MDS 158

Updated Safety and Efficacy of Venetoclax in Combination With Azacitidine for the Treatment of Patients With Treatment-Naïve Higher-Risk Myelodysplastic Syndromes: Phase 1b Results

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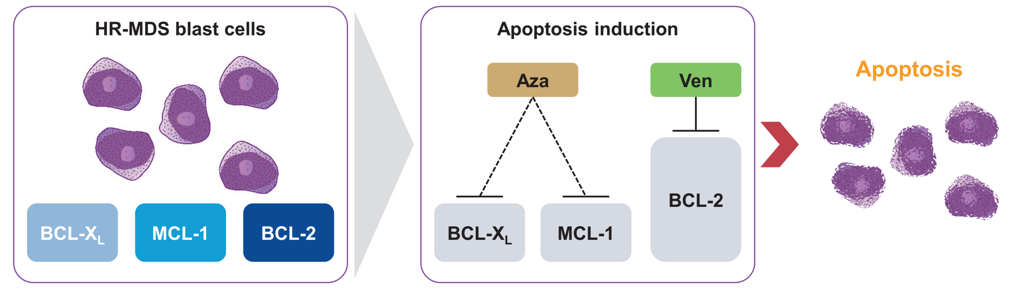
OBJECTIVE

- To update safety and efficacy findings of an ongoing, phase 1b study in patients with treatment-naïve higher-risk myelodysplastic syndromes (HR-MDS) treated with Venetoclax (Ven) + azacitidine (Aza)

BACKGROUND

- Hypomethylating agents (HMAs) are the current standard of care for patients with HR-MDS who are ineligible for allogeneic hematopoietic stem cell transplantation (HSCT)[1,2]
- Overall response rates (ORRs) remain suboptimal in patients receiving Aza, and their expected median overall survival (OS) is less than 2 years[3]
- Ven is a selective, potent, orally bioavailable B-cell lymphoma 2 (BCL-2) inhibitor, which has demonstrated synergy with HMAs in preclinical and clinical studies of myeloid malignancies[4–10]

Figure 1. Ven+Aza Mechanism of Action


HR-MDS blast cells
BCL-XL
MCL-1
BCL-2
Apoptosis induction
Aza
Ven
BCL-XL
MCL-1
BCL-2
Apoptosis

Size of rectangles indicates relative dependency on specific protein for survival.
Dotted lines indicate an indirect therapeutic effect on BCL-2 family member dependency.

Aza, azacitidine; BCL, B-cell lymphoma; HR-MDS, higher-risk myelodysplastic syndromes; MCL, myeloid cell leukemia; Ven, venetoclax.
Jilg S, et al. *Exp Hematol Oncol*. 2019;8:9; Reidel V, et al. *Oncotarget*. 2018;9(25):17270–81; Jilg S, et al. *Leukemia*. 2016;30(1):112–23.

METHODS

Study Overview

M15-531 is an ongoing, phase 1b, dose-escalation, open-label, multicenter study evaluating Ven+Aza for the treatment of patients with HR-MDS (N = 78)

PRIMARY OBJECTIVES[a]

- Safety
- Establish the recommended phase 2 dose (RP2D)

KEY SECONDARY OBJECTIVES[a]

- Overall response rate (ORR)
- Overall survival (OS)

[a]Safety and efficacy assessments were carried out on all patients who received ≥1 dose of study drug; efficacy endpoints were evaluated per International Working Group 2006 response criteria.

KEY INCLUSION CRITERIA

- Adults ≥18 years
- No prior myelodysplastic syndrome (MDS) treatment
- International Prognostic Scoring System (IPSS) ≥1.5[a]
- Bone marrow blasts <20% at screening
- Eastern Cooperative Oncology Group (ECOG) score of ≤2

