

# Biomarker results from PEVENAZA, a randomized phase 2 study of venetoclax and azacitidine +/- pevonedistat in newly diagnosed AML patients unfit for intensive chemotherapy: Increased efficacy in a subset of patients with IDH1/2 mutations and other observations

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## Background

- Acute myeloid leukemia (AML) is a very heterogeneous disease characterized by many chromosomal translocations and genetic mutations resulting in abnormal proliferation and differentiation of a clonal population of myeloid precursors.<sup>1</sup>
- Standard therapy for treating AML consists of intensive chemotherapy followed by hematological stem cell transplant to achieve complete remission (CR). Many newly diagnosed patients with AML are ineligible for intensive chemotherapy due to pre-existing comorbidities and older age.
- The phase 3 VIALE-A study established venetoclax and azacitidine combination as a new standard of care in patients with newly diagnosed AML.<sup>2</sup> The phase 2 PEVENAZA trial evaluated the combination of venetoclax plus azacitidine with the addition of pevonedistat in the newly diagnosed patient setting. Results of biomarker analyses from baseline and on-treatment bone marrow samples are presented here.

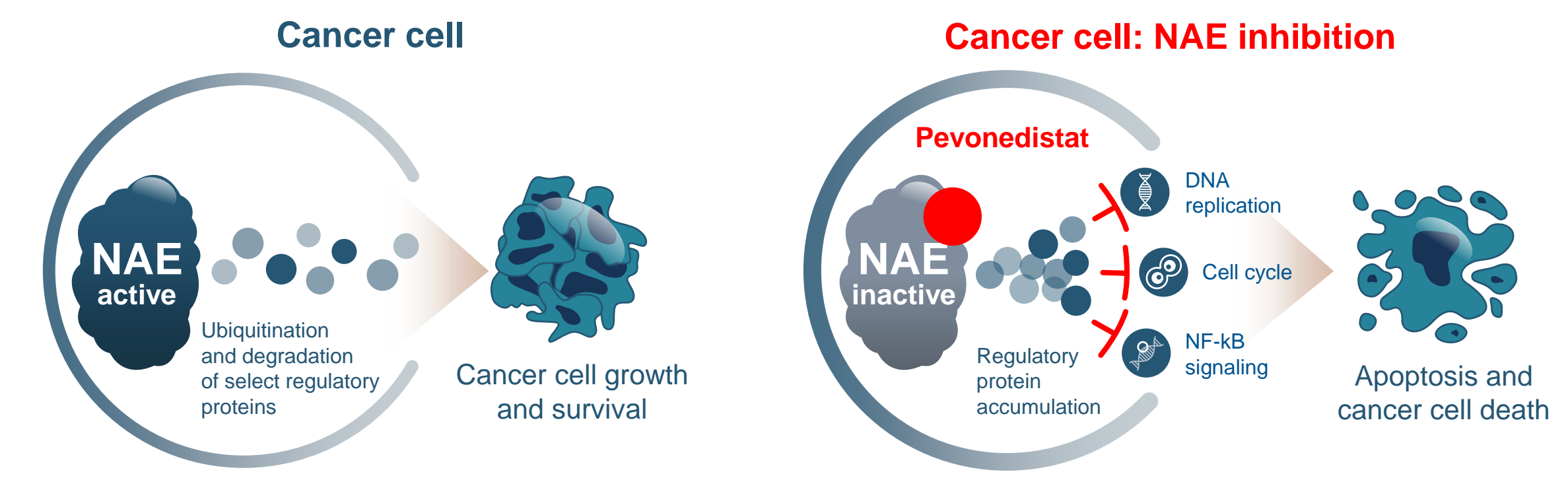
## Objectives

- The exploratory biomarker analysis in PEVENAZA trial in newly diagnosed AML aimed to determine:
  - The association between molecular mutations and clinical response
  - The expression level of AML-associated tumor antigens (TAA) such as CD33 and CD123 in AML blasts and leukemic stem cell (LSCs)
  - The effect of venetoclax + azacitidine treatment on the expression of TAAs, as well as the correlation between this expression and European LeukemiaNet (ELN) risk or molecular mutations

## Pevonedistat

- Pevonedistat is a first-in-class inhibitor of NEDD8 activating enzyme (NAE) and prevents the activation of Cullin-RING ligases necessary for proteasome mediated degradation of key regulatory proteins important in cell survival.

