Durable Response with Venetoclax in Combination with Decitabine or Azacitidine in Elderly Patients with Acute Myeloid Leukemia

AML-129

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BACKGROUND

- Acute Myeloid Leukemia (AML) has a median age of diagnosis at 68 years[1]
- Elderly patients (≥65 years) are frequently ineligible for, or refractory to, intensive induction chemotherapy[2-3]
- Anti-apoptotic BCL-2 is highly expressed in AML,[4] and is associated with chemotherapy resistance and poor outcomes[5]
- Venetoclax (Ven), an oral BCL-2 inhibitor, may offer an effective, low-intensity treatment for AML in elderly patients who are ineligible for standard induction therapy
- Ven has demonstrated synergistic anti-leukemic activity in combination with hypomethylating agents (HMA), such as decitabine (Dec) and azacitidine (Aza) in preclinical studies[6]

OBJECTIVES

- **Primary**
  - To assess the safety of venetoclax in combination with decitabine or azacitidine in patients ≥65 years of age with untreated AML who are ineligible for standard induction chemotherapy
- **Secondary**
  - To assess CR, CRi, DOR, and OS
- **Exploratory**
  - To assess the impact of venetoclax on minimal residual disease (MRD)

METHODS

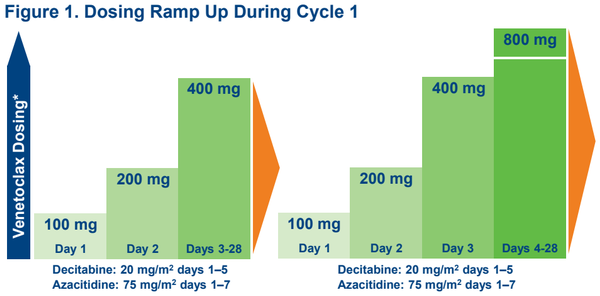
- Study Design: Phase 1b, open label, multicenter dose escalation and expansion
- Endpoints: Safety, Rates of CR/CRi, Overall Survival (OS), and Duration of Response (DOR)

Table 1. Key Patient Enrollment Criteria

Inclusion	Exclusion
▪ AML by WHO criteria ▪ Age ≥ 65 years ▪ Ineligible for standard cytarabine and anthracycline induction ▪ ECOG score 0 – 2	▪ Prior HMA or chemotherapy for antecedent hematologic disorder, CAR-T cell therapy, other experimental therapy ▪ Favorable risk cytogenetics* ▪ Active CNS involvement ▪ WBC count >25 × 10^9 per liter ▪ Infection with HIV, HBV, or HCV

* Favorable risk cytogenetics (now known as non-adverse cytogenetics) is defined as: core binding factor: inv(16), t(16;16), t(8;21), or t(15;17).
CAR-T, chimeric antigen receptor T-cell; CNS, central nervous system; ECOG, European Collaborative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NCCN, National Comprehensive Cancer Network; WBC, white blood cell; WHO, World Health Organization.

Figure 1. Dosing Ramp Up During Cycle 1



* For the 11 patients that received ramp up to 1200 mg venetoclax, that dose was administered starting on day 5.

RESULTS

Table 2. Patient Characteristics

Characteristic	N=145*
Median age (range), years	74 (65 – 86)
Male, n (%)	81 (56)
ECOG Performance Score, n (%)	
0	32 (22)
1	90 (62)
2	23 (16)
Baseline bone marrow blasts, n (%)	
≤30%	44 (30)
31 – 50%	48 (33)
>50%	53 (37)
Median months on study (range)	8.9 (0.2 – 31.7)
Baseline hydroxyurea use, n (%)	14 (10)
Age ≥75 years, n (%)	62 (43)
Cytogenetics†, n (%)	
Intermediate risk	74 (51)
Poor risk	71 (49)
Secondary AML, n (%)	36 (25)
Patient Disposition	
Deaths, n (%)	
≤30 days after Ven start	5 (3)
≤60 days after Ven start	11 (8)

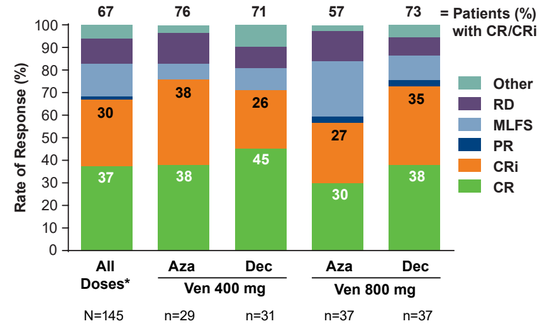
* Includes 11 patients treated with 1200 mg of venetoclax.
† Cytogenetic risk groups defined in 2014 NCCN guidelines, version 2.
Data cutoff was July 7, 2017; median months of follow up was 15.6.

