

Pevonedistat plus azacitidine versus azacitidine alone in higher-risk myelodysplastic syndromes: efficacy and safety results from study P-2001 (NCT02610777)

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Background

- Pevonedistat is an investigational, first-in-class inhibitor of the NEDD8-activating enzyme inhibitor, which blocks ubiquitination of selected proteins upstream of the proteasome.^{1,2}
- Treatment with pevonedistat disrupts protein homeostasis, leading to apoptosis and cancer cell death.^{2,3}
- For patients with higher-risk myelodysplastic syndrome (MDS) ineligible for transplant, real-world data reveal median overall survival (OS) of about 15 months with treatment, yet no novel treatments have been approved in a decade.^{4,5}
- Study P-2001, a phase 2, multicenter, global, randomized, controlled, open-label trial, (NCT02610777), compared pevonedistat + azacitidine (AZA) vs AZA alone in patients with higher-risk MDS/chronic myelomonocytic leukemia (CMML), and acute myeloid leukemia (AML) with 20–30% marrow blasts who had not previously received a hypomethylating agent.⁶
- In the intention-to-treat (ITT) population, event-free survival (EFS) trended longer (median, 21.0 vs 16.6 months; HR, 0.67; 95% CI, 0.42–1.05; $p = 0.076$) and median OS was 21.8 vs 19.0 months (HR, 0.80; 95% CI, 0.51–1.26; $p = 0.334$) with pevonedistat + AZA vs AZA alone.⁶