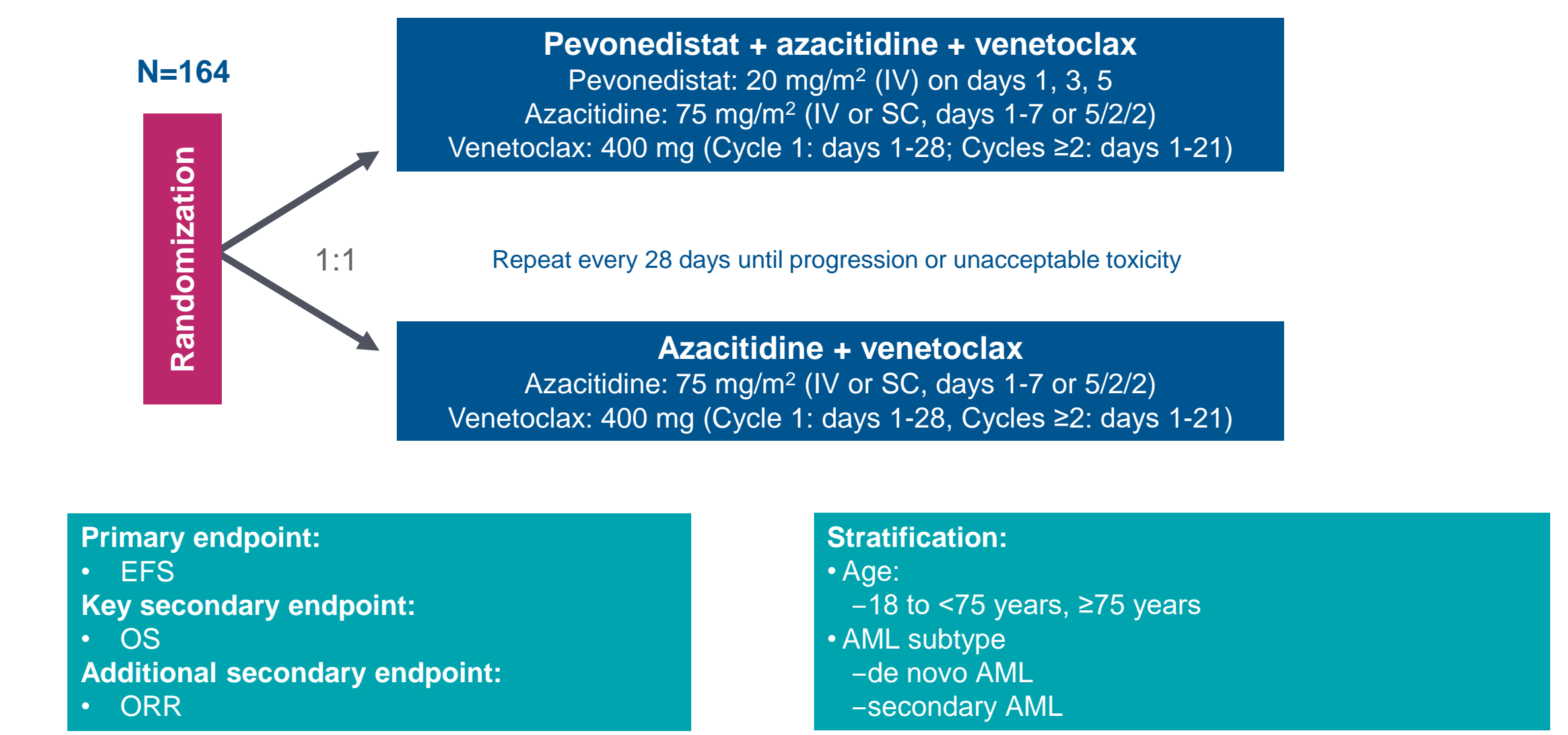
**Figure 1. Treatment with pevonedistat disrupts cell cycle progression and cell survival, leading to death of cancer cells**



## Study design and biomarker analysis schema

- PEVENAZA (NCT04266795) was a randomized, open label, phase 2 study of pevonedistat + azacitidine + venetoclax vs azacitidine + venetoclax in adult patients with newly diagnosed AML who were unfit for intensive chemotherapy.

