Indication: VENCLEXTA is indicated in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude the use of intensive induction chemotherapy.

NEW OVERALL SURVIVAL DATA

IN A PHASE 3 TRIAL

VENCLEXTA + AZACITIDINE WAS PROVEN TO HELP

1L AML PATIENTS LIVE LONGER

Median Overall Survival[1]

95% CI: (11.9, 18.7)

95% CI: (7.4, 12.7)

OS: HR=0.66; 95% CI: (0.52, 0.85); *P*<0.001

VIALE-A: A randomized (2:1), double-blind, placebo-controlled, multicenter, phase 3 study that evaluated the efficacy and safety of VENCLEXTA in combination with azacitidine (VEN+AZA; N=286) vs placebo with azacitidine (PBO+AZA; N=145) in adults with newly diagnosed AML who were ≥75 years of age, or had comorbidities that precluded the use of intensive induction chemotherapy.

1L=first line; OS=overall survival; CI=confidence interval; HR=hazard ratio.

Important Safety Information

Tumor Lysis Syndrome

- Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA.
- In patients with AML who followed the current 3-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 1.1% in patients who received VENCLEXTA in combination with azacitidine. In patients with AML who followed a 4-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 5.6% and included deaths and renal failure in patients who received VENCLEXTA in combination with low-dose cytarabine.
- VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase.
- The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function further increases the risk.
- Assess patients for TLS risk and provide appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases.
- Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during the ramp-up phase, and requires VENCLEXTA dose adjustment.

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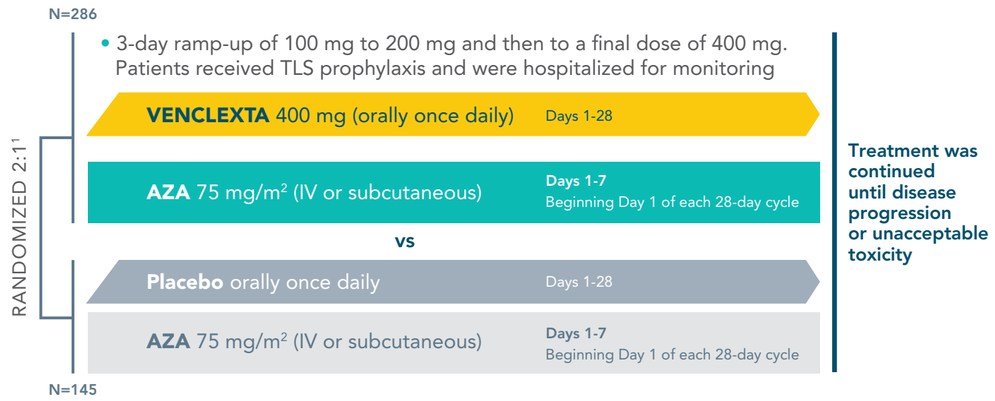
Efficacy and safety of VENCLEXTA + azacitidine (VEN+AZA) was evaluated in a pivotal phase 3 trial[1,2]

VIALE-A studied newly diagnosed AML patients who were ≥75 years of age or had comorbidities that precluded the use of intensive induction chemotherapy[1]

- Randomized (2:1), double-blind, placebo-controlled, multicenter, phase 3 study[1,2]



Comorbidities based on at least one of the following criteria[1]:

- Baseline ECOG performance status of 2-3
- Severe cardiac or pulmonary comorbidity
- Moderate hepatic impairment
- CLcr <45 mL/min
- Other comorbidities

Select clinical endpoints[1-3]

- **Primary endpoint:** overall survival
- **Select secondary endpoints:** CR, CR+CRh, CR+CRh by initiation of Cycle 2

Efficacy was based on overall survival (OS), measured from the date of randomization to death from any cause[1]

CR was defined as absolute neutrophil count (ANC) >1,000/microliter, platelets >100,000/microliter, RBC transfusion independence, and bone marrow with <5% blasts. Absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease.[1]

CRh was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).[1]

TLS=tumor lysis syndrome; IV=intravenous; ECOG=Eastern Cooperative Oncology Group; CLcr=creatinine clearance; CR=complete remission; CRh=complete remission with partial hematologic recovery; RBC=red blood cell.

Important Safety Information

Neutropenia

- In patients with AML, baseline neutrophil counts worsened in 95% to 100% of patients treated with VENCLEXTA in combination with azacitidine or decitabine or low-dose cytarabine. Neutropenia can recur with subsequent cycles.
- Monitor complete blood counts throughout the treatment period. For severe neutropenia, interrupt dosing or reduce duration based on remission status and occurrence. Consider supportive measures including antimicrobials and growth factors (e.g., G-CSF).

VIALE-A included patients with various comorbidities and different mutational and cytogenetic profiles, including *IDH1/2* and *FLT3*[1,2]

Select baseline characteristics for patients treated in the VIALE-A trial[1,2]

76
MEDIAN AGE[1]

~45%
ECOG 2-3[2]

100%
INTERMEDIATE OR POOR CYTOGENETIC RISK[1]

Additional baseline characteristics[1]

Characteristic	VEN+AZA (N=286)	PBO+AZA (N=145)
Age, years; median (range)	76 (49, 91)	76 (60, 90)
Race; %		
White	76	75
Black or African American	1	1.4
Asian	23	23
Male; %	60	60
ECOG performance status; %		
0-1	55	56
2	40	41
3	5.6	3.4
Bone marrow blast; %		
<30%	30	28
≥30% to <50%	21	23
≥50%	49	49
Disease history; %		
De novo AML	75	76
Secondary AML	25	24
Cytogenetic risk detected*; %		
Intermediate	64	61
Poor	36	39
Mutation analyses detected; n/N† (%)		
IDH1 or *IDH2*	61/245 (25)	28/127 (22)
IDH1	23/245 (9.4)	11/127 (8.7)
IDH2	40/245 (16)	18/127 (14)
FLT3	29/206 (14)	22/108 (20)
NPM1	27/163 (17)	17/86 (20)
TP53	38/163 (23)	14/86 (16)

*Per the 2016 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®).
†Number of evaluable bone marrow aspirate (BMA) specimens received at baseline.

IDH=isocitrate dehydrogenase; *FLT*=fms-like tyrosine kinase; *NPM*=nucleophosmin; *TP53*=tumor protein p53.

