HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

(S146) COMPLETED DOSE ESCALATION FROM THE FIRST-IN-HUMAN, PHASE 1/2 STUDY OF CD123 NK CELL ENGAGER, SAR443579, IN RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA OR HIGH RISK-MYELODYSPLASIA

Topic: 4. Acute myeloid leukemia - Clinical

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Background:

SAR443579 (SAR'579) is a natural killer (NK) cell engager, facilitating the formation of a cytolytic synapse between NK cells and CD123-positive tumor cells, leading to NK-cell activation and tumor cell death. Herein, we report analysis of the phase 1 portion of the on-going phase 1/2 trial (TCD17197) in adult participants (pts) with relapsed or refractory acute myeloid leukemia (R/R AML), B-cell acute lymphoblastic leukemia or high risk-myelodysplasia (HR-MDS) (NCT05086315).

Aims:

First comprehensive report of safety, efficacy, translational, and mechanistic data of SAR'579 from the completed phase 1 part of TCD17197 in adults, as the foundation for selection of recommended doses for further development in the expansion part (phase 2) of the study.

Methods:

TCD17197 is a global first-in-human, open-label, multicenter study designed to characterize the overall safety and tolerability profile of SAR'579 along with preliminary anti-leukemic activity. SAR'579 was administered intravenously during 28-day induction cycles, either twice weekly or once weekly (QW), depending on the dose level (DL) for the first 2 weeks, and then weekly for the remainder of induction cycles. Pts achieving a complete remission (CR) or CR with incomplete hematologic recovery (CRi) were eligible for maintenance dosing administered approximately once every four weeks. Bone marrow and peripheral blood samples were taken at various time points to assess treatment response and effects.

Results:

As of February 2, 2024, 59 adult pts (58 R/R AML and 1 HR-MDS) across 11 DLs encompassing 0.01 – 6 mg/kg/dose were treated. The median (range) age was 67 years (19 – 81). Pts had received a median of 2 (1 –10) prior lines of treatment, with 18 pts (30.5%) reporting prior hematopoietic stem cell transplantation and 52 pts (88.1%) with** prior exposure to venetoclax. Median white blood cell count at screening was 2.6 × 109/L (0 – 12). Median bone marrow blast burden at study entry was 47.5% (1.0 – 90.0) and 3 pts (5.2%) had extramedullary disease. Pts received a median of 2 cycles (1 – 11) with a median treatment duration of 7.9 weeks (1.0 – 66.0). Treatment-emergent adverse events (TEAEs) were reported in 58 pts (98.3%) with grade ≥3 adverse events (AEs) in 40 pts (67.8%). Serious TEAEs were reported in 35 pts (59.3%). TEAEs

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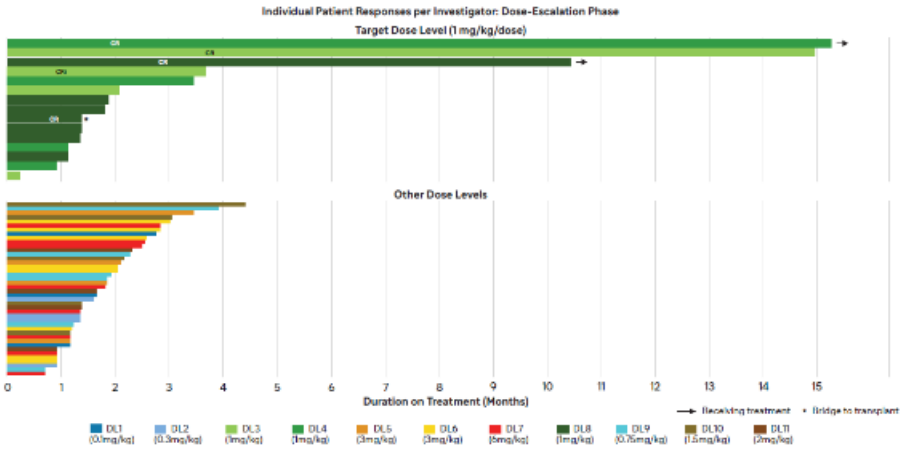
leading to the permanent discontinuation of SAR'579 were reported in 4 pts (6.8%). The most common TEAEs were infusion-related reactions (n = 33 [55.9%]) and constipation (n = 13 [22.0%]), all being ≤ grade 2 events. Treatment-related AEs occurred in 40 pts (67.8%). Cytokine release syndrome was observed in 4 pts (6.8%), with 3 cases of grade 1 at 1 mg/kg, 3 mg/kg, and 1.5 mg/kg and 1 case of grade 3 at 0.75 mg/kg. No cases of immune effector cell-associated neurotoxicity syndrome were reported. Blast reductions were observed at all dose levels. In DLs with a highest dose of 1 mg/kg QW, 5/15 (33.3%) AML pts achieved a CR (4 CR/1 CRi) (**Figure**). Mutations in responding pts included TP53, IDH2, TET2, NRAS or RUNX1. Complete remissions were observed upon completion of 1 (CR & CRi), 2, 3 and 4 cycles of treatment, and the median duration of CR/CRi was 48 weeks (~12 months), with the longest duration of response ongoing at 13+ months and one patient receiving a transplant. CD123 expression was observed in all treated patients with a high variability of receptor density at baseline and changes on treatment. High variability in effector to target (E:T) ratios was noted. The observed clinical responses over a large range of SAR'579 doses demonstrate dose-dependent bell-shaped activity that was reproduced with *in vitro* AML cell models. Predictive and prognostic markers are being explored from clinical data, including baseline NK cell numbers and fitness.

Summary/Conclusion:

SAR'579 was well tolerated up to doses of 6 mg/kg QW with observed clinical benefit in adult pts with R/R AML and a maximum response rate seen at a target dose of 1 mg/kg (33% CR/CRi). The bell-shaped dose-response curve is also observed *in vitro* in AML cell models. SAR'579 received Fast Track designation by the US FDA and these data will form the basis for selection of recommended doses for development in the phase 2 portion of TCD17197. Funding: Sanofi.



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