (1.59 incremental QALYs and $167,432 incremental costs).
Key limitations	• The sponsor excluded IC as a comparator. Clinical experts consulted for this review indicated that individuals older than 75 would be eligible to receive IC. • The sponsor incorporated a cure assumption for individuals who remain in the CR + CRi health state for more than 5 years. Clinical experts indicated that this assumption was unlikely to be correct. • A substantial portion of the QALY benefits of venetoclax plus azacitidine occurred after individuals exited the EFS state and were no longer on first-line treatment. Clinical experts indicated there was unlikely to be a substantive benefit for individuals who receive venetoclax plus azacitidine after exiting the EFS health state. • In the sponsor's model, EFS and the duration of first-line treatment were estimated independently. It is likely that EFS and treatment duration are highly correlated. • There exists substantial uncertainty surrounding the effectiveness of venetoclax plus azacitidine beyond the follow-up of the VIALE-A trial.
CADTH reanalysis results	• CADTH reanalyses included estimates for OS curves limiting the benefit of venetoclax plus azacitidine post EFS, and a cure assumption for those who remain in the CR + CRi health state for more than 10 years. In addition to these modifications, CADTH conducted several scenario analyses to quantify the uncertainty surrounding the CADTH base case. These scenario analyses included all individuals in the EFS health state being on treatment, and varying estimates of OS for venetoclax plus azacitidine. CADTH was not able to address the exclusion of IC as a comparator. • In the sequential analysis, venetoclax plus azacitidine was associated with an ICER of $125,580 per QALY compared with LDAC; LDAC was associated with an ICER of $72,232 per QALY compared with BSC. Azacitidine remained ruled out as an optimal option. • The probability that venetoclax plus azacitidine was cost-effective at a $50,000 WTP threshold compared with LDAC was 0%.

AML = acute myeloid leukemia; BSC = best supportive care; CR + CRi = complete remission plus complete remission with incomplete blood count recovery; EFS = event-free survival; IC = intensive chemotherapy; ICER = incremental cost-effectiveness ratio; LDAC = low-dose cytarabine; LY = life-year; OS = overall survival; QALY = quality-adjusted life-year; WTP = willingness to pay.

Conclusions

Based on the Clinical Review, patients treated with venetoclax plus azacitidine showed benefits in overall survival (OS), overall and early composite combined response (complete remission plus complete remission with incomplete blood count recovery [CR + CRi]), event-free survival (EFS), and complete remission compared with patients treated with azacitidine alone. An indirect treatment comparison comparing venetoclax plus azacitidine with low-dose cytarabine (LDAC) was found to be highly susceptible to bias due to the absence of randomized propensity-score comparisons.

CADTH undertook reanalyses to address limitations with the sponsor's submission. These reanalyses included: a different assumption on functional form of the OS probability for venetoclax plus azacitidine (Weibull distribution) which resulted in more plausible estimates of survival post EFS for venetoclax plus azacitidine; and changing the sponsor's assumption of disease being cured for those who remain in the CR + CRi health state from 5 years to 10 years. In the CADTH base case, best supportive care (BSC), LDAC, and azacitidine are considered optimal treatments (i.e., on the cost-effectiveness efficiency frontier). Venetoclax plus azacitidine is more effective and more costly than LDAC (incremental quality-adjusted life-year [QALY]: 1.21; incremental cost: $151,779) with an incremental cost-effectiveness ratio (ICER) of $125,580 per QALY. The probability that venetoclax plus azacitidine is cost-effective at a $50,000 willingness-to-pay (WTP) threshold compared with LDAC was 0%. There is no price reduction at which venetoclax plus azacitidine was cost-effective compared with LDAC at a WTP threshold of $50,000 per QALY, due to the cost of combination therapy and the long duration of first-line treatment. The probability that venetoclax plus azacitidine is cost-effective compared with azacitidine monotherapy at this threshold was also 0%.

The cost-effectiveness of venetoclax plus azacitidine was driven by assumptions about treatment duration and the extrapolation of OS and EFS beyond the observation period of the trial. The pharmacoeconomic model was also associated with notable structural uncertainty that appeared to confer a post-event survival benefit for venetoclax plus azacitidine that was not adequately supported by the available data. These findings taken together suggest the cost-effectiveness of venetoclax plus azacitidine compared with azacitidine monotherapy, LDAC, and BSC are uncertain and likely overestimated. The cost-effectiveness of venetoclax plus azacitidine compared with intensive chemotherapy, which the clinical experts indicated is an important comparator for those over 75 years of age, is unknown.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

One patient advocacy group, the Leukemia and Lymphoma Society of Canada (LLSC) provided input on venetoclax in combination with azacitidine for the treatment of AML. LLSC collected responses from 29 Canadian patients diagnosed with acute myeloid leukemia (AML) using an online survey conducted between December 7, 2020 and January 24, 2021. Respondents reported receiving the following front-line treatments after diagnosis: chemotherapy (n = 24), stem cell transplant or bone marrow transplant (n = 16), drug therapy (n = 6), radiation therapy (n = 5), chimeric antigen receptor (CAR) T-cell therapy (n = 1), and

liposomal daunorubicin and cytarabine (n = 1). Five of the respondents had experience with venetoclax in combination with azacitidine.

According to the respondents, the AML symptoms that impact quality of life included fatigue, suddenness of symptom development, anxiety, fear of relapse, and loss of eyesight. Moreover, the respondents reported a wide range of side effects under current treatments. Respondents highlighted that they were unable to work due to disease and associated symptoms as well as the impact on caregivers. Patients' responses to venetoclax in combination with azacitidine varied greatly, including an overall great experience (n = 1), experiences with side effects (tiredness and loss of appetite, n = 1), no side effects but relapse (n = 1), significant side effects (n = 1), and transition to transplant (n = 1). Their overall opinion of this new treatment varied greatly as well, based on diverging opinions on financial costs, efficacy, and side effects.

The LLSC survey patient respondents also reported the characteristics of new treatment options that they hoped to have, in particular, those that could maintain remission, with fewer side effects, covered by public drug plans, and accessible in wider geographic regions. The opportunity to have access to other supportive options, such as meditation, hypnosis, neuro-linguistic programming support, and awareness support (thoughts, emotions, and behaviours), was also mentioned.

Feedback from registered clinicians suggested that the options for standard of care for first-line AML treatment were azacitidine, LDAC, and supportive care. Clinicians stated that the expected goal of treatment with venetoclax plus azacitidine was an improvement in survival and quality of life, as well as transfusion independence. Clinicians remarked that very frail or very elderly patients likely would not receive venetoclax plus azacitidine, and that patients would need to travel to a clinic to receive the azacitidine component of the treatment. Clinicians also noted that younger and fit patients without significant comorbidities would be better suited for intensive induction chemotherapy.

The drug plans highlighted considerations for the implementation of venetoclax plus azacitidine that are relevant to the economic analysis. One issue is the exclusion of relevant comparators, particularly for those aged 75 years and older, where many patients may be fit to tolerate intensive chemotherapy. Another issue related to whether venetoclax can be used with alternative dosing schedules for azacitidine that some provinces currently fund (e.g., 5 to 2-2, 6 consecutive days) as it differs from the schedule included in this submission. In addition, dosing regiments for azacitidine, venetoclax, and LDAC are slightly different across indications and this was flagged by the drug plans. Another concern of the drug plans related to whether venetoclax plus azacitidine would become available to individuals who have been previously treated with azacitidine as well as a possible selection bias in the VIALE-A trial of healthier patients. It was also noted that other novel therapies are under review by CADTH for the same population.

Several of these concerns were addressed in the sponsor's model:

- The probability of remaining on remission (i.e., event-free) and the development of side effects were both incorporated in the submitted model.
- Health-related quality of life (HRQoL) estimates in the model capture some of the impact listed by patients.
- HRQoL impact of major adverse events.

CADTH was unable to address the following concerns raised from stakeholder input:

- The omission of intensive chemotherapy as a comparator in the model.
- The indirect impact to caregivers associated with AML.
- The alternative dosing schedules.
- The use of venetoclax plus azacitidine in a population that has been previously treated with azacitidine.
- No information on the labour force impact of AML was included in the pivotal trial or implemented in the economic model.

Economic Review

Economic Evaluation

The current review is for venetoclax and azacitidine for newly diagnosed AML who are 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis assessing venetoclax plus azacitidine compared with azacitidine alone, LDAC, and BSC in patients who are newly diagnosed AML for whom intensive chemotherapy is unsuitable. The modelled population was consistent with the VIALE-A clinical trial did not match the reimbursement request. Two subgroup analyses were conducted according to a bone marrow blast count of 20% to 30% with azacitidine as a comparator, and a greater than 30% blast count with azacitidine and LDAC as comparators. The cost-utility analysis was conducted from the perspective of the Canadian publicly funded health system.[5]

The recommended dose of venetoclax when used in combination with azacitidine consists of 100 mg on day 1, 200 mg on day 2, 400 mg on days 3 to 28 for the first 28-day cycle, and 400 mg administered daily on subsequent 28-day cycles.[6] The recommended dose of azacitidine when used alone or in combination with venetoclax consisted of 75 mg/m^2 on days 1 to 7 of each 28-day cycle. The recommended dose for LDAC was 20 mg/m^2 on days 1 to 10 of each 28-day cycle. BSC was not explicitly defined in the submitted report, but no drug administration was assumed for that strategy.[5]

Administration costs for venetoclax consist of pharmacy dispensing fees and physician fees for management of oral chemotherapy.[5] The administration costs for azacitidine and LDAC were associated with inpatient IV therapy administration. The total drug-acquisition cost per patient for the first 28-day cycle of venetoclax plus azacitidine is $11,724 (venetoclax: $5,585; azacitidine: $6,139) and $11,877 (venetoclax: $5,739; azacitidine: $6,139) for subsequent 28-day cycles, based on a venetoclax unit price of $70 per 100 mg tablet. The total drug-acquisition cost per patient for each 28-day cycle of azacitidine was $7,581. The total drug-acquisition cost per patient for each 28-day cycle of LDAC was $48 based on a price per vial of $4.90. The sponsor assumed no drug-acquisition costs associated with BSC.

