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POSTER ABSTRACTS

616.ACUTE MYELOID LEUKEMIAS: INVESTIGATIONAL THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Safety, Pharmacodynamic, and Anti-Tumor Activity of SL-172154 As Monotherapy and in Combination with Azacitidine (AZA) in Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML) and Higher-Risk Myelodysplastic Syndromes/Neoplasms (HR-MDS) Patients (pts)

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Background: CD47 blocking antibodies and SIRPα-Fc fusion proteins have demonstrated activity in combination with azacitidine (AZA) in previously untreated (UnTx) HR-MDS and AML pts. SL-172154 (SIRPα-Fc-CD40L), a hexameric, bi-functional fusion protein consisting of SIRPα domains linked to CD40L domains through an inert Fc linker demonstrated improved anti-tumor activity in comparison to naked CD47 blocking antibodies in pre-clinical studies [de Silva et al. Cancer Immunol Res 2020]. SL-172154, as a CD47 inhibitor, requires combination with AZA to enhance pro-phagocytic signals on leukemic stem cells/blasts thereby potentiating macrophage phagocytosis in AML/HR-MDS. Here we report the results from the Phase 1 Dose Escalation. cohorts for SL-172154 monotherapy [SL-mono] and for SL-172154 + AZA combination [SL-AZA] in pts with HR-MDS or AML.
Methods: The objectives of the dose escalation cohorts include evaluation of safety, dose-limiting toxicity (DLT), recommended phase 2 dose, pharmacokinetic and pharmacodynamic effects and efficacy per IWG 2006 for MDS and ELN 2017 for AML. SL-172154 was administered IV weekly of a 28-day cycle as monotherapy or with AZA 75 mg/m ^{2} for 7 days per cycle. mTPI-2 was used for dose escalation with a DLT threshold of 20%. Pts $\geq$ 18 years old with R/R HR-MDS or R/R AML were eligible for dose escalation cohorts. In addition, UnTx pts with TP53 mutant (TP53m)-MDS were eligible for SL-AZA cohorts.
Results: As of May 25, 2023, 37 pts were enrolled (19 in SL-mono; 18 in SL-AZA cohorts): 14 women; median age 70 years [range 44-81]. 27 pts had R/R AML (16 de novo; 11 secondary), 5 had R/R MDS, and 5 were UnTx TP53m-MDS. 23 (85%) of 27 R/R AML pts had adverse genetic abnormalities per 2017 ELN classification, including 9 (33%) with TP53m or del 17. The median number of prior lines of AML therapy was 2 [range 1-4]; 25 (93%) had received venetoclax (VEN) and 23 (85%) had received a hypomethylating agent (HMA). All 5 pts with R/R MDS had previously received HMA and 2 pts were previously treated with VEN. SL-172154 was dose escalated as monotherapy or with AZA as shown in Table 1. Infusion-related reactions (IRRs) were the most common SL-172154-related treatment-emergent AEs (TEAEs) reported in 13 (68%) and 8 (44%) pts in

SL-mono and SL-AZA cohorts, respectively. IRRs (51 events) were Grade (G) 1 or 2 except for 3 G3 events (1 each at 6 mg/kg SL-mono and SL-AZA; 1 at 3 mg/kg SL-mono). Other SL-172154-related TEAEs observed in ≥ 3 pts were AST increased (4; 21%), ALT increased (3; 16%) and nausea (3; 17%) in SL-mono cohorts, and nausea (3; 17%) in SL-AZA cohorts. All events of AST/ALT increased were transient. Only one DLT (G3 IRR in the 6 mg/kg SL-AZA cohort) was reported, which required a dose reduction to 3 mg/kg.

As of July 10, 2023, in SL-mono cohorts, 1 pt with R/R AML post 7+3, FLAG and VEN/AZA achieved Morphologic Leukemia-Free State (blast reduction from 19% to <5%) after 1 cycle of 6 mg/kg SL-172154 and proceeded to allogeneic hematopoietic cell transplant (allo-HCT) after cycle 2. In 12 evaluable pts with R/R AML receiving SL-AZA, although no objective responses (OR) were observed, relative reduction in bone marrow (BM) blasts from baseline was reported in 2/5 pts at 1 mg SL-AZA (-50%, -75%) and 5/7 pts at 3 mg SL-AZA (ranging from -35% to -90%). One pt underwent an allo-HCT. In 4 evaluable pts with UnTx TP53m-MDS, the ORs were 1 complete remission (CR), 1 marrow CR, and 2 stable disease. 2 of them proceeded to allo-HCT.

SL-172154 induced elevations in serum IL-12p40, IP-10, IL-8, IL-10, MIP3α and MCP1: greater response at 3 mg/kg compared to 1 mg/kg while similar between 3 and 6 mg/kg. In the BM, SL-172154 induced a dose-dependent increase in phagocytic cells (CD11b, HLA-DR, CD16, CD36 and CD64) within mature myeloid immune cell compartments (CD45highCD34-). Reduction in leukemic blasts (CD45lowCD34+) was associated with an increase in mature myeloid and phagocytic cell phenotypes (3 mg/kg SL-AZA > 1 mg/kg SL-AZA).

Conclusions: SL-172154 was well tolerated up to 3 mg/kg as monotherapy and in combination with AZA. Preliminary efficacy signals were detected in UnTx TP53m-MDS and R/R AML. A response to SL-172154 monotherapy, dose-dependent increases in serum cytokines and accumulation of mature myeloid cells in BM suggest a potential role for CD40 stimulation. Based on the safety, preliminary efficacy and pharmacodynamic activity, 3 mg/kg SL-172154+ AZA is being evaluated in treatment naïve pts with TP53m AML and HR-MDS.

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Table 1: Number of patients treated with SL-172154 for Each Cohort

	SL-172154 monotherapy [SL-mono] Cohorts	**SL-172154 + Azacitidine combination [SL-AZA] Cohorts**
SL-172154 Dose	Number of patients treated (n)	Number of patients treated (n)
1 mg/kg	4 3 R/R AML 1 R/R MDS	8 5 R/R AML 3 previously untreated TP53m-MDS
3 mg/kg	8 5 R/R AML 3 R/R MDS	9 8 R/R AML 1 previously untreated TP53m-MDS
6 mg/kg	7 6 R/R AML 1 R/R MDS	1 previously untreated TP53m-MDS
Total	**19** **14 R/R AML** **5 R/R MDS**	**18** **13 R/R AML** **5 previously untreated TP53m-MDS**
Median doses of SL-172154 administered [range]	7 [2-28]	8 [2-15]

Note: dose was escalated based on modified toxicity probability interval 2 (mTPI-2)
TP53m-MDS: MDS with TP53 mutation

Figure 1

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