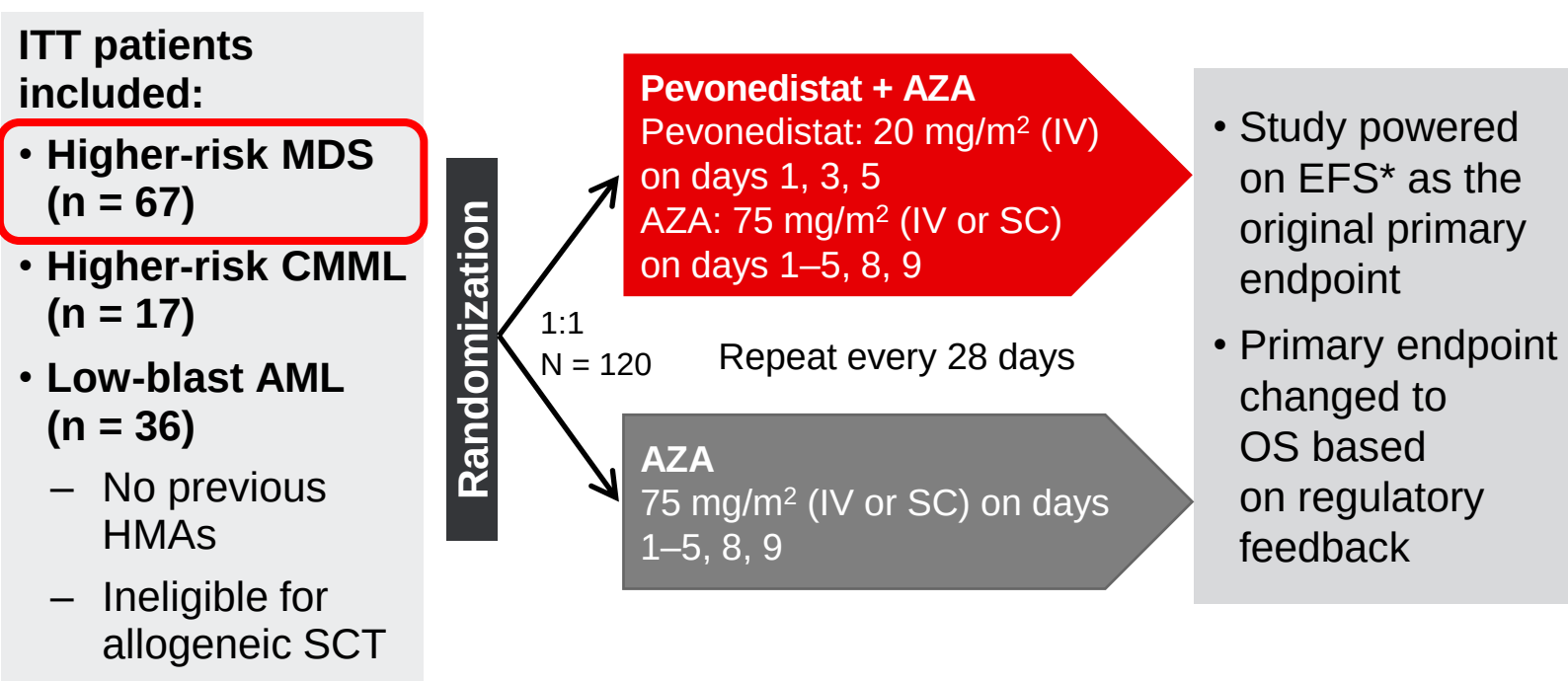
Objective

- This presentation focuses on the efficacy and safety of pevonedistat + AZA versus AZA alone in patients with higher-risk MDS from the P-2001 study.

Methods

- Analysis in patients with higher-risk MDS presented here (Figure 1).
 - Focus on clinical and cytogenetic risk (IPSS-R), and genetic factors that could impact ORR and duration of response, as well as EFS and OS.
 - Post-hoc analysis of patients with MDS assessed as high-risk according to the combined Cleveland Clinic model formula, which incorporates both clinical and genetic factors.⁷

Figure 1. P-2001: Phase 2 open-label, global, multicenter trial.



*EFS is defined as time to death or transformation to AML.
AML, acute myeloid leukemia; AZA, azacitidine; CI, confidence interval; CMML, chronic myelomonocytic leukemia; EFS, event-free survival; HMA, hypomethylating agent; HR, hazard ratio; IPSS-R, Revised International Prognostic Scoring System; ITT, intent-to-treat; IV, intravenous; MDS, myelodysplastic syndromes; ORR, overall response rate; OS, overall survival; SC, subcutaneous; SCT, stem cell transplant.

Definitions

- Higher-risk MDS:
 - Patients with higher-risk MDS had a prognostic risk category of very high (> 6 points), high (> 4.5–6 points), or intermediate (> 3–4.5 points) according to the IPSS-R.
 - Patients with intermediate-risk per IPSS-R were required to have $\geq 5\%$ bone marrow myeloblasts.
- Cleveland Clinic model formula:
 - The Cleveland Clinic model formula incorporates weighted coefficients of variables significantly associated with OS (age, IPSS-R score, and mutations in *EZH2*, *SF3B1*, and *TP53*) into the IPSS-R
 - The score is calculated according to the following formula:
 - $\text{Age} \times 0.04 + \text{IPSS-R score} \times 0.3 + \text{EZH2} \times 0.7 + \text{SF3B1} \times 0.5 + \text{TP53} \times 1$
 - The score translates into four risk groups – low (score ≤ 3), intermediate-1 (3.1–3.6), intermediate-2 (3.7–4.6), and high (≥ 4.7) – with a median OS of 37.4, 23.2, 19.9, and 12.2 months, respectively ($p < 0.001$)

Results

Efficacy

- Baseline demographic and disease characteristics were generally balanced between arms (Table 1).

Table 1. Baseline demographic and disease characteristics for patients with higher-risk MDS (n = 67).

	Pevonedistat + AZA n = 32	AZA n = 35
Higher-risk MDS		
Male/female, %	75/25	71/29
Median age, years (range)	75 (47–91)	70 (44–84)
Disease type, %		
De novo	100	97
Secondary	0	3
WHO tumor classification, %*		
RAEB-1	38	43
RAEB-2	56	51
IPSS-R risk category, %		
Intermediate	34	26
High	34	29
Very high	31	46
Median time from initial diagnosis, months (range)	2.30 (0.2–58.4)	1.74 (0.6–79.1)