The clinical outcomes modelled included QALYs and life-years. The economic analysis was undertaken over a lifetime horizon using a 28-day cycle length. The economic evaluation was conducted from the perspective of a publicly funded health care system and discounting (1.5% per year) was applied to both costs and outcomes.[5]

Model Structure

A partitioned survival model (PSM) was developed in Microsoft Excel. The PSM consisted of 3 mutually exclusive health states: EFS, progressive/relapsed disease (PD/RL), and death (Figure 1). EFS was defined as the time from treatment initiation to first progression or relapse from complete remission/complete remission with incomplete blood count recovery (CR/CRi), or treatment failure or death due to any cause. All patients enter the model in the EFS health state. Within EFS a proportion of time was assumed to be spent with CR + CRi and the remaining time in EFS without CR or CRi. Duration of first-line treatment was modelled independently from EFS, and patients could stop treatment without transitioning to another state. Patients then transition to the PD/RL state included alive patients who progressed or relapsed. After transitioning to PD/RL patients undergo subsequent treatment. Individuals remain in PD/RL until experiencing death either due to AML related mortality or due to other cause mortality. It was assumed that individuals who remain in the EFS health state with CR + CRi for more than 5 years were "cured" and no longer at risk of transitioning to PD/RL or experiencing disease-related mortality. Patients could also experience treatment-related adverse events, which were assumed to occur during the first model cycle.

Parametric survival models in combination with hazard ratios (HRs) were used to inform OS and EFS. EFS was assumed to be less than or equal to OS at all time points. The proportion of patients in the EFS health state of the model was set to be equal to the EFS curve of each treatment. 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, the cohort of patients was redistributed among the 3 health states, with death being the absorbing state.

Model Inputs

Baseline patient characteristics for the modelled population and the clinical efficacy of venetoclax plus azacitidine and azacitidine were sourced from the VIALE-A trial (data cut-off: January 4, 2020), while clinical efficacy of LDAC was based on the placebo arm data from the VIALE-C trial. The VIALE-A and VIALE-C trials were multi-centre and randomized double-blind placebo-controlled phase III trials in which patients were assigned in a 2:1 ratio either to venetoclax plus azacitidine or a comparator.[7,8] The baseline characteristics of the patient population in the VIALE-A trial consisted of a median age of 76, 21% with prior use of hypomethylating agents (HMAs) and 76% having bone marrow blast counts greater than 30%. The baseline characteristics of the patient population in the placebo arm of the VIALE-C trial consisted of a median age of 76, 21% with prior HMA use, and 76% having bone marrow blast counts greater than 30%.[8] Information on BSC efficacy in the network meta-analysis was based on NCT01074047 (Dombret) a multi-centre, randomized, open-label, phase III trial that evaluated azacitidine efficacy and safety versus conventional care regimens that consisted of patients aged 65 years and older with newly diagnosed AML who were not considered eligible for hematopoietic stem cell transplant (HSCT).[9] The median age of this arm was 78, with 100% of the 48 patients having a bone marrow blast count of greater than 30% and 0% having previously used an HMA.

Overall survival and EFS for venetoclax plus azacitidine and azacitidine were obtained using propensity score–matched parametric survival models on individual patient-level data from the VIALE-A trial, which was then extrapolated beyond the trial period. Exponential, Weibull, log-logistic, log-normal, Gompertz, and generalized gamma models were considered, and Akaike information criterion (AIC) and Bayesian information criterion (BIC) tests, visual inspection, examination of log-cumulative hazard plots, Schoenfeld residuals tests, and clinical input and external validation were used in the survival model selection process. Graphical representation of the fitted parametric distributions for EFS and OS extrapolations are shown in figures 2 to 5). For the LDAC arm, the HR method was used to evaluate their comparative effectiveness versus venetoclax plus azacitidine. To adjust for the potential difference in patient population between venetoclax plus azacitidine and LDAC, the HR was calculated via a propensity-score analysis using individual patient-level data from the VIALE-A and VIALE-C trials. The OS for BSC was estimated using a network meta-analysis with venetoclax plus azacitidine as the reference. The network meta-analysis was conducted using Bayesian mixed treatment comparison techniques. Bayesian Markov Chain Monte Carlo methods were used to estimate the posterior probability distribution and generate pairwise comparisons for treatments of interest by outcome. The proportion of time in CR + CRi for venetoclax plus azacitidine, azacitidine alone, and LDAC was estimated by the CR + CRi rate in the VIALE-A and VIALE-C trials. For the subgroup analysis of 20% to 30% blasts, parametric survival models were fitted on the VIALE-A trial data. For the subgroup analysis of greater than 30% blasts, parametric survival models were used to inform the venetoclax plus azacitidine and azacitidine estimates of OS and EFS, with the OS and EFS for LDAC estimated using an HR measure similar to the base-case analysis. The survival for the patients assumed to be cured was modelled using general population mortality based on the 2019 Canadian life table.

HRQoL in the VIALE-A and VIALE-C trials was measured using the EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L).[7,8] It was administered at cycle 1 day 1 and on day 1 of every other cycle as well as on 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. EQ-5D-5L utility scores were estimated from pooled VIALE-A and VIALE-C trial data based on individual dimension scores and using Canada preference weights.[7,10,11] 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. The linear model adjusted for the grade 3 or 4 adverse events that occurred at a prevalence rate of 5% or greater in the VIALE-A and VIALE-C trials. Adverse event utility and disutility inputs were derived from Wehler.[12] For adverse events that were not reported in the literature, values were assumed to be equal to those under the same adverse event category or the average disutility of all the adverse events. The model assumed patients could receive subsequent HSCT after initial treatment. Patients receiving subsequent HSCT were assumed to have additional HSCT disutility that would last for 365 days.[13]

The dosing schedule, dose intensity, and treatment duration for venetoclax plus azacitidine, azacitidine alone, and LDAC were obtained from the VIALE-A and VIALE-C trials. Venetoclax had a dose intensity of 73%. Azacitidine had a dose intensity of 73% when used in combination with venetoclax, and 90% when used alone. LDAC had a dose intensity of 98%. The median treatment durations for venetoclax plus azacitidine, azacitidine alone, and LDAC were obtained from the VIALE-A and VIALE-C trials and an exponential model was used to extrapolate the time on treatment beyond the trial observation period. The proportion of patients receiving subsequent treatments for each comparator were obtained from

a Canadian key opinion leader. For BSC, all patients are assumed to receive subsequent treatment of hydroxycarbamide, also based on Canadian key opinion leader input. Only the subsequent treatments with a prevalence rate greater than or equal to 5% in any of the treatment arms were considered. The dosing schedule for subsequent treatments was sourced from the VIALE-A and VIALE-C trials and Cancer Care Ontario.[14,15]The mean treatment duration of azacitidine as subsequent treatment was derived from a retrospective database study and was used as treatment duration for all subsequent therapies.[5,16] The adverse event rates for BSC were based on Dombret.[17] Only adverse events that were grade 3 or 4 with a greater than 5% prevalence rate in any of the arms were considered. The proportion of grade 3 or 4 adverse events managed on either an inpatient or outpatient basis were established based on input from a Canadian key opinion leader.[5]

The model considered the following cost components: initial treatment costs (including drug and administration), subsequent HSCT costs, subsequent pharmacological treatment costs (including drug and administration), adverse event costs associated with initial treatments, and terminal care costs. The unit drug costs of venetoclax and all other treatments were obtained from IQVIA price list (October 2020). Resource utilization and unit costs were sourced from the overall population in the VIALE-C trial, the literature, public databases, and a Canadian key opinion leader. An inpatient hospitalization cost of $1,817.86 was sourced from the Patient Cost Estimator provided by the Canadian Institute for Health Information (CIHI).[18] (A daily cost of being in an intensive care unit of $3,927.67 was sourced from a CIHI 2019 report.[19]) All patients who transitioned to death were assumed to incur terminal care costs of $86,582.31 during the last cycle before death.[20] The inpatient length of stay per cycle, the number of red blood cell transfusions per cycle and number of platelet transfusion per cycle were sourced from the key opinion leader. Monitoring costs were mostly obtained from the Ontario Schedule of Benefits for Physician Services and the Schedule of Benefits for Laboratory Services.[21] The Ontario Care Costing Initiative (OCCI) was also used to retrieve the procedure costs for bone marrow aspirates and biopsies. The cost per adverse event for both outpatient and inpatient adverse event management was obtained from the OCCI.[22] All of these costs were inflated to 2020 Canadian dollars using the all-item Consumer Price Index.

Summary of Sponsor's Economic Evaluation Results

The sponsor presented probabilistic analyses (5,000 iterations for the base case).

Base-Case Results

In the sponsor's base-case analysis for the overall population, BSC was found to have the lowest expected cost ($39,324), but also the lowest expected QALYs (0.58). The cost-effectiveness efficiency frontier included LDAC and venetoclax plus azacitidine but not azacitidine monotherapy, since azacitidine was found to be costlier and less effective than LDAC and was therefore dominated by LDAC. Compared with BSC, LDAC costs an extra $58,582 per expected QALY gained while, compared with LDAC, venetoclax plus azacitidine costs an expected extra $105,286 per QALY gained.

