653 Efficacy and Safety of Pevonedistat Plus Azacitidine Vs Azacitidine Alone in Higher-Risk Myelodysplastic Syndromes (MDS) from Study P-2001 (NCT02610777)

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Background

Pevonedistat (P), the first small-molecule inhibitor of the neural precursor cell expressed, developmentally downregulated 8 (NEDD8)-activating enzyme, disrupts proteasomal degradation of select proteins and has shown promising clinical activity and good tolerability in combination with azacitidine (A) in acute myeloid leukemia (AML).

Methods

120 pts with higher-risk MDS/chronic myelomonocytic leukemia (Revised International Prognostic Scoring System [IPSS-R] risk >3, including intermediate- [≥5% blasts], high-, or very high-risk) or low-blast AML naïve to hypomethylating agents were randomized 1:1 to receive P 20 mg/m^2 intravenously (IV) on days (d) 1, 3, 5 + A 75 mg/m^2 (IV/subcutaneously) on d 1-5, 8, 9 (n=58), or A alone (n=62), in 28-d cycles until unacceptable toxicity, relapse, transformation to AML, or progression. The study was powered for event-free survival (EFS – time from randomization to death/transformation to AML, whichever occurred first). These analyses focus on clinical, cytogenetic, and genetic factors that could impact rate, depth, and duration of response, as well as EFS and overall survival (OS), in pts with higher-risk MDS.

Results

The 67 pts with higher-risk MDS were drawn from a larger intent-to-treat (ITT) population (n=120), in which EFS trended longer (median 21.0 vs 16.6 months [mos]; hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.42-1.05; P = .076), and median OS was 21.8 vs 19.0 mos (HR 0.80; 95% CI 0.51-1.26; P =.334; median follow-up 21.4 vs 19.0 mos) with P+A vs A. In the higher-risk MDS pts, baseline characteristics were balanced between arms. Pts with higher-risk MDS received a median of 13.5 vs 10 cycles of P+A vs A, and EFS was longer with P+A vs A (median 20.2 vs 14.8 mos; HR 0.54; 95% CI 0.29-1.00; P = .045). Median OS was 23.9 vs 19.1 mos (HR 0.70; 95% CI 0.39-1.27; P = .240) with P+A vs A. Pts with MDS assessed as high-risk according to the combined Cleveland Clinic model formula [Nazha et al. *Leukemia* 2016;30:2214-20], which incorporates both clinical and genetic factors (n=16 in each arm), had a median EFS of 20.2 vs 11.7 mos (HR 0.39; 95% CI 0.17-0.90; P = .023) and a median OS of 24.2 vs 14.2 mos (HR 0.45; 95% CI 0.19-1.05; P = .056) with P+A vs A (Figure 1). In prespecified subgroup analyses of EFS among pts with IPSS-R-defined high- and very high-risk MDS, HRs favored P+A vs A (HR 0.47; 95% CI 0.19-1.18 and HR 0.53; 95% CI 0.17-1.72, respectively), as did overall response rate (complete remission [CR] + partial remission [PR] + hematologic improvement) in response-evaluable pts (79% vs 57%, with a CR rate of 52% vs 27% [P = .050] for P+A vs A). Median duration of response (CR + PR) was 34.6 vs 13.1 mos with P+A vs A (P = .106). Among pts with higher-risk MDS who were red blood cell (RBC) or platelet transfusion-dependent at baseline (P+A, n=13; A, n=19), 69.2% vs 47.4% became transfusion-independent (P = .228), and the median transfusion rate/month was 0.7 vs 2. Median duration of RBC and platelet transfusion-independence was 23.3 vs 11.6 mos (P = .016) with P+A vs A. Median time to AML transformation (range) among pts with higher-risk MDS who transformed (P+A, n=5; A, n=9) was 12.2 (4.6-12.6) vs 5.9 (1.7-14.8) mos with P+A vs A. Median dose intensity of A was 98% in both arms. Overall, P+A had a comparable safety profile to A alone and did not increase myelosuppression. In higher-risk MDS, rates of adverse events (AEs), serious AEs (SAEs), and grade ≥3 AEs normalized by the mean number of cycles dosed of A were lower with P+A

compared with A (Table 1). Clinical activity was observed with P+A in pts who had poor-risk cytogenetics and in pts with adverse-risk mutations, including TP53 (Figure 2).

