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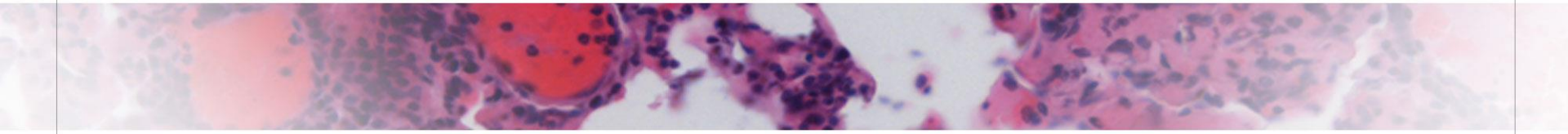

Efficacy and Safety of Pevonedistat plus Azacitidine vs Azacitidine Alone in Higher-Risk Myelodysplastic Syndromes (MDS) from Study P-2001 (NCT02610777): Abstract #653

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Oral presentation at the virtual 62nd Annual Meeting of the American Society of Hematology (ASH), December 5–8, 2020

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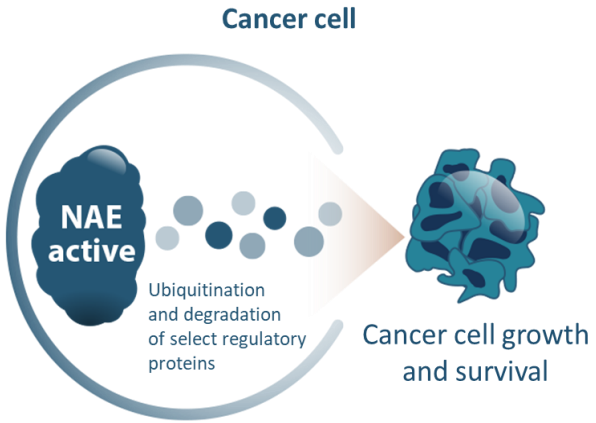
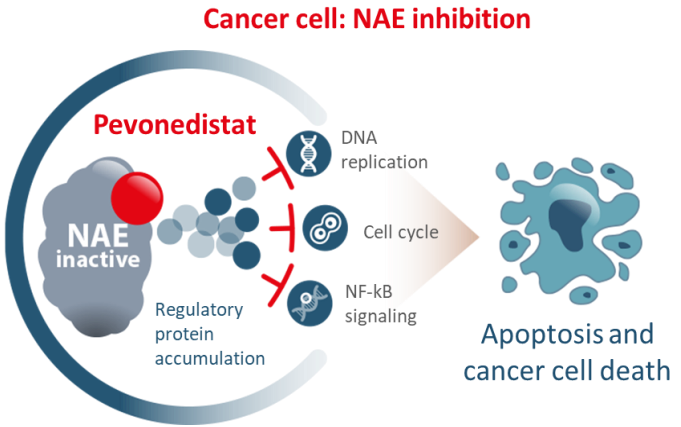
Pevonedistat: first-in-class inhibitor of the NEDD8-activating enzyme

- Inhibiting the NEDD8-activating enzyme blocks ubiquitination of select proteins upstream of the proteasome.[1,2]
- Treatment with pevonedistat disrupts cell cycle progression and cell survival, leading to cell death in cancers.[2,3]
- Pevonedistat exhibits synergistic activity in combination with azacitidine in cellular and mouse xenograft models of AML.[4]

