in which it resides. Clinical trials evaluating dual checkpoint blockade and MAPK inhibition are warranted.

Conflict-of-interest disclosure: The author has served on advisory boards from Sobi and Novartis and currently serves on the data safety monitory committee for Novalmmune. ■

REFERENCES

1. Sengal A, Velazques J, Hahne M, et al. Overcoming T-cell exhaustion in LCH: PD-1 blockade and targeted MAPK inhibition are synergistic in a mouse model of LCH. *Blood*. 2021;137(13):1777-1791.
2. Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. *Blood*. 2020;135(16):1319-1331.
3. Allen CE, Merad M, McClain KL. Langerhans-cell histiocytosis. *N Engl J Med*. 2018;379(9):856-868.
4. Gatalica Z, Bilalovic N, Palazzo JP, et al. Disseminated histiocytoses biomarkers beyond BRAFV600E: frequent expression of PD-L1. *Oncotarget*. 2015;6(23):19819-19825.
5. Chakraborty R, Hampton OA, Shen X, et al. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. *Blood*. 2014;124(19):3007-3015.
6. Diamond EL, Durham BH, Ulaner GA, et al. Efficacy of MEK inhibition in patients with histiocytic neoplasms. *Nature*. 2019;567(7749):521-524.
7. Donadieu J, Larabi IA, Tardieu M, et al. Vemurafenib for refractory multisystem Langerhans cell histiocytosis in children: an international observational study. *J Clin Oncol*. 2019;37(31):2857-2865.
8. Eckstein OS, Visser J, Rodriguez-Galindo C, Allen CE; NACHO-LIBRE Study Group. Clinical responses and persistent *BRAFV600E*$^{+}$ blood cells in children with LCH treated with MAPK pathway inhibition. *Blood*. 2019;133(15):1691-1694. *Blood*. 2019;133(15):1691-1694.
9. Paredes SEY, Almeida LY, Trevisan GL, et al. Immunohistochemical characterization of immune cell infiltration in paediatric and adult Langerhans cell histiocytosis. *Scand J Immunol*. 2020;00:e12950.
10. Mitchell JM, Berzins SP, Kannourakis G. A potentially important role for T cells and regulatory T cells in Langerhans cell histiocytosis. *Clin Immunol*. 2018;194:19-25.

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MYELOID NEOPLASIA

Comment on Stein et al, page 1792

Taking aim at IDH in fitter patients with AML

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In this issue of *Blood*, Stein et al report the feasibility of combining isocitrate dehydrogenase (IDH) inhibitors with intensive induction and consolidation therapy, paving the way for pivotal studies to explore targeted IDH therapy as standard of care for those with newly diagnosed *IDH*-mutant acute myeloid leukemia (AML).[1]

From the initial identification of IDH1^{R132C} in AML to the US Food and Drug Administration (FDA) approval of a small molecule targeting mutant IDH1 9 years later, the IDH story represents a remarkable bench-to-bedside journey.[2] IDH1^{R132} abnormalities impair decarboxylation of isocitrate to α ketoglutarate. The mutation also confers a dominant negative effect via a neomorphic gain-of-function oncometabolite called (*R*)-2-hydroxyglutarate.[3] Mutations in IDH1 and IDH2 are found in 16% to 22% of AML cases, with a higher frequency in patients with diploid karyotype and those of older age.[4]

High-throughput screening followed by hit-to-lead chemistry for inhibitors of IDH2^{R140Q} activity led to the development of enasidenib, the first-in-class inhibitor of *IDH2* mutations.[5] A phase 1 study in relapsed/refractory (R/R) AML identified 100 mg per day as the optimal dose of enasidenib. The overall response rate (ORR) was 39% (complete response [CR], 20%), and median overall survival (OS) in all patients was 9 months. Median time to best response was 4 months, and drug-specific adverse events included hyperbilirubinemia (8%) and differentiation syndrome (DS; 7%).[6] A parallel study determined ivosidenib at 500 mg per day as optimal in R/R *IDH1*-mutant AML, with an ORR of 42% (CR, 22%) and median CR duration of 8 months.[7] Median time to CR was 3 months, and key adverse events included QT prolongation (8%) and IDH DS (4%). The manageable toxicity, clinical efficacy, reduced transfusion dependency, and appeal of targeting biologically relevant mutations with an orally delivered drug led to FDA approval of both enasidenib for IDH2- (2017) and ivosidenib for IDH1-mutant (2018) R/R AML. In newly diagnosed patients with AML ineligible for intensive chemotherapy, the CR/CR with partial hematologic recovery rate for ivosidenib was 43% (CR, 30%), and median OS was 12.6 months, resulting in a label for frontline therapy.[8] Incorporating targeted therapies into the frontline setting for fit, younger patients with presumably less complex disease and greater chance of cure may maximize survival benefit, analogous to the benefits found with midostaurin, gemtuzumab, and venetoclax in AML. The addition of cytotoxic therapy could also reduce the risk of DS and shorten the time to achieve CR compared with single-agent therapy.