**Figure 2a. PEVENAZA study design**

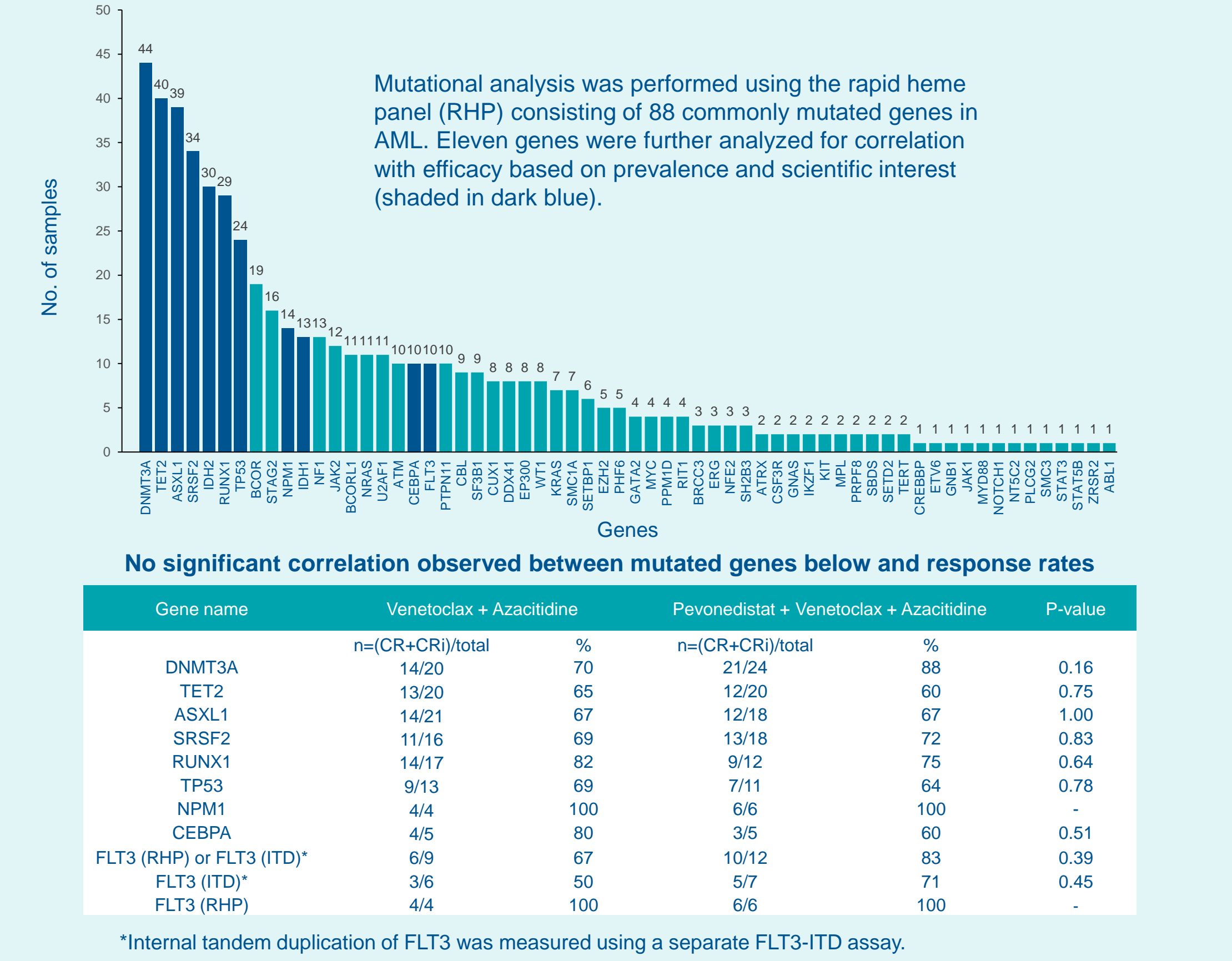


**Enrolling countries:** US, France, Italy and Poland  
EFS, event-free survival; IV, intravenous; ORR, overall response rate; OS, overall survival; SC, subcutaneous.

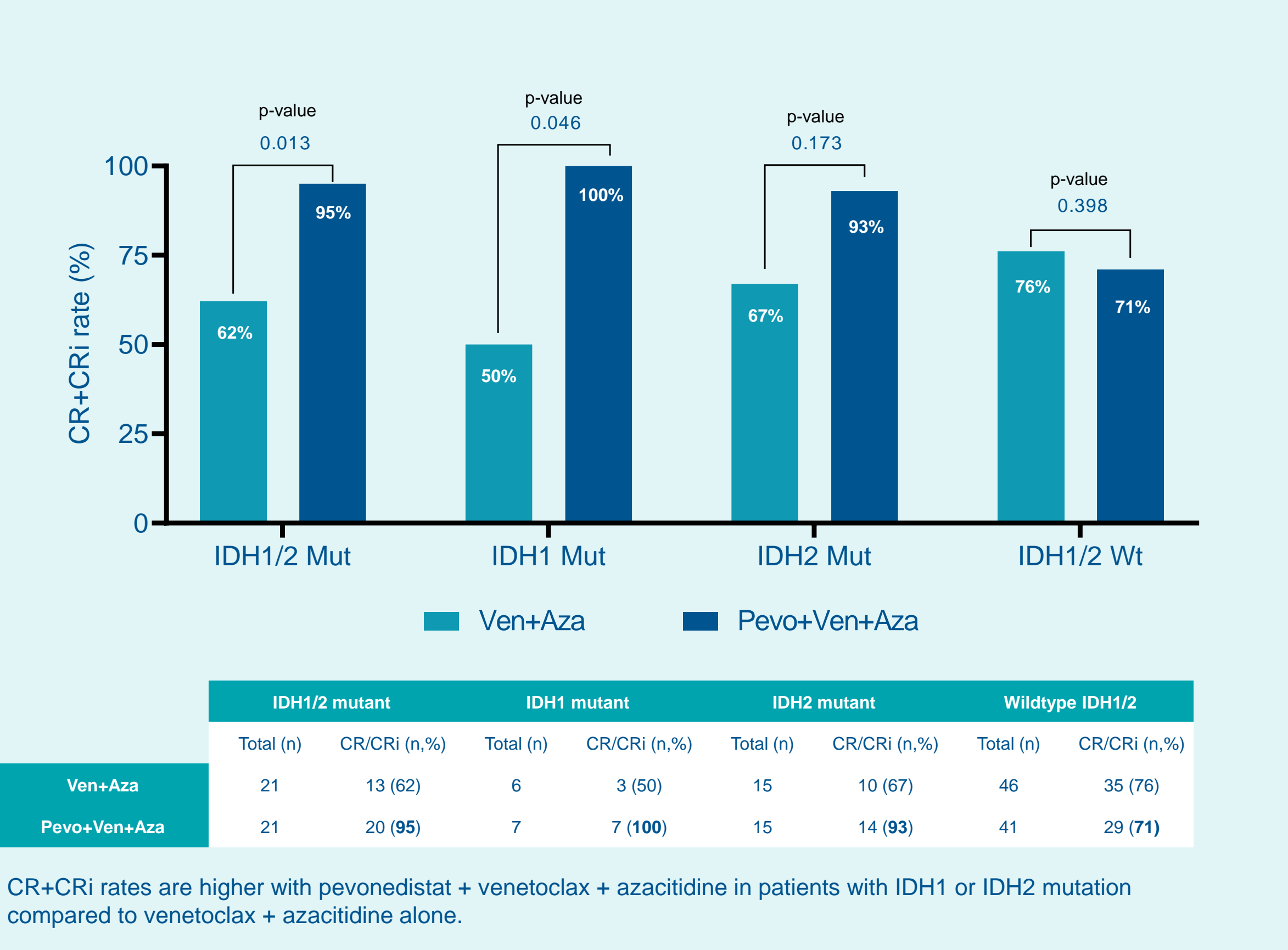
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3. Chan SM, et al. Nat Med. 2015;21(2):178-84.  
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2. Knorr KL, et al. Cell Death Differ. 2015;22(12):2133-42.

