**The First-in-Class Anti-CD47 Antibody Hu5F9-G4 is Well Tolerated and Active Alone or with Azacitidine in AML and MDS Patients: Initial Phase 1b Results**


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**BACKGROUND**

- CD47 is a “do not eat me” signal and macrophage checkpoint overexpressed on cancers that enables immune evasion.
- Cancer cells express phagocytic signals while most normal cells do not.
- Hu5F9-G4 (5F9) is a first-in-class humanized IgG4 antibody against CD47 that induces tumor cell phagocytosis but spares normal cells.
- 5F9 was well tolerated in a Phase 1 study in r/r AML (Vyas et al., 2018).

**CLINICAL TRIAL STUDY DESIGN**

**Primary objectives**

- Evaluate the tolerability and safety of 5F9 monotherapy in untreated and r/r AML
- Evaluate the tolerability and safety of 5F9 in combination with azacitidine in untreated and r/r AML

**Secondary objectives**

- Assess the efficacy of 5F9 monotherapy and combination with azacitidine in untreated and r/r AML

**Inclusion Criteria**

- Relapsed/refractory (r/r) AML/MDS (5F9 safety run-in cohort)
- Untreated AML ineligible for induction chemo or untreated MDS intermediate to very high risk by IPSS-R
- Peripheral WBC ≥ 20×10^9/L
- ECOG status of 0 to 2
- AST/ALT ≤ 5× upper limit of normal (ULN), bilirubin ≤ 1.5× ULN except for patients with Gilbert’s syndrome
- GFR ≥ 40 mL/min

**Exclusion Criteria**

- Prior systemic therapy within 2-4 weeks prior to enrollment (5F9 safety cohort)
- Prior anti-CD47 therapies (5F9+AZA cohort)
- Prior exposure to CD47 targeting agents
- Acute promyelocytic leukemia
- Known inherited or acquired bleeding disorders
- Active CNS involvement by leukemia
- Prior alkylating stem cell transplantation within 6 months or active GHD

**RESULTS**

**Safety and Tolerability**

- No MTD reached with 5F9 alone or in combination
- 5F9 profile consistent with AZA monotherapy
- Treatment discontinuation due to AE seen in only 1/4 (2%) patients
- No significant cytopenias, infections, or autoimmune AEs occurred

**Efficacy**

- All patients with CR sustained for ≥ 24 months
- No deaths within the first 60 days on 5F9+AZA treatment

**CONCLUSIONS**

- The 5F9 monotherapy ORR in r/r AML/MDS was 10%.
- The 5F9+AZA ORR in 1L MDS/AML was 100%/64%, more favorable than AZA alone.
- Hematologic improvement, cytogenetic CRs and MRD negativity is seen.
- 5/20 (25%) of responding patients received an allogeneic stem cell transplant.
- No responding patient treated with 5F9+AZA has relapsed; longest responding patient in CR 9 months and ongoing.

**REFERENCES**

- Jaiswal et al. Cell 2009; Majeti, Chao et al., Cell 2009; Chao et al., STM 2010; Liu et al., PLoS One 2015; Feng et al., ASH abs 2018

**CORRELATIVE STUDIES**

- CD47 is expressed on AML LSCs
- CD47 is a leukemia stem cell (LSC) marker on AML patients (left)
- 5F9+AZA significantly decreased or eradicated LSCs in responding AML/MDS patients (middle)
- Leukemic mutations were significantly reduced or eliminated in an 80 year old AML patient with complex cytogenetics achieving CR (9 months and ongoing).