KEY EXCLUSION CRITERIA

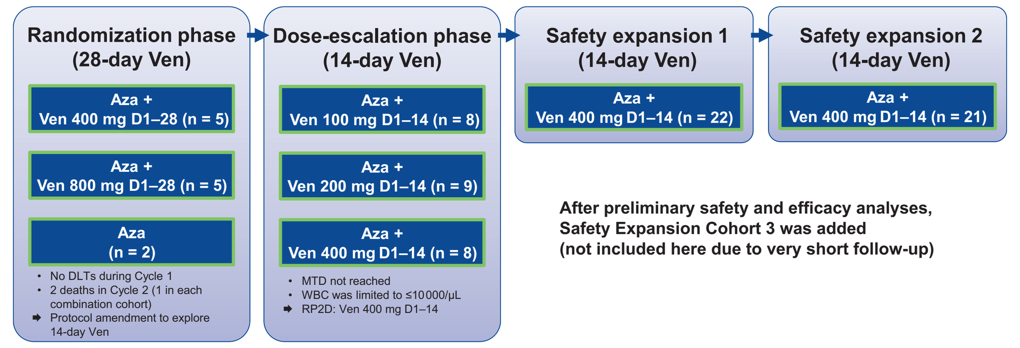
- t-MDS, chronic myelomonocytic leukemia (CMML), u-MDS/MPN
- Patients planned to undergo intensive chemotherapy or allo-HSCT[b]
- CYP3A inducers within 7 days

[a]Study protocol has been amended to allow patients with higher-risk. [b]IPSS-Revised (intermediate, high, and very high) results and patients planning to undergo allo-HSCT, allogeneic hematopoietic stem cell transplantation.
MPN, myeloproliferative neoplasm.

METHODS (CONTINUED)

STUDY DESIGN

Treatment cohorts (28-day cycles); Aza 75 mg/m² D1–7.


Randomization phase
(28-day Ven)
Aza + Ven 400 mg D1–28 (n = 5)
Aza + Ven 800 mg D1–28 (n = 5)
Aza (n = 2)
No DLTs during Cycle 1
2 deaths in Cycle 2 (1 in each combination cohort)
Protocol amendment to explore 14-day Ven
Dose-escalation phase
(14-day Ven)
Aza + Ven 100 mg D1–14 (n = 8)
Aza + Ven 200 mg D1–14 (n = 9)
Aza + Ven 400 mg D1–14 (n = 8)
MTD not reached
WBC was limited to ≤10000/μL
RP2D: Ven 400 mg D1–14
Safety expansion 1
(14-day Ven)
Aza + Ven 400 mg D1–14 (n = 22)
Safety expansion 2
(14-day Ven)
Aza + Ven 400 mg D1–14 (n = 21)
After preliminary safety and efficacy analyses, Safety Expansion Cohort 3 was added
(not included here due to very short follow-up)

Aza, azacitidine; D, Day; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; Ven, venetoclax, WBC, white blood cell.

RESULTS

Median follow-up time was 23 months (range 0.1–44.2).

Table 1. Baseline Characteristics

Characteristic	n (% of N = 78)	
Male	56 (72)	
Median age, years [range]	70 [26–87]	
ECOG performance score		
0	33 (42)	
1	38 (49)	
2	7 (9)	
Bone marrow blasts		
≤5%	7 (9)	
>5% to ≤10%	21 (27)	
>10% to ≤20%	49 (63)	
>20%	1 (1)[a]	
IPSS karyotype risk		
Good	31 (40)	
Intermediate	16 (20)	
Poor	31 (40)	
IPSS risk classification		
Intermediate-2	57 (73)	
High	21 (27)	
IPSS-R risk classification		
Intermediate	14 (18)	
High	16 (20)	
Very high	48 (62)	
Baseline cytopenias	**grade 3**	**grade 4**
Neutropenia[b]	24 (31)	22 (28)
Thrombocytopenia[c]	20 (26)	6 (8)
Leukopenia[d]	30 (38)	3 (4)
Anemia[e]	10 (13)	0

[a]Patients recruited under 2017 Initial Protocol; [b]Includes neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic sepsis, and neutropenic infection; [c]Includes platelet count decreased; [d]Includes white blood cell count decreased; [e]Includes hemoglobin count decreased. Data cutoff: Dec 15, 2020.
ECOG, Eastern Cooperative Oncology Group; IPSS, International Prognostic Scoring System; IPSS-R, International Prognostic Scoring System-Revised.

RESULTS (CONTINUED)

EXPOSURE, TOLERABILITY, AND SAFETY

- Median cycles of Aza received: 4 (range 1–27); median cycles of Ven received: 4 (range 1–27)
- 43 patients (55%) had >2 Ven dose intracycle interruptions
- Reasons for any dose interruption: non-hematologic AEs 58 (78%); hematologic toxicity 26 (35%); scheduling 21 (28%), other 42 (57%)
- 28 patients (36%) required ≥1 Ven dose reduction*
- Reasons for any Ven dose reductions: AEs 6 (21%); starting CYP3A inhibitor 21 (72%); other 7 (24%)
- 28 patients (36%) required ≥1 Aza dose reduction*
- 30-day mortality after first dose was 1%

*Dose reductions were typically 50% reduction for Ven and 33% reduction for Aza.

