Phase 1b OMNIVERSE trial: safety and tolerability of oral azacitidine in combination with venetoclax for treatment of acute myeloid leukemia

AML-370

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Introduction

- There is a need to optimize treatment options for intensive chemotherapy (IC)-ineligible patients with acute myeloid leukemia (AML)[1,2]
- Current options for this patient population generally require regular hospital or clinic visits for dose administration; as such, treatment regimens offering increased convenience and quality of life are of particular interest
- The combination of venetoclax (VEN), an oral BCL-2 inhibitor, and injectable azacitidine (Inj AZA), a hypomethylating agent, is indicated in IC-ineligible patients with newly diagnosed (ND) AML and has shown significantly improved response and survival rates versus Inj AZA alone[3]
  - This regimen can be continued until disease progression and requires subcutaneous or intravenous administration of Inj AZA (75 mg/m^2) on days 1—7 of each 28-day treatment cycle[3]
  - The relative inconvenience of Inj AZA administration may affect quality of life and result in lower levels of adherence, limiting the benefits patients may derive from treatment[4]
- In QUAZAR® AML-001, maintenance treatment with the oral formulation of AZA (Oral-AZA; 300 mg QD on days 1—14 of each 28-day treatment cycle) was well tolerated and significantly improved survival outcomes versus placebo in patients with AML in complete remission (CR) or CR with incomplete blood cell count recovery (CRi) post-IC who were not candidates for hematopoietic stem cell transplantation[5]
- Compared with Inj AZA, Oral-AZA allows for extended dosing schedules with lower cumulative drug exposure during each treatment cycle[6]

Objective

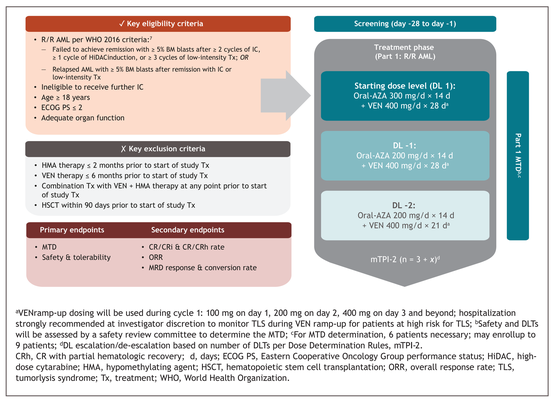
- To evaluate the safety and tolerability, and determine the maximum tolerated dose (MTD) and preliminary efficacy of Oral-AZA + VEN in patients with relapsed/refractory (R/R) AML in Part 1 of the OMNIVERSE study

Methods

Study design

- OMNIVERSE (NCT04887857) is a phase 1b, multicenter, open-label, dose-determination study evaluating Oral-AZA + VEN in patients with AML; data from the Part 1 portion of the dose-finding study in patients with R/R AML are presented here
- Eligible patients in Part 1 were adults with R/R AML who had received 1—2 prior lines of treatment, were not eligible for further IC, and had either failed to achieve remission or had relapsed with ≥ 5% bone marrow (BM) blasts (**Figure 1**)
- A modified toxicity probability interval-2 (mTPI-2) design was used to determine the MTD in R/R AML
- Dose-limiting toxicities (DLTs) were assessed for Oral-AZA + VEN dose levels (DL) and were used to determine DL de-escalation
- Measurable residual disease (MRD) was measured using multiparameter flow cytometry (0.1% threshold)

Figure 1. Key inclusion/exclusion criteria, endpoints, and Oral-AZA + VEN DLs



[a]VENramp-up dosing will be used during cycle 1: 100 mg on day 1, 200 mg on day 2, 400 mg on day 3 and beyond; hospitalization strongly recommended at investigator discretion to monitor TLS during VEN ramp-up for patients at high risk for TLS; [b]Safety and DLTs will be assessed by a safety review committee to determine the MTD; [c]For MTD determination, 6 patients necessary; may enrollup to 9 patients; [d]DL escalation/de-escalation based on number of DLTs per Dose Determination Rules, mTPI-2.
CRh, CR with partial hematologic recovery; d, days; ECOG PS, Eastern Cooperative Oncology Group performance status; HiDAC, high-dose cytarabine; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; ORR, overall response rate; TLS, tumorlysis syndrome; Tx, treatment; WHO, World Health Organization.

Endpoints

- **Primary endpoints:** evaluate safety and tolerability, and establish the MTD of Oral-AZA + VEN in patients with R/R AML
  - MTD was assessed (and DLTs were evaluated; NCI CTCAE v.5.0) from first dose to the end of cycle 1 (or last DLT assessment)
  - Safety was assessed through incidence, seriousness, and severity of adverse events (AEs; NCI CTCAE v.5.0), AE relationship to study drug, and clinical laboratory evaluations from informed consent to 28 days after last dose
- **Secondary endpoints:** assessment of preliminary investigator-determined response rates per ELN 2017 AML response criteria[8] for CR, CRi, CR with partial hematologic recovery, and overall response

