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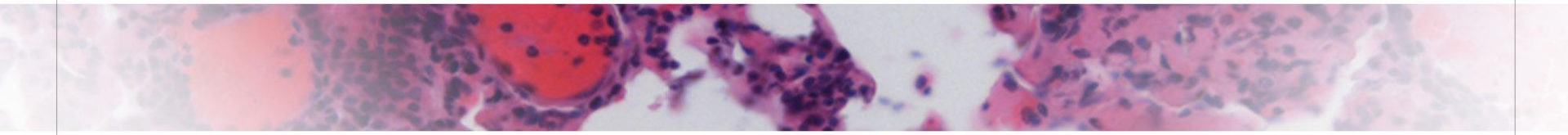

# A Randomized, Phase 2 Study of Pevonedistat, Venetoclax, and Azacitidine Versus Venetoclax plus Azacitidine in Adults with Newly Diagnosed Acute Myeloid Leukemia (AML) Who Are Unfit for Intensive Chemotherapy

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**For questions or comments please contact Dr Nicholas Short: nshort@mdanderson.org**

# Disclosures

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**Co-author disclosures:**

**FS, DZ, OT, SF, DVF:**

- Employment: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

**Off-label drug use:**

- This presentation contains information about investigational use of pevonedistat. Safety and efficacy have not been determined.

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# Unmet need in AML

- More than 50% of patients with AML are ineligible for intensive chemotherapy.[1]
- Outcomes are poor with lower-intensity treatments, such as the hypomethylating agents azacitidine and decitabine:[2–4]
  - Low response rates (10–30%)
  - Median OS less than 1 year.

- Some improvements, compared with single-agent hypomethylating agents, have been achieved using combination regimens.[5]
- The combination of venetoclax plus azacitidine is emerging as a standard of care for older patients ineligible for standard induction therapy, based on the results of the VIALE-A study:[6]
  - Improved OS with venetoclax + azacitidine vs azacitidine alone (median 14.7 vs 9.6 months; HR 0.66 [95% CI 0.52–0.85]; p<0.001).

**Despite recent advances, novel combinations are needed that can improve patient outcomes without increasing toxicity**

AML, acute myeloid leukemia; CI, confidence interval; HR, hazard ratio; OS, overall survival.

1. Griffiths EA, et al. Leuk Res 2020;91:106339; 2. Dombret H, et al. Blood 2015;126:291–9; 3. Kantarjian HM, et al. J Clin Oncol 2012;30:2670–7; 4. Cashen AF, et al. J Clin Oncol 2010;28:556–61; 5. Short NJ, et al. Cancer Discov 2020;10:506–25; 6. DiNardo CD, et al. N Engl J Med 2020;383:617–29.

# Pevonedistat

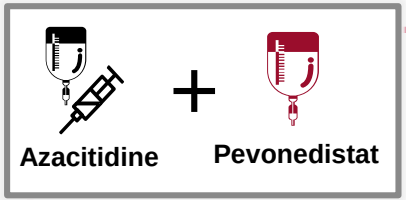
- Pevonedistat is the first-in-class small-molecule inhibitor of the NEDD8-activating enzyme (NAE).[1]
- Inhibiting NAE blocks ubiquitination of select proteins upstream of the proteasome.[1,2]
- Treatment with pevonedistat disrupts cell cycle progression and cell survival, leading to cell death in cancers, including myeloid malignancies.[1,3]


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

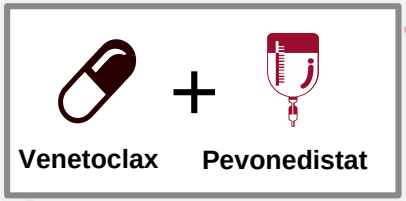
1. Soucy TA, et al. Nature 2009;458:732–6; 2. Brownell JE, et al. Mol Cell 2010;37:102–11; 3. Soucy TA, et al. Clin Cancer Res 2009;15:3912–6.

# PEVENAZA: study rationale

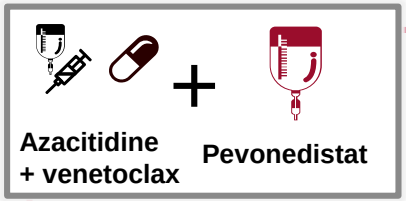
Pevonedistat has shown synergistic effects in combination with venetoclax and azacitidine in multiple studies.