Table 2. Summary of Adverse Events

AEs, n (%)	Any grade	Grade 3	Grade 4
Neutropenia[a]	65 (83)	47 (60)	47 (60)
Febrile neutropenia	38 (49)	34 (44)	6 (8)
Nausea	43 (55)	1 (1)	0
Constipation	42 (54)	0	0
Diarrhea	38 (49)	2 (3)	0
Thrombocytopenia[b]	38 (49)	9 (11)	30 (38)
Vomiting	32 (41)	1 (1)	0
Leukopenia[c]	30 (38)	12 (15)	23 (29)
Anemia[d]	23 (29)	18 (23)	1 (1)
Fatigue	20 (26)	0	0
Hypokalemia	17 (22)	6 (8)	1 (1)
Dyspnea	16 (21)	1 (1)	0

Serious AEs, n (%)	57 (73)
Neutropenia[a]	38 (49)
Febrile neutropenia	35 (45)
Pneumonia	5 (6)
Sepsis	4 (5)
Diverticulitis	4 (5)

AEs reported in ≥20% of patients for any grade. SAEs reported in ≥5% of patients.
[a]Includes neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic sepsis, and neutropenic infection; [b]Includes platelet count decreased; [c]Includes white blood cell count decreased; [d]Includes hemoglobin count decreased.
AEs, adverse events; Aza, azacytidine; SAEs, serious adverse events; Ven, venetoclax.

EFFICACY

23% of the study population moved to post-study allogeneic HSCT[e] prior to other post-study systemic cancer therapies.

Figure 3. Overall Response Rate

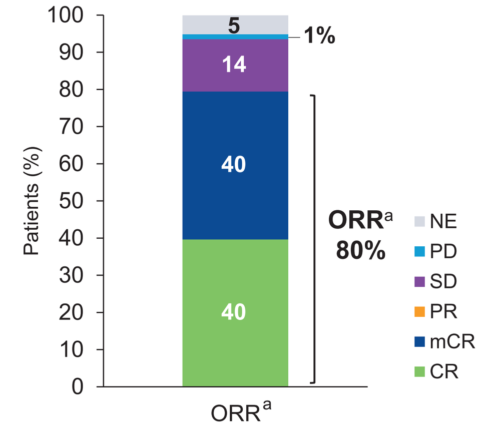

Patients (%)
100
90
80
70
60
50
40
30
20
10
0
5
1%
14
40
40
ORR[a]
80%
ORR[a]
NE
PD
SD
PR
mCR
CR

