



Piezo1 protein (Uniprot Q92508) amino acids 602 to 2521 and known mutations in *PIEZO1* encoding amino acid substitutions. Er blood group antigens encoded by *PIEZO1* are given in red and as detailed by Karamatic Crew et al.<sup>1</sup> Gly2394 is required for expression of the high-prevalence antigen Er<sup>A</sup>, whereas Ser2394 encodes the antithetical low-prevalence antigen Er<sup>B</sup>. Proposed novel high-prevalence antigens Er4 and Er5 are associated, respectively, with Gln2407 and Arg2245 in Piezo1. One Er3-negative allele encodes wild-type Gly2394 (Er<sup>B</sup>) with a nearby Glu2392Lys mutation. Exemplary mutations of *PIEZO1* with resulting amino acid exchanges reported for patients with DHS are given in blue and are del756, Pro1358, Arg2225, Thr2020, and His2456. Exemplary mutations of *PIEZO1* with resulting amino acid exchanges reported for patients with LMPHM6 are given in black and are Ter755, Ter1630, and Phe2171. All Er blood group antigens cluster in the carboxy-terminal loop of Piezo1. Dominant mutations causing DHS and LMPHM6 mutations following a recessive mode of inheritance may be observed throughout all parts of Piezo1. The position of the *PIEZO1* mutations suggest coding of disease-associated alleles for blood group antigens and, vice versa, blood group antigens that may simultaneously represent disease-associated alleles. However, this hypothesis requires further research. Graphic generated in Protter.

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## CLINICAL TRIALS AND OBSERVATIONS

Comment on *de Botton et al*, page 156

# IDH2 inhibition in AML

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**Donald's life was ending. As an 80-year old with relapsed IDH2-mutant acute myeloid leukemia (AML) the leukemia cutis erupting on his skin served as a visual reminder of his battered and blastic bone marrow. With limited standard treatment options he sought to enroll in a clinical trial with enasidenib, a potent inhibitor of mutant IDH2. Preclinically, enasidenib reliably led to the differentiation of malignant myeloblasts in vitro.<sup>1</sup> Would enasidenib be the first approved differentiation agent since the discovery of all-trans retinoic acid in the 1980s? After a long discussion Donald consented, screened and enrolled in the phase 1 trial of enasidenib for relapsed and refractory AML.**

IDH2 mutations occur in 10% to 15% of patients with AML, increase in incidence as patients age, and exert their leukemogenic effect through the neomorphic production of  $\beta$ -hydroxyglutarate, an oncometabolite that poisons TET enzymes and leads to a subsequent block in myeloid differentiation.<sup>2,3</sup> Enasidenib, a potent and selective inhibitor of mutant IDH2, led to a

reduction in  $\beta$  hydroxyglutarate, myeloid differentiation, and clinical responses in a phase 1/2 clinical study.<sup>4,5</sup> That study demonstrated a rate of complete remission (CR) and CR with partial hematologic recovery (CRh) of 23%, a median duration of remission of 8.2 months, and conversion of 34% of patients from transfusion dependent to independent. Based on these results,

the US Food and Drug Administration approved enasidenib for the treatment of relapsed and refractory IDH2 mutant AML in 2017. In this issue of *Blood*, de Botton and colleagues report the results of the logical successor study, a randomized phase 3 study of enasidenib vs “conventional care regimens” in patients 60-years of age or older with IDH2-mutant relapsed and refractory AML.<sup>6</sup> In this study, patients with relapsed or refractory AML after 2-3 lines of prior treatment were randomized in an open-label fashion to receive enasidenib or 1 of 4 conventional care regimens: intermediate dose cytarabine, azacitidine, low dose cytarabine or best supportive care alone. The results are unexpected. Despite improvements in the overall response rate, time to treatment failure, and a modest improvement in event free survival, all favoring enasidenib, the overall survival between enasidenib and the conventional care arm was equivalent. How is this possible? How is it that a differentiation agent that avoids myelosuppression fails to improve survival over myelosuppressive therapy or no treatment at all? Perhaps more importantly, should we interpret these results to mean that patients with relapsed and refractory IDH2 mutant AML should not get enasidenib?

The answer to this conundrum can be found in a detailed look at the CONSORT diagram in the study results. 12.4% of the patients randomly assigned to the conventional care arm dropped out of the study before receiving their allotted treatment compared with only 1 patient randomly assigned to enasidenib. Similarly, 34 patients allocated to the conventional care regimen were discontinued from treatment by their physician because of “no treatment benefit,” something that did not happen to any patient randomly assigned to enasidenib. 24 patients self-discontinued treatment in the conventional care regimen compared with only 10 patients in the enasidenib arm. In total nearly 50% of patients allocated to the conventional care arm did not actually receive a full course of conventional care.

It is easy then, to understand what may have happened. Because of the open-label nature of the study, patients

randomly assigned to a conventional care regimen chose to receive other therapy—perhaps even enasidenib itself—rather than their allotted treatment. Because of this, the overall survival results are hopelessly confounded and should not be used to guide clinical practice toward or away from enasidenib.

One final question that needs to be answered is the relevance of the regimens included in conventional care in 2022. Despite a lack of randomized data, the totality of the clinical data suggests that patients with IDH-mutant AML may be particularly sensitive to the combination of azacitidine and the BCL2 inhibitor venetoclax, even in the relapsed and refractory setting.<sup>7,8</sup> A more useful and practical clinical study would involve randomly assigning patients with IDH2-mutant relapsed and refractory AML to enasidenib or azacitidine-venetoclax in a placebo controlled manner, and then assessing for both event-free and overall survival.

Donald ultimately enrolled in the clinical study of enasidenib back in 2014. His leukemia cutis and marrow both cleared up, and he remains in CR while receiving enasidenib in 2022. The promise of enasidenib remains alive.

*Conflict-of-interest disclosure:* The author declares no competing financial interests. ■

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## CLINICAL TRIALS AND OBSERVATIONS

Comment on *Dampier et al*, page 168

# Ups and downs in the treatment of sickle cell disease

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**Despite promising early results, in this issue of *Blood*, Dampier et al<sup>1</sup> report the negative results of rivipansel, a predominantly E-selectin antagonist, in treating hospitalized vaso-occlusive crisis (VOC) in patients with sickle cell disease (SCD). Although these results are disappointing for patients and physicians, important lessons can nevertheless be learned.**