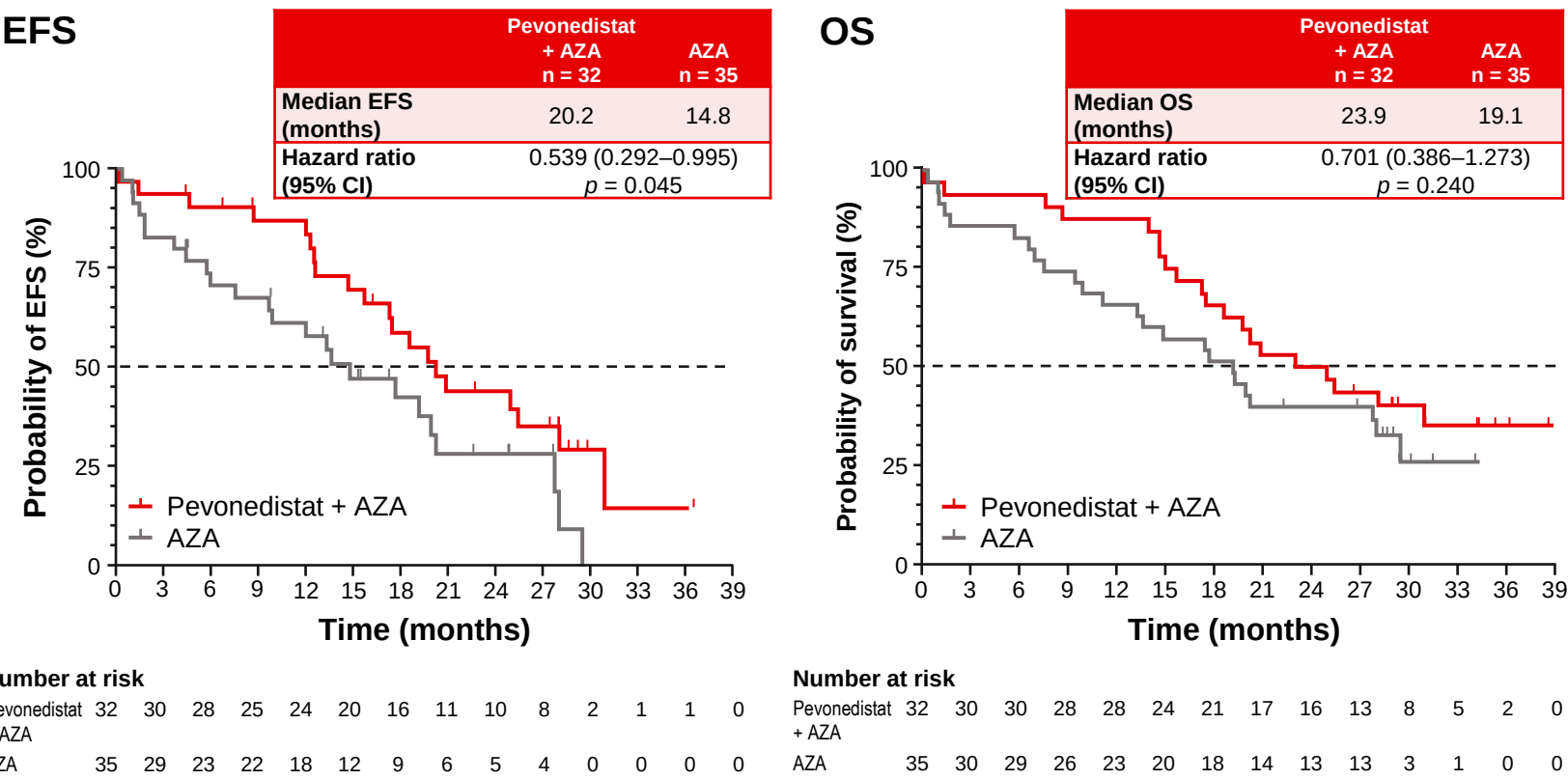
Note: percentages may not sum to 100 due to rounding.

*Missing or NA in two patients in each arm.

AZA, azacitidine; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; NA, not available; RAEB, refractory anemia with excess blasts; WHO, World Health Organization.

- EFS and OS favored pevonedistat + AZA among patients with higher-risk MDS according to IPSS-R (Figure 2).
- Among patients with high-risk MDS according to the Cleveland Clinic model formula, for those treated with pevonedistat + AZA vs AZA alone:
 - EFS was longer (median, 20.2 vs 11.7 months; HR, 0.388; 95% CI, 0.166–0.902; $p = 0.023$).
 - OS trended longer (median, 24.2 vs 14.2 months; HR, 0.447; 95% CI, 0.190–1.050; $p = 0.056$)
- CR rate was nearly doubled, and median DOR was almost tripled with pevonedistat + AZA (Figure 3).
- Rate and duration of RBC and platelet transfusion independence was increased (Figure 4).
- Median time to AML transformation was delayed in patients with higher-risk MDS (Figure 5).