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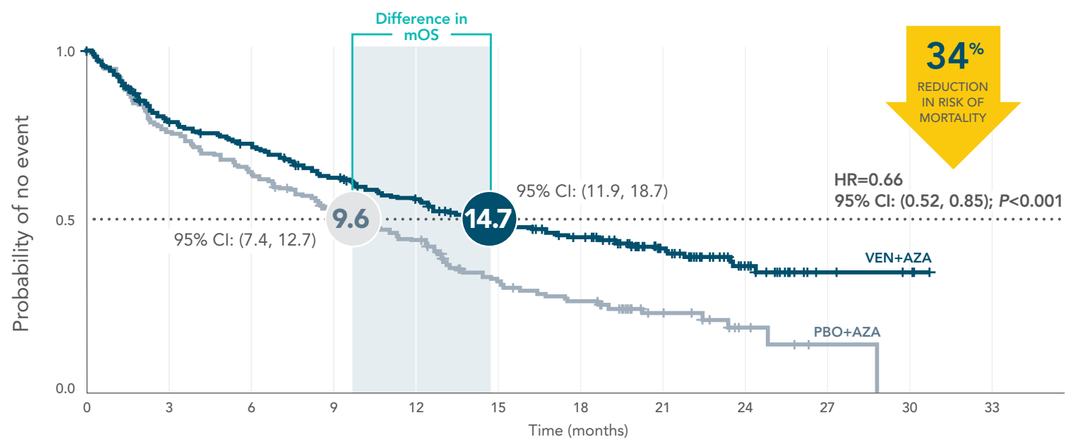
VEN+AZA demonstrated superior overall survival vs PBO+AZA[1]

PRIMARY ENDPOINT: OVERALL SURVIVAL[1]

Median OS was extended by 5.1 months in patients treated with VEN+AZA vs PBO+AZA[1]



Number of patients at risk

VEN+AZA	286	219	198	168	143	117	101	54	23	5	3
PBO+AZA	145	109	92	74	59	38	30	14	5	1	

- Median follow-up for OS was approximately 20.5 months (range: <0.1-30.7 months)[2]
  - Median follow-up was estimated using reverse Kaplan-Meier methodology

mOS=median overall survival.

Important Safety Information

Infections

- Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with VENCLEXTA. Monitor patients for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 infection until resolution and resume at same or reduced dose based on occurrence.

Immunization

- Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. Advise patients that vaccinations may be less effective.

Embryo-Fetal Toxicity

- VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for at least 30 days after the last dose.

Increased Mortality in Patients with Multiple Myeloma when VENCLEXTA is Added to Bortezomib and Dexamethasone

- In a randomized trial (BELLINI; NCT02755597) in patients with relapsed or refractory multiple myeloma, the addition of VENCLEXTA to bortezomib plus dexamethasone, a use for which VENCLEXTA is not indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with VENCLEXTA in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

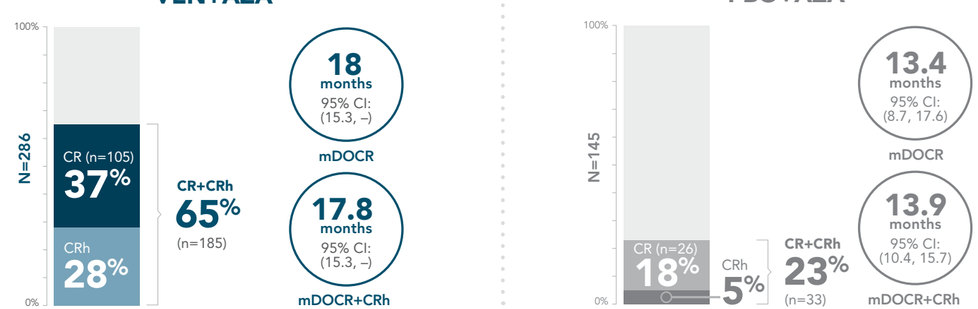
Adverse Reactions

- **In patients with AML receiving combination therapy with azacitidine,** the most frequent serious adverse reactions (≥5%) were febrile neutropenia (30%), pneumonia (22%), sepsis (excluding fungal; 19%), and hemorrhage (6%). The most common adverse reactions (≥30%) of any grade were neutrophils decreased (98%), platelets decreased (94%), lymphocytes decreased (91%), hemoglobin decreased (61%), nausea (44%), diarrhea (43%), febrile neutropenia (42%), musculoskeletal pain (36%), pneumonia (33%), fatigue (31%), and vomiting (30%). Fatal adverse reactions occurred in 23% of patients who received VENCLEXTA in combination with azacitidine, with the most frequent (≥2%) being pneumonia (4%), sepsis (excluding fungal; 3%), and hemorrhage (2%).

Almost 3× more remissions, longer mDOR, and greater transfusion independence observed with VEN+AZA vs PBO+AZA[1]

SECONDARY ENDPOINTS: CR, CR+CRh[1,2]

Powerful, durable remissions[1]



- CR, 95% CI: (31, 43); *P*<0.001
- CR+CRh, 95% CI: (59, 70); *P*<0.001

- CR, 95% CI: (12, 25)
- CR+CRh, 95% CI: (16, 30)

TRANSFUSION INDEPENDENCE CONVERSION, TRANSFUSION INDEPENDENCE MAINTENANCE[1]

Greater transfusion independence conversion and/or maintenance rates were observed with VEN+AZA vs PBO+AZA

Transfusion independence conversion (conversion from dependent to independent)

VEN+AZA	PBO+AZA
49%	27%
(76/155)	(22/81)

RBC and PLATELET

Patients were dependent on RBC and/or platelet transfusions at baseline

Transfusion independence maintenance (independent from baseline to post-baseline period)

VEN+AZA	PBO+AZA
69%	42%
(90/131)	(27/64)

RBC and PLATELET

Patients were independent of both RBC and platelet transfusions at baseline

DOCR (duration of CR) is defined as the number of days from the date of first response of CR to the date of earliest evidence of confirmed morphologic relapse, confirmed progressive disease, or death due to disease progression.[1]

DOCR+CRh (duration of CR+CRh) is defined as the number of days from the date of first response of CR+CRh (the first of either CR or CRh) to the date of earliest evidence of confirmed morphologic relapse, confirmed progressive disease, or death due to disease progression.[1]

Transfusion independence was defined as no RBC and platelet transfusion during any consecutive ≥56-day post-baseline period.[1]

Transfusion dependence is defined as RBC counts for hemoglobin ≤7-8 g/dL or per institutional guidelines or symptoms of anemia; platelets for patients with platelets <10,000/microliter or with any signs of bleeding.[4]

mDOR=median duration of response; mDOCR=median duration of complete remission; mDOCR+CRh=median duration of complete remission and complete remission with partial hematologic recovery; TI=transfusion independence.

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Overall survival outcomes in different mutational subgroups[2,3]

Overall survival was statistically significant in the consolidated *IDH1/IDH2* group of patients in the VEN+AZA arm[3]

