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Lower residual mutation load following treatment with pevonedistat + azacitidine versus azacitidine alone: Comparative analysis of study arms in P-2001, a randomized phase 2 trial

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Novel targets in MDS

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Disclosures

- Sharon Friedlander, *employed by Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited*
- Andrew Krueger, *employed by Millennium Pharmaceuticals, Inc.*
- Kevin Galinsky, *employed by Millennium Pharmaceuticals, Inc.*
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- Douglas V. Faller, *employed by Millennium Pharmaceuticals, Inc.*
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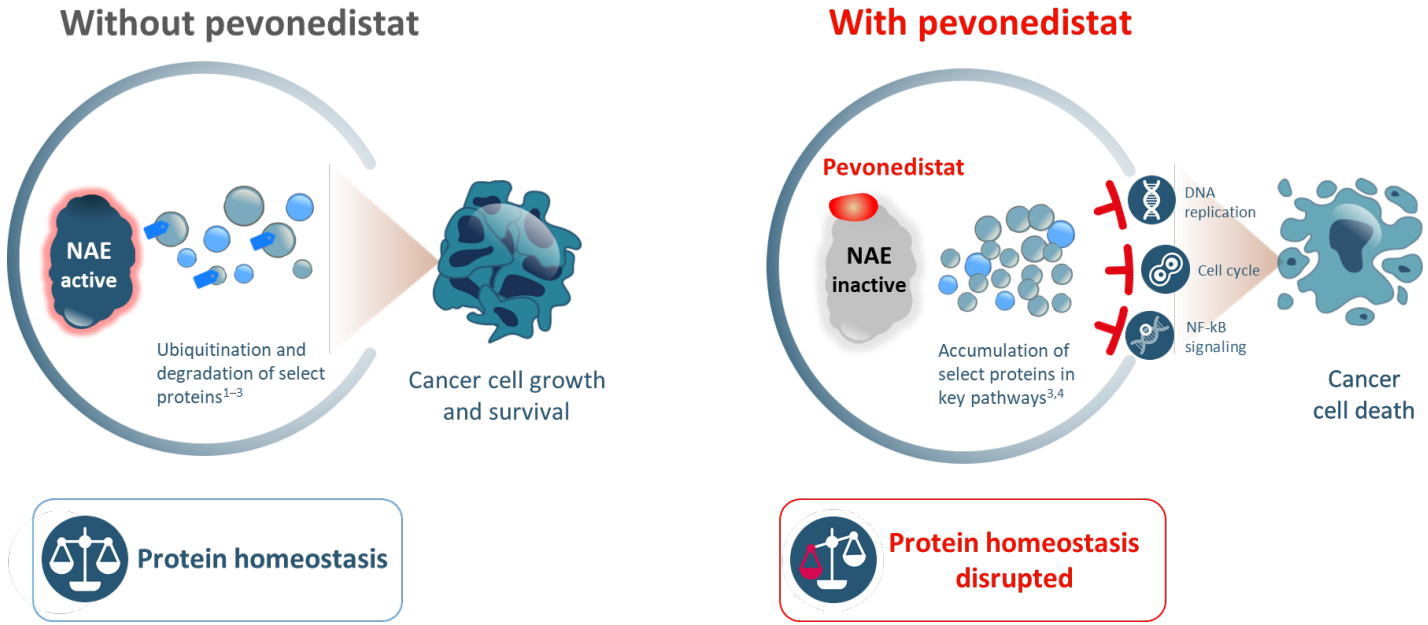
Introduction

- MDS and AML share foundational biology, molecular mutations that drive disease, and clinical features[1–4]
- Lower intensity therapy for MDS and AML with 20–30% blasts includes a backbone of HMAs[5]
- Novel, effective therapies that do not worsen myelosuppression are needed

Pevonedistat is a selective NEDD8-activating enzyme (NAE) inhibitor that leads to cancer cell death by disrupting protein homeostasis[6–9]



AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; HMA, hypomethylating agent; MDS, myelodysplastic syndromes; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NEDD8, neural-precursor-cell-expressed developmentally down-regulated protein 8.