Analysis population

- Safety and efficacy variables were analyzed descriptively unless otherwise specified
- A minimum of 6 evaluable patients at a given DL was required to determine MTD of Oral-AZA + VEN
- Safety events and DLTs were reviewed by a safety review committee to determine the MTD:
  - Safety population: patients who received ≥ 1 dose of Oral-AZA + VEN
  - DLT-evaluable population: patients who received ≥ 1 dose of Oral-AZA + VEN and either had a DLT during cycle 1, or had no DLT and completed 75% of the planned Oral-AZA + VEN doses during cycle 1
- The efficacy population comprised patients who received ≥ 1 dose of Oral-AZA + VEN and had ≥ 1 post-baseline response assessment

Results

Patient characteristics

- Data from Part 1 are available for 6 patients (3 female; aged 21—80 years; **Table 1**)
- Four patients had 1 prior line of treatment and 2 patients had 2 prior lines of treatment

Table 1. Patient demographics and disease characteristics in OMNIVERSE (Part 1)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Patient characteristics						
Age, years	77	80	51	65	70	21
Sex	Female	Male	Female	Male	Female	Male
Race	White	White	Asian	White	White	Black/African American
Ethnicity	Not Hispanic/Latino	Not Hispanic/Latino	Not Hispanic/Latino	Not Hispanic/Latino	Not Hispanic/Latino	Not Hispanic/Latino
ECOG PS	1	1	1	1	0	1
Cytogenetic risk at diagnosis[9]	Intermediate (Normal)	Intermediate (Normal)	Intermediate (Normal)	Adverse (Trisomy 8 and 21)	Intermediate (Normal)	Adverse (Complex[a])
Mutations at diagnosis	*NPM1*, *FLT3*-ITD,[b] *IDH2*	*JAK* 2V617F	*NPM1*, *FLT3*-ITD,[b] *DNMT3A*, *NRAS*	*RUNX1*, *ASXL1*, *TET2*, *IDH1*, *ZRSR2*, *BCOR*, *EZH2*	Not detected	*RUNX1*
AML classification[7]	Primary AML with recurrent genetic abnormalities	Secondary AML with MDS-related changes	Primary AML with recurrent genetic abnormalities	Primary AML with MDS-related changes	Primary AML, NOS	Primary AML, NOS
Prior AML treatment						
Prior lines of treatment	1 **Ind.**: Cytarabine + idarubicin **Consol.**: Cytarabine **Maint.**: Thioguanine + etoposide	1 **Ind.**: Inj AZA + sabatolimab	2 **Ind.**: Cytarabine + daunorubicin **Consol.**: HiDAC + midostaurin **2nd ind.**: Gilteritinib **HSCT**: Haplo-HSCT **Maint.**: Gilteritinib	1 Ind.: LDAC + VEN + midostaurin[c]	2 **Ind.**: Cytarabine + idarubicin + etoposide Consol.: Cytarabine **2nd ind.**: Cytarabine + idarubicin **2nd consol.**: IDAC	1 **Ind**: Cytarabine + daunorubicin + cladribine **Consol.**: HiDAC **HSCT**: Haplo-HSCT (cord) **Maint.**: Low-dose decitabine
Best response achieved[d]	MLFS	PR	CR (MRD negative)	PR	CRi	CR (MRD positive)
Blood parameters at screening						
Hb (g/L)	114	131	98	85	102	98
WBC (G/L)	27.3	1.83	4.33	0.99	0.87	3.91
ANC (G/L)	1.09	1.1	0.13	0.12	0.17	2.08
PLT (G/L)	76	180	78	17	136	101
PB blasts (%)	84	0	26	24	0	0
BM blasts at screening, %	76.0	15.5	50.0	53.0	27.0	14.0
Cytogenetic risk at screening[9]	Intermediate (Trisomy 11)	Intermediate (Normal)	Adverse (Complex[a])	Intermediate (Normal)	Intermediate (Normal)	Adverse (Complex[a])
Mutations at screening	*NRAS* (VAF: 0.16), *IDH2* (VAF: 0.48), *SRSF2* (VAF: 0.50), *ASLXl* (VAF: 0.04)	Not detected	*NPM1*, *FLT3*-ITD	IDH1	Not detected	Not detected

[a]Karyotype: (47–51,X,IDIC(Y)(q11.23),+IDIC(Y)x1–5,T(16;21)(P11.2;Q22)[CP8]/46, SL,-DER(16;21)[2]/48–49,XY,+10,+14,T(16;21),+22[CP7]/47,XY,+8,T(16;21)[CP3].ISH(DXZ1x1,SRYx4–12); [b]Low allelic ratio; [c]Treatment received in the context of a clinical trial; [d]During last prior line of treatment received; [e]Karyotype: [46 X, del (X) (q22-24q25-27),t (2,5) (q 32;q11.1) del (13) (q12q14), add (17) (p12) [3]/45-46, XX, add (1) (q42), del (7) (q11.1) del (13) (q12q22)+r, inc [cp4]]; [f]Karyotype: (47–49,X,IDIC(Y)(Q11.23),+IDIC(Y)X1–3,T(15;18)(Q22;Q23),T(16;21)(P11.2;Q22)[CP13]//46,XY[7]].
ANC, absolute neutrophil count; consol, consolidation; CR, complete remission; haplo, haploidentical; Hb, hemoglobin; ind, induction; ITD, internal tandem duplication; LDAC, low-dose cytarabine; maint, maintenance; MLFS, morphologic leukemia-free state; MDS, myelodysplastic syndromes; NOS, not otherwise specified; PB, peripheral blood; PLT, platelet; PR, partial remission; TKD, tyrosine kinase domain; VAF, variant allele frequency; WBC, white blood cell.