- **Tolerable and clinically active** in patients aged ≥60 years with untreated AML.[1]
- Improved EFS and OS, **did not increase myelosuppression**, and maintained azacitidine dose intensity in patients with higher-risk MDS/CMML or low-blast AML.[2]




- **Synergistic cytotoxic effects** in AML cell lines and primary clinical AML samples.[3]
- Resistance to venetoclax may be overcome through pevonedistat-induced neutralization of pro-survival proteins, including MCL-1.[4]



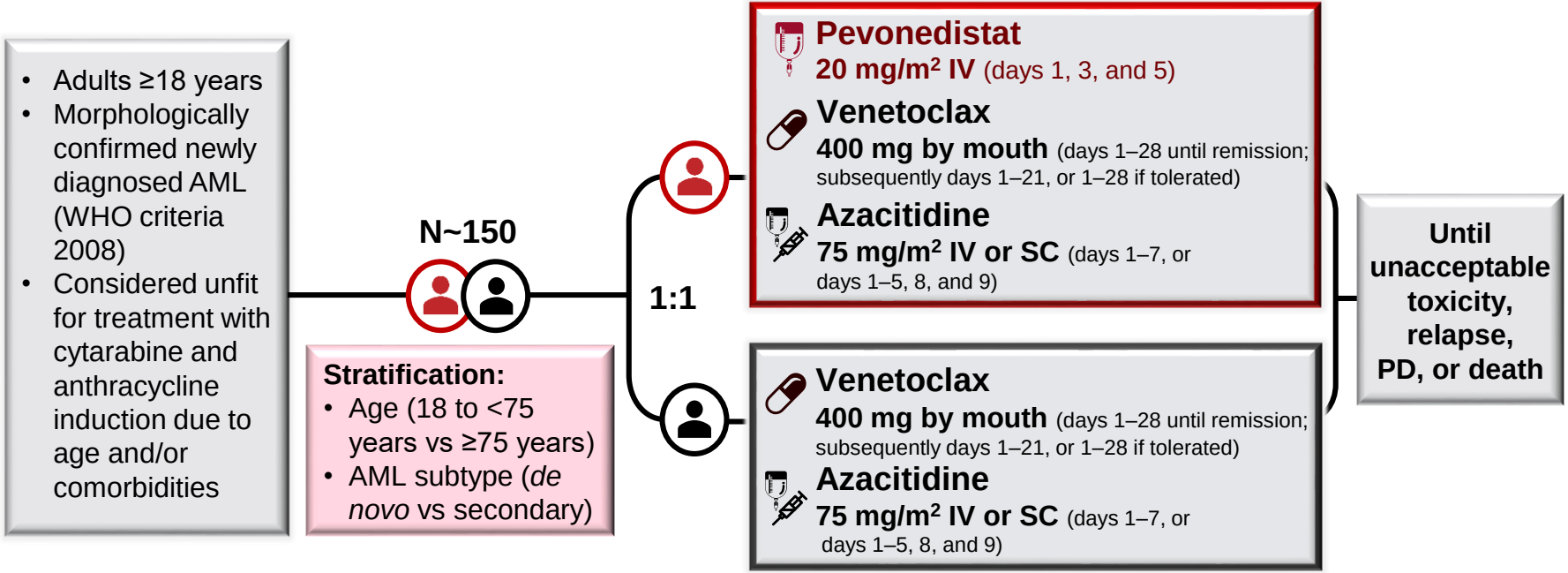

- **High response rate** demonstrated and RP2D established in a phase 1/2 study of the triplet combination of pevonedistat, venetoclax, and azacitidine in secondary AML.[5]

CMML, chronic myelomonocytic leukemia; EFS, event-free survival; MCL-1, myeloid leukemia cell differentiation protein; MDS, myelodysplastic syndromes; RP2D, recommended phase 2 dose.

1. Swords RT, et al. Blood 2018;131:1415–24; 2. Ades L, et al. J Clin Oncol 2020;38(15_suppl):abstract 7506; 3. Knorr KLB, et al. Cell Death Differ 2015;22:2133–42; 4. Niu X, et al. Clin Cancer Res 2016;22:4440–51; 5. Short N, et al. Hemasphere 2020;4(Suppl. 1):abstract EP557.

