330 The First-in-Class Anti-CD47 Antibody Magrolimab Combined with Azacitidine Is Well-Tolerated and Effective in AML Patients: Phase 1b Results

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Introduction

Magrolimab (Hu5F9-G4) is an antibody blocking CD47, a macrophage immune checkpoint and "don't eat me" signal on cancers. Magrolimab induces tumor phagocytosis and eliminates leukemia stem cells (LSCs). Azacitidine (AZA) synergizes with magrolimab by inducing "eat me" signals on leukemic blasts, thereby enhancing phagocytosis. Magrolimab + AZA has been shown to be clinically effective in acute myeloid leukemia (AML) and myelodysplastic syndrome. We report here updated phase 1b data of this combination in untreated AML, including *TP53*-mutant AML.

Methods

The phase 1b data represent treatment-naive AML patients unfit for intensive chemotherapy. A magrolimab priming/intrapatient dose-escalation regimen (1-30 mg/kg IV weekly followed by 30 mg/kg Q2W dosing in cycle 3 and beyond) was utilized to mitigate on-target anemia. AZA dosing was 75 mg/m^2 on days 1-7 on a 28-day cycle. Responses were assessed by European LeukemiaNet 2017 criteria.

Results

Fifty-two AML patients with a median age of 73 years (range 31 to 89) were treated with magrolimab+AZA. The majority (64%) had poor risk cytogenetics. Further, 65% of patients had *TP53* mutations, which were specifically enriched for this trial. 64% of all patients had complex cytogenetics, including 83% of *TP53*-mutant AML patients. Magrolimab+AZA was well tolerated with a safety profile similar to AZA monotherapy. Treatment-related adverse events (AEs) (≥15% of patients) for magrolimab+AZA were anemia (31%), fatigue (19%), blood bilirubin increase (19%), neutropenia (19%), thrombocytopenia (17%), and nausea (15%). On-target anemia was generally transient and reversible with no observed grade 4 or 5 AEs, and 56% of AML patients became red blood cell transfusion independent on therapy. No immune-related AEs associated with magrolimab were observed. Treatment-related febrile neutropenia occurred in only 2 (3.8%) patients. Only 2 (3.8%) patients discontinued due to a treatment-related AE. Thirty-four patients were evaluable for efficacy at time of data cut. Of these patients, 22 (65%) achieved an objective response; 15 (44%) achieved complete remission (CR), 4 (12%) with CR with incomplete count recovery (CRi), 1 (3%) with partial response, 2 (6%) with morphological leukemia-free state (MLFS), 11 (32%) with stable disease (SD), and 1 (3%) with progressive disease (PD). Time to response was more rapid (median 2.04 months) than expected for AZA alone. For those with abnormal cytogenetics at baseline, 7/15 (47%) achieved a cytogenetic CR, and 7/19 (37%) of patients with CR/CRi became minimal residual disease negative by flow cytometry.
In *TP53*-mutant AML patients, 15/21 (71%) achieved an objective response; 10 (48%) achieved a CR, 4 (19%) with CRi, 1 (5%) with MLFS, 5 (24%) with SD, and 1 (5%) with PD. The median duration of response was 9.9 months (range 0.03+ to 15.1+ mo ongoing); 89% of patients continued in response at 6 months. The median overall survival (OS) for *TP53*-mutant AML patients (n=34) was 12.9 months (95% CI: 6.24 mo – not reached). The median OS for *TP53* wild-type AML patients (n=16) was 18.9 months (95% CI: 4.34 mo – not reached). The median follow-up for *TP53*-mutant and wild-type patients was 4 and 12 months, respectively.
CD47 expression is enriched on AML LSCs, and magrolimab has demonstrated LSC targeting activity preclinically. Thus, the impact of magrolimab therapy on LSCs was evaluated. Putative bone marrow LSCs, as defined by CD34+CD38- expression, were eliminated by magrolimab+AZA in 71% of all responding AML patients. Additional correlative studies, including the impact of therapy on *TP53* mutational burden and immune cell composition, are in progress.

Conclusions

Magrolimab is a novel immunotherapy and LSC-targeting agent that blocks a key macrophage checkpoint. Magrolimab+AZA is well tolerated with no immune-related AEs observed in relation to magrolimab. On-target anemia is mitigated by a priming/maintenance dose strategy. Efficacy is seen in both *TP53*-mutant and wild-type AML patients. While sample size and follow-up are limited, efficacy is particularly encouraging in *TP53*-mutant AML with a 71% response rate, 48% CR rate, and median OS of 12.9 months. Expansion cohorts in AML are ongoing (NCT03248479) and a phase 3 trial evaluating magrolimab+AZA in untreated *TP53*-mutant AML patients is planned. Additional patients, follow-up, and correlative studies will be reported at time of presentation.