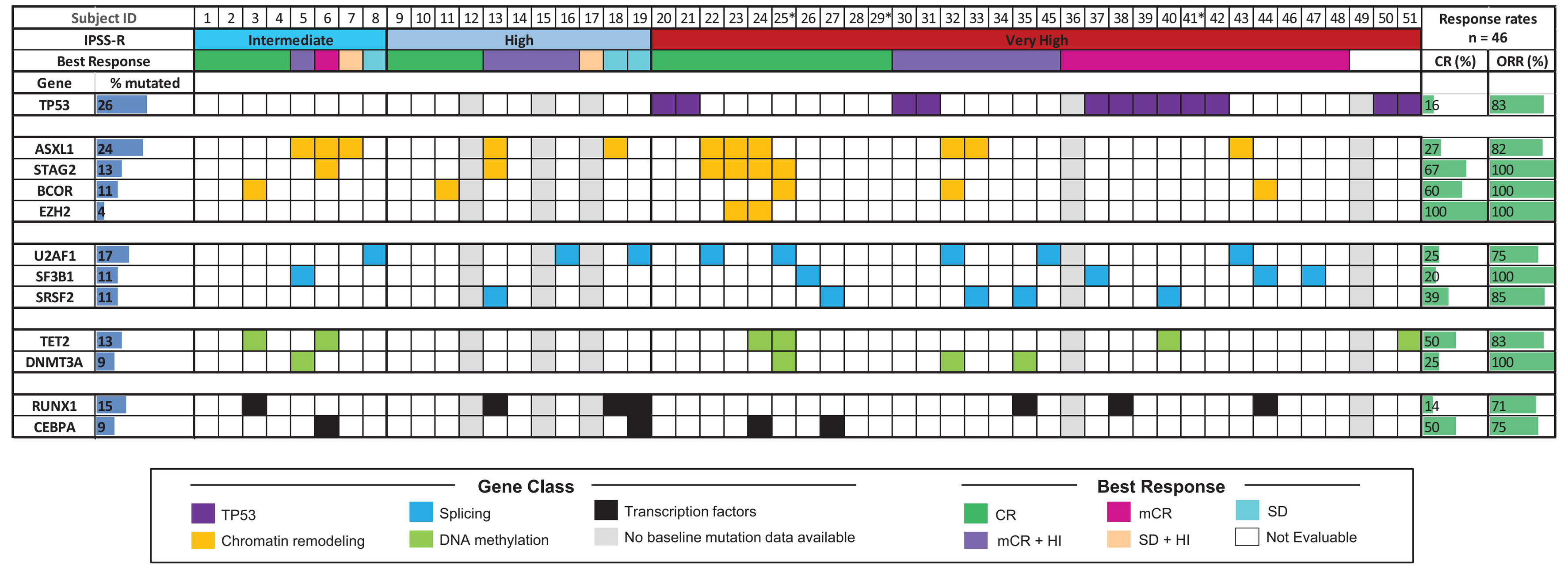
Table 3. Efficacy Summary

	n (% of N = 78)
Overall Response Rate[a]	62 (80%)
CR	31 (40%)
mCR	31 (40%)
mCR + hematologic improvement[b] n/N (%)	13/31 (42%)
Transfusion Independence Rate[c] n/N (%)	20/43 (46.5%)
[95% CI]	[31.2, 62.3]
	Months [95% CI]
Median time on study	23 [16.9, 24.5]
Overall Survival, median	28.2 [17.7, NE]
Overall Survival for CR, median[d]	28.6 [27.5, NE]
Duration of Response for CR, median	13.8 [8.9, NE]
Median time to CR, months (range)	2.6 (1.2–19.6)
Median time to mCR, months (range)	0.9 (0.7–4.6)

[a]ORR = CR+mCR+PR; PR n = 0; per IWG 2006; [b]Hematologic improvement (HI) includes patients who are eligible for HI evaluations and achieved neutrophil, erythroid, or platelet responses; [c]Defined as no transfusion ≥8 weeks; calculated for patients who were transfusion-dependent on RBC or platelet at baseline; [d]mOS for mCR+HI has not been reached; [e]Including bone marrow and peripheral blood stem cell.
CI, confidence interval; CR, complete remission; DoR, duration of response; mCR, marrow complete remission; NE, not estimable; ORR, overall response rate; PD, disease progression; PR, partial remission; SD, stable disease.

Figure 4. Clinical Activity Was Observed in Patients With HR-MDS Harboring Poor Prognostic Mutations