- OS in *IDH1/IDH2* was a prespecified secondary endpoint

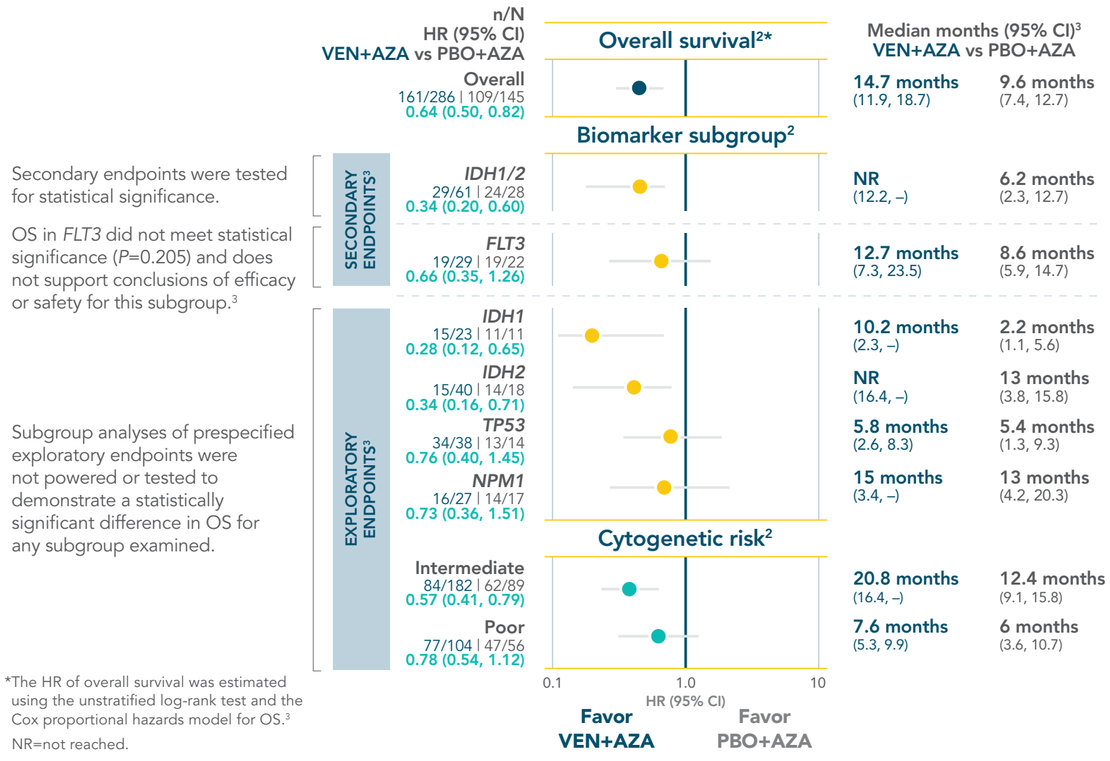
65%
REDUCTION IN RISK OF MORTALITY[2]

HR=0.35; 95% CI: (0.20, 0.60)
P<0.0001

- In the VEN+AZA arm, median OS in the *IDH1/IDH2* group (N=61) was not reached (95% CI: 12.2, –)[3]
- In the PBO+AZA arm, median OS in the *IDH1/IDH2* group (N=28) was 6.2 months (95% CI: 2.3, 12.7)[3]

Descriptive prespecified analysis of OS in secondary and exploratory endpoints[3]

- OS in the *IDH1/2* and *FLT3* subgroups was a prespecified secondary endpoint. Other select biomarker subgroups (*IDH1*, *IDH2*, *TP53*, and *NPM1*) and cytogenetic risk were prespecified exploratory endpoints[3]



Secondary endpoints were tested for statistical significance.

OS in *FLT3* did not meet statistical significance (*P*=0.205) and does not support conclusions of efficacy or safety for this subgroup.[3]

Subgroup analyses of prespecified exploratory endpoints were not powered or tested to demonstrate a statistically significant difference in OS for any subgroup examined.

*The HR of overall survival was estimated using the unstratified log-rank test and the Cox proportional hazards model for OS.[3]

NR=not reached.

Important Safety Information

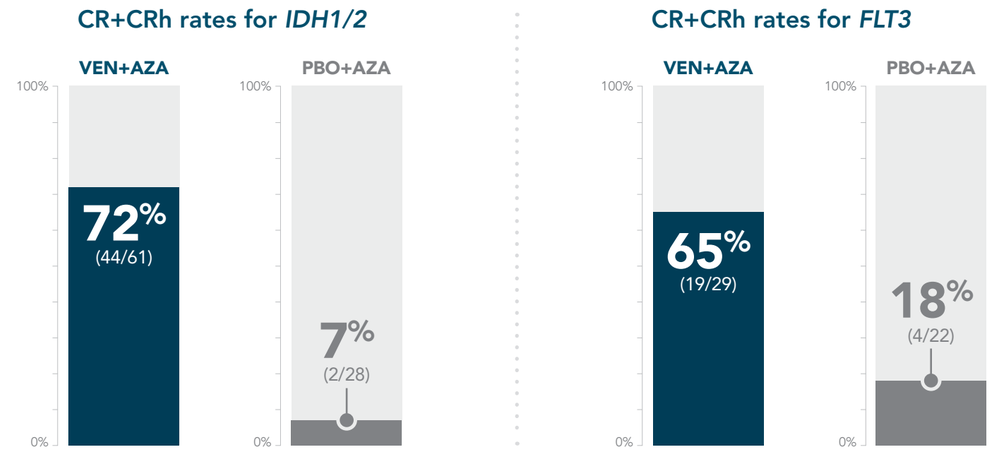
Drug Interactions

- Concomitant use with a P-gp inhibitor or a strong or moderate CYP3A inhibitor increases VENCLEXTA exposure, which may increase VENCLEXTA toxicities, including the risk of TLS. Consider alternative medications or adjust VENCLEXTA dosage and monitor more frequently for adverse reactions. Resume the VENCLEXTA dosage that was used prior to concomitant use of a P-gp inhibitor or a strong or moderate CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

Remission was achieved in different mutational subgroups, including *IDH1/2* and *FLT3*[3]

More than half of patients with an *IDH1/2* or *FLT3* mutation achieved remission in the VEN+AZA group

- CR+CRh rates for *IDH1/2* and *FLT3* were prespecified secondary endpoints



Important Safety Information

Drug Interactions (cont'd)

- Patients should avoid grapefruit products, Seville oranges, and starfruit during treatment as they contain inhibitors of CYP3A.
- Avoid concomitant use of strong or moderate CYP3A inducers.
- Avoid concomitant use of VENCLEXTA with a P-gp substrate. If concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA.
- Monitor international normalized ratio (INR) more frequently in patients receiving warfarin.

Lactation

- Advise nursing women not to breastfeed during treatment with VENCLEXTA and for 1 week after the last dose.

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A tolerable, manageable, and predictable adverse reaction profile[1]

No additional warnings or precautions for VENCLEXTA were observed in the AML trials

The safety profile of VEN+AZA was consistent with the known side effect profile of both agents

Adverse reactions (≥10%) in patients with AML who received VEN+AZA with a difference between arms of ≥5% for all grades or ≥2% for Grade 3 or 4 reactions compared with PBO+AZA*

Adverse reaction by body system					
		VEN+AZA (N=283)		PBO+AZA (N=144)	
Body system	**Adverse reaction**	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Gastrointestinal disorders	Nausea	44	2	35	<1
	Diarrhea†	43	5	33	3
	Vomiting†	30	2	23	<1
	Stomatitis†	18	1	13	0
	Abdominal pain†	18	<1	13	0
Blood and lymphatic system disorders	Febrile neutropenia	42	42	19	19
Musculoskeletal and connective tissue disorders	Musculoskeletal pain†	36	2	28	1
General disorders and administration site conditions	Fatigue†	31	6	23	2
	Edema†	27	<1	19	0
Vascular disorders	Hemorrhage†	27	7	24	3
	Hypotension†	12	5	8	3
Metabolism and nutrition disorders	Decreased appetite†	25	4	17	<1
Skin and subcutaneous tissue disorders	Rash†	25	1	15	0
Infections and infestations	Sepsis (excluding fungal)	22	22	16	14
	Urinary tract infection†	16	6	9	6
Respiratory, thoracic and mediastinal disorders	Dyspnea†	18	4	10	2
Nervous system disorders	Dizziness†	17	<1	8	<1

*Patients who received at least one dose of either treatment.
†Includes multiple adverse reaction terms.