1. DiNardo CD, *et al. Am J Hematol* 2016;91:227–32; 2. Solary E. *Blood* 2017;130:126–36; 3. Catenacci DV, Schiller GJ. *Blood Rev* 2005;19:301–19; 4. Cheson BD. *Oncologist* 1997;2:28–39; 5. Bewersdorf JP, *et al. Ther Adv Hematol* 2020;11:1–228; 6. Soucy TA, *et al. Genes Cancer* 2010;1:708–16; 7. Soucy TA, *et al. Nature* 2009;458:732–6; 8. Brownell JE, *et al. Mol Cell* 2010;37:102–111; 9. Swords RT, *et al. Blood* 2010:115:3796–800;
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Study P-2001 (NCT02610777): Phase 2, randomized, open-label, global, multicenter study[1]

ITT patients included those with:
- **higher-risk MDS (n=67)**
- **higher-risk CMML (n=17)**
- **LB-AML (n=36)**

AND who:
- had no previous HMAs
- were ineligible for allogeneic SCT

Randomization

1:1
N=120

Pevonedistat + azacitidine
Pevonedistat: 20 mg/m^2 (IV) on days 1, 3, 5
Azacitidine: 75 mg/m^2 (IV or SC) on days 1–5, 8, 9

Repeat every 28 days

Azacitidine
75 mg/m^2 (IV or SC) on days 1–5, 8, 9

- **Endpoints:**
  - OS
  - EFS (defined as time to death or transformation to AML)

CI, confidence interval; CMML, chronic myelomonocytic leukemia; EFS, event-free survival; HR, hazard ratio; ITT, intent-to-treat; IV, intravenous; LB-AML, low-blast AML; OS, overall survival; SC, subcutaneous; SCT, stem-cell transplant.

1. Sekeres MA, *et al*. *Leukemia* 2021; doi:10.1038/s41375-021-01125-4.
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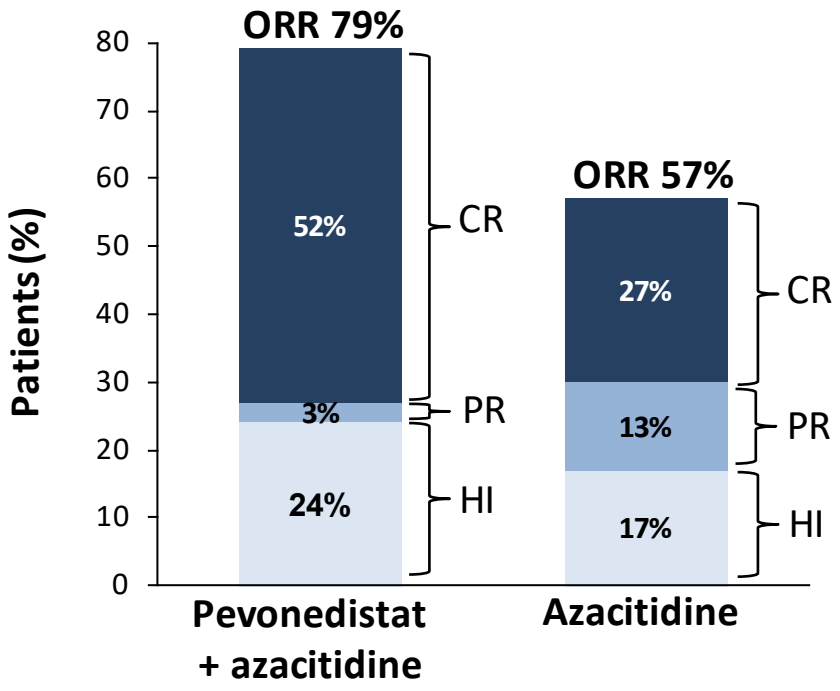
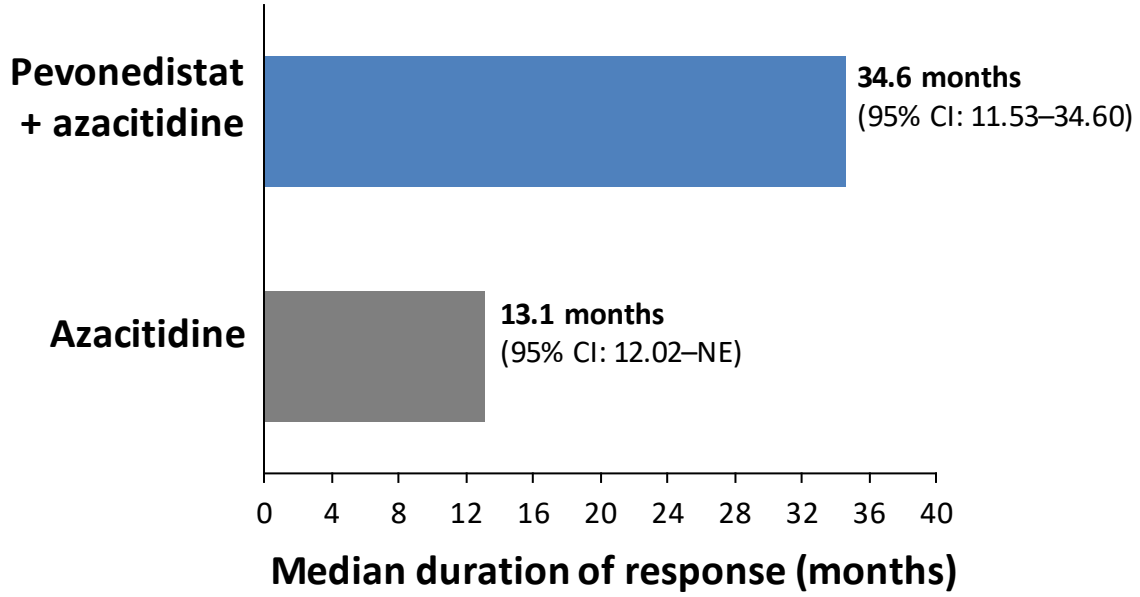
Encouraging clinical efficacy with pevonedistat + azacitidine in patients with higher-risk MDS: Results from study P-2001

