Abstract: P773

Title: PHASE 1B STUDY OF SL-172154, A BI-FUNCTIONAL FUSION PROTEIN TARGETING CD47 AND CD40, WITH AZACITIDINE IN PREVIOUSLY UNTREATED ACUTE MYELOID LEUKEMIA AND HIGHER-RISK MYELODYSPLASTIC SYNDROMES

Abstract Type: Poster Presentation

Topic: Myelodysplastic syndromes - Clinical

Background:

SL-172154 (SIRPα-Fc-CD40L, 154), 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 CD47 blocking antibodies in preclinical studies. The dose escalation results showed that 154+azacitidine (AZA) was tolerable in higher-risk myelodysplastic syndromes (HR-MDS)/ acute myeloid leukemia (AML) and supported 3 mg/kg dose for further investigation [Daver 2023 ASH].

Aims:

The objectives of the Dose expansion cohorts were to evaluate the safety, efficacy (per IWG 2006 for HR-MDS, ELN 2017 for AML) and pharmacodynamic effects of 154 (3 mg/kg) + AZA.

Methods:

Previously untreated HR-MDS or TP53 mutant (TP53m) AML patients (pts) consented to participate in this study. 154 was administered IV qwk during the first 2 cycles and q2wks from the 3rd cycle onwards (28 day/cycle) + AZA until disease progression or unacceptable toxicity. Baseline and longitudinal minimal residual disease (MRD) were centrally assessed by multiparameter flow cytometry (MFC) with negative MRD defined as <0.02%. NGS analysis is ongoing and will be presented at the meeting.

Results:

As of 1 Feb 2024, 39 pts (24 HR-MDS, 15 TP53m-AML) of median age 74 yrs [range 42-89] were enrolled. Of 24 pts with HR-MDS, 20 (83%) had TP53m, 21 (88%) had complex karyotype (CK) defined by ≥ 3 cytogenetic abnormalities; 7 (29%) had therapy-related MDS. IPSS-R risk was very high (n=10)/high (n=14). All 15 pts with TP53m-AML had CK, including 11 (73%) secondary AML. The 60-day mortality in HR-MDS was 8% (2/24-sepsis and AML) and in TP53m AML was 27% (4/15- cardiac arrest, sepsis, pneumonia and AML). 154-related adverse event (AE) was reported in 31/39 (80%) pts. Infusion related reaction (IRR), 18 (46%), was the most common AE; all were Grade (G) 1/2 except for 2 (5%) G3 events. Other 154-related AEs (all Grade in ≥10%) were fatigue (5; 13%) and hypokalemia (4; 10%). Cytokine release syndrome was reported in 2 pts with HR-MDS (G2 and G3 each). 11 (28%) pts experienced at least one G3/4 154-related AE, with fatigue, febrile neutropenia, and IRR as the most common (in 2 pts each). 2 pts had drug discontinuations that were possibly related to 154: one G4 event (myocardial infarction) and one G5 event (cardiac arrest). Both pts had a history of significant cardiovascular disease, adverse risk factors, and other comorbidities. In HR-MDS, objective response (OR) rate was 15/23 (65%), see Table 1. 9/23 (39%) pts achieved CR with the median [range] time to CR of 16 [4-30] weeks. Duration of CR ranged from 0.1+ to 42+ weeks. None of the pts with CR progressed as of 1 Feb 2024. Cytogenetic CRs were observed in 6/8 pts who had abnormal cytogenetics at baseline. MRD by MFC was negative in 10/12 pts with CR or mCR+HI. 16/24 pts are ongoing treatment. In TP53m-AML, OR rate was 36% (2 CR, 1 CRi, 2 PR). MRD up to C3 was positive in 3 pts with CR/CRi: 2/3 pts proceeded to HCT, 1/3 pt is ongoing (MRD 0.02% at cycle 4). The median time to CR was 8.7 [8.4-9.0] weeks; duration of CR ranged from 2+ to 12+ weeks. None of the responders progressed as of 1 Feb 2024. Of 15 pts, 6 pts are ongoing treatment; 4 responders (1 CR, 1 CRi, 2 PR) discontinued treatment to undergo hematopoietic cell transplantation (HCT). Median duration of response and overall survival has not been reached in both HR-MDS and TP53m AML as of the data cut date.

Summary/Conclusion: The combination of 3 mg/kg 154+AZA showed an acceptable safety profile. Preliminary efficacy results suggest that the combination of 154+AZA provides encouraging CR rates in previously untreated HR-MDS and TP53m AML pts and successfully bridged responding TP53m AML pts to HCT.

Table 1

	***TP53wt*-HR-MDS** (N=4)	***TP53m*-HR-MDS** (N=20)	**HR-MDS In total[a]** (N=24)		***TP53m*-AML** (N=15)
N (response evaluable)[b]	4	19	23	N (response evaluable)[b]	14
CR	2 (50%)	7 (37%)	9 (39%)	CR	2 (14%)
mCR	1 (25%)	4 (21%)	5 (22%)	CRi	1 (7%)
mCR+HI	1 (25%)	2 (11%)	3 (13%)	PR	2 (14%)
SD+HI	0	1 (5%)	1 (4%)	**CR+CRi**	**3 (21%)**
OR (CR, mCR, or SD+HI)	**3 (75%)**	**12 (63%)**	**15 (65%)**	**OR** (CR, CRi, or PR)	**5[c] (36%)**

OR: objective response; CR: complete remission; mCR: marrow CR; HI: hematologic improvement; SD: stable disease; CRi: CR with incomplete hematologic recovery; PR: partial remission; DOR; duration of OR; TP, TP53wt: TP53 wild type; TP53m: TP53 mutant

[a]Includes one pt with previously untreated HR-MDS from the Dose-escalation cohort, who was treated with the same dose of 154 and AZA.

[b]Response evaluable population includes pts who had at least one on-study disease assessment or progress/die before the first on-study disease assessment.

[c]4 out of 5 pts (except for 1 pt achieving CR) discontinued the study drug to proceed with an allogeneic hematopoietic cell transplantation.

Keywords: MDS, AML, Phase I, TP53