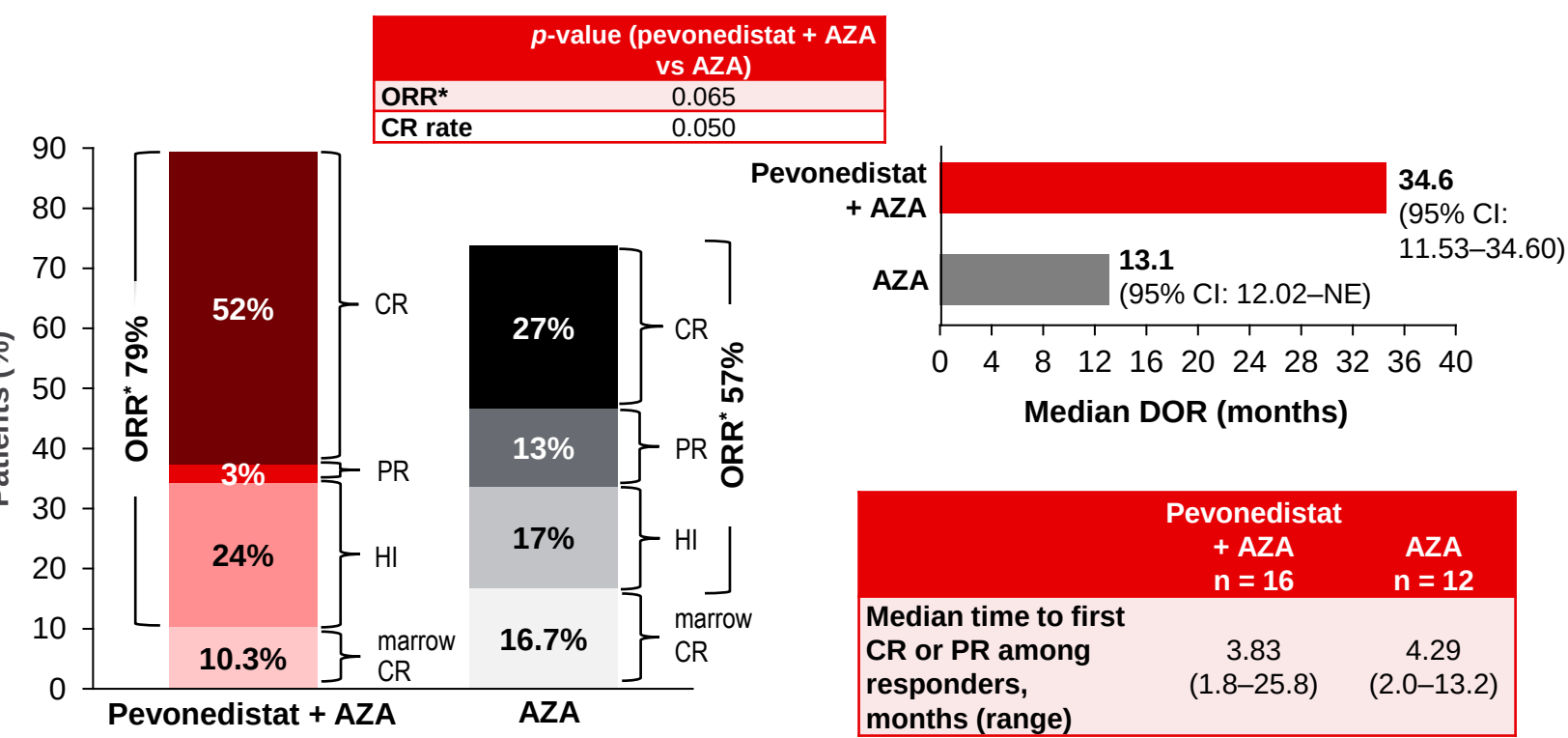
Figure 2. EFS* and OS in patients with higher-risk MDS according to IPSS-R.



*EFS defined as time to death or transformation to AML in higher-risk MDS.

EFS, event-free survival; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; OS, overall survival.