Hematologic laboratory abnormalities

New or worsening Grade 3 or 4 hematologic laboratory abnormalities in VIALE-A ≥2% VEN+AZA compared with PBO+AZA, respectively: neutrophils decreased 98% vs 81%, platelets decreased 88% vs 80%, lymphocytes decreased 71% vs 39%, hemoglobin decreased 57% vs 52%.

Duration of exposure and occurrence of adverse reactions[1,2]

Patients maintained treatment with VEN+AZA for a median of 7.6 months[1]

Median duration of exposure

VEN+AZA[1]

7.6

months

(range: <0.1-30.7)

Median number of cycles

VEN+AZA[2]

7.0

cycles

(range: 1.0-30.0)

Rate of serious adverse reactions				
	VEN+AZA[1]		PBO+AZA[2]	
	(%) occurrence	Most frequent adverse reaction(s)	(%) occurrence	Most frequent adverse reaction(s)
Serious ARs	83	≥5%: febrile neutropenia (30%), pneumonia (22%), sepsis (excluding fungal; 19%), hemorrhage (6%)	73	≥5%: pneumonia (22%), febrile neutropenia (10%), sepsis (8%)
Fatal ARs	23	≥2%: pneumonia (4%), sepsis (excluding fungal; 3%), hemorrhage (2%)	–	–
Discontinuation, reduction, and interruption rates				
ARs leading to permanent drug discontinuation	24	≥2%: sepsis (excluding fungal; 3%), pneumonia (2%)	20	–
ARs leading to dose reductions	2	pneumonia (0.7%)	4	–
ARs leading to dose interruptions	72	≥5%: febrile neutropenia (20%), neutropenia (20%), pneumonia (14%), sepsis (excluding fungal; 11%), thrombocytopenia (10%)	57	–

- Among patients who achieved bone marrow clearance of leukemia, 53% underwent dose interruptions for ANC <500/microliter in the VEN+AZA arm[1]
- Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia, VENCLEXTA or placebo was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥50 × 10^3/microliter[1]
- Azacitidine was resumed on the same day as VENCLEXTA or placebo following interruption[1]
- Azacitidine dose reduction was implemented in the clinical trial for management of hematologic toxicity[1]

AR=adverse reaction.

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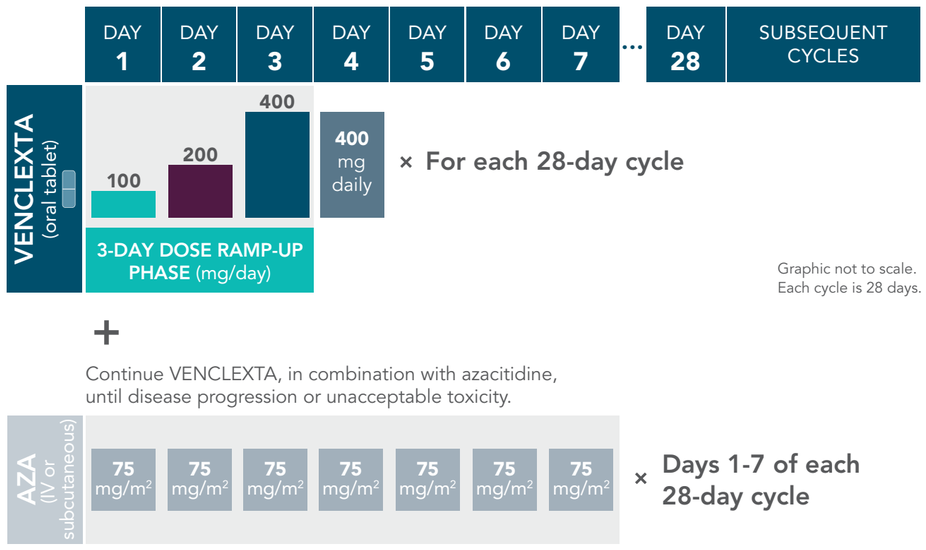
Dose ramp-up is designed to allow patients to safely attain the recommended daily dose[1]

- Assess patient-specific factors for level of risk of tumor lysis syndrome (TLS) and provide prophylactic hydration and anti-hyperuricemics to patients prior to first dose of VENCLEXTA to reduce risk of TLS
- Instruct patients to take VENCLEXTA tablets with a meal and water at approximately the same time each day. VENCLEXTA tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing

Pretreatment TLS risk assessment and prophylaxis

- All patients should have white blood cell count less than 25 × 10^9/L prior to initiation of VENCLEXTA. Cytoreduction prior to treatment may be required
- Prior to first VENCLEXTA dose, provide all patients with prophylactic measures including adequate hydration and anti-hyperuricemic agents and continue during ramp-up phase
- Assess blood chemistry and correct pre-existing abnormalities prior to initiation of treatment with VENCLEXTA
- Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during ramp-up, and 24 hours after reaching final dose
- For patients with risk factors for TLS, consider additional measures, including increased laboratory monitoring and reducing VENCLEXTA starting dose

VENCLEXTA is taken orally in combination with AZA



- If using VENCLEXTA in combination with decitabine, follow the dose ramp-up schedule for VENCLEXTA and administer decitabine at 20 mg/m^2 intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1, Day 1
- If using VENCLEXTA in combination with low-dose cytarabine, follow the dose ramp-up schedule for VENCLEXTA and administer cytarabine at 20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1, Day 1
- In patients with AML who followed the current 3-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 1.1% in patients who received VENCLEXTA in combination with azacitidine (VIALE-A). In patients with AML who followed a 4-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 5.6% and included deaths and renal failure in patients who received VENCLEXTA in combination with low-dose cytarabine (VIALE-C)

VENCLEXTA dose should be modified for concomitant use with certain medications[1,5,6]

VENCLEXTA is metabolized by the CYP3A enzyme; the dose should be reduced when used with P-gp inhibitors or strong or moderate CYP3A inhibitors

Dose modifications for managing potential interactions

Coadministered drug	Initiation and ramp-up phase	Steady daily dose after ramp-up phase
Posaconazole	Day 1: 10 mg Day 2: 20 mg Day 3: 50 mg Day 4: 70 mg	Reduce the VENCLEXTA dose to 70 mg
Other strong CYP3A inhibitor Clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, telaprevir, voriconazole*	Day 1: 10 mg Day 2: 20 mg Day 3: 50 mg Day 4: 100 mg	Reduce the VENCLEXTA dose to 100 mg
Moderate CYP3A inhibitor Aprepitant, ciprofloxacin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, verapamil*	Reduce the VENCLEXTA dose by at least 50%	
P-gp inhibitor Amiodarone, carvedilol, clarithromycin, cyclosporine, dronedarone, itraconazole, ketoconazole, quinidine, ranolazine, ritonavir, verapamil*		

- Adjust the VENCLEXTA dose and monitor more frequently for adverse reactions. Resume the VENCLEXTA dosage that was used prior to concomitant use of a strong or moderate CYP3A inhibitor or a P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor[1]
- Avoid grapefruit products, Seville oranges, and starfruit during treatment with VENCLEXTA, as they contain inhibitors of CYP3A[1]
- Concomitant use of VENCLEXTA with strong CYP3A inducers decreases VENCLEXTA exposure, which may decrease VENCLEXTA efficacy. Avoid concomitant use of VENCLEXTA with strong CYP3A inducers or moderate CYP3A inducers[1]
- Concomitant use of VENCLEXTA increases warfarin exposure, which may increase the risk of bleeding. Monitor international normalized ratio (INR) more frequently in patients using warfarin concomitantly with VENCLEXTA[1]
- Concomitant use of VENCLEXTA increases exposure of P-gp substrates, which may increase toxicities of these substrates. Avoid concomitant use of VENCLEXTA with a P-gp substrate. If concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA[1]

Dose modifications for patients with severe hepatic impairment[1]

- Reduce the VENCLEXTA once daily dose by 50% for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for adverse reactions

*This is not an exhaustive list and is intended only to complement, not replace, clinical judgment during treatment of patients with VENCLEXTA. Please refer to the FDA website for more examples.