Response-evaluable patients with higher-risk MDS (n=59)[1,2]





Treatment with pevonedistat + azacitidine was associated with nearly triple the median DOR and nearly double the CR in patients with higher-risk MDS (n=67)

CI, confidence interval; CR, complete response; DOR, duration of response; HI, hematological improvement; NE, not evaluable; ORR, overall response rate; PR, partial response.

1. Sekeres MA, *et al*. *Leukemia* 2021; doi: 10.1038/s41375-021-01125-4; 2. Sekeres MA, *et al*. Presented at the 62nd Annual Meeting and Exposition of the American Society of Hematology, Dec 5–8, 2020 [abstract 653]

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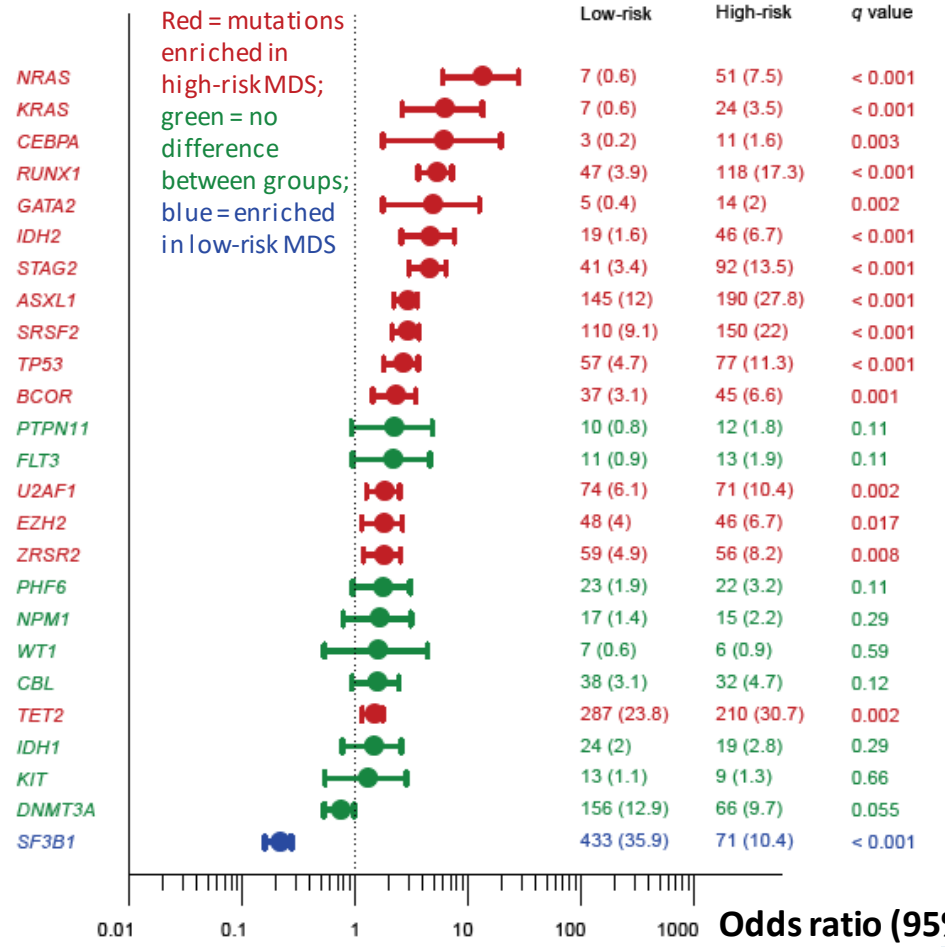
Mutations associated with leukemic transformation and disease progression are enriched in high-risk vs low-risk MDS

- MDS and secondary AML involve cells that harbor mutations in many of the same genes and functional categories; hence, they are perceived to be a disease continuum[1–3]
  - Mutations in MAP kinase signaling and myeloid transcription factor genes are associated with disease progression and leukemic transformation[4]
- **Based on the clinical findings in P-2001, we hypothesized that treatment with pevonedistat + azacitidine would induce a deeper and more persistent molecular response than azacitidine alone; having an impact on mutation profiles**

Univariate analysis of frequency of mutations (odds ratio) between low- vs high-risk MDS[5]



MAP, mitogen-activated protein.