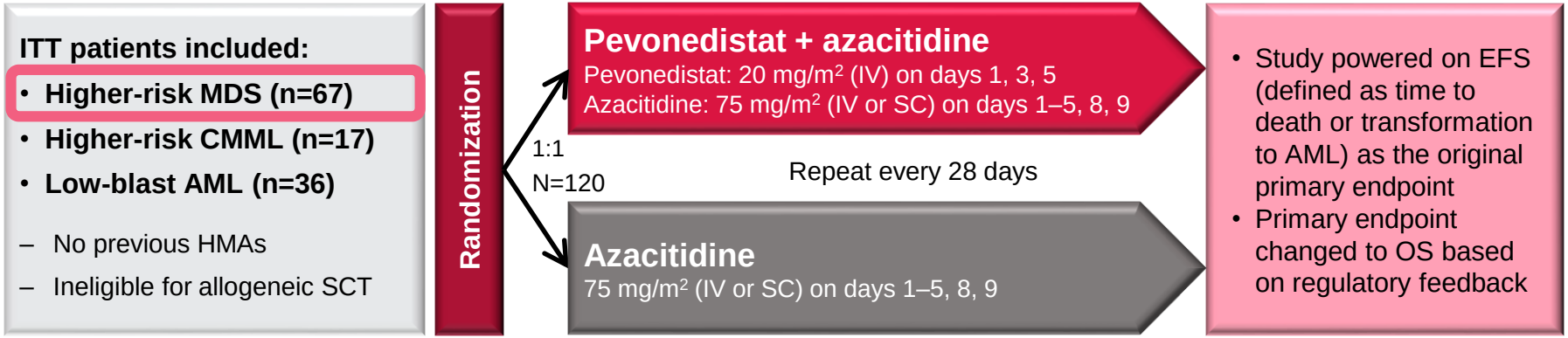




AML, acute myeloid leukemia; NAE, NEDD8-activating enzyme; NEDD8, neural precursor cell expressed, developmentally downregulated 8; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells.

1. Brownell JE, et al. Mol Cell 2010;37:102–11; 2. Soucy TA, et al. Nature 2009;458:732–6; 3. Soucy TA, et al. Clin Cancer Res 2009;15:3912–16. 4. Smith PG, et al. Blood 2011;118:abstract 578.

NCT02610777: phase 2, randomized, open-label, global, multicenter study



Results in the ITT population:[1]

- **Median EFS:** 21.0 vs 16.6 months (HR: 0.67; 95% CI: 0.42–1.05; P=0.076)
- **Median OS:** 21.8 vs 19.0 months (HR: 0.80; 95% CI: 0.51–1.26; P=0.334)

Analyses in patients with higher-risk MDS presented here:

- 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[2]

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.

1. Ades L, et al. J Clin Oncol 2020;38(15_suppl):abstract 7506; oral presentation at ASCO 2020;
2. Nazha A, et al. Leukemia 2016;30:2214–20.

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 ≥5% bone marrow myeloblasts

Cleveland Clinic model formula[1]

- 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:

Age × 0.04 + IPSS-R score × 0.3 + *EZH2* × 0.7 + *SF3B1* × 0.5 + *TP53* × 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)

1. Nazha A, et al. Leukemia 2016;30:2214–20.

Baseline demographics and disease characteristics were generally balanced between arms

		Pevonedistat + azacitidine	Azacitidine
Higher-risk MDS		**n=32**	**n=35**
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.
NA, not available; RAEB, refractory anemia with excess blasts; WHO, World Health Organization.

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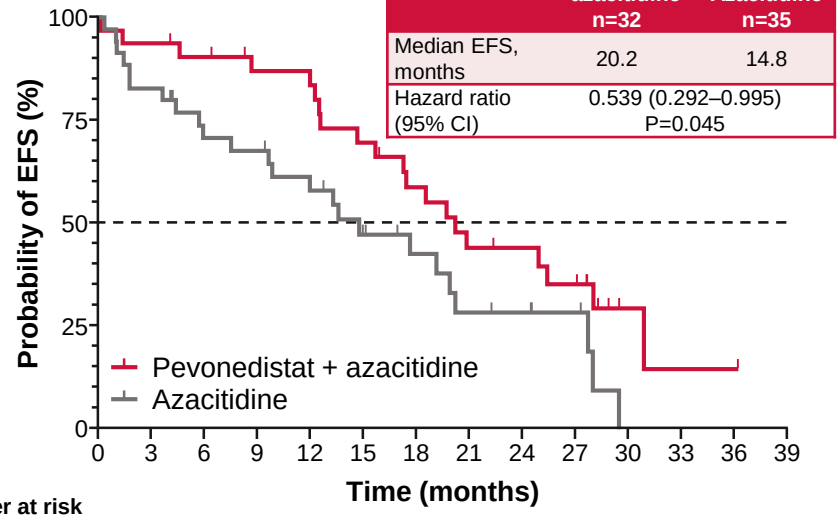
EFS and OS favored pevonedistat + azacitidine among patients with higher-risk MDS according to IPSS-R