The initial treatment costs were the key cost driver for venetoclax plus azacitidine and azacitidine (63% and 55% of total costs respectively), while medical costs were the key cost drivers for LDAC and BSC (79% and 91% of total costs respectively). Medical costs, particularly in the PD/RL health state, were also a major cost driver for venetoclax plus azacitidine (17% of total costs), since patients on venetoclax plus azacitidine experienced longer OS compared with other treatment options. Consequently, patients in the venetoclax plus azacitidine arm experienced more QALYs than the comparators (2.53 QALYs for

venetoclax plus azacitidine compared with 0.58 to 0.94 QALYs for the other treatments). At a WTP threshold of $50,000 per QALY, there was a 0% probability that venetoclax plus azacitidine is cost-effective compared with LDAC. The probability that venetoclax plus azacitidine is cost-effective compared with azacitidine monotherapy at this threshold was also 0%.

Additional results from the sponsor's submitted economic evaluation base case are presented in Appendix 4 (Table 11).

Sensitivity and Scenario Analysis Results

The sponsor conducted a subgroup analysis on the subgroup of patients with a bone marrow blast count of between 20% and 30% and patients with a blast count greater than 30%. The incremental cost per QALY gained for venetoclax plus azacitidine when compared with azacitidine in the 20% to 30% subgroup analysis was $85,091 per QALY. In the greater than 30% subgroup analysis, azacitidine was dominated, and the incremental cost per QALY gained for venetoclax plus azacitidine when compared with LDAC was $96,294 per QALY. The sponsor performed scenario analyses related to the duration of treatment, the inclusion of cure assumption, and time horizon. The results of these analyses are presented in Appendix 4 (Table 12).

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **Exclusion of intensive chemotherapy as a comparator:** The model submitted by the sponsor did not include intensive chemotherapy as a comparator. The indication consisted of individuals newly diagnosed with AML who are 75 years or older or who have comorbidities that preclude the use of intensive chemotherapy. The sponsor stated that patients over age 75 would by definition be ineligible for intensive chemotherapy. However, according to clinical experts' feedback, a notable proportion of patients (upward of 30%) aged 75 or older would receive intensive chemotherapy in Canada. The pivotal trial data excluded people who were eligible for intensive chemotherapy; consequently, the cost-effectiveness of venetoclax plus azacitidine compared with intensive chemotherapy remains unknown.
    - CADTH was unable to address this limitation in its reanalysis.
- **Cure assumption for those who remain in the CR + CRi state for more than 5 years:** The sponsor's model assumed that individuals who remain in CR + CRi for more than 5

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Best supportive care	39,324	0.58	Reference
Low-dose cytarabine	60,259	0.94	58,582 vs. best supportive care
Azacitidine	95,629	0.88	Dominated by low-dose cytarabine
Venetoclax plus azacitidine	227,691	2.53	105,286 vs. low-dose cytarabine

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[5]

Note: Dominated refers to a treatment having a higher total cost and lower total QALYs when compared with the previous less costly treatment.

years are cured and are only at risk of dying from causes unrelated to the disease. Clinical experts indicated this is not likely to be the case, as individuals in clinical practice can still relapse and die from the disease after 5 years.

  - As a response to this limitation, CADTH revised the base case with the assumption that individuals need to remain in the CR + CRi for 10 years before being considered "cured."

- **Modelling approach produces biased estimate of incremental QALYs:** In the submission, individuals who receive venetoclax plus azacitidine and survive for more than a year exit the EFS health state and are no longer on first-line treatment. The QALY benefits observed in venetoclax plus azacitidine after EFS (0.84 QALYs in the PD/RL health state) are comparable to the total QALY estimates for azacitidine, LDAC, and BSC (0.88, 0.94, and 0.58 total QALYs, respectively). CADTH asked the sponsor to provide clinical evidence supporting the implied post-event benefit of first-line venetoclax plus azacitidine. CADTH's Clinical Review team and clinical experts evaluated the response from the sponsor, and concluded there was insufficient evidence to justify the 0.84 QALYs accrued after progression or relapsed disease in the venetoclax plus azacitidine arm.
  - To address this limitation, CADTH revised the base case by selecting Weibull as the survival distribution for venetoclax plus azacitidine OS. The Weibull distribution was selected by first limiting the candidate survival distributions for venetoclax plus azacitidine OS to those whose life-years after EFS were less than 1 (Weibull and exponential). From these 2 curves, the Weibull distribution was selected based on fit estimates (BIC and AIC). As a scenario analysis, CADTH considered the exponential distribution for OS in the venetoclax plus azacitidine arm.
- **EFS and duration of first-line treatment estimated independently:** The sponsor's model estimates time receiving first-line treatment and time in the event-free state independently. This is likely to be incorrect for 2 reasons. First, in the sponsor's definition of EFS, if an individual experienced treatment failure, they would no longer be in EFS. Second, time spent on treatment and the risk of PD/RL are likely to be correlated. One consequence of independently estimating and extrapolating the risk of ending treatment and the risk of disease progression is that individuals in the model can be considered off treatment but remain in the EFS state for unrealistic durations. Conversely, for some iterations of the probabilistic analysis, patients could be on treatment and in the PD/RL health state if values from the EFS parameters are randomly drawn in such a way that the mean EFS is lower than the mean duration of first-line treatment. This limitation has 2 possible effects: a possible bias on the extrapolated outcomes, and an effect on the uncertainty associated with both the EFS and the treatment-related parameter.
  - CADTH conducted a scenario analysis in which patients were assumed to remain on treatment if they were in the EFS health state (i.e., duration of treatment was assumed to be equal to EFS).
- **Uncertainty surrounding the extrapolation of parametric survival models:** Due to the limited follow-up and sample size of the VIALE-A trial, efficacy was estimated beyond the trial period. The uncertainty associated with the selection of parametric distribution for all survival probabilities in the model was not explored in the submission.
  - CADTH conducted a scenario analysis where the second best–fitting curves (according to BIC) for all distributions of all comparators was used instead.

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (See Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Gamma distribution not considered.	The sponsor did not implement the gamma distribution in the submitted model. CADTH was not able to assess the impact of not including that distribution on the outcomes of the economic analysis. However, the gamma distribution did not provide the best-fitting curve according to BIC or AIC for any of the treatments.
The EFS was artificially restricted such that it remained under OS. This is a by-product of OS and EFS being independently modelled.	When a partitioned survival model is used, the OS and EFS curves are typically modelled independently. In situations where either of the 2 probabilities is non-zero by the end of the trial follow-up, this assumption is particularly problematic, as it can result in biased estimates. The bias is amplified in the context of a probabilistic analysis where restrictions that are introduced in the model, such as the EFS being artificially restricted to be lower than OS, can amplify the bias. This is a structural assumption shared by all partitioned survival models.
The sponsor did not define what BSC consisted of in the submission.	This limits the usefulness of the model with regard to the comparator arm in decision-making. However, experts agreed that BSC is an unlikely treatment option.
Incomplete administration costs.	According to the product monograph, treatment with venetoclax requires preparatory steps, including anti-hyperuricemic drugs, cytoreduction before treatment, assessment and monitoring of blood chemistry, and laboratory monitoring. These additional steps are associated with additional administration costs. The sponsor's model assumed the administration costs for venetoclax were limited to pharmacy dispensing fees and physician monitoring for chemotherapy regimens. This is likely to underestimate the initial treatment costs for venetoclax and the estimates of the cost-effectiveness of venetoclax plus azacitidine as a result.
The sponsor did not consider an alternative reference treatment when estimating the OS under BSC using NMA input.	When estimating an absolute effect size (e.g., probability of event) using estimates from an NMA, a reference treatment needs to be assumed. In the submitted model, the reference treatment when estimating BSC OS was assumed to be venetoclax plus azacitidine. However, the choice of venetoclax plus azacitidine as a reference treatment is arbitrary. Ideally, the sponsor would want to assess the sensitivity of the results on that reference treatment assumption by choosing a different reference treatment. However, the sponsor did not conduct such a sensitivity analysis on this assumption.
Hospitalization costs were accrued based on time in state, not on treatment-specific.effects	The sponsor assumed that hospitalizations were dependent on time in a specific health state, not treatment-specific risks of inpatient hospitalization. However, experts agreed there is limited evidence on the inpatient hospitalization risks for the treatments considered.
Did not consider vial sharing.	The sponsor assumed no vial sharing, generating uncertainty in the treatment cost estimates.

AIC = Akaike information criterion; BIC = Bayesian information criterion; BSC = best supportive care; EFS = event-free survival; NMA = network meta-analysis; OS = overall survival.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

To address limitations identified within the economic model, the CADTH base case was derived by making changes in model parameter values and assumptions, in consultation with clinical experts (Table 5).

CADTH's base-case results for the main population are presented in Table 6 and stepped reanalysis in Table 13. Disaggregated results of the CADTH reanalysis are presented in Table 14. In CADTH's base case, venetoclax plus azacitidine was associated with the highest total discounted costs ($205,367) and QALYs (1.97) over the lifetime time horizon. According to the sequential analysis, BSC is preferred for WTP thresholds below $72,232, LDAC for WTP thresholds of between $72,232 and $125,580, and venetoclax plus azacitidine for WTP thresholds above $125,580. Azacitidine was extendedly dominated by LDAC and venetoclax plus azacitidine. The probability that venetoclax plus azacitidine was a cost-effective strategy compared with LDAC was 0% at a WTP threshold of $50,000 per QALY. In the CADTH base case, 44% of the QALYs were accrued after the duration of the VIALE-A trial for venetoclax plus azacitidine (0.87 QALYs).

CADTH did not consider any subgroup analysis, given the minimal differences in the point estimates of the identified subgroups.

