Clinical Trial

Major Finding: This combination was safe and met its primary efficacy endpoint of complete remission rate.

Concept: Efficacy of this combination in patients with *TP53*-mutated myelodysplastic syndrome was also demonstrated.

Impact: The results of this trial suggest further evaluation of this combination in the currently underway phase III trial.

MAGROLIMAB PLUS AZACITIDINE IS SAFE AND EFFICACIOUS IN HIGH-RISK MDS

Patients with high-risk myelodysplastic syndromes (MDS) have poor prognosis and are at increased risk of progression to acute myeloid leukemia. The most common frontline therapy for this disease is hypomethylating agents (HMA), like azacitidine, but complete remission (CR) rates with single-agent HMAs are low. Preclinical studies indicated that azacitidine along with magrolimab, a first-in-class monoclonal antibody targeting CD47, which is overexpressed on blasts in MDS, led to increased phagocytosis of myeloid cells, suggesting potential clinical benefit of this combination. In order to assess the safety and tolerability of this combination along with its efficacy in patients, Sallman and colleagues conducted an open-label, single-arm, multicenter phase Ib clinical trial in 95 patients with higher-risk MDS. The primary endpoints of this study were adverse events as well as CR rate. The most common all-grade treatment-emergent adverse events (TEAE) were constipation, thrombocytopenia, anemia, neutropenia, nausea, and diarrhea, with anemia, neutropenia, and thrombocytopenia being the most common grade 3/4 TEAEs. Ten patients had to discontinue treatment due to TEAEs. Evaluation of efficacy revealed that the primary efficacy endpoint of CR was achieved with an overall response rate of 74.7%. Median CR duration was 11.1 months, while the median objective response (OR) duration was 9.8 months. Moreover, median progression-free survival and overall survival (OS) were 11.6 months and not reached, respectively. In the 25 patients with *TP53* mutation, 10 patients (40%) achieved CR with a median CR duration of 7.6 months. Additionally, median OR duration was 9.2 months, while median OS was 16.3 months for this patient population. Overall, the results of this study show that magrolimab plus azacitidine was well tolerated with potential efficacy, including in *TP53*-mutated MDS, and suggest the benefit of continuing the phase III trial of this combination that is currently underway in patients with high-risk MDS. ■

Sallman DA, Al Malki MM, Asch AS, Wang ES, Jurcic JG, Bradley TJ, et al. Magrolimab in combination with azacitidine in patients with high-risk myelodysplastic syndromes: final results of a phase Ib study. J Clin Oncol 2023 Mar 8 [Epub ahead of print].

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Leukemia

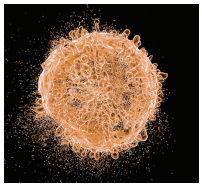
Major Finding: Revumenib is well tolerated with clinical efficacy, and mutations in *MEN1* mediate acquired resistance.

Concept: Mutations block inhibitor binding but not *KMT2A*–menin association and chromatin binding.

Impact: These results suggest clinical use of revumenib in acute leukemia with monitoring of *MEN1* mutation status.

REVUMENIB IS SAFE AND EFFICACIOUS, BUT *MEN1* MUTATIONS MEDIATE RESISTANCE

Rearrangements in *KMT2A* (*KMT2A*r) as well as mutations in *NPM1* are common in acute leukemias, with the adapter protein menin being needed to sustain their aberrant leukemogenic gene expression programs. These mutations have been associated with poor prognosis in acute leukemias, but targeted therapies that target *KMT2A*r or *NPMI*-mutated acute leukemias are still needed. In two complementary studies, Issa and colleagues along with Perner, Stein, and colleagues sought to evaluate revumenib, a potent, oral inhibitor of the menin–*KMT2A* interaction, in a first-in-human clinical trial along with potential mechanisms of acquired resistance to this small molecule. Issa and colleagues conducted a first-in-human, phase I clinical trial in 68 patients with relapsed/refractory acute leukemia to evaluate the safety, the maximum tolerated dose, and the recommended phase II dose of revumenib. A low frequency of grade 3 or higher treatment-related adverse events was demonstrated, with asymptomatic prolongation of the QT interval on electrocardiography being the only dose-limiting toxicity noted. Additionally, a complete remission/complete remission with partial hematologic recovery rate of 30% was observed, and remissions were seen in patients who were refractory to multiple previous lines of therapy. Building upon these results, the study by Perner, Stein, and colleagues investigated potential mechanisms of resistance to revumenib and revealed that somatic mutations in *MEN1*, which encodes for menin, at the revumenib–menin interface lead to acquired resistance, as indicated by patient genetic data, patient-derived xenografts, and unbiased base-editor screens. These mutations were found to typically occur at residues M327, G331, T349, and S160 of menin, which were revealed to be crucial for small-molecule binding but not for *KMT2A* association with menin. Thus, the structural perturbations induced by these mutations decrease affinity of menin–inhibitor interactions, which prevents inhibitor-induced displacement of the menin–*KMT2A* complex from the chromatin and fails to suppress menin–*KMT2A* target gene expression. Together, the results of these two studies indicate that revumenib is well tolerated with potential clinical efficacy and reveal potential mechanisms of acquired resistance. ■



Issa GC, Aldoss I, DiPersio J, Cuglievan B, Stone R, Arellano M, et al. The menin inhibitor revumenib in KMT2A*-rearranged or* NPM1*-mutant leukaemia. Nature 2023;615:920–4.*

Perner F, Stein EM, Wenge DV, Singh S, Kim J, Apazidis A, et al. MEN1 *mutations mediate clinical resistance to menin inhibition. Nature 2023;615:913–9.*

doi: 10.1158/2159-8290.CD-RW2023-046