1. DiNardo CD, *et al. Hematology Am Soc Hematol Educ Program* 2016;1:348–55; 2. Murati A, *et al. BMC Cancer* 2012;12:304; 3. Caponetti GC, *et al. Int J Lab Hematol* 2020;42:671–84; 4. Higgins A, *et al. Genes* 2020;11:749; 5. Makishima H, *et al. Nat Genet* 2017;49:204–12. Figure reproduced with permission from the author.

Residual mutation load: Prespecified comparative analysis of study arms in P-2001

Collected at screening

Baseline bone marrow aspirate samples (n=96), including:
- 55 patients with higher-risk MDS
- 15 patients with higher-risk CMML
- 26 patients with LB-AML

Baseline analysis

NGS of DNA

Targeted panel,[a] incorporating 123 myeloid genes
Sensitivity: 1% VAF

Collected at selected timepoints (day 22 of cycle 2, 4 and 7, and at relapse)

Longitudinal bone marrow aspirate samples (n=58), including:
- 33 patients with higher-risk MDS
- 7 patients with higher-risk CMML
- 18 patients with LB-AML

Longitudinal analysis

Ultra-deep duplex DNA sequencing

Targeted panel[a] of 54 myeloid genes
Sensitivity: <0.02% VAF

Developed in collaboration with Dr. R. Coleman Lindsley at Dana-Farber Cancer Institute and the Broad Institute in Boston, MA, USA

[a]Samples were sequenced with a mean target coverage of 9500x using a TruSeq Hybrid Capture Panel incorporating 123 myeloid genes. Single-nucleotide variants and insertions and deletions (indels) were identified with MuTect.
NGS, next-generation sequencing; VAF, variant allele frequency.
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The duplex sequencing cohort was representative of the general study population

Treatment arm	DUPLEX SEQUENCING COHORT (n=45)		STUDY POPULATION (n=120)	
	Pevonedistat + azacitidine (n=22)	Azacitidine (n=23)	Pevonedistat + azacitidine (n=58)	Azacitidine (n=62)
Higher-risk MDS, n (%)	11 (50)	16 (70)	32 (55)	35 (56)
CMML, n (%)	4 (18)	3 (13)	9 (16)	8 (13)
LB-AML, n (%)	7 (32)	4 (17)	17 (29)	19 (31)
Male/female, n (%)	34 (76)/11 (24)		83 (69)/37 (31)	
Age, years, median (range)	73 (44–91)		72 (34–91)	
IPSS-R risk score for patients with MDS+CMML, n (%)	Intermediate: 20 (59) High: 6 (18) Very high: 8 (23)		Intermediate: 29 (35) High: 27 (32) Very high: 28 (33)	
ELN category for patients with AML, n (%)	Adverse: 7 (64) Intermediate: 1 (9) Indeterminate: 3 (27)		Adverse: 15 (62) Intermediate: 3 (13) Indeterminate: 6 (25)	

Results in the ITT population[1]

Pevonedistat + azacitidine versus azacitidine

- **Median EFS:** 21.0 versus 16.6 months (HR: 0.67; 95% CI: 0.42–1.05; P=0.076)

Results in duplex sequencing population

Pevonedistat + azacitidine versus azacitidine

- **Median EFS:** 20.3 versus 16.9 months (HR: 0.12; 95% CI: 0.024-0.6; P=0.01)