Scenario Analysis Results

Price-reduction analyses were conducted using both the sponsor and CADTH base case (Table 7). In the price-reduction scenarios, CADTH varied the price of venetoclax, keeping the price of azacitidine constant. Within the CADTH base case and the sponsors base case, there was no price reduction that resulted in venetoclax plus azacitidine being considered cost-effective at a WTP threshold of $50,000 per QALY. This is due to the cost of combination therapy and the long duration of first-line treatment for individuals who receive venetoclax plus azacitidine. In particular, the significant cost of azacitidine implied that even if venetoclax was offered at a price of $0, the cost of combination therapy would not be low enough for venetoclax plus azacitidine to be considered cost-effective at a WTP threshold of $50,000 per QALY. Exploratory price-reduction analyses were performed to estimate the necessary

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
LDAC drug-acquisition costs: The sponsor used a lower drug cost for LDAC based on an expired wholesale price. CADTH has selected the available pricing in the IQVIA database for the concentration of LDAC based on its product monograph (100 mg/mL).		
Changes to derive the CADTH base case		
1. Cure assumption for those who remain in the CR + CRi state for more than 5 years	Cure assumption for those who remain in the CR + CRi state for more than 5 years.	Cure assumption for those who remain in the CR + CRi state for more than 10 years.
2. Substantial benefit of venetoclax plus azacitidine occurring after EFS	OS distribution for venetoclax plus azacitidine: Log-normal	OS distribution for venetoclax plus azacitidine (Weibull)
CADTH base case	Combined revisions 1 + 2	

CR + CRi = complete remission plus complete remission with incomplete blood count recovery; EFS = event-free-survival; LDAC = low-dose cytarabine; OS = overall survival.

price reduction to reach a $50,000 per QALY threshold for the combination of venetoclax plus azacitidine (72%), and the additional reduction of the azacitidine price (45%) if the price of venetoclax were reduced by 100%.

CADTH also performed a set of scenario analyses. The scenarios included selecting the exponential distribution for venetoclax plus azacitidine OS, assuming that all patients in the EFS state were on active therapy, using the second best–fitting OS and EFS curves (according to BIC). Additionally, CADTH conducted exploratory analyses considering venetoclax plus LDAC as a comparator as well as using a shortened time horizon. Detailed results are presented in Appendix 4 (Table 15).

Based on the sequential analysis, all the scenarios considered altered the ICER for venetoclax plus azacitidine versus other comparators. The 2 largest impacts were assuming that all

Table 6: Summary of the CADTH Reanalysis Results

Drug	Total costs ($)	Total QALYs	ICER vs. BSC ($/QALY)	Sequential ICER ($/QALY)
CADTH base case				
BSC	36,180	0.52	Reference	Reference
LDAC	53,588	0.76	72,232	72,232 vs. BSC
Venetoclax plus azacitidine	205,367	1.97	116,680	125,580 vs. LDAC
Azacitidine	95,659	0.87	169,939	Extendedly dominated

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LDAC = low-dose cytarabine; QALY = quality-adjusted life-year.
Note: Reanalyses are based on publicly available prices of the comparator treatments.

Table 7: CADTH Price-Reduction Analyses

ICERs for venetoclax plus azacitidine vs. comparators	ICERs for venetoclax plus azacitidine vs. LDAC ($/QALY)	
Price reduction (%)	**Sponsor base case ($)**	**CADTH reanalysis ($)**
No price reduction	103,995	131,933
10	100,021	126,227
20	96,048	120,521
30	92,074	114,816
40	88,101	109,110
50	84,128	103,404
60	80,154	97,699
70	76,181	91,993
80	72,208	86,287
90	68,234	80,582
100	64,261	74,876

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LDAC = low-dose cytarabine; QALY = quality-adjusted life-year.
Note: Only non-dominated strategies are presented. Reanalyses are based on publicly available prices for the comparator treatments.

individuals who are in the EFS health state were on first-line treatment (ICER for venetoclax plus azacitidine versus LDAC = $273,764 per QALY) and setting the model time horizon equal to that of the VIALE-A trial (ICER for venetoclax plus azacitidine versus azacitidine = $411,828 per QALY).

Taken together, the findings within the CADTH base-case reanalysis and scenario analyses suggest that in the absence of long-term data, the cost-effectiveness of venetoclax plus azacitidine remains highly uncertain. The CADTH base-case and scenario results suggest that the magnitude of incremental effectiveness appears to be driven by 2 principal factors: the benefit of venetoclax plus azacitidine after EFS, and the duration an individual can remain in the EFS health state while being off treatment. The model findings were sensitive to changes in the parametric extrapolation assumptions for OS and EFS, as seen by the second best–fit scenario analysis. In particular, although most of the distributions for OS and EFS that were implemented in the submitted model fitted the observed data well, they diverged considerably in extrapolations beyond the trial follow-up time. The distributional assumptions made by CADTH ensured that post-event survival is similar between strategies, since an assumption of a post-event survival benefit for venetoclax plus azacitidine was not supported by the submitted evidence or by the clinical feedback from experts consulted by CADTH.

Issues for Consideration

- CADTH is currently evaluating venetoclax in combination with LDAC. These 2 reviews were conducted independently; however, if both venetoclax plus azacitidine and venetoclax plus LDAC are approved, they would be considered comparators. An exploratory analysis was conducted to estimate the cost-effectiveness of venetoclax plus azacitidine if venetoclax plus LDAC were available as a comparator, but these results are subject to limitations within the efficacy evidence in the VIALE-C trial that are not discussed within this report.

Overall Conclusions

Based on the CADTH Clinical Review of the VIALE-A study results and a sponsor-submitted indirect treatment comparison, treatment with venetoclax plus azacitidine increased OS and EFS compared with LDAC and BSC among patients with newly diagnosed AML who have comorbidities that preclude the use of intensive induction chemotherapy over the trial's follow-up (median 20 months). The extrapolated difference in EFS and OS between venetoclax plus azacitidine and both LDAC and BSC were the key drivers of incremental effectiveness in the economic analysis. The duration of first-line treatment was a key driver of costs in the economic analysis. The CADTH Clinical Review found that the OS benefit beyond progression that was observed in the economic analysis is not supported by evidence or clinical experience. Intensive chemotherapy was excluded as a comparator, despite the indication from clinical experts that a notable proportion (upward of 30%) of those 75 years or older would receive intensive chemotherapy in Canada.

CADTH undertook reanalyses to address limitations with the sponsor's submission. These reanalyses included: a different assumption on the functional form of the OS probability for venetoclax plus azacitidine (Weibull distribution) that limits the benefit of venetoclax plus azacitidine post EFS, and changing the sponsor's assumption of disease being cured for those who remain in the CR + CRi health state from 5 years to 10 years. In the CADTH base case, BSC, LDAC, and venetoclax plus azacitidine were considered optimal treatments (i.e., on the cost-effectiveness efficiency frontier). The results of the CADTH reanalysis were broadly aligned with the sponsor's submission. Venetoclax plus azacitidine was more effective and

more costly than LDAC (incremental QALY: 1.21; incremental cost: $151,779), with an ICER of $125,580 per QALY. The probability that venetoclax plus azacitidine was cost-effective at a $50,000 WTP threshold compared with LDAC was 0%. There was no price reduction at which venetoclax plus azacitidine was cost-effective compared with LDAC at a WTP threshold of $50,000 per QALY, due to the cost of combination therapy and the long duration of first-line treatment. The probability that venetoclax plus azacitidine is cost-effective compared with azacitidine monotherapy at this threshold was also 0%.

The CADTH base-case results are associated with substantial uncertainty for multiple reasons. First, the modelling approach followed by the sponsor did not address the dependence between EFS and treatment duration. This, in turn, resulted in uncertainty in the extrapolation of the treatment duration. The sponsor provided limited evidence on the probability of stopping treatment over time, so CADTH was not able to adequately assess what the duration of treatment would be. In a scenario analysis where individuals were assumed to be on treatment throughout the EFS, the ICER of venetoclax plus azacitidine versus LDAC increased to $273,764 per QALY.

The model had several further limitations that prevented CADTH from estimating an unbiased estimate of cost-effectiveness. The exclusion of intensive chemotherapy as a comparator and the benefit accrued after EFS, as noted earlier, provided insufficient clinical evidence to support such a finding. The EFS and OS were estimated independently, which likely resulted in unrealistic scenarios in the extrapolation of the model (e.g., EFS probability > OS probability). Taken together, these findings suggest the cost-effectiveness results were driven primarily by assumptions about the relationship between time to treatment discontinuation, EFS, and OS, which were uncertain within the trial data.

The cost-effectiveness of venetoclax plus azacitidine compared with intensive chemotherapy is unknown.

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Appendix 1: Cost Comparison Table

Note that this appendix has not been copy-edited.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s) and drug plans. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Acute Myeloid Leukemia

Treatment	Strength/ concentration	Form	Price ($)	Recommended dosage	28-day cycle cost ($)	Average annual cost ($)
Venetoclax (VENCLEXTA) + low-dose cytarabine (CYTOBAR)						
Venetoclax (Venclexta)[b]	**10 mg** **50 mg** **100 mg**	**Tablet**	**7.0000[a]** **35.0000[a]** **70.0000[a]**	**100 mg on day 1; 200 mg on day 2; 400 mg on day 3; 400 mg on day 4 and onward**	**Cycle 1: 7,490** **Cycle 2+: 7,840**	**101,850 to 102,200**
Azacitidine[b,c]	**100 mg**	**Vial for powdered suspension**	**599.9900** **(5.9999 per mg)**	**75 mg/m² on days 1 to 7**	**8,400**	**109,498**
Venetoclax + azacitidine					**Cycle 1: 15,890** **Cycle 2+: 16,240**	**211,348**
Non-intensive chemotherapies						
Azacitadine[c]	100 mg	Powdered suspension	599.9900 (5.9999 per mg)	75 mg/m² daily for days 1 to 7	8,400	109,498
Low-dose cytarabine[d]	100 mg/mL (5 mL vial)	Injectable solution	76.8500 (15.37 per mL)	20 mg/m², days 1 to 10	769	10,018
	100 mg/mL (20 mL vial)	Injectable solution	306.5000 (15.3250 per mL)			
Induction therapy (7 + 3)[e]						
Cytarabine	100 mg/mL (5 mL vial)	Injectable solution	76.8500 (15.37 per mL)	100 mg/m², days 1 to 7 200 mg/m², days 1 to 7 [f]	538	NA
	100 mg/mL (20 mL vial)	Injectable solution	306.5000 (15.3250 per mL)			
Daunorubicin	20 mg	Powdered solution	91.0000	60 mg/m² IV days 1 to 3[e]	1,638	NA
Idarubicin	1 mg/mL (5 mL vial)	IV solution	211.5200 (42.304 per mL)	12 mg/m² on days 1, 2, and 3[e,f]	3,173	NA
7 + 3 induction therapy (cytarabine 100 or 200 mg/m² + daunorubicin 60 mg/m²)[f]					2,176	NA
7 + 3 induction therapy (cytarabine 200 mg/m² + idarubicin 12mg/m²)[f]					3,711	NA

