Exploring Dose-Response Relationship of a Novel CD123 NK Cell Engager SAR443579 in Acute Myeloid Leukemia (AML) Models

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INTRODUCTION

- SAR443579 (SAR'579) is a trifunctional anti-CD123 natural killer (NK) cell engager (NKCE) which is currently in a phase 1/2 trial in patients with relapsed or refractory AML (R/R AML)), B-cell acute lymphoblastic leukemia (B-ALL) or high risk-myelodysplasia (HR-MDS), or Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) (NCT05086315).
- SAR'579 binds to CD123 tumor-associated antigen (highly expressed in R/R AML) and co-engages NK cells through the activating NK cell receptors NKp46 and CD16a, leading to the formation of an immunological synapse followed by NK cell activation, degranulation with release of cytotoxic granules, and ultimately killing of CD123-positive tumor cells (1).

Here, we investigated the *in vitro* and *in vivo* dose-response relationship of SAR'579 over a broad range of doses.

Figure 1. SAR'579: trifunctional anti-CD123 NKp46×CD16 NK cell engager

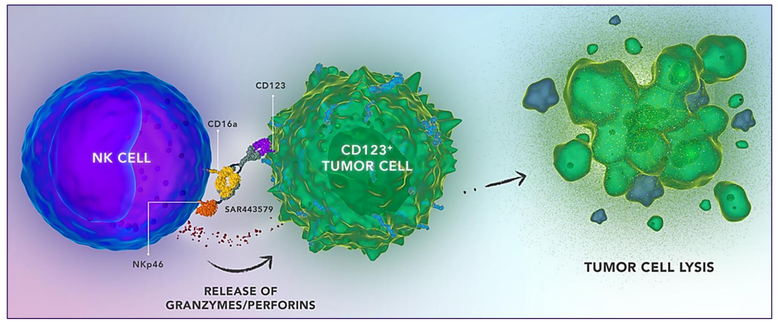
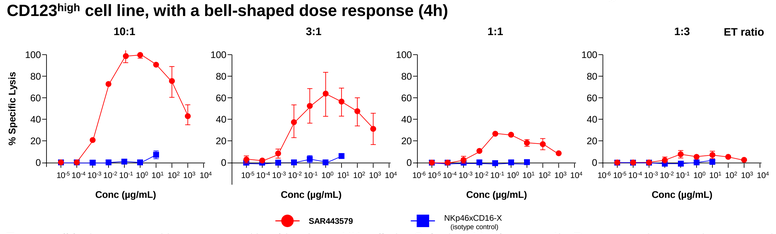


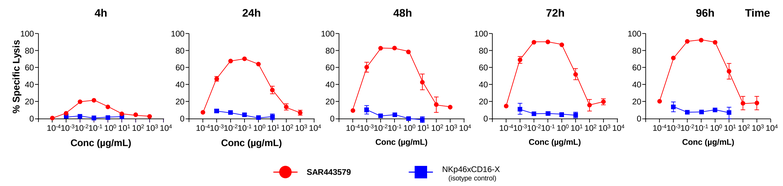
Figure 2. Potent SAR'579 cytotoxic activity in a time- & Effector-to-Target (E:T) ratio-dependent manner with a bell-shaped dose response up to high concentrations

SAR'579 exhibits potent cytotoxic activity in an E:T ratio-dependent manner against MOLM-13 CD123^{high} cell line, with a bell-shaped dose response (4h)



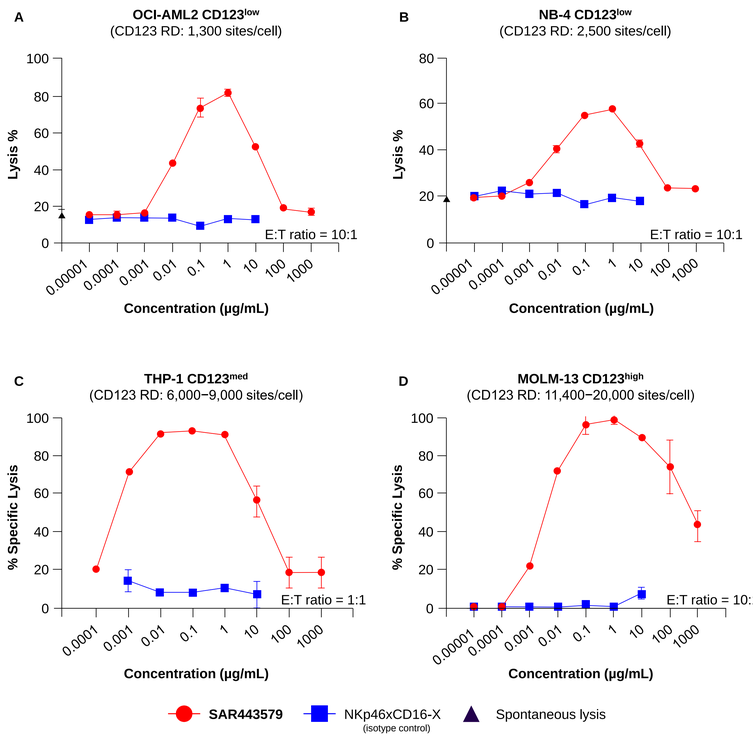
Tumor cell lysis measured in presence of healthy donor NK cells by Calcein-AM release at 4h. Representative experiment out of 4 independent NK donors.