Table 3. Treatment-Emergent Adverse Events (AEs)

AEs in ≥25% of Patients	Any Grade	Grade 3/4
Any event, n (%)	145 (100)	141 (97)
Nausea	88 (61)	2 (1)
Diarrhea	76 (52)	7 (5)
Constipation	70 (48)	2 (1)
Febrile neutropenia	63 (43)	63 (43)
Fatigue	54 (37)	8 (6)
Hypokalemia	49 (34)	15 (10)
Decreased appetite	48 (33)	3 (2)
Decreased WBC count	45 (31)	45 (31)
Vomiting	44 (30)	0
Platelet count decreased	42 (30)	35 (24)
Anemia	40 (28)	36 (25)
Cough	41 (28)	0
Peripheral edema	41 (28)	0
Serious AEs in ≥3% of Patients	**N=145**	
Any event, n (%)	102 (70)	
Febrile neutropenia	46 (32)	
Pneumonia	17 (12)	
Bacterial Infection	9 (6)	
Lung Infection	7 (5)	
Sepsis	6 (4)	
Hypotension	5 (3)	
Mental Status Changes	4 (3)	
Gastrointestinal Hemorrhage	4 (3)	
Mucosal Inflammation	4 (3)	

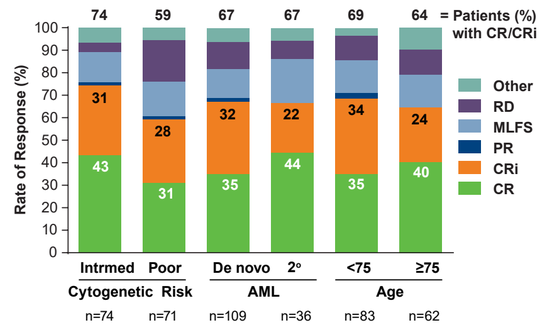
- Rates of AEs between patients treated with Dec or Aza were similar at respective Ven doses
- No events of laboratory or clinical tumor lysis syndrome (TLS) were observed

Figure 2. Response Rates by Treatment



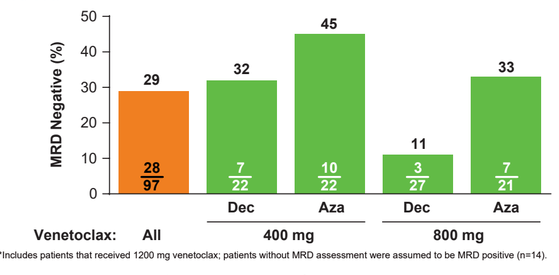
* All doses includes 11 patients that received 1200 mg venetoclax.
CR, complete remission; CRi, CR with incomplete blood count recovery; PR, partial remission; MLFS, morphogenic leukemia free state; RD, resistant disease. Other, disease progression, or discontinued prior to assessment.

Figure 3. Response Rates by Patient Subgroups



CR, complete remission; CRi, CR with incomplete blood count recovery; PR, partial remission; MLFS, morphogenic leukemia free state; RD, resistant disease. Other, disease progression, or discontinued prior to assessment.

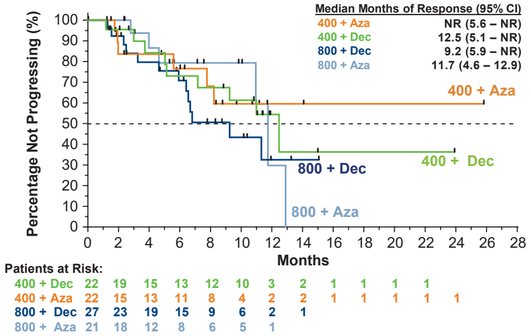
Figure 4. Minimal Residual Disease (MRD) Negativity in Those with CR/CRi



*Includes patients that received 1200 mg venetoclax; patients without MRD assessment were assumed to be MRD positive (n=14).

- MRD negativity was defined as less than 10^{-3} leukemic cells at any measurement, as detected at a central laboratory by multicolor flow cytometry in bone marrow aspirates

Figure 5. DOR for Patients after CR/CRi



Abbreviations: 400, 400 mg venetoclax; 800, 800 mg venetoclax; NR, not reached; NA, not available.

Figure 6. Duration of Response by Patient Subgroups

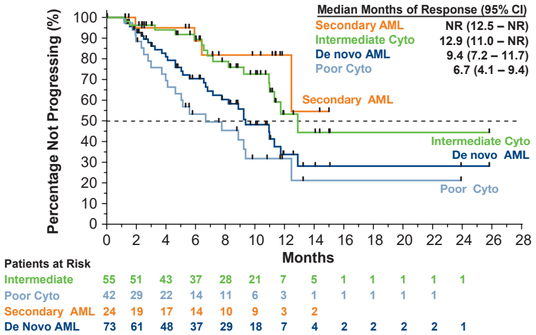
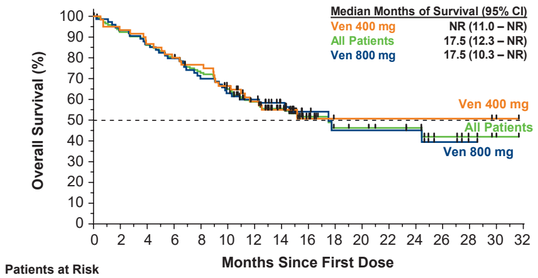


Figure 7. Overall Survival



CONCLUSIONS

- Venetoclax plus Dec or Aza demonstrated a tolerable safety profile
- Preliminary data suggest that 400 mg of venetoclax has the optimal benefit-risk profile in combination with decitabine or azacitidine
- Responses were promising across high risk subgroups; poor risk cytogenetics, secondary AML and age older than 75 years
- With median 15.6 months of follow up, the observed median OS was 17.5 months, with approximately 50% survival at 1 year
- MRD negativity was achieved in >45% of patients treated with Ven 400 mg and azacitidine
- Deep responses and durable outcomes were achieved with venetoclax combined with either hypomethylating agent, azacitidine or decitabine

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DISCLOSURES & ACKNOLEDGEMENTS

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