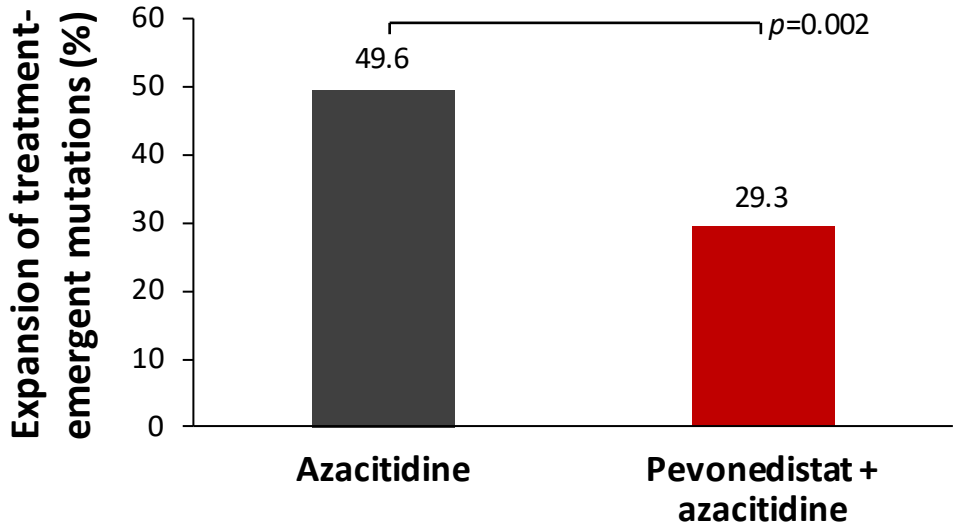
ELN, European LeukemiaNet; HR, hazard ratio; IPSS-R, Revised International Prognostic Scoring System.

1. Sekeres MA, *et al*. *Leukemia* 2021; doi:10.1038/s41375-021-01125-4.

Friedlander S, *et al*. EHA 2021. Abstract code S166. @MikkaelSekeres

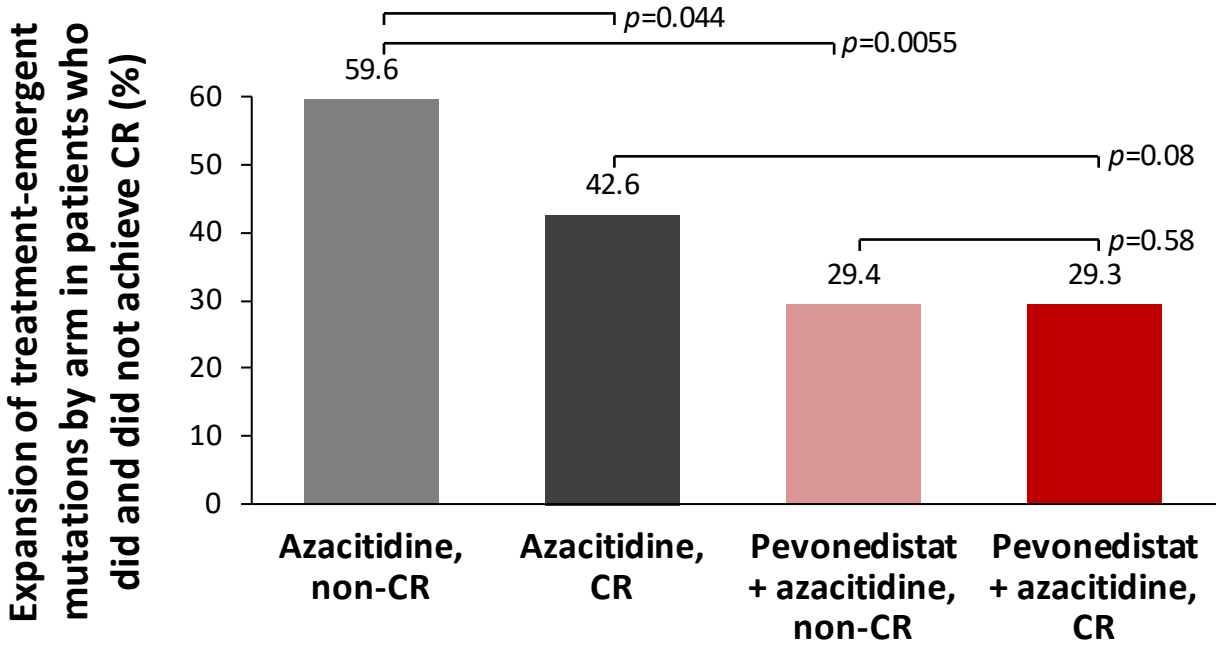
Addition of pevonedistat to azacitidine improved control of clonal expansion, even in patients who did not achieve CR

Pevonedistat + azacitidine was associated with significantly less expansion of treatment-emergent mutations than azacitidine alone[a]



	Azacitidine	Pevonedistat + azacitidine
Expanding, n	63	27
Non-expanding, n (data not shown)	64	65
P=0.002	0.496	0.293