Conclusions

In pts with higher-risk MDS, P+A led to longer EFS and a higher CR rate compared with A; the effect on EFS was particularly evident in pts with IPSS-R high- and very-high-risk disease. This finding was associated with longer duration of response, later transformation to AML, increased rate of transfusion-independence and lower transfusion rates with P+A vs A. AEs, SAEs, and grade ≥3 AEs per A cycle dosed appeared lower with P+A vs A. Clinical activity was observed in pts with a variety of adverse-risk mutations, and a prognostic risk model that incorporates both clinical and genetic risk factors revealed potential clinical benefit among pts with high-risk MDS. Further evaluation of P+A vs A is ongoing in a randomized phase 3 trial (NCT03268954).

Figure 1. Combined Cleveland Clinic model formula in patients with myelodysplastic syndromes. Improved event-free survival and overall survival in patients at risk category "High" with pevonedistat + azacitidine vs azacitidine

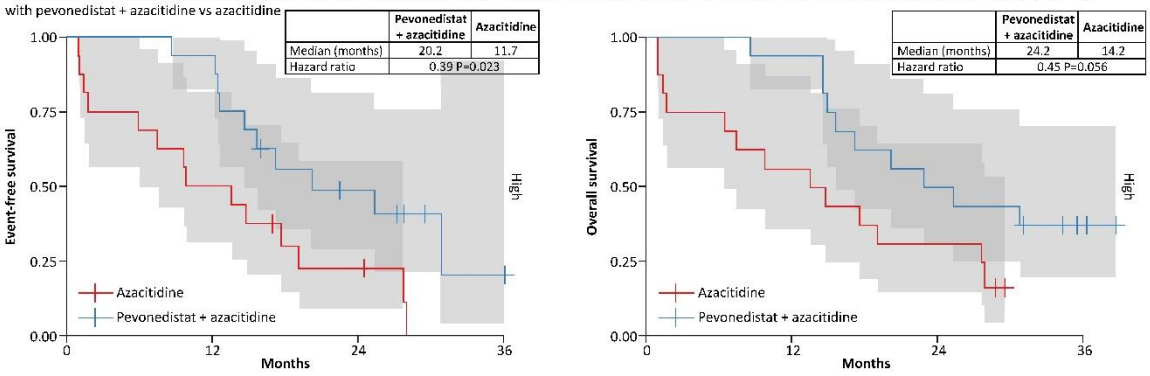

Figure 2. Clinical activity was observed with pevonedistat + azacitidine in patients with higher-risk myelodysplastic syndrome harboring poor-prognostic mutations. CR, complete remission; HI, hematologic improvement; ORR, overall response rate; PR, partial remission.

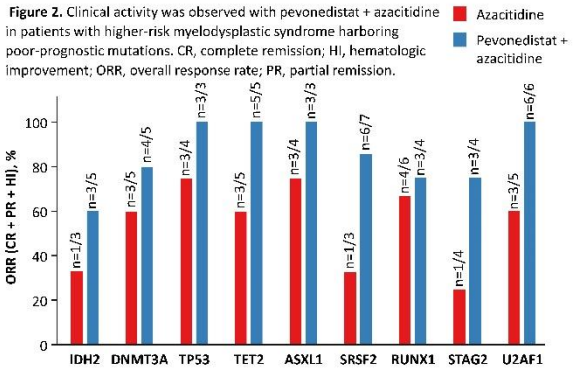

Table 1. Adverse events in patients with higher-risk myelodysplastic syndromes normalized by mean number of azacitidine cycles dosed. Normalized n=AE (n)/azacitidine cycles dosed (mean). AE, adverse event; SAE, serious adverse event.

	Pevonedistat + azacitidine n=32	Azacitidine alone n=35
Azacitidine cycles dosed (mean)	16.3	10.7
Any AE, n (normalized n)	32 (1.96)	35 (3.27)
Treatment-related AE, n (normalized n)	22 (1.35)	27 (2.52)
SAE, n (normalized n)	24 (1.47)	20 (1.87)
Treatment-related SAE, n (normalized n)	4 (0.25)	3 (0.28)
Grade ≥3 AE, n (normalized n)	30 (1.84)	29 (2.71)