CYP3A=cytochrome P450 3A; P-gp=P-glycoprotein.

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Responses for CR and CRh were reached at different times throughout treatment; management of Grade 4 neutropenia or thrombocytopenia may differ before and after remission is achieved[1]

In VIALE-A, bone marrow assessment was conducted following Cycle 1 treatment. Once bone marrow assessment confirmed a remission,* VENCLEXTA or placebo was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥50 × 10^3/microliter.

For patients with resistant disease at the end of Cycle 1, a bone marrow assessment was performed after Cycle 2 or 3 and as clinically indicated.[1]

Select secondary endpoints: CR, CR+CRh[1,2]

Endpoint	VEN+AZA (N=286)	PBO+AZA (N=145)
CR, n (%), (95% CI)	**105 (37), (31, 43)**	**26 (18), (12, 25)**
***P* value**	<0.001	
Median DOCR (months), (95% CI)	18 (15.3, –)	13.4 (8.7, 17.6)
CR+CRh, n (%), (95% CI)	**185 (65), (59, 70)**	**33 (23), (16, 30)**
***P* value**	<0.001	
Median DOCR+CRh (months), (95% CI)	17.8 (15.3, –)	13.9 (10.4, 15.7)

The median time to first response of CR or CRh was 1.0 months (range 0.6-14.3 months) with VEN+AZA treatment; some patients achieved CR/CRh in later cycles[1,3]

Secondary endpoint: CR+CRh by initiation of Cycle 2[3]

- **40%** (n=114/286) with VEN+AZA (95% CI: [34, 46]; *P*<0.001)

In an exploratory post hoc analysis of CR+CRh in the VEN+AZA ITT population[3]:

- **47%** (134/286) achieved CR+CRh by the beginning of Cycle 3
- **50%** (143/286) achieved CR+CRh by the beginning of Cycle 4

*Defined as less than 5% leukemia blasts with cytopenia.

ITT=intention to treat.

Important Safety Information

Females and Males of Reproductive Potential

- Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for at least 30 days after the last dose.
- Based on findings in animals, VENCLEXTA may impair male fertility.

Renal Impairment

- Patients with reduced renal function (CLcr <80 mL/min, calculated by Cockcroft-Gault formula) require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with VENCLEXTA.

Hepatic Impairment

- Reduce the dose of VENCLEXTA for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more frequently for signs of adverse reactions. No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Recommended dose modifications for cytopenias and non-hematologic adverse reactions in AML[1]

- Monitor blood counts frequently through resolution of cytopenias. Dose modification and interruptions for cytopenias are dependent on remission status

Managing Grade 4 neutropenia with or without fever or infection, or Grade 4 thrombocytopenia

Occurrence before remission*† is achieved	After remission*† is achieved: Occurrence lasting at least 7 days
STAY ON VENCLEXTA REGIMEN: In most instances, do not interrupt the VENCLEXTA regimen due to cytopenias	**DELAY** subsequent cycle of VENCLEXTA regimen and monitor blood counts **For 1st occurrence** **RESUME VENCLEXTA** therapy at 400 mg‡ in combination with azacitidine or decitabine upon resolution to Grade 1 or 2 and resume 28-day treatment cycle **For subsequent occurrences** **RESUME VENCLEXTA** therapy at 400 mg‡ in combination with azacitidine or decitabine upon resolution to Grade 1 or 2 and reduce treatment cycle by 7 days for each subsequent cycle *(eg, for 2nd occurrence, VENCLEXTA would be dosed for 21 days of a 28-day cycle)*

In an exploratory post hoc analysis:

- 75% of patients in remission (139/186) had at least 1 pause in dosing lasting 7+ days[3]

Non-Hematologic Adverse Reactions		
Grade 3 or 4 non-hematologic toxicities	Any occurrence	Interrupt VENCLEXTA if not resolved with supportive care. Upon resolution to Grade 1 or baseline level, resume VENCLEXTA at the same dose.

*Recommend bone marrow evaluation.
†Defined as <5% leukemia blasts with cytopenia.
‡Dose may vary based on drug-drug interactions or severe hepatic impairment.

In VIALE-A:

- Among patients who achieved bone marrow clearance of leukemia, 53% underwent dose interruptions for ANC <500/microliter
- Once bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia, VENCLEXTA or placebo was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥50 × 10^3/microliter

AR=adverse reaction.

Please see additional Important Safety Information on pages 16 and 17.
Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclexta.pdf.

VENCLEXTA® venetoclax tablets 10mg, 50mg, 100mg

Additional efficacy from a phase 3 clinical trial of VEN+LDAC vs PBO+LDAC[1]

Study VIALE-C: VENCLEXTA in combination with LDAC vs PBO+LDAC

- The efficacy and safety of VENCLEXTA in combination with low-dose cytarabine (VEN+LDAC) (N=143) versus placebo with low-dose cytarabine (PBO+LDAC) (N=68) was evaluated in VIALE-C, a double-blind randomized trial in patients with newly diagnosed AML
- At baseline, patients were ≥75 years of age, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity

Dosing in VIALE-C

- Patients received VENCLEXTA 600 mg orally once daily on Days 1-28 following completion of the ramp-up dosing schedule or placebo in combination with cytarabine 20 mg/m^2 subcutaneously once daily on Days 1-10 of each 28-day cycle beginning on Cycle 1, Day 1
- During the 4-day ramp-up phase, patients received TLS prophylaxis and were hospitalized for monitoring

Bone marrow assessment in VIALE-C

- A bone marrow assessment was performed following Cycle 1 of treatment. If bone marrow assessment confirmed a remission, defined as less than 5% leukemia blasts with cytopenia, VENCLEXTA or placebo was interrupted up to 14 days or until ANC ≥500/microliter and platelet count ≥50 × 10^3/microliter
- For patients with resistant disease at the end of Cycle 1, a bone marrow assessment was performed after Cycle 2 or 3 and as clinically indicated
- LDAC was resumed on the same day as VENCLEXTA or placebo following interruption
- Patients continued to receive treatment until disease progression or unacceptable toxicity

Baseline Characteristics

VEN+LDAC: (N=143)