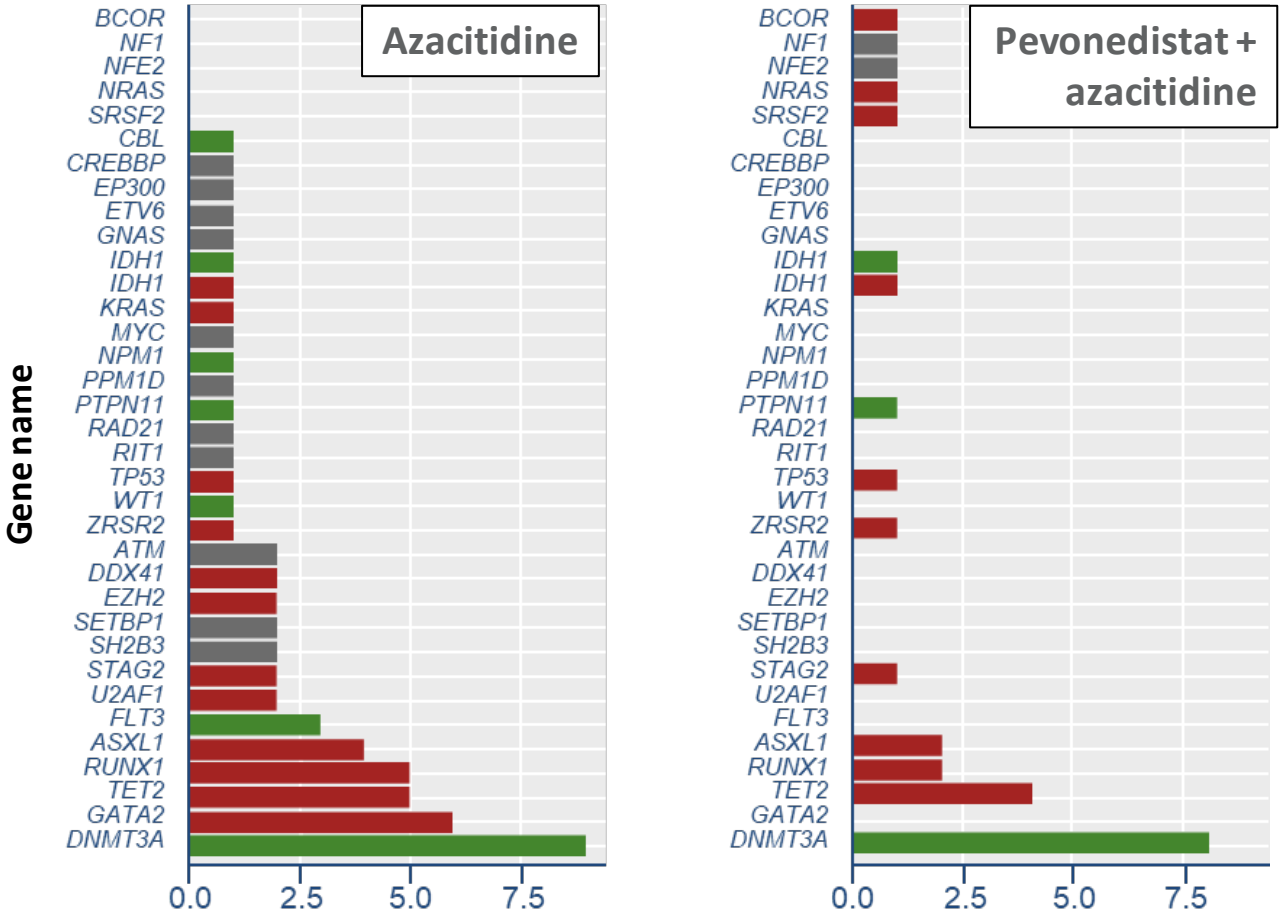
Pevonedistat controlled clonal expansion in patients who did and did not achieve CR, mCR or CRi