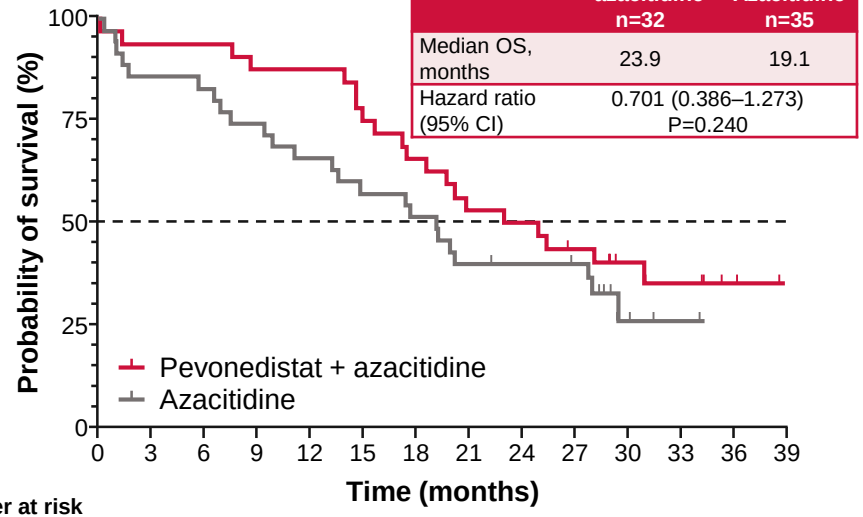
EFS*



	Pevonedistat + azacitidine n=32	Azacitidine n=35
Median EFS, months	20.2	14.8
Hazard ratio (95% CI)	0.539 (0.292–0.995) P=0.045	

Number at risk														
Pevonedistat + azacitidine	32	30	28	25	24	20	16	11	10	8	2	1	1	0
Azacitidine	35	29	23	22	18	12	9	6	5	4	0	0	0	0

OS



	Pevonedistat + azacitidine n=32	Azacitidine n=35
Median OS, months	23.9	19.1
Hazard ratio (95% CI)	0.701 (0.386–1.273) P=0.240	

Number at risk														
Pevonedistat + azacitidine	32	30	30	28	28	24	21	17	16	13	8	5	2	0
Azacitidine	35	30	29	26	23	20	18	14	13	13	3	1	0	0

- Longer EFS was particularly evident in patients with IPSS-R-defined very-high-risk MDS (n=26; HR: 0.47; 95% CI: 0.19–1.18) and high-risk MDS (n=21; HR: 0.53; 95% CI: 0.17–1.72)

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

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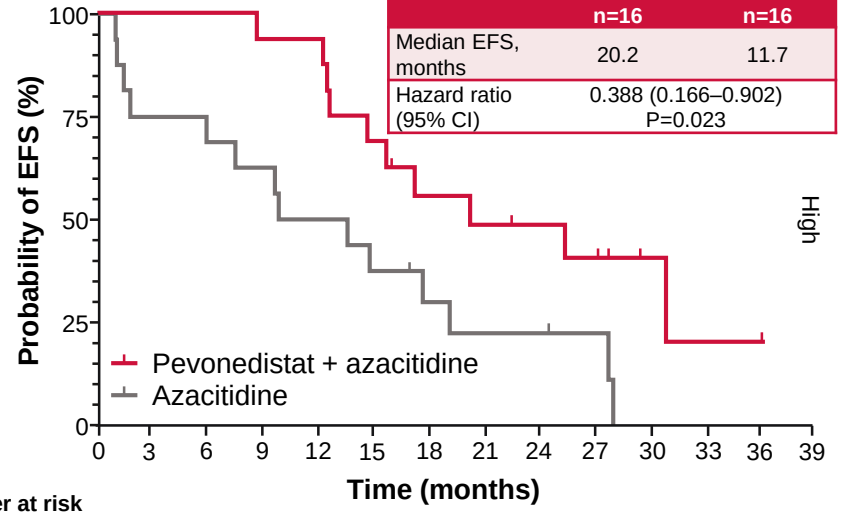
EFS was longer and OS trended longer in patients with high-risk MDS according to Cleveland Clinic model formula[1]