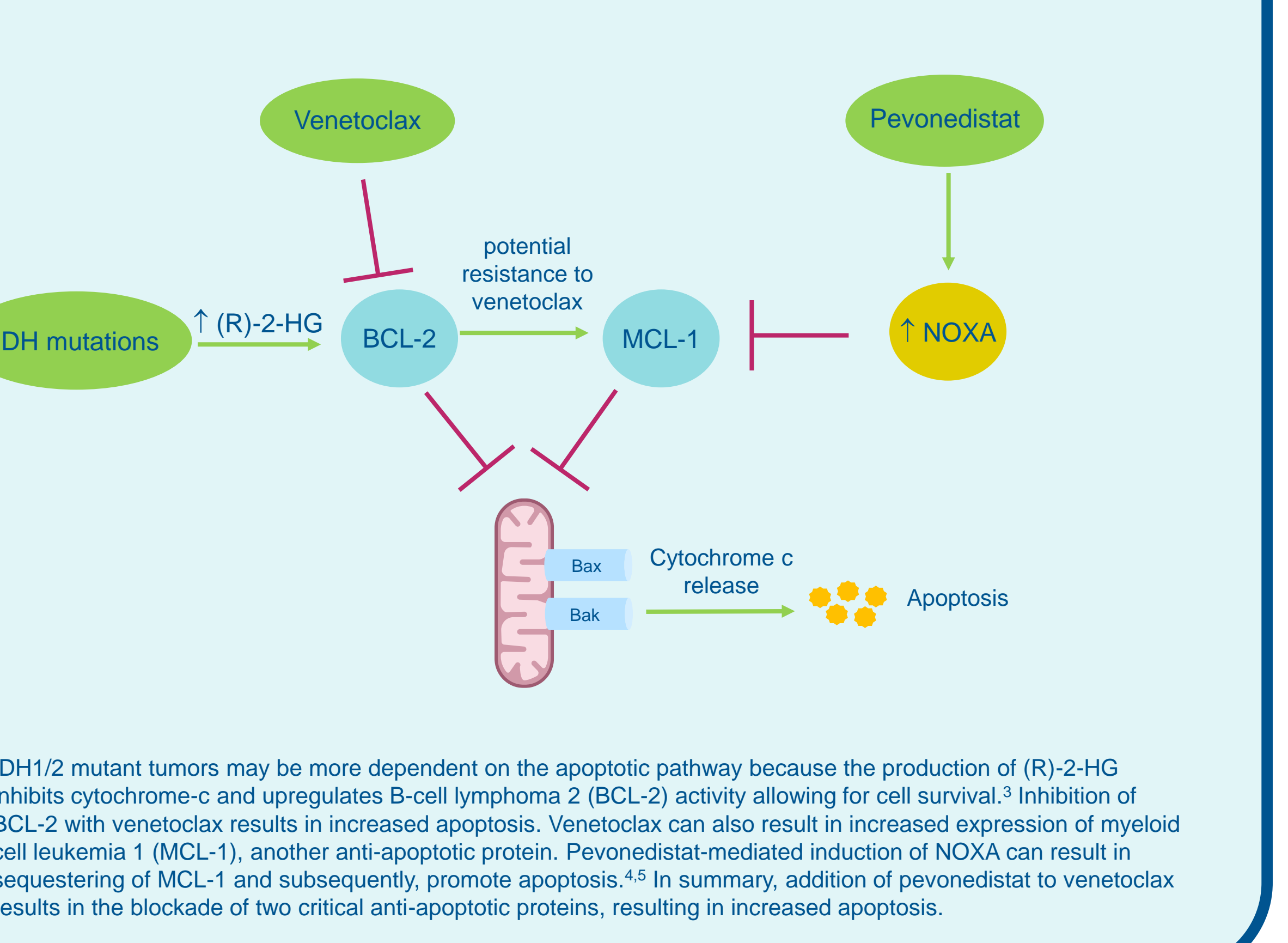
## Mutation landscape of most prevalent genes mutated in AML in response-evaluable patients