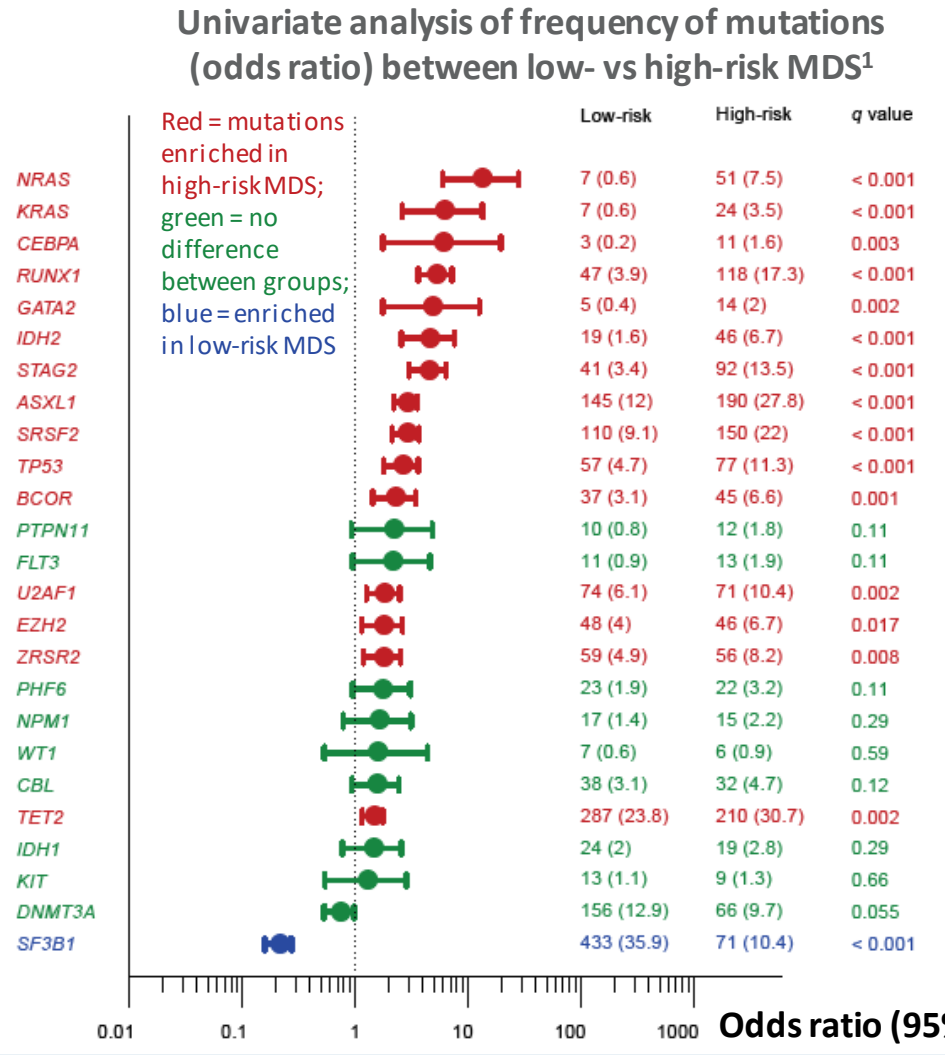


Trend p-value=0.0008

[a]Expansion of treatment-emergent mutations was defined as either newly detected or numerically increased VAF after treatment.
CRi, CR with incomplete blood-count recovery; mCR, marrow CR.

Treatment effect was seen across genes associated with both lower- and higher-risk MDS



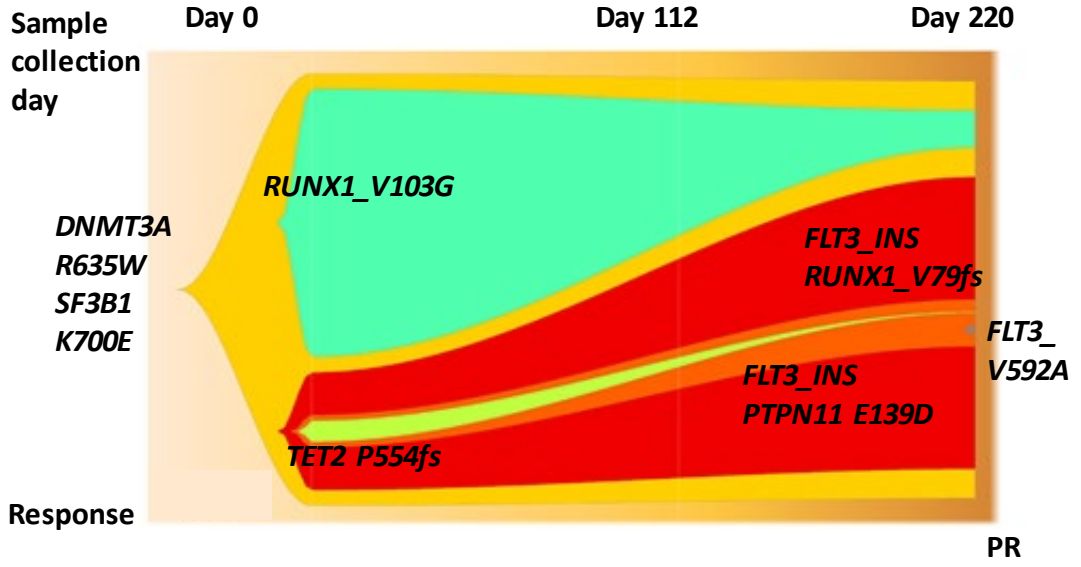


[a]Expansion of treatment-emergent mutations was defined as either newly detected or increasing VAF after treatment. [b]Non-expanding data not shown.