# PEVENAZA: study design

**Randomized, open-label, controlled, phase 2 study (NCT04266795)[1]**




IV, intravenous; PD, progressive disease; SC, subcutaneous; WHO, World Health Organization.

1. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04266795.

# PEVENAZA: study endpoints

## Primary endpoint: EFS

Defined as time from randomization to the date of: failure to achieve CR/CRi (i.e. discontinuing treatment without achieving CR/CRi), relapse from CR or CRi, or death from any cause, whichever occurs first[1]

## Key secondary endpoint: OS

Defined as time from randomization to death from any cause

## Other secondary endpoints:

- 6-month, 1-year, and 2-year survival rates
- 30- and 60-day mortality
- EFS after cycle 6
- Response rates
- Duration of response
- Time to first response
- Time to relapse from CR/CRi or death
- Health-related QoL
- PK
- Rate of hospitalization
- Safety

## Exploratory endpoints:

- Molecular characterization of bone marrow aspirates for MRD and MoA studies
- Assessment of elimination of leukemic stem cells
- Identification of predictive biomarkers of response

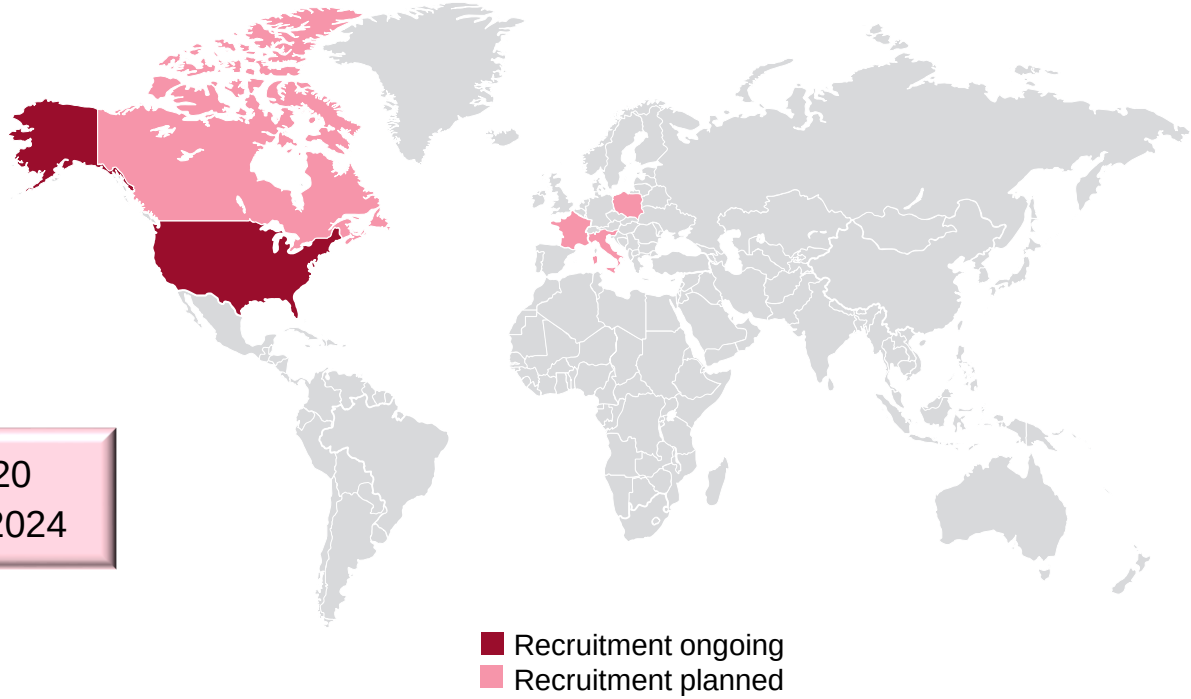
CR, complete remission; CRi, CR with incomplete blood count recovery; MoA, mechanism of action; MRD, measurable residual disease; PK, pharmacokinetics; QoL, quality of life.

1. Döhner H, et al. Blood 2017;129:424–47.

# PEVENAZA: study locations

- The study is planned to enroll ~150 patients at ~85 sites globally.
- Recruitment is ongoing in the United States, and planned in Canada, Italy, Poland, and France (other countries may be added).

**Study start date:** October 9, 2020
**Estimated completion:** March 2024



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