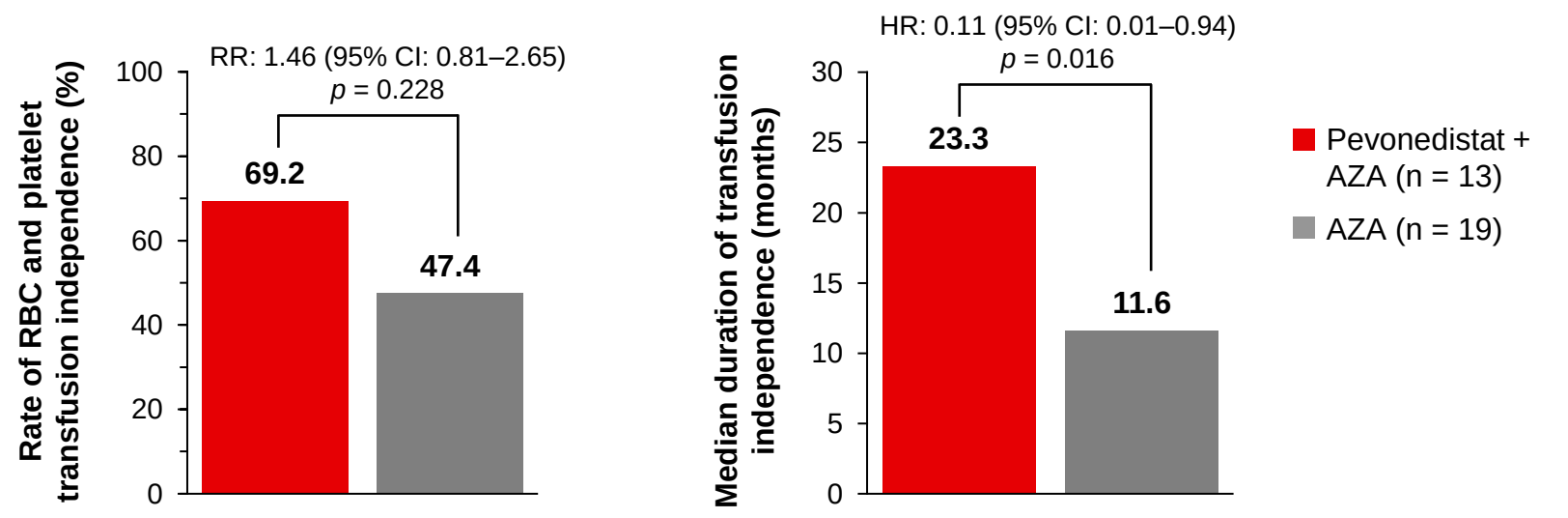
Figure 3. CR rate and median DOR in response-evaluable patients with higher-risk MDS (n = 59).



*ORR = (CR + PR + HI)

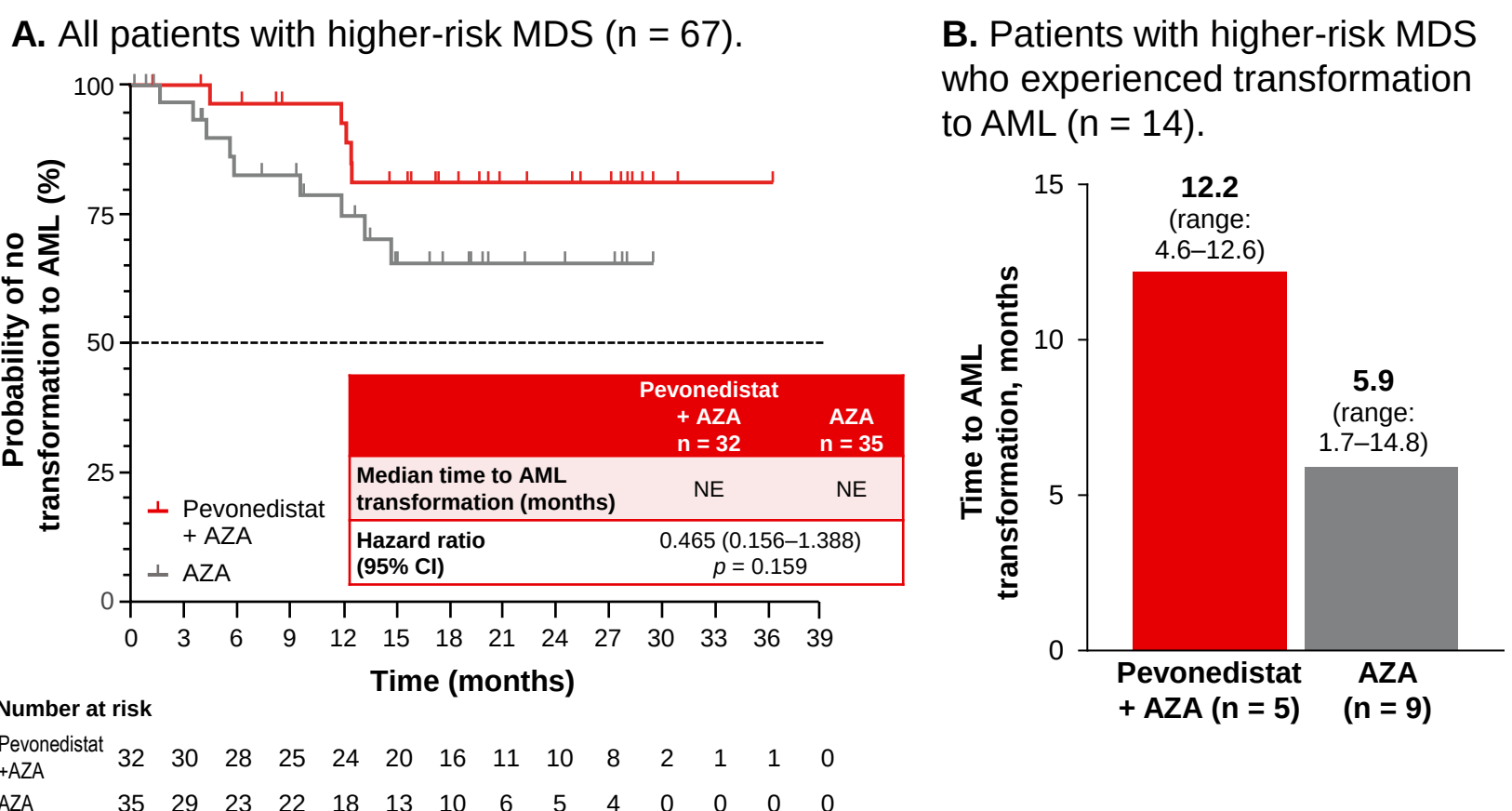
AZA, azacitidine; CR, complete response; DOR, duration of response; HI, hematological improvement; MDS, myelodysplastic syndromes; NE, not evaluable; ORR, overall response rate; PR, partial response.

