THE FIRST-IN-CLASS ANTI-CD47 ANTIBODY HU5F9-G4 IS ACTIVE AND WELL TOLERATED ALONE OR IN COMBINATION WITH AZACITIDINE IN AML AND MDS PATIENTS: INITIAL PHASE 1B RESULTS

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Background
Novel and effective therapies are needed in patients with myeloid malignancies. Hu5F9-G4 (5F9) is a first-in-class antibody targeting CD47, a macrophage immune checkpoint and “don’t eat me” signal on cancers, that induces tumor cell phagocytosis. CD47 is also a leukemia stem cell (LSC) marker in AML. Pre-clinically, CD47 blockade induces phagocytosis of AML cells and eliminates LSCs in animal models. Azacitidine (AZA) synergizes with 5F9 to eliminate AML by inducing pro-phagocytic signals on AML, thus enhancing phagocytosis. This trial clinically investigated 5F9 alone or with AZA in AML/MDS patients and is the first report of a clinical study combining a CD47 targeting agent with a hypomethylating/cytotoxic agent.

Aims
The primary objectives of this study were to evaluate the safety and efficacy of 5F9 treatment in relapsed/refractory (r/r) AML/MDS and 5F9 in combination with AZA in untreated AML and MDS patients.

Methods
This Phase 1b trial enrolled: 1) relapsed/refractory (r/r) AML/MDS patients with 5F9 alone; and 2) untreated AML (induction ineligible) and intermediate-very high risk MDS patients with 5F9+AZA. A 5F9 priming/intra-patient dose escalation regimen (1-30 mg/kg weekly) was used to mitigate on-target anemia. Standard AZA dosing was used.

Results
10 (6 AML, 4 MDS) r/r pts received 5F9 (median 2 prior therapies (range 1-6). 24 untreated pts (15 AML, 9 MDS) received 5F9+AZA. In total, median age was 73, 62% of AML pts were intermediate or poor cytogenetic risk (38% unknown), all MDS pts were intermediate or high risk by IPSS-R. 5F9 alone or with AZA was well-tolerated with no MTD reached. 5F9 did not potentiate AZA toxicities. Treatment-related AEs (>10% of pts) for 5F9+AZA were anemia (25%), thrombocytopenia (20%), and infusion reactions (15%). In 25 efficacy evaluable pts, 8/15 (53%) untreated AML/MDS pts had a CR/CRi to 5F9+AZA (5/10 (50%) in AML, 3/5 (60%) in MDS). 1/10 (10%) r/r AML/MDS pts had a response (MLFS) to 5F9 alone. LSCs were reduced/eliminated in the majority of 5F9+AZA responders. 50% of all responders were minimal residual disease (MRD) negative by flow cytometry. 4/10 (40%) previously red cell dependent AML pts became RBC transfusion independent and 4/5 (80%) MDS pts had hematologic improvement. Time to response was more rapid (median 1.9 mos) than expected for AZA alone. As of Jan 2019, no responder has relapsed (median follow-up

of 3.4 mos (range 1.1 – 6.8 mos). 2 pts had successful allogeneic transplant. Additional patients and follow up will be reported.

Conclusion

5F9+AZA is a novel immunotherapy blocking a key macrophage/cancer checkpoint. It is well tolerated with promising activity in AML/MDS patients including rapid CRs with MRD negativity. Adding 5F9 to cytotoxic agents may be a promising treatment strategy. An expansion cohort is ongoing (NCT03248479). Funded by Forty Seven and California Institute for Regenerative Medicine.