## Increased efficacy (CR+CRi) observed in patients with IDH1/2 mutation when pevonedistat is combined with venetoclax and azacitidine

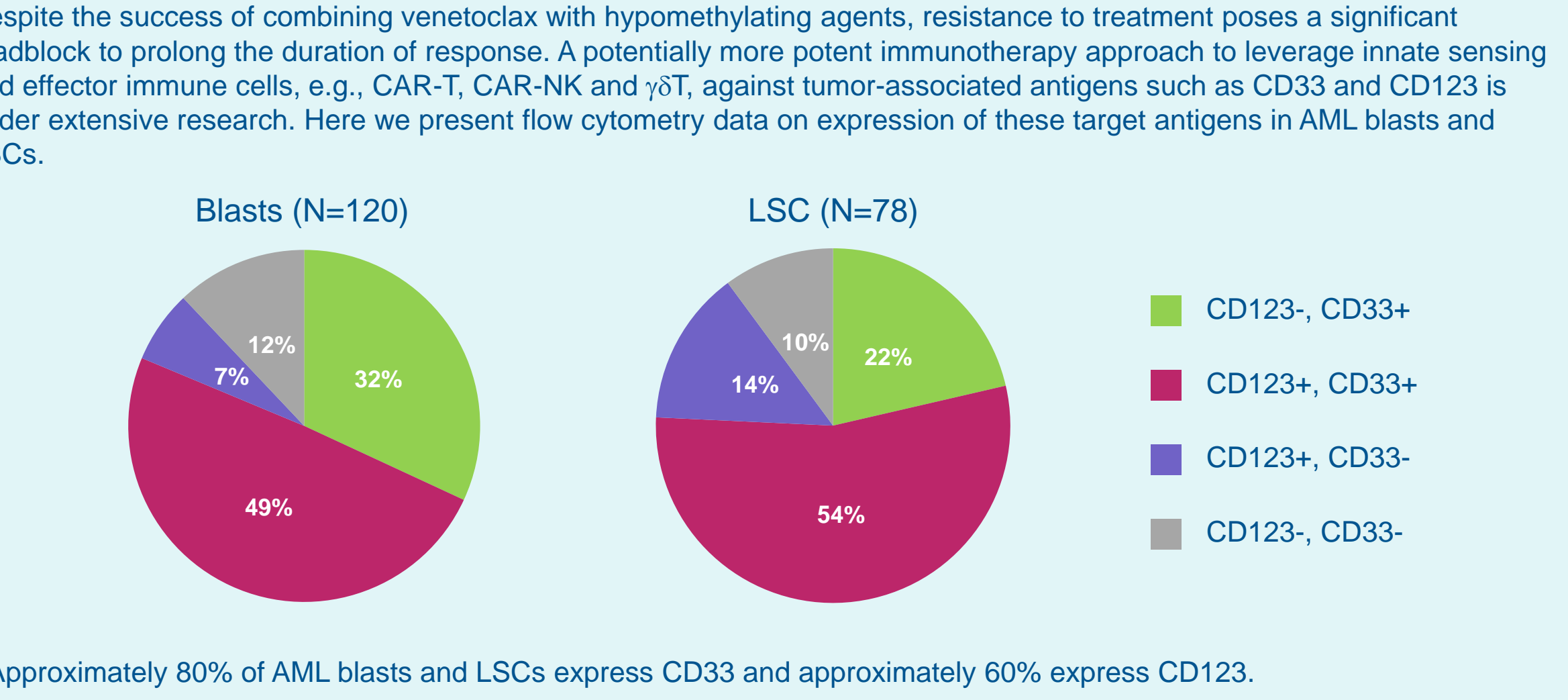


## Proposed mechanism of increased efficacy in IDH mutant population with pevonedistat

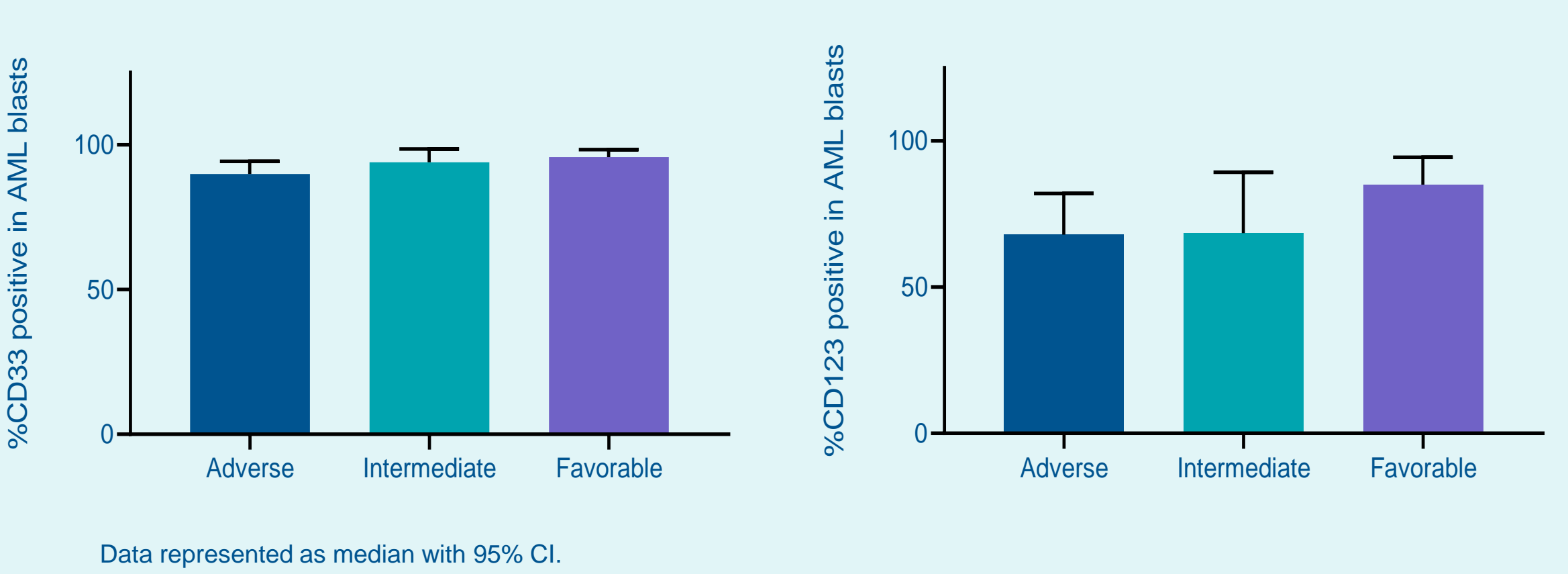


IDH1/2 mutant tumors may be more dependent on the apoptotic pathway because the production of (R)-2-HG inhibits cytochrome-c and upregulates B-cell lymphoma 2 (BCL-2) activity allowing for cell survival.