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This differentiation block will not stand, man: ivosidenib for MDS

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Comment on DiNardo et al, page 4209

In this issue of *Blood Advances*, DiNardo et al[1] report the results of a phase 1, open-label, single-arm study of patients with isocitrate dehydrogenase 1 (*IDH1*)-mutated relapsed/refractory (R/R) myelodysplastic syndrome (MDS) treated with ivosidenib. The authors should be commended for enrolling a population enriched for this genetic abnormality, as *IDH1* mutations occur uncommonly in MDS (~2%-5%).[2,3] It bears mentioning that the US Food and Drug Administration (FDA)–granted ivosidenib full regulatory approval based on safety/efficacy data drawn from 19 patients. Therefore, we should be cautious to make broad, sweeping generalizations as to the efficacy and safety of ivosidenib in *IDH1*-mutant MDS. Follow-up studies to confirm the disease-modifying activity of ivosidenib, particularly in patients who were not represented in the phase 1 trial (ie, individuals of different races, ethnicities, International Prognostic Scoring System [IPSS] scores, and cytogenetic risk), are still merited. Despite this, the achievement of a durable response in the setting of R/R MDS is highly valuable information for the MDS field. Understanding that before ivosidenib, there were no FDA-approved medications nor an established standard-of-care approach for the treatment of patients with MDS refractory to hypomethylating agents (HMAs).[4,5]

As DiNardo et al report, ivosidenib is clearly clinically active in *IDH1*-mutant MDS, with a complete response (CR) rate of 38.9% (7/18), a median time to CR of 1.87 months, an estimated probability of remaining in a CR for 5 years of 68.6%, and a median overall survival of 35.7 months. Important limitations of the study include the nonrandomized design and the small sample size. In addition, they show that 72.7% (7/11) of patients who were either platelet and/or red blood cell transfusion dependent at baseline went on to become transfusion independent while receiving ivosidenib. This is an important finding because reducing the burden of red blood cell and platelet transfusions remains a major unmet need in patients with MDS, and the achievement of transfusion independence has been shown to improve quality-of-life and economic outcomes for patients with MDS.[6,7] Importantly, ivosidenib was well-tolerated in this trial, with no grade 3 adverse events (AEs) related to ivosidenib. Notably, only 10.5% (2/19) of patients experienced differentiation syndrome, and no patient permanently discontinued ivosidenib because of an AE.[1]

Studies have shown that *IDH1*-mutant MDS is associated with worse outcomes in patients with MDS, including an increased risk for transformation to acute myeloid leukemia (AML).[2,3,8] So perhaps incorporating *IDH1* inhibitors like ivosidenib earlier in the treatment regimen for MDS may lead to a disease-modifying effect and prevent this cohort of patients from progressing to AML. Interestingly, in AML, patients with an *IDH1* mutation have been shown to have higher response rates and enhanced overall survival when treated with HMAs and venetoclax therapy in combination vs HMA monotherapy.[9,10] In addition, in the phase 3 AGILE trial, the combination of ivosidenib and azacitidine was shown to be superior to azacitidine alone, leading to the FDA approval of ivosidenib in combination with azacitidine for newly diagnosed *IDH1*-mutant AML.[11] The combination of HMA and venetoclax has demonstrated encouraging activity for the treatment of patients with high-risk MDS in the frontline and the phase 3 VERONA study (NCT04401748) is ongoing.[12] Therefore, an area for future research is to discover how to incorporate and sequence ivosidenib for the treatment of *IDH1*-mutated MDS to maximize efficacy and minimize toxicity.

Our understanding of MDS genetics has advanced significantly because of the widespread adoption of next-generation sequencing (NGS). With the use of NGS and the subsequent ability to identify and target key driver mutations, like *IDH1*, there has been a better comprehension of the evolutionary path

of this disease. Although the presence of a somatic *IDH1* mutation at baseline presents a potential target for therapeutic intervention, the pathogenesis of MDS remains complex and multifactorial.[4,5] As DiNardo et al show in this study, 11.1% (2/18) of patients progressed to AML, and notably these patients still had detectable *IDH1* mutations when they progressed. One interpretation is that the *IDH1* mutation was not the primary clonal driver of the disease but a passenger mutation in these patients. Therefore, the field of MDS/AML will continue to benefit from research that specifically evaluates patients with a somatic *IDH1* mutation (ie, detected on a NGS panel) and their responses to *IDH1* inhibitor therapy. In particular, obtaining more data regarding variant allele frequencies (VAFs) are required, especially because DiNardo et al show that VAF levels obtained at baseline and throughout the study, had an association with clinical responses.

Importantly, ivosidenib does have a multitude of drug-drug interactions. It is classified as a substrate of CYP3A4 and P-glycoprotein, an inhibitor of the P-glycoprotein/organic anion transporter 3, and it also induces multiple hepatic enzymes, including CYP3A4, CYP2C9, CYP2B6, and CYP2C8. Accordingly, it has been shown to decrease the concentrations of antifungal agents such as voriconazole, in some cases to undetectable levels. Such interactions are likely due to the induction of CYP2C9 by ivosidenib.[13] However, the FDA-approved package insert still recommends reducing the dose of ivosidenib when prescribed with moderate/strong CYP3A4 inhibitors such as voriconazole or posaconazole, even though this does not reflect the dosing used in the phase 1 study by DiNardo et al[13,14] Therefore, it is critically important to consider drug interactions in patients being prescribed ivosidenib, including consultation with clinical pharmacy specialists.

Overall, *IDH1*-mutated MDS is a rare patient cohort with limited treatment options. The approval of ivosidenib for R/R MDS is promising. However, we believe that this approval now prompts the development of novel research strategies and also necessitates further validation through real-world data to reinforce these phase 1 discoveries. In the coming years, we anticipate that the MDS field will be transformed by the availability of molecularly targeted agents that may have the potential to add to or displace HMA monotherapy in first-line treatments. Specific to ivosidenib, we are aware of a multitude of clinical trials further investigating its safety and efficacy as monotherapy (NCT03503409) or in combination with azacitidine and venetoclax (NCT03471260 and NCT03471260), standard intensive chemotherapy (NCT03839771), checkpoint inhibition (NCT04044209), and with CPX-351 (NCT04493164). Together, it is hoped that results yielded from these studies will ultimately improve the care and outcomes of patients with *IDH1*-mutated MDS.

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