EFS

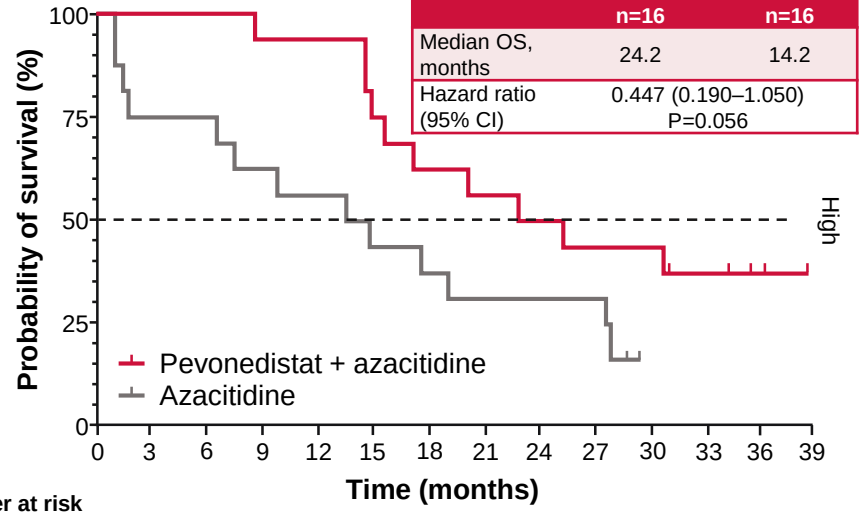


	Pevonedistat + azacitidine n=16	Azacitidine n=16
Median EFS, months	20.2	11.7
Hazard ratio (95% CI)	0.388 (0.166–0.902) P=0.023	

Number at risk

Pevonedistat + azacitidine	16	16	16	15	15	11	8	7	6	5	2	1	1
Azacitidine	16	12	11	10	8	6	4	3	3	2	0	0	0

OS



	Pevonedistat + azacitidine n=16	Azacitidine n=16
Median OS, months	24.2	14.2
Hazard ratio (95% CI)	0.447 (0.190–1.050) P=0.056	

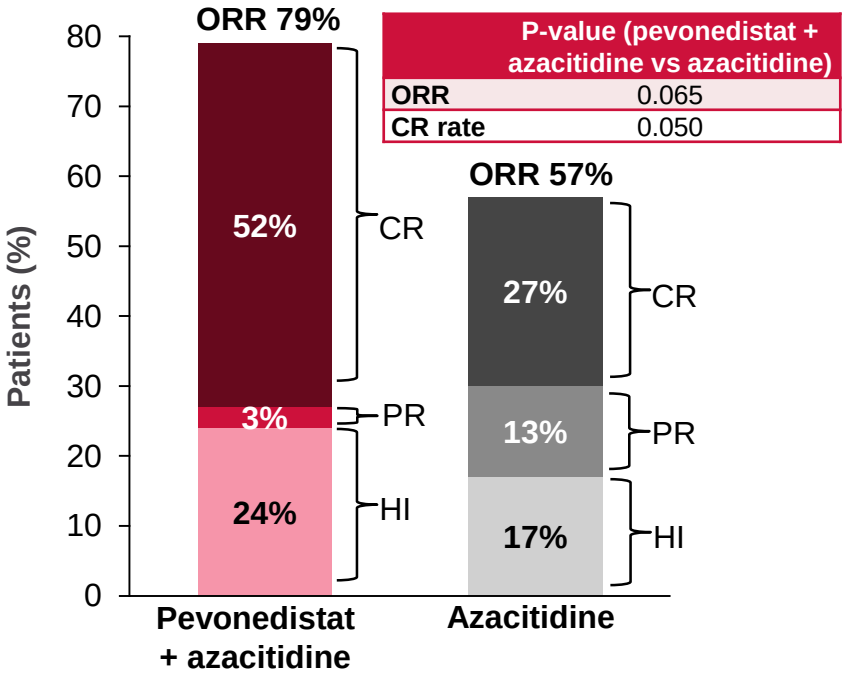
Number at risk

Pevonedistat + azacitidine	16	16	16	15	15	12	10	9	8	7	7	4	2
Azacitidine	16	12	12	10	9	7	6	5	5	5	0	0	0

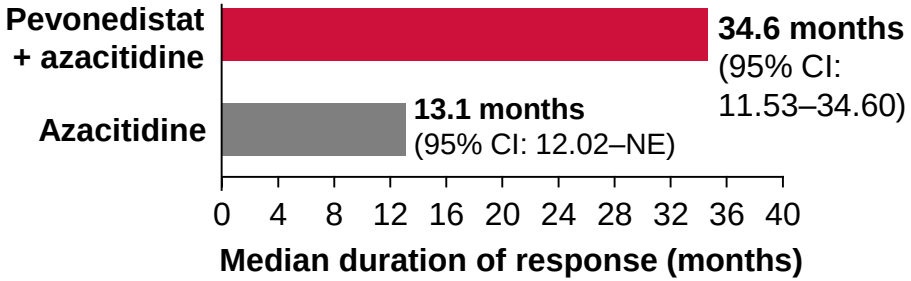
1. Nazha A, et al. Leukemia 2016;30:2214–20.