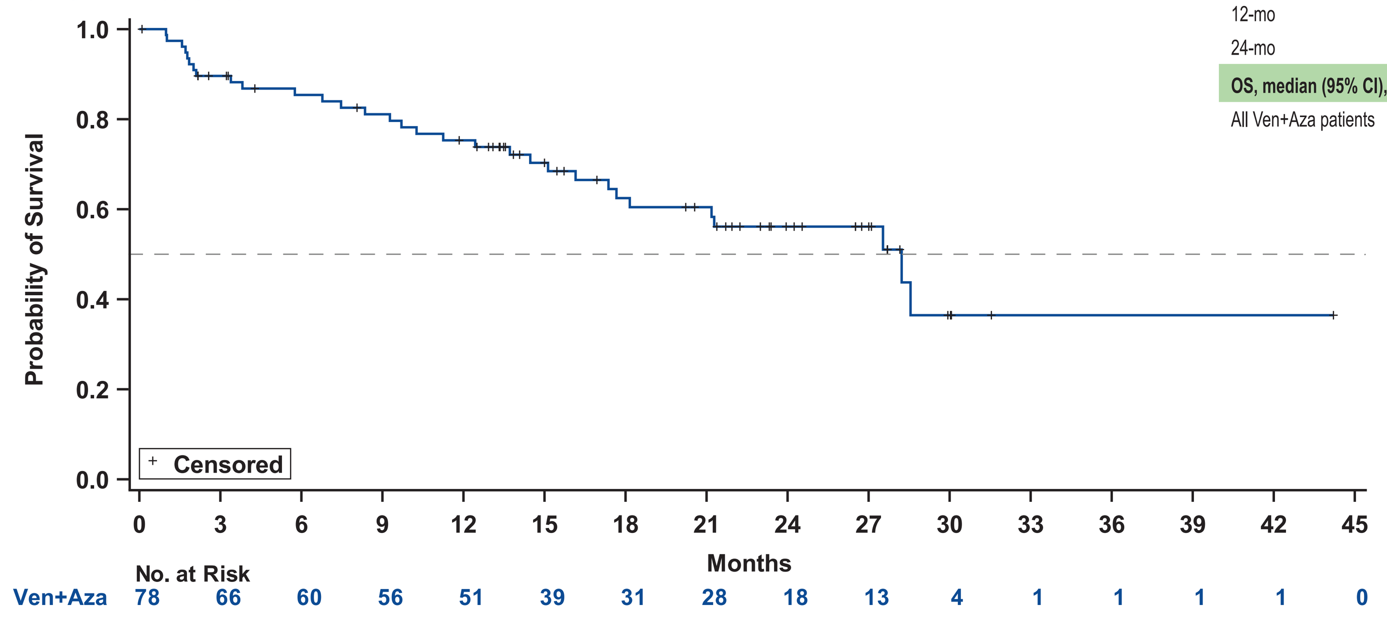
- Clinical responses were independent of baseline genetic mutation status
- ORR = CR+mCR+PR


Subject ID
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25* 26 27 28 29* 30 31 32 33 34 35 45 36 37 38 39 40 41* 42 43 44 46 47 48 49 50 51
IPSS-R
Intermediate
High
Very High
Best Response
Gene
% mutated
Response rates
n = 46
CR (%)
ORR (%)
TP53 26 16 83
ASXL1 24 27 82
STAG2 13 67 100
BCOR 11 60 100
EZH2 4 100 100
U2AF1 17 25 75
SF3B1 11 20 100
SRSF2 11 39 85
TET2 13 50 83
DNMT3A 9 25 100
RUNX1 15 14 71
CEBPA 9 50 75
Gene Class
TP53
Chromatin remodeling
Splicing
DNA methylation
Transcription factors
No baseline mutation data available
Best Response
CR
mCR + HI
mCR
SD + HI
SD
Not Evaluable

Mutations assessed using BMA at screen using Archer Variant Plex Myeloid Gene Panel except for those with patients with * in which mutations were assessed using peripheral blood at SCR using Illumina TruSight Myeloid Gene Panel.
% mutated is calculated based on the 46 patients who have baseline mutations performed. Response rates based on IWG 2006 response criteria; Analysis of patients receiving RP2D and response rates are from Dec 2020 data cut.
CR, complete remission; HI, Hematologic Improvement; mCR, marrow complete remission; Mut, mutant; ORR, overall response rate; SD, stable disease.

Median time on the study: 23 months (range 0.1–44.2).