Treatment	Strength/ concentration	Form	Price ($)	Recommended dosage	28-day cycle cost ($)	Average annual cost ($)
FLAG-IDA (first-line and salvage therapy)						
Filgrastim	0.30 mg/0.5 mL	Pre-filled syringe	144.3135 (per 0.5 mL pre-filled syringe)	0.30 mg days 1 to 4	577	7,525
	0.30 mg/mL	Vial	176.1330			
	0.480 mg/0.8 mL	Pre-filled syringe	230.9000 230.9017			
	0.480 mg/1.6 mL	Vial	230.9000			
	0.600 mg/mL	Vial	352.2650 (mL in 10 × 0.8 mL pen) 352.2660 (mL in 10 × 0.5 mL pen)			
Idarubicin	1 mg/mL (5 mL vial)	IV solution	211.5200 (42.3040 per mL)	10 mg/m^2 days 1 to 2	1,692	22,059
Fludarabine	10 mg	Tablet	40.0760[h]	30 mg/m^2 days 1 to 4	962	12,538
Cytarabine	100 mg/mL (5 mL vial)	Injectable solution	76.8500 (15.37 per mL)	2,000 mg/m^2 days 1 to 4	2,452	31,964
	100 mg/mL (20 mL vial)	Injectable solution	306.5000 (15.3250 per mL)			
FLAG-IDA (first-line and salvage therapy)					5,683	74,082

AML = acute myeloid leukemia; FLAG = fludarabine, cytarabine, granulocyte colony-stimulating factor; FLAG-IDA = fludarabine, cytarabine, granulocyte colony-stimulating factor plus idarubicin; LDAC = low-dose cytarabine; NA = not applicable (due to being a single cycle for induction —see regimen monograph).

Note: All prices are from the IQVIA (DeltaPA database) (accessed March 26, 2021), unless otherwise indicated, and do not include dispensing fees. Where applicable, assumes 1.81 m^2 and no vial sharing.

[a]Sponsor-submitted price.

[b]Based on 28-day cycles as per the Venclexta product monograph.[6]

[c]Azacitidine product monograph.[23]

[d]Cytarabine dosing as per British Columbia Cancer Agency protocol.[24]

[e]3 + 7 protocol as per Cancer Care Ontario.[25]

[f]As per clinical expert input from CADTH's review of Vyxeos.

[g]Every 28 days as per Cancer Care Ontario regimen monograph FLAG-IDA.[26]

[h]Price obtained from the Ontario Drug Benefit Formulary.[27]

Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

Table 9: Submission Quality

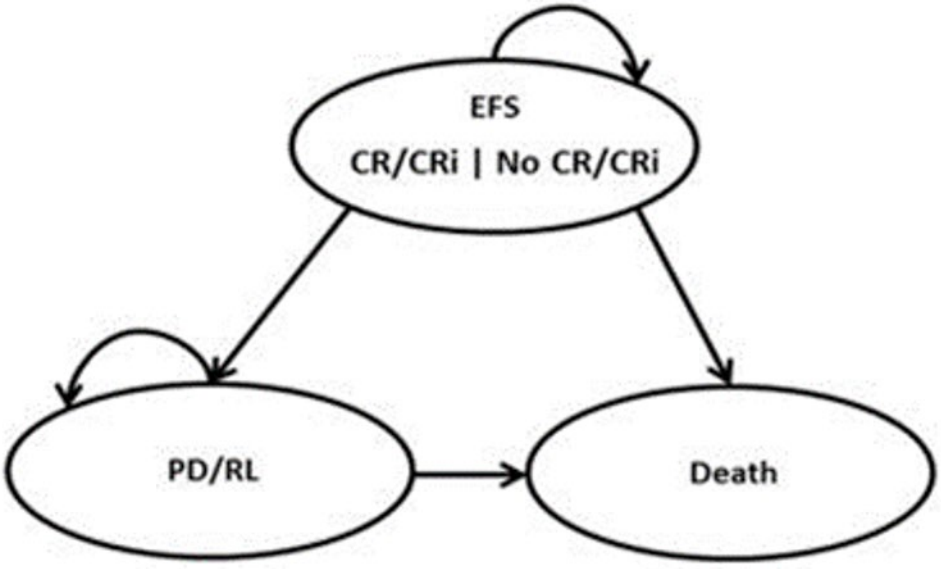
Description	Yes/No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	No	Model population does not match reimbursement request. The reimbursement request is for venetoclax plus azacitidine for newly diagnosed AML who are 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. The modelled population was patients who are newly diagnosed with AML for whom IC is unsuitable. The model excludes IC as a comparator. Clinical experts indicated that those over the age of 75 would be eligible to receive IC.
Model has been adequately programmed and has sufficient face validity	No	The sponsor used numerous IFERROR statements in their model. IFERROR statements lead to situations in which the parameter value is overwritten with an alternative value without alerting the user to the automatized overwriting. The systematic use of IFERROR statements makes thorough auditing of the sponsor's model impossible, as it remains unclear whether the model is running inappropriately by overriding errors. Best programming practices are such that any errors alert the user to a specific error.
Model structure is adequate for decision problem	No	The PSM has a structural assumption that EFS and OS are independent, this can result in substantial benefits after individuals have exited the event-free state and are no longer on first-line treatment.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	Yes	NA
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	Yes	NA
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough detail)	Yes	NA

AML = acute myeloid leukemia; EFS = event-free survival; IC = intensive chemotherapy; OS = overall survival; PSM = partitioned survival model; NA = not applicable

Appendix 3: Additional Information on the Submitted Economic Evaluation

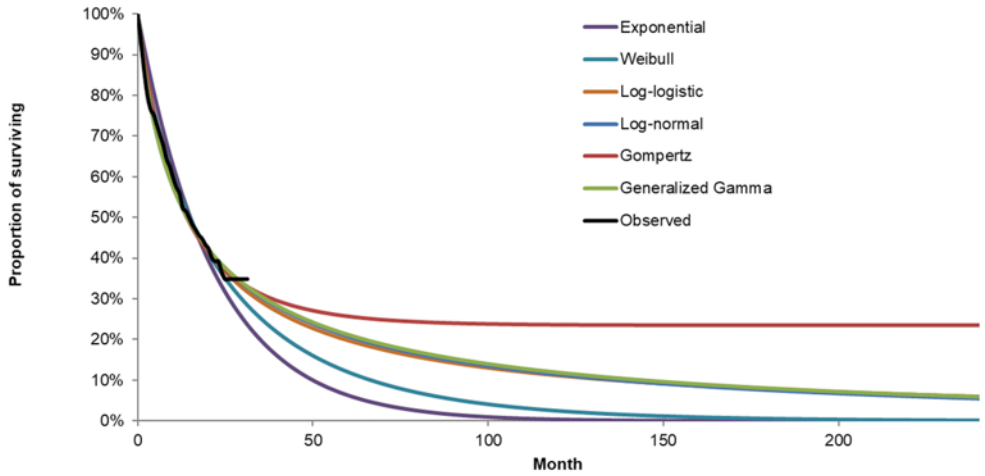
Note that this appendix has not been copy-edited.

Figure 1: Model Structure



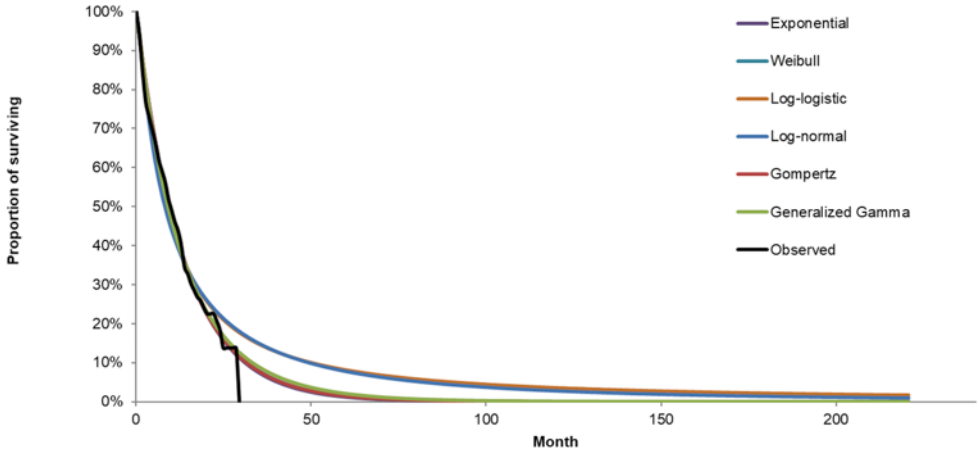
Source: Sponsor's economic submission.[5]

Figure 2: Observed and Extrapolated Event-Free Survival — Venetoclax Plus Azacitidine



