Abstract: P475

Title: EXPLORING DOSE-RESPONSE RELATIONSHIP OF A NOVEL CD123 NK CELL ENGAGER SAR443579 IN ACUTE MYELOID LEUKEMIA (AML) MODELS

Abstract Type: Poster Presentation

Topic: Acute myeloid leukemia - Biology & translational research

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Background:

SAR443579 (SAR'579) is a trifunctional anti-CD123 natural killer (NK) cell engager, currently in a phase 1/2 trial in patients with relapsed or refractory (R/R) AML, B-cell acute lymphoblastic leukemia or high risk-myelodysplasia (HR-MDS) (NCT05086315). SAR'579 acts by targeting CD123 antigen, which is highly expressed in hematological malignancies such as R/R AML, and by co-engaging NKp46 and CD16a activating receptors on NK cells. SAR'579 facilitates the formation of an immunological synapse between NK cells and CD123-positive tumor cells leading to NK cell activation, degranulation and tumor cell killing. The anti-tumor activity of SAR'579 in preclinical models has been described previously (1).

Aims:

To document SAR'579 mechanism of action *in vitro* and *in vivo* over a broad range of doses.

Methods:

The cytotoxic activity of SAR'579 was evaluated *in vitro* over a broad range of concentrations against different AML cell lines exhibiting low (OCI-AML2 and NB-4 cells, ~1300 and 2500 sites/cells, respectively), medium (THP-1 cells, ~6000-9000 sites/cells) or high (MOLM-13 cells, ~11000-20000 sites/cells) CD123 receptor density, in the presence of healthy donor NK cells at different effector (E) to target (T) (E:T) ratios and different time points. Cytotoxic activity was measured using the Calcein-AM release assay, by live-cell imaging analysis (Incucyte system) or by flow cytometry measuring tumor cell viability after Cell Trace Violet (CTV)-Propidium iodide (PI) staining. The effect of SAR'579 on NK cell activation was evaluated by flow cytometry. A surrogate SAR'579 antibody which binds to murine NKp46 on mouse NK cells was used for *in vivo* studies in SCID mice intravenously (IV) injected with human MOLM-13 AML cells. The surrogate SAR'579 antibody was tested at single doses ranging from 0.05 to 30 mg/kg via intraperitoneal administrations.

Results:

In vitro, SAR'579 demonstrated potent cytotoxic activity in an E:T ratio and time-dependent manner against the 4 AML cell lines tested, regardless of CD123 receptor density. A bell-shaped dose-response curve was observed upon treatment with SAR'579 in all AML cell lines. Interestingly, for all cell lines the maximum cytotoxic effect was reached within the same range of concentrations (ECmax range from 0.08 to 0.66 µg/ml geometric mean), irrespective of the E:T ratio, the duration of treatment or the level of CD123 expression. *In vivo*, the SAR'579 surrogate NK cell engager also demonstrated potent anti-tumor efficacy with bell-shaped dose-dependent activity with decreased activity at the 2 highest doses tested, 10 and 30 mg/kg.

Additional data from mechanistic analyses will be presented.

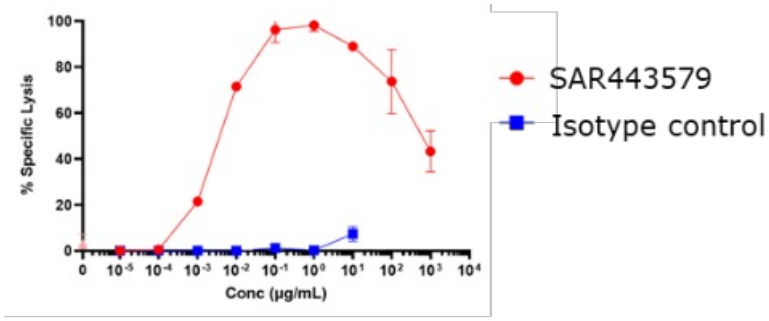
Conclusion:

SAR'579 demonstrates potent anti-tumor activity against AML tumor cells expressing low, medium or high CD123 antigen densities, with a bell-shaped dose-response up to high concentrations *in vitro*, regardless of CD123 receptor density or E:T ratio. A similar bell-shaped dose-effect was observed *in vivo* in mice, as already

described for some other immune cell engagers.

Figure:

Cytotoxicity against MOLM-13 AML cells



Reference:

1. L. Gauthier, A. Virone-Oddos et al., Nature Biotechnol. 2023; https://doi.org/10.1038/s41587-022-01626-2

Keywords: NK cell, Acute myeloid leukemia, Cancer immunotherapy, Cytotoxicity