1. Makishima H, *et al. Nat Genet* 2017;49:204–12. Figure reproduced with permission from the author.

Higher-risk MDS: Expansion of genes associated with disease progression and leukemic transformation in the azacitidine arm

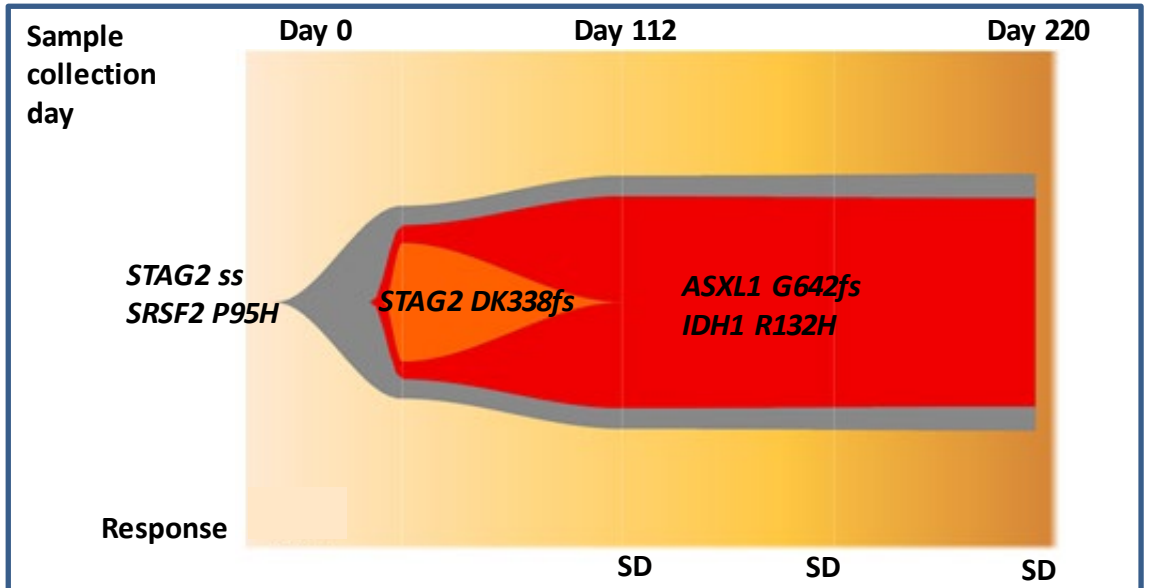
Patient with higher-risk MDS treated with azacitidine



Age, years	73
IPSS-R score	6.5 (very high risk)
Transfusion dependent status at baseline	No
Pancytopenia status at baseline	No
DOR, months	2.8
EFS (time to AML transformation or death), months	9.6
OS, months	14.9

Genes associated with disease progression and leukemic transformation, including MAP kinase signaling (*FLT3*, *PTPN11*) and myeloid transcription factors (*RUNX1*)

Patient with higher-risk MDS treated with pevonedistat + azacitidine



Age, years	81
IPSS-R score	7.5 (very high risk)
Transfusion dependent status at baseline	Yes
Pancytopenia status at baseline	No
DOR (PD), months	16.9
EFS (time to AML transformation or death), months	21.7
OS, months	21.7

Clearance of the *STAG2 Dk338fs* clone and sustainability of a subclone harboring genes associated with DNA methylation/chromatin modification (*ASXL1* and *IDH1*)

C, cycle; DOR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease.

Conclusions

- Consistent with clinical findings in P-2001, these data suggest that pevonedistat + azacitidine reduces mutation burden compared with azacitidine alone, with the following potential clinical benefits
  - Lesser likelihood of treatment-emergent resistance
  - Controlled expansion of mutations associated with higher-risk MDS and AML transformation
  - Increased durability of treatment response
- These findings will be further assessed in the following clinical trials:

Trial	Phase	NCT number	Patients	Treatment
PANTHER	3	NCT03268954	Patients with higher-risk MDS, AML (20–30% blasts) or CMML	Pevonedistat + azacitidine versus azacitidine alone
PEVOLAM	3	NCT04090736	Patients with newly diagnosed AML who are unfit for intensive chemotherapy	Pevonedistat + azacitidine versus azacitidine alone
PEVENAZA	2	NCT04266795	Patients with newly diagnosed AML who are unfit for intensive chemotherapy	Pevonedistat + venetoclax + azacitidine versus venetoclax + azacitidine

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