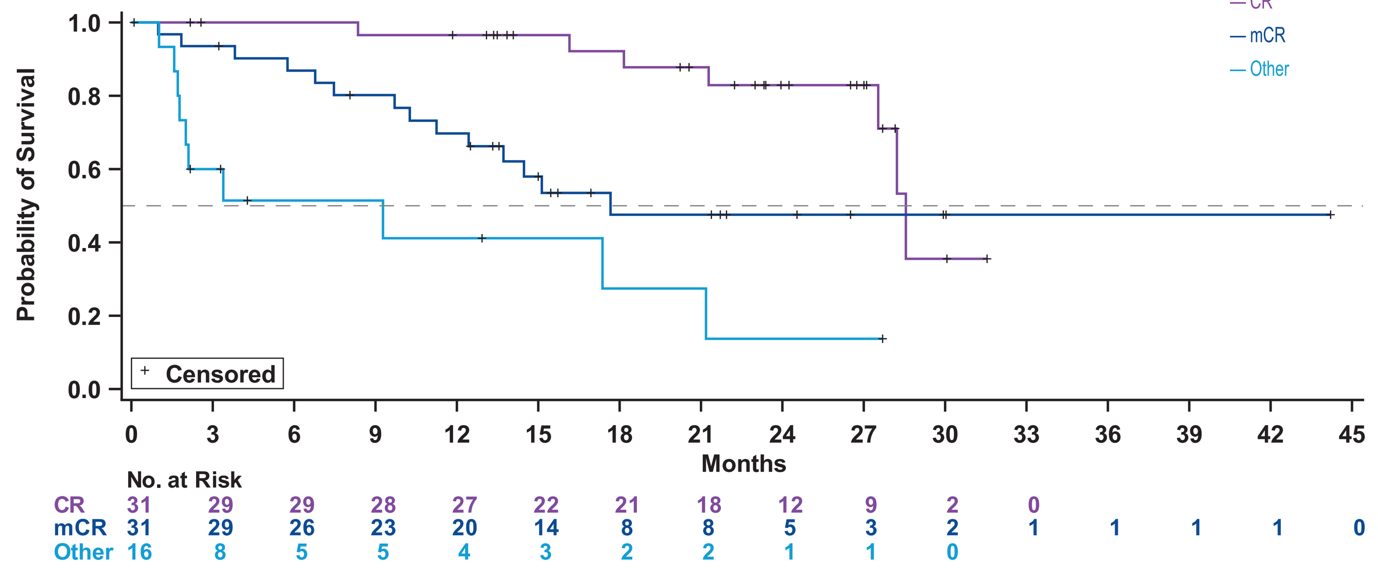
Figure 5. Overall Survival for All Patients


Probability of Survival
1.0
0.8
0.6
0.4
0.2
0.0
Censored
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45
Months
No. at Risk
Ven+Aza 78 66 60 56 51 39 31 28 18 13 4 1 1 1 1 0

Survival estimates, % (95% CI)	
12-mo	75.3 (63.6, 83.7)
24-mo	56.1 (42.5, 67.7)
OS, median (95% CI), months	
All Ven+Aza patients	28.2 (17.7, NR)

Aza, azacitidine; CI, confidence interval; NR, not reached; OS, overall survival; RP2D, recommended phase 2 dose; Ven, venetoclax.

Figure 6. Overall Survival by Response


Probability of Survival
1.0
0.8
0.6
0.4
0.2
0.0
Censored
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45
Months
No. at Risk
CR 31 29 29 28 27 22 21 18 12 9 2 0
mCR 31 29 26 23 20 14 8 8 5 3 2 1 1 1 1 0
Other 16 8 5 5 4 3 2 2 1 1 0

OS, median (95% CI), months	
— CR	28.6 (27.5, NR)
— mCR	17.7 (11.3, NR)
— Other	9.3 (1.7, 21.2)

CI, confidence interval; CR, complete remission; mCR, marrow CR; NR, not reached; OS, overall survival.

CONCLUSIONS

- The combination of Ven+Aza was associated with a rapid and durable response, promising efficacy including remission rates and OS, and an acceptable safety profile for patients with HR-MDS
- Patients who achieved complete remission (CR) had median time to CR of 2.6 months and median duration of response was 13.8 months
- A Safety Expansion Cohort 3 was added, enrollment has concluded, and future analyses will include those data
- A phase 3 study (VERONA[a]) is currently recruiting patients to evaluate safety and efficacy in Ven+Aza in newly diagnosed patients with HR-MDS

[a]NCT04401748. Available at: https://clinicaltrials.gov/ct2/show/NCT04401748.

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REFERENCES

1. NCCN Guidelines®. Myelodysplastic Syndromes. V3.2021.
2. Fenaux P, et al. *Lancet Oncol*. 2009;10(3):223–32.
3. Sekeres MA, et al. *J Clin Oncol*. 2017;35(24):2745–53.
4. DiNardo CD, et al. *Lancet Oncol*. 2018;19(2):216–28.
5. Wei AH, et al. *J Clin Oncol*. 2019;37(15):1277–84.
6. DiNardo CD, et al. *Am J Hematol*. 2018;93(3):401–7.
7. Jilg S, et al. *Exp Hematol Oncol*. 2019;8:9.
8. Jin S, et al. *Clin Cancer Res*. 2020;26(13):3371–83.
9. Reidel V, et al. *Oncotarget*. 2018;9(25):17270–81.
10. Wei AH, et al. *Blood*. 2020;135(24):2137–45

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