- The median age of patients treated with VEN+LDAC was 76 years (range: 36-93 years). ECOG performance status at baseline was 0-1 for 52% of patients, 2 for 44% of patients, and 3 for 4.2% of patients
- Mutations identified were as follows: *TP53*—20% (22/112); *IDH1* or *IDH2*—19% (21/112); *FLT3*—18% (20/112); and *NPM1*—16% (18/112). Intermediate or poor cytogenetic risk was present in 63% and 33% of patients, respectively

PBO+LDAC: (N=68)

- The median age of patients treated with PBO+LDAC was 76 years (range: 41-88 years). ECOG performance status at baseline was 0-1 for 50% of patients, 2 for 37% of patients, and 3 for 13% of patients
- Mutations identified were as follows: *TP53*—17% (9/52); *IDH1* or *IDH2*—23% (12/52); *FLT3*—17% (9/52); and *NPM1*—13% (7/52). Intermediate or poor cytogenetic risk was present in 63% and 29% of patients, respectively

Efficacy was based on the rate of CR and duration of CR with supportive evidence of rate of CR+CRh, duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence[1]

CR

- VEN+LDAC: 27% (95% CI: 20, 35)
  mDOCR: 11.1 months (95% CI: 6.1, –)
- PBO+LDAC: 7.4% (95% CI: 2.4, 16)
  mDOCR: 8.3 months (95% CI: 3.1, –)

CR+CRh

- VEN+LDAC: 47% (95% CI: 39, 55)
  mDOCR+CRh of 11.1 months
- PBO+LDAC: 15% (95% CI: 7.3, 25)
  mDOCR+CRh of 6.2 months

TTFR

- The median time to first response of CR or CRh was 1.0 month (range: 0.7-5.8 months) with VEN+LDAC treatment

- VEN+LDAC did not significantly improve OS versus PBO+LDAC. HR for OS was 0.75 (95% CI: 0.52, 1.07); *P*=0.114. The median OS for the VEN+LDAC arm was 7.2 months (95% CI: 5.6, 10.1) and for the PBO+LDAC arm was 4.1 months (95% CI: 3.1, 8.8)

TTFR=time to first response.

Important Safety Information

Tumor Lysis Syndrome

- Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA.

Adverse Reactions

- **In patients with AML receiving combination therapy with low-dose cytarabine,** the most frequent serious adverse reactions (≥10%) were pneumonia (17%), febrile neutropenia (16%), and sepsis (excluding fungal; 12%). The most common adverse reactions (≥30%) of any grade were platelets decreased (97%), neutrophils decreased (95%), lymphocytes decreased (92%), hemoglobin decreased (63%), nausea (42%), and febrile neutropenia (32%). Fatal adverse reactions occurred in 23% of patients who received VENCLEXTA in combination with LDAC, with the most frequent (≥5%) being pneumonia (6%) and sepsis (excluding fungal; 7%).

Safety information from VIALE-C[1]

A predictable, tolerable, and manageable safety profile

No additional warnings or precautions for VENCLEXTA were observed in the AML trials.

Serious ARs

Serious adverse reactions were reported in 65% of patients who received VEN+LDAC, with the most frequent (≥10%) being pneumonia (17%), febrile neutropenia (16%), and sepsis (excluding fungal; 12%).

Fatal ARs

Fatal adverse reactions occurred in 23% of patients who received VENCLEXTA in combination with LDAC, with the most frequent (≥5%) being pneumonia (6%) and sepsis (excluding fungal; 7%).

Adverse reactions leading to discontinuation, dose reductions, and dose interruptions

Adverse reactions led to permanent discontinuation of VENCLEXTA in 25% of patients, dose reductions in 9%, and dose interruptions in 63%. Among patients who achieved bone marrow clearance of leukemia, 32% underwent dose interruptions for ANC <500/microliter. The most frequent adverse reaction (>2%) which resulted in permanent discontinuation of VENCLEXTA was pneumonia (6%). Adverse reactions which required a dose reduction in ≥1% of patients were pneumonia (1%) and thrombocytopenia (1%), and the adverse reactions which required a dose interruption in ≥5% of patients included neutropenia (20%), thrombocytopenia (15%), pneumonia (8%), febrile neutropenia (6%) and sepsis (excluding fungal; 6%).

Adverse reactions (≥10%) in patients with AML who received VEN+LDAC with a difference between arms of ≥5% for all grades or ≥2% for Grade 3 or 4 compared with PBO+LDAC in VIALE-C*

		VEN+LDAC (N=142)		PBO+LDAC (N=68)	
	Adverse reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Gastrointestinal disorders	Nausea	42	1	31	0
	Diarrhea	28	3	16	0
	Vomiting	25	<1	13	0
	Abdominal pain†	15	<1	9	3
	Stomatitis†	15	1	6	0
Blood and lymphatic system disorders	Febrile neutropenia	32	32	29	29
Infections and infestations	Pneumonia†	29	19	21	21
Vascular disorders	Hemorrhage†	27	8	16	1
	Hypotension†	11	5	4	1
Musculoskeletal and connective tissue disorders	Musculoskeletal pain†	23	3	18	0
General disorders and administration site conditions	Fatigue†	22	2	21	0
Nervous system disorders	Headache	11	0	6	0

*Patients who received at least one dose of either treatment.
†Includes multiple adverse reaction terms.

Hematologic laboratory abnormalities

New or worsening Grade 3 or 4 hematologic laboratory abnormalities in VIALE-C ≥2% VEN+LDAC compared with PBO+LDAC respectively: platelets decreased 95% vs 90%, neutrophils decreased 92% vs 71%, lymphocytes decreased 69% vs 24%, hemoglobin decreased 57% vs 54%.

For dose modifications for drug-drug interactions and management of adverse reactions specific to VEN+LDAC regimen, please see section 2 of the full Prescribing Information.

Please refer to following pages for additional efficacy data.

Please see additional Important Safety Information on pages 16 and 17.
Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclexta.pdf.

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M14-358: VEN+AZA or DEC

Additional efficacy from a phase 1b trial of VEN+AZA or DEC[1,7]

Study M14-358: VENCLEXTA in combination with AZA or DEC[1]

- VENCLEXTA was studied in a non-randomized, open-label trial (NCT02203773) that evaluated the efficacy of VENCLEXTA in combination with AZA (N=84) or DEC (N=31) in patients with newly diagnosed AML
- Of those patients, 67 who received AZA combination and 13 who received DEC combination were 75 years or older, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline ECOG performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, CLcr <45 mL/min, or other comorbidity

Dosing in M14-358[1]

- Patients received VENCLEXTA 400 mg orally once daily following completion of the ramp-up dosing schedule in combination with azacitidine (75 mg/m^2 either intravenously or subcutaneously on Days 1-7 of each 28-day cycle beginning on Cycle 1, Day 1) or decitabine (20 mg/m^2 was administered intravenously on Days 1-5 of each 28-day cycle beginning on Cycle 1, Day 1)
- During the ramp-up phase, patients received TLS prophylaxis and were hospitalized for monitoring
- Treatment was continued until disease progression or unacceptable toxicity

M14-358: VEN+DEC

Baseline characteristics[1]