CR rate was nearly doubled and median duration of response was almost tripled with pevonedistat + azacitidine

Response-evaluable patients with higher-risk MDS (n=59):



	P-value (pevonedistat + azacitidine vs azacitidine)
ORR	0.065
CR rate	0.050



	Pevonedistat + azacitidine n=16	Azacitidine n=12
Median time to first CR or PR among responders, months (range)	3.83 (1.8–25.8)	4.29 (2.0–13.2)

CR, complete response; HI, hematologic improvement; NE, not evaluable; PR, partial response.

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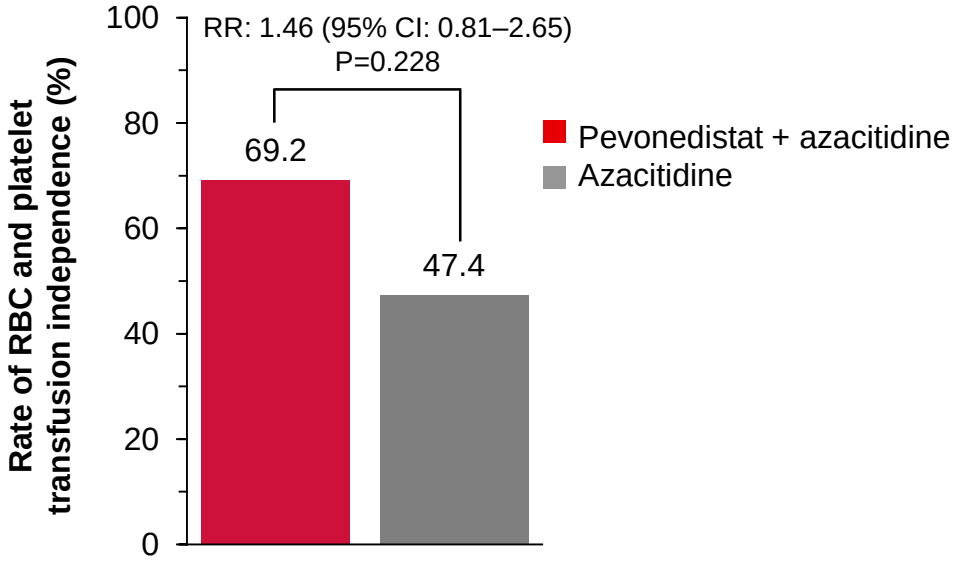
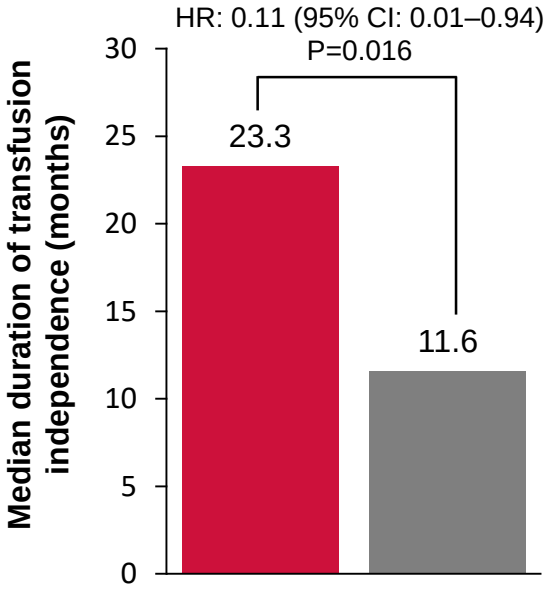
Rate and duration of RBC and platelet transfusion independence* was increased

Among patients with higher-risk MDS who were RBC or platelet transfusion dependent at baseline (pevonedistat + azacitidine, n=13; azacitidine, n=19):





*RBC and platelet transfusion independence includes patients who became either RBC or platelet transfusion independent.
RBC, red blood cell; RR, relative risk.