<sup>3</sup> Inhibition of BCL-2 with venetoclax results in increased apoptosis. Venetoclax can also result in increased expression of myeloid cell leukemia 1 (MCL-1), another anti-apoptotic protein. Pevonedistat-mediated induction of NOXA can result in sequestering of MCL-1 and subsequently, promote apoptosis.<sup>4,5</sup> In summary, addition of pevonedistat to venetoclax results in the blockade of two critical anti-apoptotic proteins, resulting in increased apoptosis.

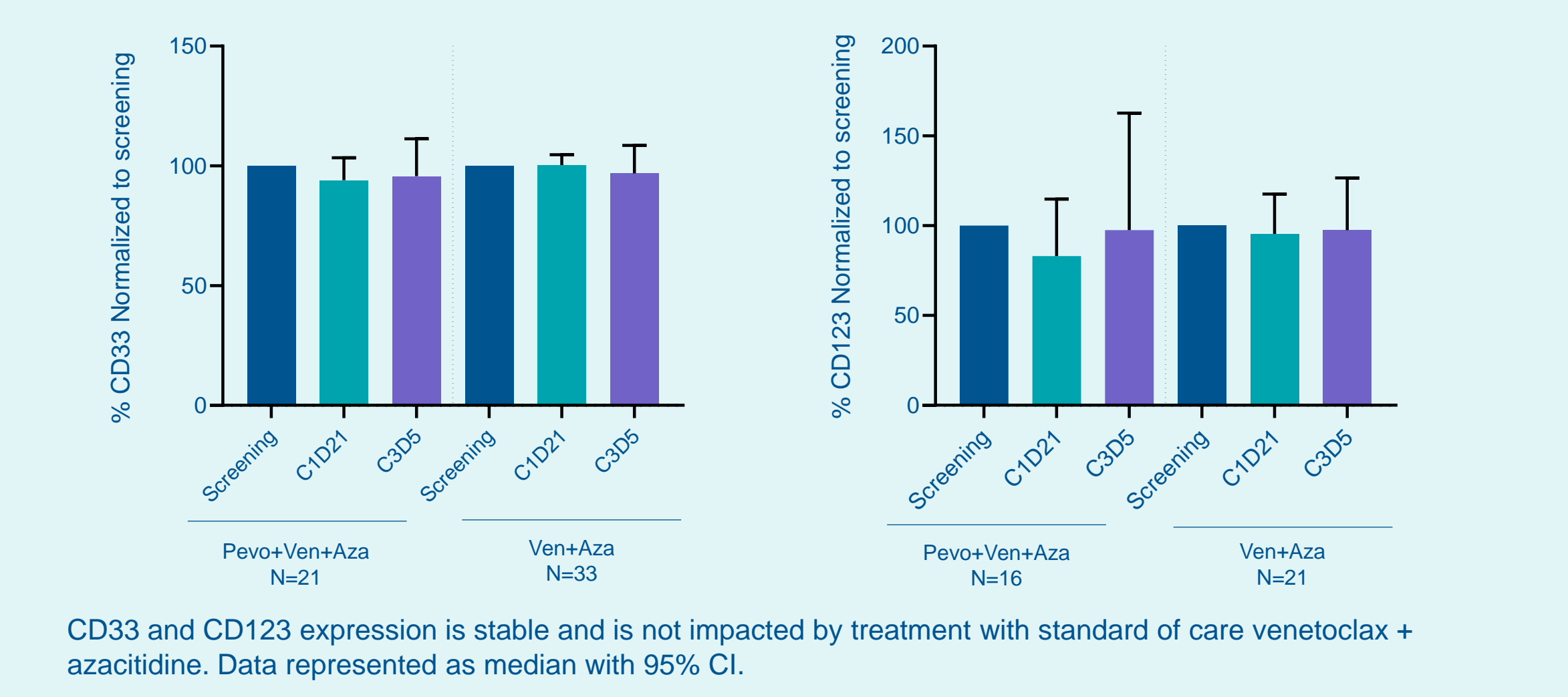
## Distribution of CD33 and CD123 expression in AML blasts and LSCs