SAR'579 exhibits potent cytotoxic activity in a time-dependent manner against THP-1 CD123^{med} cell line, with bell-shaped dose-effect response (E:T ratio 1:1)



Tumor cell lysis measured in presence of healthy donor NK cells by Incucyte live-cells analysis system. Kinetics from a representative experiment out of 4 NK independent donors.

Figure 3. Potent SAR'579 cytotoxic activity with a bell-shaped dose response against AML cell models expressing low to high CD123 receptor density



Tumor cell lysis measured in presence of healthy donor (HD) NK cells by flow cytometry with Cell Trace Violet (CTV)-Propidium iodide (PI) at 24 hours (A & B), Incucyte live-cells analysis system up to 96h (C) or by Calcein-AM release at 4h (D). Representative experiment out of 3-4 independent NK donors.

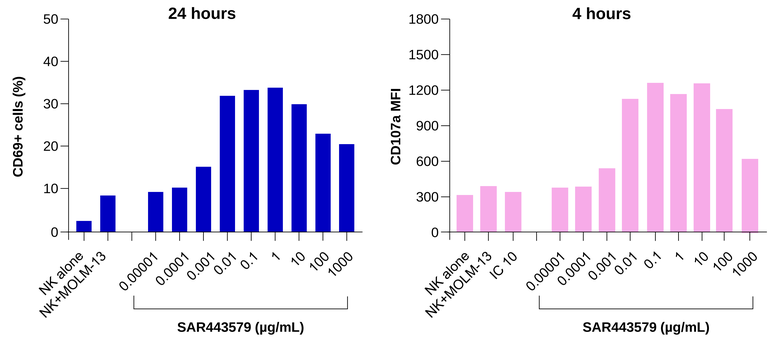
Table 1. SAR'579 maximum cytotoxic effect (EC$_{max}$) reached within the same range of concentrations irrespective of CD123 receptor density

	MOLM-13 CD123^{high}		THP-1 CD123^{med}	OCI-AML2 CD123^{low}	NB-4 CD123^{low}
CD123 receptor density	11,400-20,000		6,000-9,000	1,300	2,500
E:T ratio	10:1	3:1	1:1	10:1	10:1
EC$_{max}$ (µg/mL) geo mean [CI 95%]	0.35 [0.09 – 1.36]	0.43 [0.04 – 4.24]	0.08 [0.02 – 0.26]	0.62 [0.12 – 3.17]	0.66 [0.15 – 2.88]

EC$_{max}$ expressed as the geometric mean [CI 95%] for n=3 (NB-4) or 4 (MOLM-13, THP-1 or OCI-AML-2) healthy donor NK

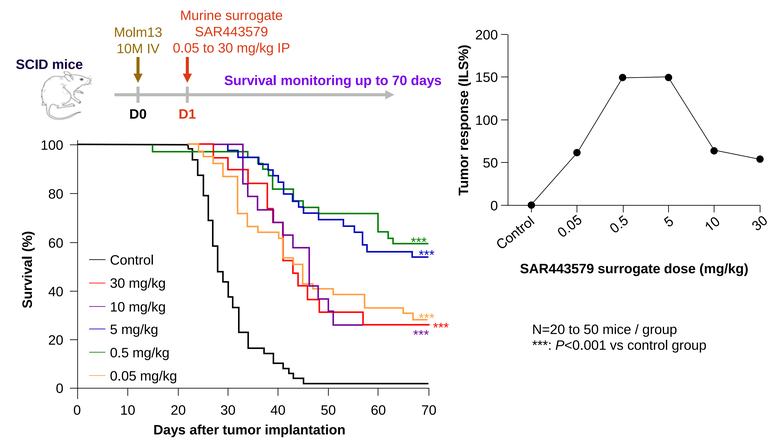
Geo mean, geometric mean; CI, confidence interval.

Figure 4. SAR'579 leads to NK cell activation/degranulation in a dose-dependent manner with a bell-shaped dose response (MOLM-13 CD123^{high} cells)



NK cell activation assessed by flow cytometry. Representative experiment out of 4 independent NK donors.

Figure 5. Potent antitumor activity of SAR'579 murine surrogate with optimal efficacy at 0.5 & 5 mg/kg doses against MOLM-13 CD123^{high} AML model



N=20 to 50 mice / group
***: *P*<0.001 vs control group

- **SAR'579 murine surrogate leads to a bell-shaped dose-response in mice**

SAR'579 treatment induced a moderate and dose-dependent decrease of NK cell number in blood and spleen, suggesting NK cell redistribution and recruitment.

CONCLUSIONS

- **The trifunctional anti-CD123 NKCE SAR'579 demonstrated potent anti-tumor activity against AML tumor cells expressing low to high CD123 antigen densities.**
- **A bell-shaped dose-response after treatment with SAR'579 over a broad range of concentrations was observed *in vitro*, regardless of receptor density or E:T ratio.**
- **Similar bell-shaped dose-effect observed *in vivo* in mice, as previously described for other immune cell engagers.**

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DISCLOSURES:
Nouguier C and **Abbadessa G** were employees of Sanofi during the conduct of this study and may have held stock and/or stock options. Rest all authors are employed by Sanofi and may hold stock and/or stock options.

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REFERENCES:
(1) L. Gauthier, A. Virone-Oddos et al., Control of acute myeloid leukemia by a trifunctional NKp46-CD16a-NK cell engager targeting CD123, *Nature Biotechnol*. 41, 1296–1306 (2023).

ABBREVIATIONS:
CD, cluster of differentiation; NK, natural killer; E:T ratio, Effector-to-Target Ratio; ILS, increase in life span; IP, intraperitoneal; IV, intravenous; RD, receptor density.