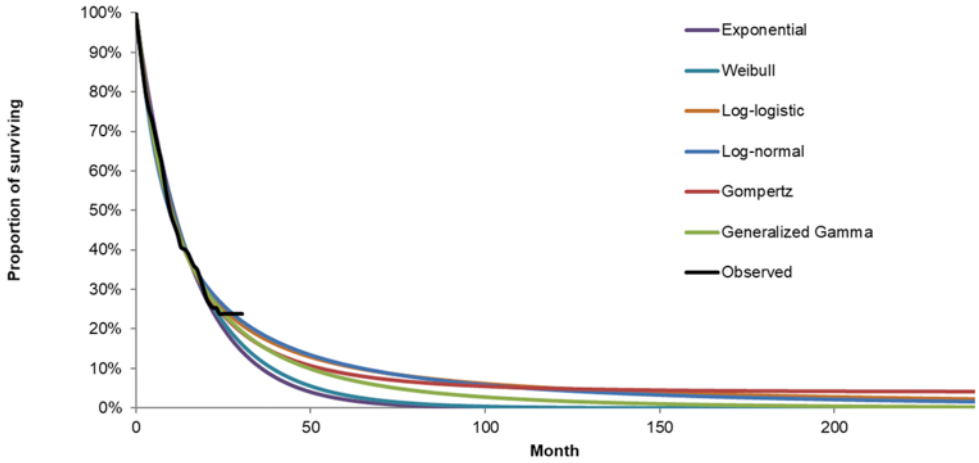
Source: Sponsor's economic submission.[5]

Figure 3: Observed and Extrapolated Event-Free Survival: Azacitidine



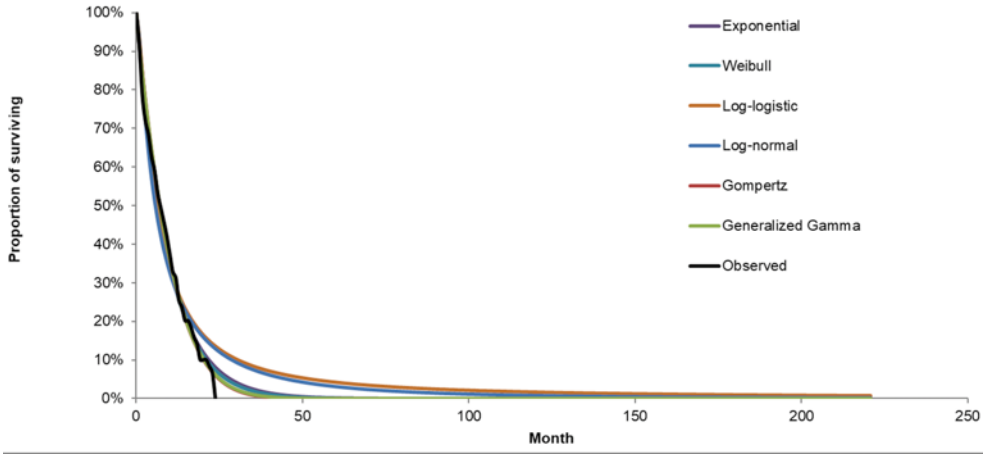
Source: Sponsor's economic submission.[5]

Figure 4: Observed and Extrapolated Event-Free Survival — Venetoclax Plus Azacitidine



Source: Sponsor's economic submission.[5]

Figure 5: Observed and Extrapolated Event-Free Survival: Azacitidine



Source: Sponsor's economic submission.[5]

Table 10: Total Drug-Acquisition and Administration Cost per Treatment

Treatment	Median treatment duration (cycle)	Source of treatment duration	Drug and administration costs for the first cycle ($)	Drug and administration costs for subsequent cycles ($)
VEN-AZA	8.26	VIALE-A trial[84]	12,627.20	12,780.92
AZA	4.67	VIALE-A trial[84]	8,449.85	8,449.85
LDAC	1.85	VIALE-A trial[84]	1,441.82	1,441.82

AZA = azacitidine; LDAC = low-dose cytarabine; VEN-AZA = venetoclax in combination with azacitidine.

Table 11: Disaggregated Summary of Sponsor's Submitted Economic Evaluation Results

Treatment	Component	Value	Incremental (vs. BSC)
Discounted LY			
BSC	Event-free survival	0.32	NA
	PD/RL	0.44	NA
	Total LYs	0.75	NA
LDAC	Event-free survival	0.52	0.20
	PD/RL	0.62	0.18
	Total LYs	1.14	0.39
VEN-AZA	Event-free survival	1.77	1.45
	PD/RL	0.89	0.45
	Total LYs	2.66	1.91

Treatment	Component	Value	Incremental (vs. BSC)
AZA	Event-free survival	0.80	0.48
	PD/RL	0.32	−0.12
	Total LYs	1.12	0.37
Discounted QALYs			
BSC	Event-free survival with CR/CRi	0.00	NA
	Event-free survival without CR/CRi	0.25	NA
	PD/RL	0.32	NA
	Total QALYs	0.57	NA
LDAC	Event-free survival with CR/CRi	0.06	0.06
	Event-free survival without CR/CRi	0.36	0.11
	PD/RL	0.45	0.13
	Total QALYs	0.87	0.3
VEN-AZA	Event-free survival with CR/CRi	0.91	0.91
	Event-free survival without CR/CRi	0.52	0.27
	PD/RL	0.65	0.33
	Total QALYs	2.07	1.50
AZA	Event-free survival with CR/CRi	0.16	0.16
	Event-free survival without CR/CRi	0.48	0.23
	PD/RL	0.23	−0.09
	Total QALYs	0.87	0.30
Discounted costs ($)			
BSC	Initial treatment costs	0	NA
	Subsequent treatment costs	880	NA
	Subsequent HSCT costs	0	NA
	Adverse event	2,599	NA
	Medical costs	35,492	NA
	Total costs	38,972	NA
LDAC	Initial treatment costs	3,117	3,117
	Subsequent treatment costs	4,837	3,957
	Subsequent HSCT costs	0	0
	Adverse event costs	4,496	1,897
	Medical costs	45,033	9,541
	Total costs	57,484	18,512

Treatment	Component	Value	Incremental (vs. BSC)
VEN-AZA	Initial treatment costs	144,001	144,001
	Subsequent treatment costs	369	−511
	Subsequent HSCT costs	1,296	1,296
	Adverse event costs	5,743	3,144
	Medical costs	64,170	28,678
	Total costs	215,579	176,607
AZA	Initial treatment costs	52,414	52,414
	Subsequent treatment costs	831	−49
	Subsequent HSCT costs	1,294	1,294
	Adverse event costs	3,743	1,144
	Medical costs	37,320	1,828
	Total costs	95,603	56,631
		Sequential ICER ($/QALY)	**ICER vs. SOC ($/QALY)**
BSC		Reference	Reference
LDAC		61,707 vs. BSC	61,707
VEN-AZA		131,746 vs. LDAC	117,738
AZA		Extendedly dominated	188,770

AZA = azacitidine; HSCT = hematopoietic stem cell transplant; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; VEN-AZA = venetoclax in combination with azacitidine; vs. = versus ; NA = not applicable

Table 12: Sponsor's Submitted Scenario Analysis Results

Scenario		ICER for LDAC vs. BSC ($/QALY)	ICER for AZA vs. BSC ($/QALY)	ICER for VEN-AZA vs. BSC ($/QALY)
Base case		61,707	188,770	117,738
1	Median treatment duration	66,636	Dominated	98,807
2	Excluding cure assumption	60,206	Dominated	108, 374
3	10-year time horizon	61,774	Extendedly dominated	131,640

AZA = azacitidine; BSC = best supportive care; CR = complete remission; ICER = incremental cost-effectiveness ratio; LDAC = low-dose cytarabine; QALY = quality-adjusted life-year; VEN = venetoclax; vs. = versus .

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has not been copy-edited.

Detailed Results of the CADTH Base Case

Table 13: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Scenario	Drug	Total costs ($)	Total QALYs	Sequential ICER ($/QALY)
Sponsor's base case	BSC	39,324	0.58	Reference
	LDAC	60,259	0.94	58,582 vs. BSC
	VEN-AZA	227,691	2.53	105,286 vs. LDAC
	AZA	95,629	0.88	Dominated
1. Cure assumption = 10 year	BSC	39,119	0.58	Reference
	LDAC	61,477	0.93	64,494 vs. BSC
	VEN-AZA	232,333	2.54	105,796 vs. LDAC
	AZA	95,659	0.87	Dominated
2. OS VEN-AZA Weibull distribution	BSC	36,180	0.52	Reference
	LDAC	53,478	0.76	71,617 vs. BSC
	VEN-AZA	203,857	2.02	119,775 vs. LDAC
	AZA	95,641	0.88	Extendedly dominated
3. CADTH base case (1 + 2)	BSC	36,180	0.52	Reference
	LDAC	53,588	0.76	72,232 vs. BSC
	VEN-AZA	205,367	1.97	125,580 vs. LDAC
	AZA	95,659	0.87	Extendedly dominated

AZA = azacitidine; BSC = best supportive care ICER = incremental cost-effectiveness ratio; LDAC = low-dose cytarabine; LY = life-year; OS = overall survival; QALY = quality-adjusted life-year; Reference = this treatment was used as the reference; VEN-AZA = venetoclax in combination with azacitidine; vs. = versus.