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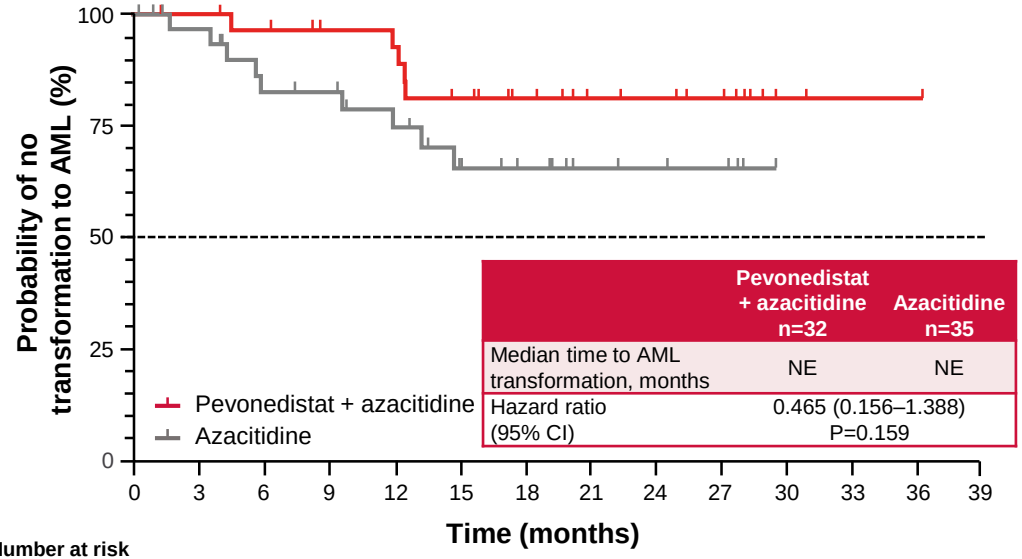
Median time to AML transformation* was delayed in patients with higher-risk MDS

All patients with higher-risk MDS (n=67):



	Pevonedistat + azacitidine n=32	Azacitidine n=35
Median time to AML transformation, months	NE	NE
Hazard ratio (95% CI)	0.465 (0.156–1.388) P=0.159	

Number at risk

Pevonedistat +azacitidine	32	30	28	25	24	20	16	11	10	8	2	1	1	0
Azacitidine	35	29	23	22	18	13	10	6	5	4	0	0	0	0

*Transformation to AML defined according to WHO classification as >20% blasts in blood or marrow and 50% increase in blast count from baseline.
StD, standard deviation.

Patients with higher-risk MDS who experienced transformation to AML (n=14):

	Pevonedistat + azacitidine n=5	Azacitidine n=9
Median time to AML transformation, months (range)	12.2 (4.6–12.6)	5.9 (1.7–14.8)
Mean time to AML transformation, months (StD)	10.76 (3.47)	7.88 (4.65)

Median OS:

- 2.56 months (95% CI: 0.01–10.78) from time of transformation to AML
- 27.7 months in patients who did not experience transformation to AML (n=53) versus 13.6 months among those who did (n=14; HR: 0.289; 95% CI: 0.145–0.576; P=0.0002)

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Exposure-adjusted AE rates were lower with pevonedistat + azacitidine, without added myelosuppression

- Median number of azacitidine treatment cycles: 13.5 (pevonedistat + azacitidine) versus 10.0 (azacitidine).
- Median azacitidine dose intensity: 98% in both treatment arms.

Rates of AEs, SAEs, and grade ≥3 AEs normalized by the mean number of azacitidine cycles dosed:

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

*Normalized n=AE (n)/azacytidine cycles dosed (mean)
AE, adverse event; SAE, serious adverse event.

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Frequency of poor prognostic and frequently mutated genes

Mutation frequency, %	Pevonedistat + azacitidine (n=24)	Azacitidine (n=25)
SRSF2	29.2	12.0
U2AF1	25.0	20.0
DNMT3A	20.8	20.0
TET2	20.8	20.0
IDH2	20.8	12.0
RUNX1	16.7	24.0
STAG2	16.7	16.0
ASXL1	12.5	16.0
TP53	12.5	16.0
IDH1	8.3	16.0
BCOR	8.3	4.0
EZH2	8.3	4.0
ETV6	4.2	12.0
SF3B1	4.2	8.0
CEBPA	4.2	4.0
ZRSR2	4.2	4.0
NRAS	4.2	0.0
FLT3-ITD	0.0	4.0