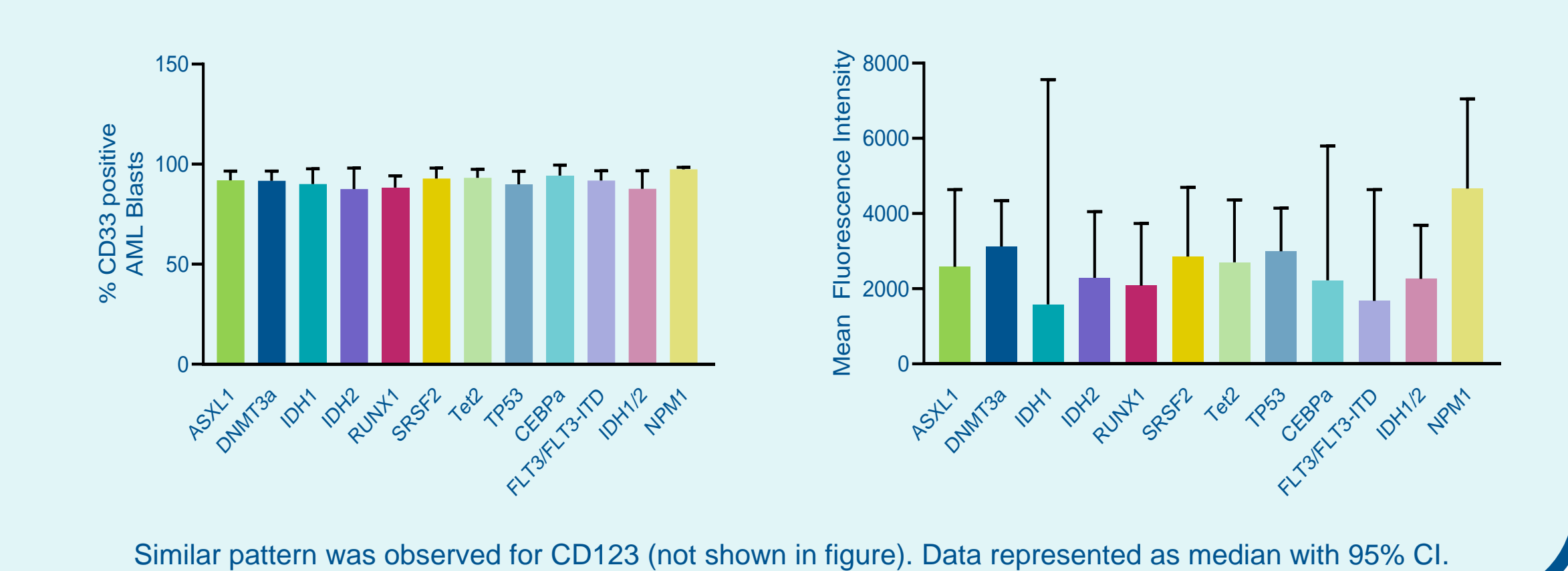
## Baseline CD33 and CD123 (% expression) in AML blasts is independent of ELN risk category