In their study reported in this issue of *Blood*, Stein et al explored IDH targeting in fit patients with AML undergoing first-line intensive 7 + 3 induction with intermediate- or high-dose cytarabine-based consolidation therapy. The study population was predominantly ≥60 years of age, consistent with the higher frequency of *IDH* mutations in older age groups. After confirming the safety of ivosidenib at 500 mg or enasidenib at 100 mg per day, commencing on day 1 of induction chemotherapy, the study was expanded to include a total of 60 and 91 patients in the ivosidenib and enasidenib arms, respectively.

In the ivosidenib arm, 15% received 2 induction cycles, 58% were consolidated, 32% received maintenance therapy, and 47% proceeded to hematopoietic stem cell transplantation (HSCT). The time to median neutrophil (>0.5 10^9/L) or platelet (>50 × 10^9/L) recovery during induction did not seem prolonged (28 days). Although any-grade QT prolongation during induction was 27% (grade ≥3 in 10%) and seemed higher than reported in the phase 1 study, the potential impact of concomitant medications could not be excluded. The end-of-induction CR rate was 55% in the ivosidenib arm, and the combined

CR/CR with incomplete hematologic recovery (CRi)/CR with incomplete platelet recovery (CRp) rate was 72%.

In the enasidenib arm, 24% received 2 induction cycles, 49% were consolidated, 26% received maintenance therapy, and 47% proceeded to HSCT. Median time to neutrophil or platelet recovery after induction was 34 or 29 days, respectively. The rate of hyperbilirubinemia during induction was 50% (grade ≥3 in 16%), but this was not considered problematic. The end-of-induction CR rate was 47% in the enasidenib arm, and the combined CR/CRi/CRp rate was 62%.

Early (30-day) mortality in both arms was not increased (5%). Although IDH DS was uncommon (3%), 3 of the 4 cases were grade ≥3 in severity and occurred between days 29 and 48, suggesting that patients should be monitored even after discharge. In a limited subset of 46 patients, clearance of mutant *IDH1/2* by digital polymerase chain reaction was 39% and 23%, respectively. This study included 4 patients in the ivosidenib arm and 17 patients in the enasidenib arm with secondary AML with prior hypomethylating agent exposure, with a CR/CRi/CRp rate (at any time) of 59%. The overall study follow-up time was short (median, 9.3 months) for a frontline induction study, thus preventing conclusions regarding survival. On the basis of this feasibility study, an international phase 3 randomized trial investigating ivosidenib and enasidenib with standard intensive chemotherapy led by the Heamato Oncology Foundation for Adults in the Netherlands (HOVON) and German-Austrian AML Study Group (AMLSG) has commenced (registered at www.clinicaltrials.gov as #NCT03839771). The rarity of the disease will require an international effort to screen thousands of patients to enroll the target number of 968 with IDH1/2-mutant AML.

Although the next steps for IDH targeting seemed straightforward, recent studies have raised questions. Preliminary results from an ongoing phase 2 randomized study comparing enasidenib with or without azacitidine as first-line treatment for AML patients unfit for intensive chemotherapy showed an improved response rate and event-free survival, but not OS, for patients in the combination arm.[9] Although 21% of patients in the azacitidine-alone arm received enasidenib at relapse, this raises the question of whether the optimal approach is to use IDH2-targeted therapy at diagnosis or in the salvage setting. Likewise, the phase 3 IDHENTIFY trial in IDH2-mutant AML, which enrolled patients for whom 2 or 3 lines of therapy had failed, reported no survival improvement with enasidenib compared with standard of care. Although the details have not been released, these results heighten the importance of the results presented by Stein et al and the ongoing phase 3 HOVON/AMLSG trial. Many regulatory jurisdictions require a randomized study to support the case for reimbursement of IDH inhibitors. Therefore, worldwide access to IDH2 inhibitors may be limited until such pivotal studies are completed.

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REFERENCES

1. Stein EM, DiNardo CD, Fathi AT, et al. Ivosidenib or enasidenib combined with intensive chemotherapy in patients with newly diagnosed AML: a phase 1 study. *Blood*. 2021; 137(13):1792-1803.
2. Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. *N Engl J Med*. 2009; 361(11):1058-1066.
3. Zhao S, Lin Y, Xu W, et al. Glioma-derived mutations in IDH1 dominantly inhibit IDH1 catalytic activity and induce HIF-1α. *Science*. 2009;324(5924):261-265.
4. Medeiros BC, Fathi AT, DiNardo CD, Pollyea DA, Chan SM, Swords R. Isocitrate dehydrogenase mutations in myeloid malignancies. *Leukemia*. 2017;31(2):272-281.
5. Yen K, Travins J, Wang F, et al. AG-221, a first-in-class therapy targeting acute myeloid leukemia harboring oncogenic IDH2 mutations. *Cancer Discov*. 2017;7(5):478-493.
6. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia. *Blood*. 2017; 130(6):722-731.
7. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-2398.
8. Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood*. 2020;135(7): 463-471.
9. DiNardo C, Schuh AC, Stein EM, Femandez P. Enasidenib plus azacitidine significantly improves complete remission and overall response compared with azacitidine alone in patients with newly diagnosed acute myeloid leukemia (AML) with isocitrate dehydrogenase 2 (IDH2) mutations: interim phase II results from an ongoing, randomized study. Presented at the *61st American Society of Hematology Annual Meeting and Exposition*. 7-10 December 2019. Orlando, FL.

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