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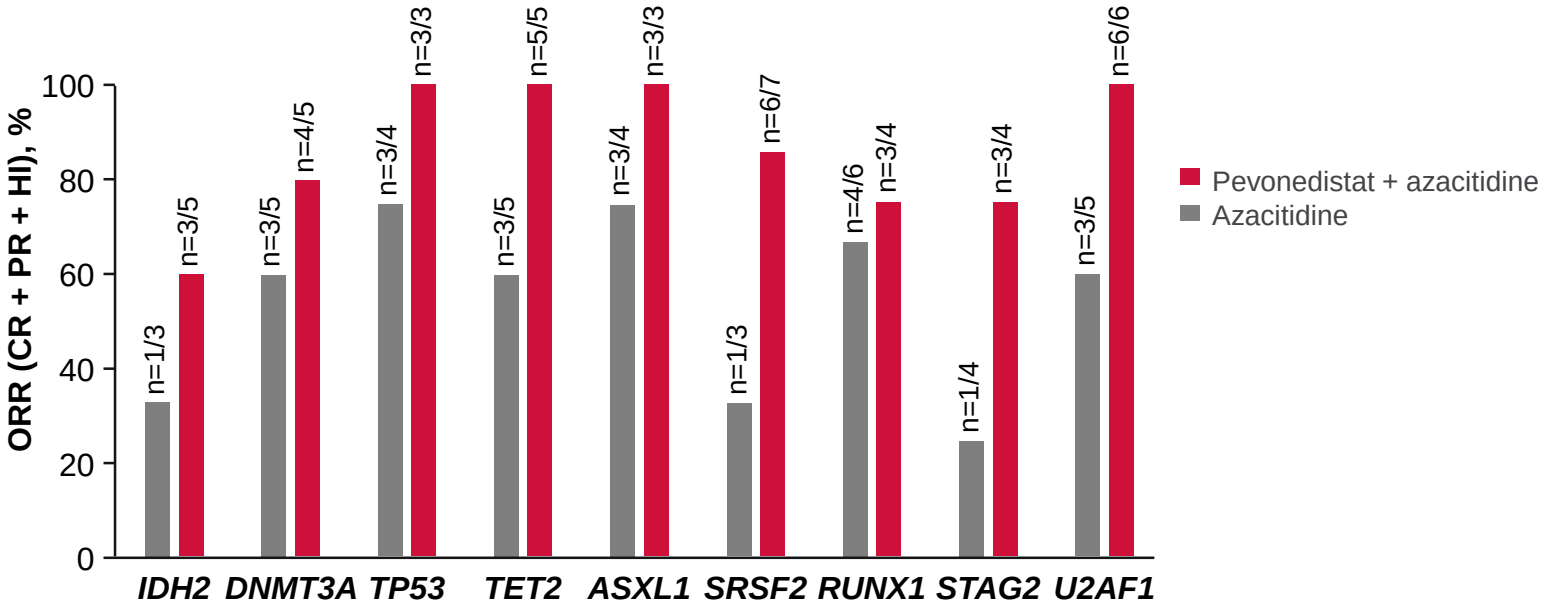
Clinical activity was observed in patients with higher-risk MDS who had poor-risk cytogenetics and in patients with adverse-risk mutations, including TP53



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Conclusions

- Encouraging efficacy was observed with pevonedistat + azacitidine in patients with higher-risk MDS in the P-2001 study.
- Longer EFS and encouraging OS with pevonedistat + azacitidine versus azacitidine 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 + azacitidine 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 + azacitidine, without added myelosuppression.
- The phase 3 PANTHER trial (NCT03268954) of pevonedistat + azacitidine is fully enrolled and will further clarify these findings.

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Acknowledgements

- **We thank all of the patients and their families, and the investigators and staff at all clinical sites, for their participation in the study.**

- We would also like to acknowledge Helen Kitchen of FireKite, an Ashfield company, part of UDG Healthcare plc, for writing support during the development of this presentation, which was funded by Millennium Pharmaceuticals, Inc., and complied with Good Publication Practice 3 ethical guidelines (Battisti et al. Ann Intern Med 2015;163:461–4), and editorial support from Marcel Kuttab, PharmD (Millennium Pharmaceuticals, Inc.).

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