Table 14: Disaggregated Summary of CADTH's Economic Evaluation Results

Treatment	Component	Value	Incremental (vs. BSC)
Discounted LY			
BSC	Event-free survival	0.32	NA
	PD/RL	0.36	NA
	Total LYs	0.67	NA
LDAC	Event-free survival	0.53	0.21
	PD/RL	0.46	0.10
	Total LYs	0.98	0.31

Treatment	Component	Value	Incremental (vs. BSC)
VEN-AZA	Event-free survival	2.00	1.68
	PD/RL	0.49	0.14
	Total LYs	2.49	1.82
AZA	Event-free survival	0.79	0.47
	PD/RL	0.33	−0.03
	Total LYs	1.12	0.45
Discounted QALYs			
BSC	Event-free survival with CR/CRi	0.00	NA
	Event-free survival without CR/CRi	0.25	NA
	PD/RL	0.26	NA
	Total QALYs	0.52	NA
LDAC	Event-free survival with CR/CRi	0.05	0.05
	Event-free survival without CR/CRi	0.37	0.11
	PD/RL	0.34	0.07
	Total QALYs	0.76	0.24
VEN-AZA	Event-free survival with CR/CRi	1.03	1.03
	Event-free survival without CR/CRi	0.58	0.32
	PD/RL	0.36	0.10
	Total QALYs	1.97	1.45
AZA	Event-free survival with CR/CRi	0.16	0.16
	Event-free survival without CR/CRi	0.47	0.22
	PD/RL	0.24	−0.02
	Total QALYs	0.87	0.36
Discounted costs ($)			
BSC	Initial treatment costs	$0	NA
	Subsequent treatment costs	$892	NA
	Subsequent HSCT costs	$0	NA
	Adverse event costs associated with initial treatment	$2,612	NA
	Medical costs	$32,676	NA
	Total costs	$36,180	NA

Treatment	Component	Value	Incremental (vs. BSC)
LDAC	Initial treatment costs	$4,648	$4,648
	Subsequent treatment costs	$4,887	$3,995
	Subsequent HSCT costs	$0	$0
	Adverse event costs associated with initial treatment	$4,537	$1,925
	Medical costs	$39,516	$6,839
	Total costs	$53,588	$17,408
VEN-AZA	Initial treatment costs	$144,002	$144,002
	Subsequent treatment costs	$387	$-505
	Subsequent HSCT costs	$1,304	$1,304
	Adverse event costs associated with initial treatment	$5,708	$3,096
	Medical costs	$53,965	$21,288
	Total costs	$205,367	$169,186
AZA	Initial treatment costs	$52,414	$52,414
	Subsequent treatment costs	$833	$-58
	Subsequent HSCT costs	$1,306	$1,306
	Adverse event costs associated with initial treatment	$3,716	$1,104
	Medical costs	$37,389	$4,712
	Total costs	$95,659	$59,479
		Sequential ICER ($/QALY)	**ICER vs. BSC ($/QALY)**
BSC		Reference	Ref.
LDAC		$72,232 vs. BSC	$72,532
VEN-AZA		$125,580 vs. LDAC	$116,680
AZA		Extendedly dominated	$169,939

AZA = azacitidine; BSC = best supportive care; EFS = event-free-survival; HSCT = hematopoietic stem cell transplant; ICER = incremental cost-effectiveness ratio; LDAC = low-dose cytarabine; LY = life-year; OS = overall survival; QALY = quality-adjusted life-year; VEN-AZA = venetoclax in combination with azacytidine; NA = not applicable.

Scenario Analyses

Table 15: Summary of the CADTH Scenario Analysis

Scenario		Drug	Sequential ICER ($/QALY)
1	VEN-AZA OS survival estimate: Exponential not Weibull.	BSC	—
		LDAC	$76,594
		VEN-AZA	$133,637
		AZA	Extendedly dominated

Scenario		Drug	Sequential ICER ($/QALY)
2	For all treatments, time on first-line treatments is the same as time event-free.	BSC	—
		LDAC	$114,062
		VEN-AZA	$273,764
		AZA	Extendedly dominated
3	Second best–fitting curves according to BIC (except for VEN-AZA consider only subset of candidate curves which generate < 1 LY benefit post EFS). PFS exponential for VEN-AZA and AZA. OS: Weibull VEN-AZA, exponential VEN.	BSC	—
		LDAC	$74,875
		VEN-AZA	$168,363
		AZA	Extendedly dominated

AZA = azacitidine; BIC = Bayesian information criterion; BSC = best supportive care; EFS = event-free survival; ICER = incremental cost-effectiveness ratio; LDAC = low-dose cytarabine; LY = life-year; OS = overall survival; QALY = quality-adjusted life-year; VEN-AZA = venetoclax in combination with azacitidine.

Additionally, CADTH conducted 2 exploratory scenario analyses. The first set the model time horizon to that of the pivotal trial to quantify the amount of health and cost outcomes incurred during that period. The second exploratory analysis included venetoclax in combination with LDAC as a comparator, as CADTH experts indicated there may be potential overlap in the population that would receive either venetoclax plus azacitidine or venetoclax plus LDAC. The results of these analyses are presented below.

Table 16: Summary of the CADTH Exploratory Analyses

Exploratory Scenario		Drug	Sequential ICER ($/QALY)
1	Considering VEN + LDAC a comparator.	BSC	—
		VEN + LDAC	$62,231 vs. BSC
		VEN-AZA	$180,591 vs. VEN-LDAC
		LDAC	Extendedly dominated
		AZA	Dominated
2	Time horizon is equal to that of the pivotal trial (2 years).	BSC	—
		LDAC	$95,159
		AZA	$282,233
		VEN-AZA	$411,827

AZA = azacitidine; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LDAC = low-dose cytarabine; LY = life-year; QALY = quality-adjusted life-year; VEN-AZA = venetoclax in combination with azacitidine; VEN-LDAC = venetoclax in combination with LDAC vs. = versus .

Appendix 5: Submitted Budget Impact Analyses and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 17: Summary of Key Takeaways

Key Takeaways of the BIA

• CADTH identified the following key limitations with the sponsor's analysis:
  ◦ There was uncertainty with several epidemiological inputs used to derive the market size.
  ◦ The sponsor's market share uptake assumptions of venetoclax in the new drug scenario does not reflect the expectations of the clinical experts consulted for this review. The estimated market shares remain uncertain with the potential availability of venetoclax in combination with low-dose cytarabine.
• The CADTH reanalyses included revising market share estimates for venetoclax in the new drug scenario, revising the epidemiological inputs to derive the market size, allowing for drug wastage; removing patient co-payments, and aligning BIA model inputs to those applied in the pharmacoeconomic analysis.
• Based on the CADTH reanalysis, the budget impact from the venetoclax in combination with azacitidine would result in an incremental budget impact of $16,784,064 in year 1, $21,182,961 in year 2, and $32,039,516 in year 3, for a total budget impact of $70,006,541. The results were primarily driven by the market share uptake of venetoclax plus azacitidine, number of patients eligible for treatment, and proportion of patients ineligible for induction chemotherapy.

Summary of Sponsor's BIA

In the submitted budget impact analysis (BIA), the sponsor assessed the venetoclax in combination with azacitidine (VEN-AZA)for adults with newly diagnosed AML who are 75 years or older, or who are between the ages of 18 and 74 who have comorbidities that preclude the use of intensive induction chemotherapy.[28] The BIA was undertaken from the perspective of the public health care payer in the Canadian setting (excluding Quebec) over a 3-year time horizon.[28] In the reference scenario, the sponsor assumed that these patients would be eligible to receive either azacytidine monotherapy, or LDAC. In the new drug scenario, (VEN-AZA) was assumed to displace market share from azacitidine monotherapy.[28]

By leveraging data from multiple sources in the literature and assumptions based on clinical expert input, the sponsor estimated the eligible population size using an epidemiological approach. Only drug-acquisition costs were considered, and no drug wastage was assumed for azacitidine monotherapy and LDAC.[28]

Key inputs to the BIA are documented in Table 18.

Table 18: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Target population	
Incidence	0.004%
Proportion ineligible for induction chemotherapy	50%
Percentage of patients aged less than 65 years	12%
Percentage of patients aged less than 65 years, covered by public drug plans	58.9%
Percentage of patients aged 65 years and over	88%

Parameter	Sponsor's estimate (reported as year 1 / year 2 / year 3 if appropriate)
Percentage of patients aged 65 years and over, covered by public drug plans	100%
Number of patients eligible for drug under review	544 / 552 / 559
Market Uptake (3 years)	
Uptake (reference scenario)	83.8% / 83.8% / 83.8%
Azacitidine monotherapy	9.5% / 9.5% / 9.5%
LDAC	4.8% / 4.8% / 4.8%
BSC	1.9% / 1.9% / 1.9%
Other	
Uptake (new drug scenario)	20.0% / 40.0% / 55.0%
VEN + AZA Azacitidine monotherapy	63.8% / 43.8% / 28.8%
LDAC	9.5% / 9.5% / 9.5%
BSC	4.8% / 4.8% / 4.8%
Other	1.9% / 1.9% / 1.9%
Cost of treatment (per patient)	
Cost of treatment per treatment course[a]	$84,008.40
Venetoclax plus azacitidine	$42,735.06
Azacitidine monotherapy	$356.53
LDAC	$0
BSC	$0
Other	

BSC = best supportive care; LDAC = low-dose cytarabine.

[a]Based on mean number of treatment cycles, as per the sponsor's base case.[28]

Summary of the Sponsor's BIA Results

Results of the sponsor's base-case analysis suggested that venetoclax in combination with azacitidine (VEN + AZA) in patients with newly diagnosed AML who are 75 years or older, or who are between the ages of 18 and 74 who have comorbidities that preclude the use of intensive induction chemotherapy would result in incremental costs of $11,367,049 in year 1, $23,043,115 in year 2, $32,114,958 in year 3, for a total incremental cost of $66,525,123 over the 3-year time horizon.[28]

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Exclusion of relevant comparators:** As per the Health Canada indication and the sponsor's submitted reimbursement request, the submitted pharmacoeconomic model for VEN-AZA is indicated for the treatment of patients with newly diagnosed AML who are 75 years or older, or who are between the ages of 18 and 74 who have comorbidities that preclude the use of intensive induction chemotherapy. Feedback from clinical experts consulted by CADTH for this review indicates that induction chemotherapy is a common first-line treatment option for AML patients over the age of 75. These experts estimated that as many as 50% of patients 75 years or older would likely receive intensive chemotherapy if Venclexta-based approaches were not available. As such, CADTH considers intensive chemotherapy a relevant comparator for both combination treatments: venetoclax plus azacitidine and venetoclax plus LDAC.
  - CADTH was unable to address this limitation.