- The median age of patients treated with VEN+DEC was 75 years (range: 68-86 years). ECOG performance status at baseline was 0-1 for 92% of patients and 2 for 7.7% of patients
- Of the 13 patients in the VEN+DEC arm, those who had mutations identified were as follows: 31% with *TP53*, 15% with *NPM1*, 23% with *FLT3*, and no patients with *IDH1* or *IDH2*. Intermediate or poor cytogenetic risk was present in 38% and 62% of patients, respectively

First-line efficacy and fast remissions with VEN+DEC[1]

- CR was 54% (n=7); 95% CI: (25, 81)
- CRh was 7.7% (n=1); 95% CI: (0.2, 36)
- Median duration of response of CR was 12.7 months (95% CI: [1.4, –])
- Median time to first response (CR or CRh) was 1.9 months (range: 0.8-4.2)

Descriptive prespecified exploratory analysis of CR+CRh rates in different mutational and cytogenetic risk subgroups[7]

- CR+CRh rates were 33% (n=1/3; 95% CI: [0.8, 91]) for *FLT3*, 100% (n=2/2; 95% CI: [16, 100]) for *NPM1*, 75% (n=3/4; 95% CI: [19, 99]) for *TP53*, 60% (n=3/5; 95% CI: [15, 95]) for the intermediate cytogenetic risk group, and 63% (n=5/8; 95% CI: [25, 92]) for the poor cytogenetic risk group
- CR rates were 50% (n=2/4; 95% CI: [7, 93]) for *TP53* and 50% (n=4/8; 95% CI: [16, 84]) for the poor cytogenetic risk group. CR rates for *FLT3*, *NPM1*, and the intermediate cytogenetic risk group were the same as rates seen for CR+CRh
- No patients had an *IDH1/2* mutation
- 4 patients had insufficient sample for analysis. Patients could have expressed one or more, or none, of the identified mutations
- The subgroup analyses were not powered or tested to demonstrate a statistically significant difference in outcomes for any subgroup examined

Important Safety Information

Tumor Lysis Syndrome

- Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA.

Adverse Reactions

- **In patients with AML receiving combination therapy with decitabine,** the most frequent serious adverse reactions (≥10%) were sepsis (excluding fungal; 46%), febrile neutropenia (38%), and pneumonia (31%). The most common adverse reactions (≥30%) of any grade were febrile neutropenia (69%), fatigue (62%), constipation (62%), musculoskeletal pain (54%), dizziness (54%), nausea (54%), abdominal pain (46%), diarrhea (46%), pneumonia (46%), sepsis (excluding fungal; 46%), cough (38%), pyrexia (31%), hypotension (31%), oropharyngeal pain (31%), edema (31%), and vomiting (31%). One (8%) fatal adverse reaction of bacteremia occurred within 30 days of starting treatment.

Please see additional Important Safety Information on pages 16 and 17.
Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclexta.pdf.

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Safety information from a phase 1b trial of VEN+DEC[1]

A predictable, tolerable, and manageable safety profile

No additional warnings or precautions for VENCLEXTA were observed in the AML trials.

Adverse reactions reported in ≥30% (any grade)

- The most common adverse reactions (≥30%) were febrile neutropenia (69%), fatigue (62%), constipation (62%), musculoskeletal pain (54%), dizziness (54%), nausea (54%), abdominal pain (46%), diarrhea (46%), pneumonia (46%), sepsis (excluding fungal; 46%), cough (38%), pyrexia (31%), hypotension (31%), oropharyngeal pain (31%), edema (31%), and vomiting (31%)
- The most common hematologic laboratory abnormalities (≥30%) were neutrophils decreased (100%), lymphocytes decreased (100%), white blood cells decreased (100%), platelets decreased (92%), hemoglobin decreased (69%)
- The median duration of exposure for patients taking VEN+DEC was 8.4 months (range: 0.5-39.0 months)

Treatment events and occurrence rates

- Serious adverse reactions were reported in 85% of patients
- The most frequent serious adverse reactions (≥10%) were sepsis (excluding fungal; 46%), febrile neutropenia (38%), and pneumonia (31%)
- One (8%) fatal adverse reaction of bacteremia occurred within 30 days of starting treatment
- Permanent discontinuation due to adverse reactions occurred in 38% of patients
- The most frequent adverse reaction leading to permanent discontinuation (≥5%) was pneumonia (8%)
- Dosage interruptions due to adverse reactions occurred in 69% of patients
- The most frequent adverse reactions leading to dose interruption (≥10%) were:
  – neutropenia (38%), febrile neutropenia (23%), leukopenia (15%), and pneumonia (15%)
- Dosage reductions due to adverse reactions occurred in 15% of patients
- The most frequent adverse reaction leading to dose reduction (≥5%) was neutropenia (15%)

For dose modifications for drug-drug interactions and management of adverse reactions specific to VEN+DEC regimen, please see section 2 of the full Prescribing Information.

Important Safety Information

Tumor Lysis Syndrome

- Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA.
- In patients with AML who followed the current 3-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 1.1% in patients who received VENCLEXTA in combination with azacitidine. In patients with AML who followed a 4-day ramp-up dosing schedule and the TLS prophylaxis and monitoring measures, the rate of TLS was 5.6% and included deaths and renal failure in patients who received VENCLEXTA in combination with low-dose cytarabine.
- VENCLEXTA can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of VENCLEXTA and at each dose increase.
- The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function further increases the risk.
- Assess patients for TLS risk and provide appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases.
- Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during the ramp-up phase, and requires VENCLEXTA dose adjustment.

Neutropenia

- In patients with AML, baseline neutrophil counts worsened in 95% to 100% of patients treated with VENCLEXTA in combination with azacitidine or decitabine or low-dose cytarabine. Neutropenia can recur with subsequent cycles.
- Monitor complete blood counts throughout the treatment period. For severe neutropenia, interrupt dosing or reduce duration based on remission status and occurrence. Consider supportive measures including antimicrobials and growth factors (e.g., G-CSF).

Infections

- Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with VENCLEXTA. Monitor patients for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 infection until resolution and resume at same or reduced dose based on occurrence.

Immunization

- Do not administer live attenuated vaccines prior to, during, or after treatment with VENCLEXTA until B-cell recovery occurs. Advise patients that vaccinations may be less effective.

Embryo-Fetal Toxicity

- VENCLEXTA may cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for at least 30 days after the last dose.

Increased Mortality in Patients with Multiple Myeloma when VENCLEXTA is Added to Bortezomib and Dexamethasone

- In a randomized trial (BELLINI; NCT02755597) in patients with relapsed or refractory multiple myeloma, the addition of VENCLEXTA to bortezomib plus dexamethasone, a use for which VENCLEXTA is not indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with VENCLEXTA in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

Adverse Reactions

- **In patients with AML receiving combination therapy with azacitidine,** the most frequent serious adverse reactions (≥5%) were febrile neutropenia (30%), pneumonia (22%), sepsis (excluding fungal; 19%), and hemorrhage (6%). The most common adverse reactions (≥30%) of any grade were neutrophils decreased (98%), platelets decreased (94%), lymphocytes decreased (91%), hemoglobin decreased (61%), nausea (44%), diarrhea (43%), febrile neutropenia (42%), musculoskeletal pain (36%), pneumonia (33%), fatigue (31%), and vomiting (30%). Fatal adverse reactions occurred in 23% of patients who received VENCLEXTA in combination with azacitidine, with the most frequent (≥2%) being pneumonia (4%), sepsis (excluding fungal; 3%), and hemorrhage (2%).
- **In patients with AML receiving combination therapy with decitabine,** the most frequent serious adverse reactions (≥10%) were sepsis (excluding fungal; 46%), febrile neutropenia (38%), and pneumonia (31%). The most common adverse reactions (≥30%) of any grade were febrile neutropenia (69%), fatigue (62%), constipation (62%), musculoskeletal pain (54%), dizziness (54%), nausea (54%), abdominal pain (46%), diarrhea (46%), pneumonia (46%), sepsis (excluding fungal; 46%), cough (38%), pyrexia (31%), hypotension (31%), oropharyngeal pain (31%), edema (31%), and vomiting (31%). One (8%) fatal adverse reaction of bacteremia occurred within 30 days of starting treatment.