Figure 4. Rate and duration of RBC and platelet transfusion independence* among patients with higher-risk MDS.



*RBC and platelet transfusion independence includes patients who became either RBC or platelet transfusion independent after dependence at baseline.
AZA, azacitidine; HR, hazard ratio; MDS, myelodysplastic syndromes; RBC, red blood cell; RR, relative risk.

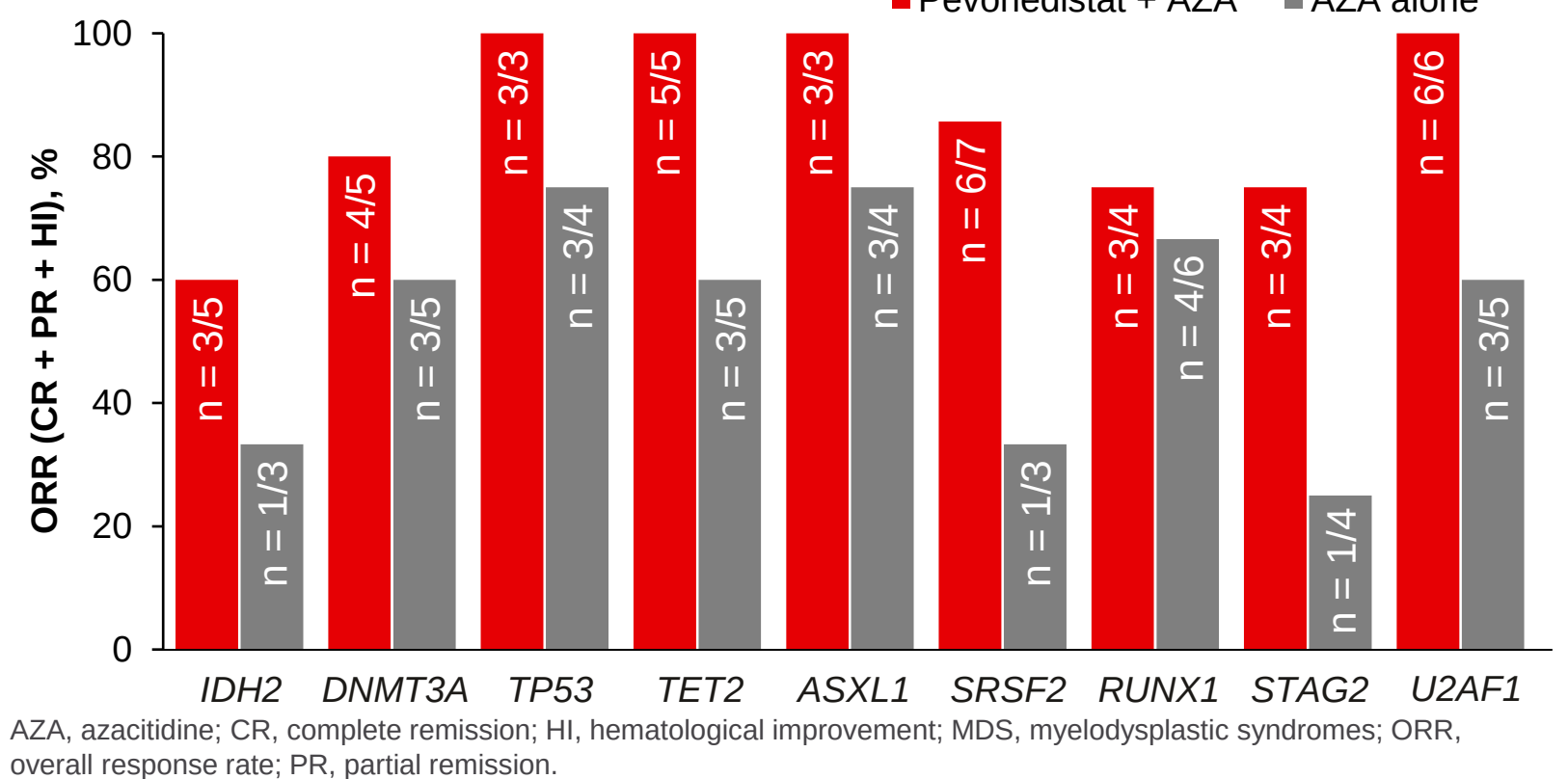
Figure 5. Median time of transformation to AML* in patients with higher-risk MDS.



*Transformation to AML defined according to WHO classification as > 20% blasts in blood or marrow and 50% increase in blast count from baseline.
AML, acute myeloid leukemia; AZA, azacitidine; MDS, myelodysplastic syndromes.

- Median OS from time of transformation to AML was 2.56 months (95% confidence interval [CI] 0.01–10.78).
- In patients who did not experience transformation to AML (n = 53) the median OS was 27.7 months versus 13.6 months among those who did (n = 14; HR: 0.289; 95% CI: 0.145–0.576; $p = 0.0002$).
- Clinical activity was observed in patients with higher-risk MDS who had poor-risk cytogenetics and in patients with adverse-risk mutations, including *TP53* (Figure 6).

Figure 6. Clinical activity in patients with higher-risk MDS who had adverse-risk mutations.



Safety

- Exposure-adjusted AE rates were lower with pevonedistat + AZA than with AZA alone without added myelosuppression (Table 2).
 - Patients received a higher mean number of treatment cycles with pevonedistat + AZA than with azacitidine alone (mean; 16.3 cycles vs 10.7 cycles).
- Median dose intensity of AZA was 98% in both arms.

Table 2. Exposure-adjusted AE rates in patients with higher-risk MDS.

	Pevonedistat + AZA (n = 32)	AZA alone (n = 35)
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)

Normalized n = n/mean number of cycles dosed.

AE, adverse event; AZA, azacitidine; MDS, myelodysplastic syndromes; SAE, serious adverse event.

Conclusions

- Encouraging efficacy was observed with pevonedistat + AZA in patients with higher-risk MDS in the P-2001 study.
- Longer EFS and favorable OS with pevonedistat + AZA versus AZA was associated with:
 - Double the CR rate.
 - Nearly tripled the median duration of response.
 - Delayed transformation to AML.
 - Increased rate of transfusion independence.
 - Lower transfusion rates.
- EFS and OS favored pevonedistat + AZA among patients with MDS assessed as high-risk by the combined Cleveland Clinic model formula.
- Clinical activity was observed in patients with adverse-risk mutations, including *TP53*.
- Exposure-adjusted AE rates were lower with pevonedistat + AZA, without added myelosuppression.
- The phase 3 PANTHER trial (NCT03268954) of pevonedistat + AZA is fully enrolled and will further clarify these findings.

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