- **Uncertainty in the uptake of venetoclax in combination with azacitidine: The** sponsor anticipated that VEN + AZA would capture 20%, 40%, and 55% of the market share distribution in years 1, 2, and 3, by displacing market share only from patients receiving azacitidine monotherapy. CADTH's clinical experts noted uncertainty in the uptake rate of VEN + AZA, as they expected a higher uptake across all 3 years. Uncertainty was further raised regarding the market share distribution of in a world where venetoclax plus LDAC was also publicly funded.
  - CADTH addressed this limitation by revising the market share uptake of venetoclax plus azacitidine to 40% in year 1, 50% in year 2, and 75% in year 3.
- **Uncertainty regarding the number of patients eligible to receive venetoclax in combination with azacitidine:** The sponsor used an epidemiological approach to identify the patient population eligible to receive VEN-AZA which resulted in a total number of 544, 552, and 559 patients in years 1, 2, and 3, respectively. The clinical experts consulted by CADTH indicated that these numbers appeared to be lower than expected, and they noted several areas of uncertainty with the estimates and assumptions used to derive the market size. First, the sponsor used an incident approach and did not consider prevalence statistics as part of their methodological approach to estimating the market size, which would include the proportion of patients who are currently being treated for the condition and eligible for the treatment (i.e., those who are currently on azacitidine or LDAC). Second, the sponsor assumed that approximately 59% of patients less than 65 years of age who would be eligible for publicly funded coverage across Canada, however, CADTH's clinical experts expressed their uncertainty with this estimate, noting that they felt it was high. Lastly, the sponsor assumed that approximately 50% of patients would be ineligible for induction chemotherapy, however, CADTH's clinical experts noted that this was likely overestimated since approximately 10% of patients over the age of 75 are expected to receive induction chemotherapy in Canadian clinical practice rather than none. As such, approximately 10% fewer newly diagnosed patients with AML were expected to be ineligible to receive induction chemotherapy, and a range of 30% to 50% of patients may be ineligible.
  - CADTH partially addressed this limitation by revising the proportion of newly diagnosed patients who were ineligible for induction chemotherapy to 40%. In a scenario analysis, CADTH explored the assumption that (i) 30% and (ii) 50% of newly diagnosed patients were ineligible for induction chemotherapy. To further address the uncertainty in the estimated market size, CADTH conducted scenario analyses to decrease the proportion of patients less than the age of 65 years covered by public drug plans by 10%, and varied the target population by plus or minus 10%.
- **Misalignment of drug cost inputs between the sponsor-submitted pharmacoeconomic and budget impact analyses:** Several drug cost inputs affecting cost calculations in the sponsor-submitted BIA did not align with drug cost inputs in the pharmacoeconomic analysis. First, the sponsor applied a cost for LDAC based on an expired wholesale price in the IQVIA database rather than based on the available wholesale price aligned with the concentration in the product monograph for cytarabine for injection. To align with CADTH's cost comparison table, the price for LDAC was corrected to reflect available pricing, at $76.85 per vial. Second, while sponsor appropriate assumed drug wastage in the pharmacoeconomic analysis (i.e., no vial sharing for both, azacitidine monotherapy and LDAC), in contrast, vial sharing was assumed in the BIA. Drug wastage should be assumed for IV treatments as it is unlikely for patients to share vials, and without accounting for drug wastage, the total daily cost for these comparator treatments would be underestimated. Third, the dosing schedule for LDAC in the submitted BIA was based on a dose of 100 mg/m^2 rather than 20 mg/m^2 as in the pharmacoeconomic analysis, and the median time on treatment was selected in the pharmacoeconomic analysis to extrapolate time on treatment over the model time horizon rather than the mean time on treatment. The dose for LDAC was adjusted to reflect the dosing schedule in the pharmacoeconomic analysis, and the median time on treatment was further selected rather than mean time on treatment.
  - CADTH addressed this limitation by correcting the cost of LDAC, assuming drug wastage for the comparator regimens, and selecting the median time on treatment to calculate treatment duration.

CADTH Reanalyses of the BIA

A table noting the changes made to the sponsor's BIA as part of CADTH's reanalysis is available in Table 19.

Table 19: CADTH Revisions to the Submitted BIA

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Market share estimates in the new drug scenario (across years 1 to 3)	VEN-AZA: 20% / 40% / 55% AZA: 63.8% / 43.8% / 28.8% LDAC: 9.5% / 9.5% / 9.5% BSC: 4.8% / 4.8% / 4.8% Other: 1.9% / 1.9% / 1.9%	VEN + AZA: 40% / 50% / 75% AZA: 45.7% / 35.7% / 10.7% LDAC: 9.5% / 9.5% / 9.5% BSC: 4.8% / 4.8% / 4.8% Other: 0.0% / 0.0% / 0.0%
2. Approach to derive market size	Proportion of newly diagnosed patients ineligible for induction chemotherapy = 50%	Proportion of newly diagnosed patients ineligible for induction chemotherapy = 40%
3. Alignment of drug cost inputs	a. Lower cost of LDAC = $6.75 per mL (20 mg/mL in 5 mL vial) b. Drug wastage = excluded c. Daily dose of LDAC = 100 mg/m^2 d. Time on treatment based on the mean treatment duration	a. Cost of LDAC = $76.85 per vial (or $15.37 per mL [100 mg/mL in 5 mL vial]) b. Drug wastage = included c. Daily dose of LDAC = 20 mg/m^2 d. Time on treatment revised to reflect the median treatment duration
CADTH base case	**Reanalysis 1 + 2 + 3**	

AZA = azacitidine; BSC = best supportive care; LDAC = low-dose cytarabine.

The results of the CADTH stepwise reanalysis are presented in summary format in Table 20 and Table 21.

Table 20: Summary of the CADTH Reanalyses of the BIA

Stepped analysis	Three-year total ($)
Submitted base case	66,525,123
CADTH reanalysis 1	96,678,220
CADTH reanalysis 2	53,220,098
CADTH reanalysis 3	60,204,555
CADTH base case	70,006,541

BIA = budget impact analysis.

CADTH also conducted additional scenario analyses to address the remaining uncertainty regarding the potential size of the eligible population:

1. Assumed fewer patients less than the age of 65 years may be eligible for public drug plan coverage by decreasing the proportion by (a) 10% and (b) 25%.
2. Assumed that (a) 30% and (b) 50% of newly diagnosed AML patients may be ineligible for induction chemotherapy.
3. Explored the impact of varying the estimated market size by +/− 10%.
4. Assumed that the treatment duration was reflected by the mean time on treatment to calculate drug-acquisition costs.
5. Applied a price reduction of 72% for venetoclax and a price reduction of 72% for azacitidine.

Table 21: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation) ($)	Year 1 ($)	Year 2 ($)	Year 3 ($)	Three-year total ($)
Submitted base case	Reference	19,248,209	19,509,844	19,775,036	20,043,831	59,328,711
	New drug	19,248,209	30,876,893	42,818,151	52,158,790	125,853,834
	Budget impact	0	11,367,049	23,043,115	32,114,958	66,525,123
CADTH base case	Reference	14,156,118	14,348,538	14,543,573	14,741,259	43,633,370
	New drug	14,156,118	31,132,602	35,726,534	46,780,775	113,639,911
	Budget impact	0	16,784,064	21,182,961	32,039,516	70,006,541
CADTH scenario analysis 1a	Reference	13,977,486	14,167,477	14,360,051	14,555,243	43,082,772
	New drug	13,977,486	30,739,748	35,275,710	46,190,461	112,205,919
	Budget impact	0	16,572,270	20,915,659	31,635,218	69,123,147
CADTH scenario analysis 1b	Reference	13,709,486	13,895,835	14,084,717	14,276,166	42,256,718
	New drug	13,709,486	30,150,354	34,599,346	45,304,821	110,054,521
	Budget impact	0	16,254,519	20,514,629	31,028,655	67,797,803
CADTH scenario analysis 2a	Reference	10,617,089	10,761,403	10,907,680	11,055,944	32,725,027
	New drug	10,617,089	23,349,451	26,794,901	35,085,581	85,229,933
	Budget impact	0	12,588,048	15,887,221	24,029,637	52,504,906
CADTH scenario analysis 2b	Reference	17,695,148	17,935,672	18,179,466	18,426,574	54,541,712
	New drug	17,695,148	38,915,752	44,658,168	58,475,969	142,049,889
	Budget impact	0	20,980,080	26,478,702	40,049,395	87,508,176
CADTH scenario analysis 3 (+ 10%)	Reference	14,156,118	15,783,392	15,997,930	16,215,385	47,996,707
	New drug	14,156,118	34,245,862	39,299,188	51,458,852	125,003,902
	Budget impact	0	18,462,470	23,301,257	35,243,467	77,007,195
CADTH scenario analysis 4 (−10%)	Reference	14,156,118	12,913,684	13,089,216	13,267,133	39,270,033
	New drug	14,156,118	28,019,342	32,153,881	42,102,697	102,275,920
	Budget impact	0	15,105,658	19,064,665	28,835,564	63,005,887
CADTH scenario analysis 5	Reference	22,103,496	22,403,942	22,708,472	23,017,141	68,129,555
	New drug	22,103,496	32,259,906	42,688,338	50,862,879	125,811,122
	Budget impact	0	9,855,964	19,979,866	27,845,738	57,681,568
CADTH scenario analysis	Reference	14,156,118	14,348,538	14,543,573	14,741,259	43,633,370
	New drug	14,156,118	14,371,483	14,490,350	14,493,514	43,355,347
	Budget impact	0	22,945	−53,223	−247,745	−278,023

BIA = budget impact analysis.