

Impact Of Magrolimab in Combination With Azacitidine on Red Blood Cells (RBCs) in Patients With Higher-Risk Myelodysplastic Syndromes (HR MDS)

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Context: Magrolimab is an antibody blocking CD47, a “don’t eat me” signal expressed on cancer cells, to escape immune surveillance and macrophage-mediated clearance. Preclinical studies found that CD47 is critical to RBC homeostasis, with CD47 deficiency decreasing RBC half-life. Fc-mediated opsonization also depletes RBCs, raising concerns that potential on-target anemia could result from the use of anti-CD47 agents. Several clinical trials demonstrated that magrolimab can be safely administered as monotherapy, with an initial lower “priming” dose yielding transient anemia with compensatory reticulocytosis and no anemia observed at higher maintenance doses. However, the underlying mechanism has not been fully defined. **Objective:** To describe manageable anemia in magrolimab-treated patients and further investigate the underlying mechanisms in preclinical models. **Design:** Prospective analysis from a phase 1 trial of magrolimab+azacitidine (NCT03248479). Complete blood counts (CBCs), peripheral blood, and bone marrow (BM) were collected from patients at prespecified time points. CBCs were measured, and blood and BM samples were analyzed by flow cytometry for CD47 expression on RBCs and white blood cells (WBCs). Preclinical modeling studies were conducted with intact and Fc-deficient anti-mouse CD47 (MIAP410) and anti-human CD47 (magrolimab) antibodies in murine models, including C57BL/6J B-hSIRPA/hCD47 mice. **Patients:** 57 patients with HR MDS. **Interventions:** Magrolimab IV 1 mg/kg (priming) then 30 mg/kg QW, then Q2W (maintenance). Azacitidine 75 mg/m² days 1-7 (each 28-day cycle). **Results:** Treatment with magrolimab+azacitidine resulted in tolerable anemia that correlated with rapid, near-complete loss of CD47 in RBCs but not WBCs. The initial 1-mg/kg priming dose was sufficient for CD47 loss, which persisted with subsequent 30-mg/kg maintenance doses. Both findings are consistent with prior clinical observations of magrolimab monotherapy in patients with solid tumors and magrolimab+rituximab in patients with lymphoma. Our preclinical studies with mouse models revealed that CD47 removal is mechanistically independent of previously described RBC antigen modulation mechanisms and cellular compartments. Instead, this CD47 loss requires anti-CD47 cross-linking between RBCs and non-RBCs. **Conclusions:** These results support the idea that on-target magrolimab-mediated anemia is mitigated by a near-complete loss of RBC CD47. Patients with HR MDS treated with magrolimab+azacitidine had tolerable anemia with priming and maintenance doses. **Keywords:** MDS, myelodysplastic syndromes, magrolimab, azacitidine, CD47, red blood cells.