Adverse Reactions (cont'd)

- **In patients with AML receiving combination therapy with low-dose cytarabine,** the most frequent serious adverse reactions (≥10%) were pneumonia (17%), febrile neutropenia (16%), and sepsis (excluding fungal; 12%). The most common adverse reactions (≥30%) of any grade were platelets decreased (97%), neutrophils decreased (95%), lymphocytes decreased (92%), hemoglobin decreased (63%), nausea (42%), and febrile neutropenia (32%). Fatal adverse reactions occurred in 23% of patients who received VENCLEXTA in combination with LDAC, with the most frequent (≥5%) being pneumonia (6%) and sepsis (excluding fungal; 7%).

Drug Interactions

- Concomitant use with a P-gp inhibitor or a strong or moderate CYP3A inhibitor increases VENCLEXTA exposure, which may increase VENCLEXTA toxicities, including the risk of TLS. Consider alternative medications or adjust VENCLEXTA dosage and monitor more frequently for adverse reactions. Resume the VENCLEXTA dosage that was used prior to concomitant use of a P-gp inhibitor or a strong or moderate CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.
- Patients should avoid grapefruit products, Seville oranges, and starfruit during treatment as they contain inhibitors of CYP3A.
- Avoid concomitant use of strong or moderate CYP3A inducers.
- Avoid concomitant use of VENCLEXTA with a P-gp substrate. If concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before VENCLEXTA.
- Monitor international normalized ratio (INR) more frequently in patients receiving warfarin.

Lactation

- Advise nursing women not to breastfeed during treatment with VENCLEXTA and for 1 week after the last dose.

Females and Males of Reproductive Potential

- Advise females of reproductive potential to use effective contraception during treatment with VENCLEXTA and for at least 30 days after the last dose.
- Based on findings in animals, VENCLEXTA may impair male fertility.

Renal Impairment

- Patients with reduced renal function (CLcr <80 mL/min, calculated by Cockcroft-Gault formula) require more intensive prophylaxis and monitoring to reduce the risk of TLS when initiating treatment with VENCLEXTA.

Hepatic Impairment

- Reduce the dose of VENCLEXTA for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more frequently for signs of adverse reactions. No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

References: 1. VENCLEXTA [package insert]. North Chicago, IL: AbbVie Inc. **2.** DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629. **3.** Data on file, ABVRRTI71211. AbbVie Inc. **4.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.1.2021—October 14, 2020. © National Comprehensive Cancer Network, Inc 2020. All rights reserved. Accessed October 15, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc. **5.** Drug development and drug interactions: table of substrates, inhibitors and inducers. US Food and Drug Administration website. https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm. Updated March 6, 2020. Accessed October 15, 2020. **6.** CRESEMBA [package insert]. Northbrook, IL: Astellas Pharma. **7.** Data on file, ABVRRTI67697. AbbVie Inc.

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In a phase 3 trial, VENCLEXTA + azacitidine was proven to help 1L AML patients live longer

In patients who were ≥75 years of age or had comorbidities that precluded the use of intensive induction chemotherapy[1]

FDA-approved regardless of mutation status. No need to wait for biomarker test results.

LONGER OVERALL SURVIVAL[1]	VEN+AZA	PBO+AZA
• VEN+AZA improved overall survival vs PBO+AZA **(HR=0.66; 95% CI: [0.52, 0.85]; *P*<0.001)**		
mOS	**14.7 months** 95% CI: (11.9, 18.7)	**9.6 months** 95% CI: (7.4, 12.7)
LASTING IMPACT[1]		
• Almost 3× more remissions and longer mDOR vs PBO+AZA		
CR *P*<0.001	**37%** 105/286 patients 95% CI: (31, 43)	**18%** 26/145 patients 95% CI: (12, 25)
mDOCR	**18 months** 95% CI: (15.3, –)	**13.4 months** 95% CI: (8.7, 17.6)
CR+CRh *P*<0.001	**65%** 185/286 patients 95% CI: (59, 70)	**23%** 33/145 patients 95% CI: (16, 30)
mDOCR+CRh	**17.8 months** 95% CI: (15.3, –)	**13.9 months** 95% CI: (10.4, 15.7)

LEVERAGE 3-STEP APPROACH FOR TREATMENT WITH VENCLEXTA[1]

Initiation

- Evaluate TLS risk in all patients and provide prophylactic measures
- 3-day dose ramp-up and monitor blood chemistries
- Dose-reduce for concomitant use with P-gp inhibitors or strong or moderate CYP3A inhibitors or for severe hepatic impairment

Assessment

- Assess and monitor for common and serious adverse reactions (ARs)
- Bone marrow assessment as clinically indicated
  - In VIALE-A, bone marrow assessment was conducted following Cycle 1 treatment to assess for remission

Management

- Manage hematologic ARs with dose modifications based on remission status*
  - May include VENCLEXTA pause or change in VENCLEXTA duration
- Manage non-hematologic ARs with dose modifications*

*See Table 6 in the full Prescribing Information for dose modifications.

Select Important Safety Information

- Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with VENCLEXTA. Assess patients for risk, including evaluation of tumor burden and comorbidities, and provide prophylaxis for TLS, including hydration and anti-hyperuricemics. Reduced renal function further increases the risk. Monitor blood chemistries and manage abnormalities promptly. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases.
- Concomitant use of VENCLEXTA with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, which may increase the risk of TLS at initiation and during ramp-up phase, and requires VENCLEXTA dose adjustment.
- Grade 3 or 4 neutropenia occurred in patients treated with VENCLEXTA. Monitor blood counts and for signs of infection; manage as medically appropriate.
- Baseline neutrophil counts worsened in 95% to 100% of patients treated with VENCLEXTA in combination with azacitidine or decitabine or low-dose cytarabine. Neutropenia can recur with subsequent cycles.
- Fatal and serious infections such as pneumonia and sepsis have occurred in patients with VENCLEXTA. Monitor patients for signs and symptoms of infection and treat promptly. Withhold VENCLEXTA for Grade 3 and 4 infection until resolution.
- Do not administer live attenuated vaccines prior to, during, or after treatment until B-cell recovery occurs.
- VENCLEXTA may cause embryo-fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for at least 30 days after the last dose.

Please see additional Important Safety Information on pages 16 and 17.
Please see accompanying full Prescribing Information or visit www.rxabbvie.com/pdf/venclexta.pdf.

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