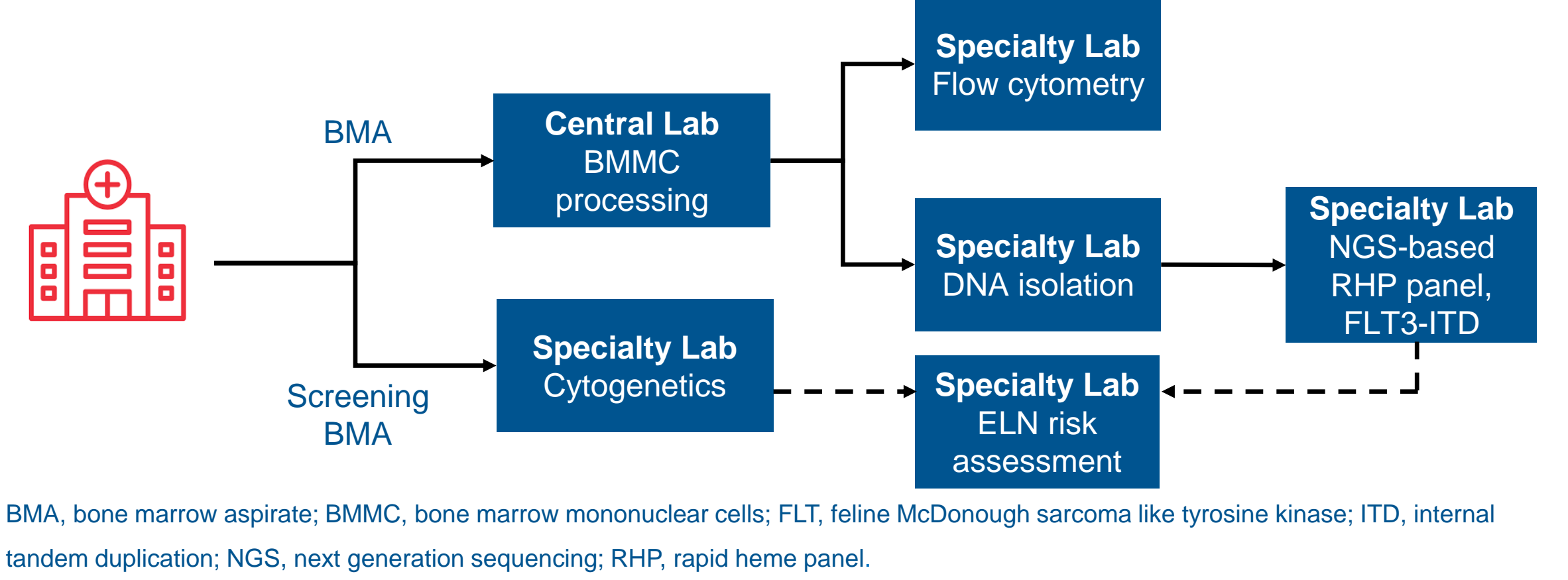
## CD33 and CD123 expression in AML blasts and LSCs is not significantly altered by Ven + Aza treatment



## Baseline CD33 (% expression and MFI) in AML blasts is independent of molecular mutations



**Figure 2b. Sample workflow for biomarker assessment**



BMA, bone marrow aspirate; BMMC, bone marrow mononuclear cells; FLT, feline McDonough sarcoma like tyrosine kinase; ITD, internal tandem duplication; NGS, next generation sequencing; RHP, rapid heme panel.

## Results

- In patients with newly diagnosed AML, the addition of pevonedistat to venetoclax/azacitidine increased CR + CRi with incomplete count recovery (CRi) rates in the IDH1/2 mutant population (95% Pev+Ven+Aza compared to 62% Ven +Aza) (p=0.013). No other statistically significant correlations were observed in patients with mutations in FLT3, NPM1, or seven other genes.
- Analysis of baseline blasts and LSCs across all patients for CD33 and CD123 suggest that targeting CD33 could reach ~70-80% of blasts/LSCs and ~60% of blasts/LSCs, respectively, while targeting both CD33/CD123 could reach up to 90% of blasts/LSCs.
- Expression of CD33 and CD123 did not show significant changes post-treatment with venetoclax + azacitidine (+/- pevonedistat), supporting the development of therapeutic agents against these potential targets for patients with relapsed/refractory AML who have progressed on venetoclax / azacitidine.
- Expression of CD33 and CD123 (mean fluorescence intensity [MFI] or % expression) did not correlate with ELN risk category or specific molecular mutations.

## Conclusions

- Analyses of biomarker samples from the PEVENAZA trial resulted in several insights for the pevonedistat program.
- The observation that newly diagnosed patients with IDH1/2 mutations may benefit from the addition of pevonedistat to venetoclax + azacitidine is certainly hypothesis-generating and will require further follow-up with larger number of patients.
- Consistent expression of CD33 and CD123 at baseline and during venetoclax + azacitidine treatment on blasts and LSCs supports the development of therapeutic agents that specifically target these proteins in both first- and second-line settings for AML.

## Disclosures

**RR, SL, SF, FS:** Employment: Takeda. **XF:** Independent Contractor: Takeda. **LA:** Advisory Board: Takeda. **NS:** Independent Contractor, Grant/Contractor: Takeda Oncology. **TY:** Employment, Stock, Patent: Takeda. **CP:** no conflicts of interest.

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