Safety

- No DLTs were observed
- Oral-AZA + VEN was given for a median of 4 (range: 1—14) cycles (**Table 2**). Of the 6 patients, 4 reported ≥ 1 any grade drug-related treatment-emergent AE (TEAE), the most common of which were grade 1—3 diarrhea (2 patients) and grade 1—2 nausea (2 patients)
  - Grade 3 diarrhea (1 patient) resolved within 48 hours and did not require study drug modification
- Grade 3 febrile neutropenia, deemed a serious AE (SAE) and not related to Oral-AZA or VEN treatment, was reported in 4 patients (6 episodes total; **Table 2**)
  - Other grade 3/4 TEAEs that occurred in 1 patient each were: anemia, thrombocytopenia, scrotal cellulitis, pneumonia, fungal infection, influenza, chronic obstructive pulmonary disease exacerbation, pleural effusion, respiratory distress, respiratory failure, dyspnea, diarrhea, neutropenic colitis, syncope, and congestive heart failure
  - Other SAEs that occurred in 1 patient each were: scrotal cellulitis, Morganella infection, influenza, congestive heart failure, syncope, neutropenic colitis, and dyspnea
- In 1 patient (Patient 1), Oral-AZA was reduced to 200 mg QD × 14 days from cycle 4 due to grade 2 intermittent diarrhea and grade 2 nausea
- In 4 patients (Patients 1, 2, 5, and 6), VEN was reduced per protocol (due to co-treatment with a strong CYP3A inhibitor) to 70 mg QD × 28 days from cycle 2
- Four patients discontinued treatment due to a TEAE (n = 2 [neutropenic colitis and dyspnea, n = 1 each]), progressive disease (n = 1), or lack of response (n = 1)
- Three patients died after treatment discontinuation due to progressive disease, an AE (neutropenic colitis), or unknown causes (n = 1 each)

MTD

- MTD of Oral-AZA + VEN was determined to be Oral-AZA 300 mg QD × 14 days + VEN 400 mg QD × 28 days

Preliminary efficacy

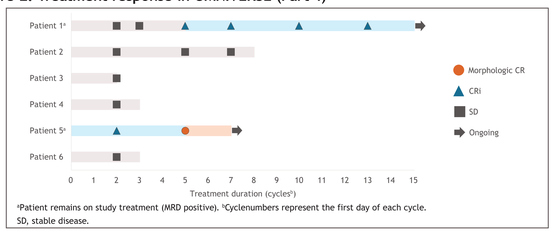
- Best response achieved was morphologic CR (MRD positive) in 1 patient, CRi (MRD positive) in 1 patient and stable disease in 4 patients (**Figure 2**)
- As of July 2023, 2 patients remain on study treatment

Table 2. Treatment and safety outcomes in OMNIVERSE (Part 1)

Preferred term	Patients with R/R AML receiving Oral-AZA + VEN (N = 6)
Treatment duration	
Mean number of cycles	5.3
Median number of cycles	4
Range, cycles	1—14
Patients experiencing ≥ 1 DLT, n (%)	**0 (0)**
Patients with ≥ 1 SAE, n (%)	**4 (67)**
Patients with ≥ 1 grade 3/4 TEAE (≥ 2 patients), n (%)	**5 (83)**
Febrile neutropenia	4 (67)
Patients with ≥ 1 any grade drug-related TEAE, n (%)	**4 (67)**
Diarrhea (grade 1—3)	2 (33)
Nausea (grade 1—2)	2 (33)
Ageusia (grade 1)	1 (17)
Decreased appetite (grade 1)	1 (17)
Hypokalemia (grade 1)	1 (17)
Hypophosphatemia (grade 2)	1 (17)
Stomatitis (grade 1)	1 (17)
Vomiting (grade 1)	1 (17)
Patients with dose reduction due to TEAE, n (%)	**1 (17)**
Oral-AZA	1 (17)
VEN	0 (0)

AE; serious adverse event; TEAE, treatment-emergent adverse event.

Figure 2. Treatment response in OMNIVERSE (Part 1)



[a]Patient remains on study treatment (MRD positive). [b]Cyclenumbers represent the first day of each cycle.
SD, stable disease.

Conclusions

- These results indicate that, in patients with R/R AML, a MTD of Oral-AZA 300 mg QD × 14 days + VEN 400 mg QD × 28 days has a manageable safety profile consistent with known profiles of the individual agents
- No DLTs were observed during the study
- An all-oral combination regimen of Oral-AZA + VEN could represent a convenient treatment strategy in AML and warrants further evaluation in this patient population

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