Preliminary Pharmacokinetics (PK) and Pharmacodynamic (PD) Analysis of the CD123 NK Cell Engager (NKCE) SAR443579 in Patients (pts) with Relapsed or Refractory Acute Myeloid Leukemia (R/R AML), B-cell Acute Lymphoblastic Leukemia (B-ALL) or High Risk-Myelodysplasia (HR-MDS)

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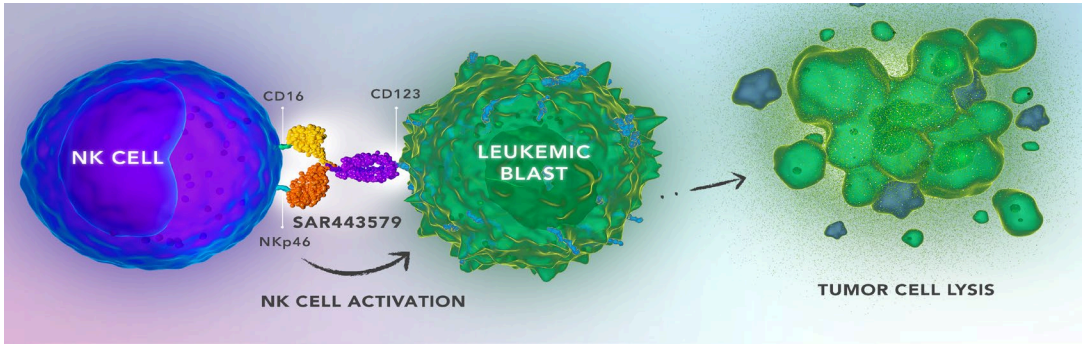
Disclosures

- No conflicts of interest to declare

Background

- CD123 is widely expressed in hematological malignancies[1-4]
- T cell engagers targeting CD123 have displayed some preliminary clinical efficacy but show some safety concerns of cytokine release syndrome and neurotoxicity[5]



- SAR443579 (SAR'579) is a trifunctional anti-CD123 NKp46xCD16 natural killer cell engager (NKCE) targeting CD123 antigen and co-engaging NKp46 and CD16a on natural killer (NK) cells triggering tumor cell death
- A Phase 1/2 trial (NCT05086315) is evaluating SAR'579 in patients with relapsed or refractory acute myeloid leukemia (R/R AML), B-cell acute lymphoblastic leukemia (B-ALL) or high risk-myelodysplasia (HR-MDS)
- Early clinical results noted SAR'579 was well tolerated up to 3000 µg/kg/infusion QW with no dose limiting toxicities and clinical remissions identified at a maximal target dose of ≥1000 µg/kg/infusion[6]
- Here we report the pharmacokinetics (PK) / pharmacodynamics (PD) in the same cohort[6]

1. Lyapichev KA, et al. *Clin Lymph Myel Leuk*. 2021; 21(4): e317-e320. 2. Patnaik MM, et al. *Leuk Lymphoma*. 2021; 62(11):2568-86. 3. Uckun FM, et al. *Front Aging*. 2021; 2:757276.
4. El Achi H, et al. *Cancers (Basel)*. 2020;12(11):3087. 5. Uy GL, et al. *Blood*. 2021;137(6):751-62. 6. Stein AS, et al, *J Clin Oncol*, (2023) (suppl 16): 7005. CD, cluster of differentiation; QW, once weekly

First-in-Human Dose Escalation & Enrollment

Dose Escalation Part

Determine maximum tolerated or administered dose based on incidence of dose-limiting toxicity in cycle 1 (28-day cycles)

R/R-AML, HR-MDS, B-ALL
6 initial dose levels (Bayesian Logistic Regression Model)

IV Dose in µg/kg	DL1	DL2	DL3	DL4	DL5	DL6
Day 1	10	30	100	300	1000	3000
Day 4	30	100	300	/	/	/
Day 8	100	300	1000	1000	3000	3000
Day 11	100	300	/	/	/	/
Day 15	100	300	1000	1000	3000	3000
Day 22	100	300	1000	1000	3000	3000

- Additional cycles (28 days) allowed using Day 22 dose (QW)
- Participants achieving CR/CRi eligible for maintenance schedule (Q4W)

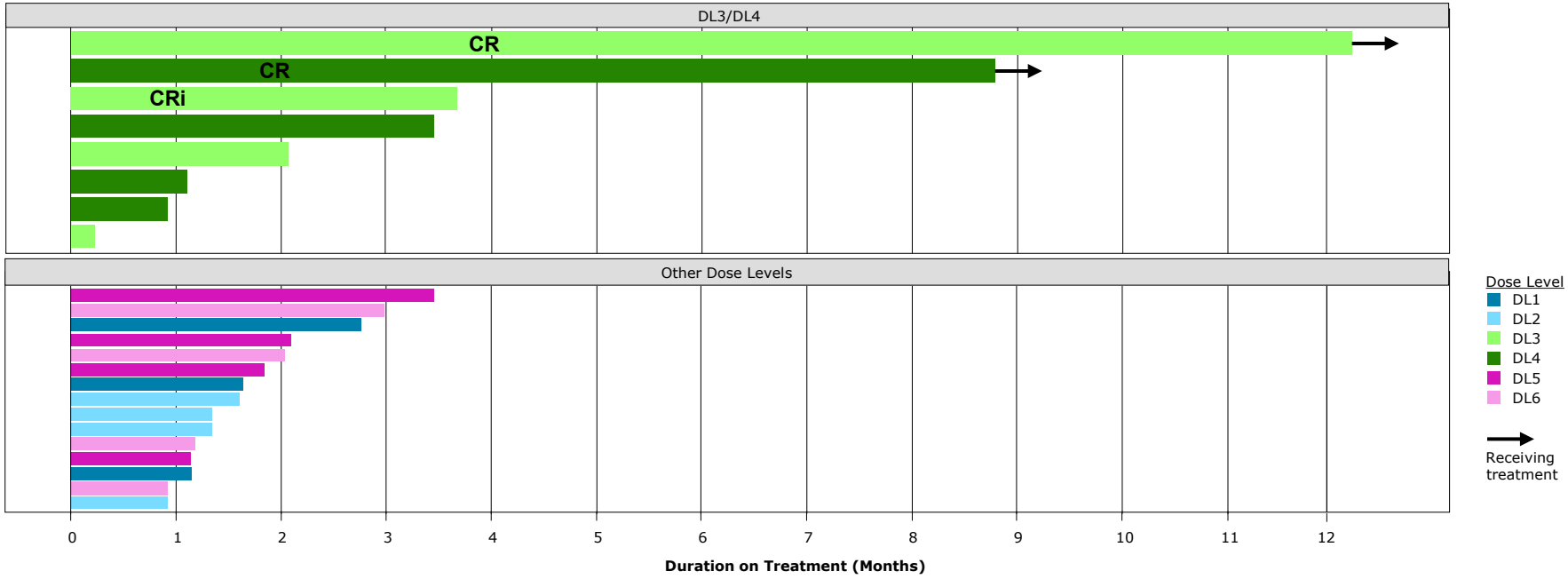
23 participants
(DL1=3; All other DLs=4)*†

- On treatment=2 (8.7%)
- Discontinued=21 (91.3%)
  - Progressive disease=17 (73.9%)
  - Adverse event=1 (4.3%)^
  - Participant withdrawal=1 (4.3%)
  - Other=2 (8.7%)

*Data cut-off; August 7, 2023 for included participants. †Previously disclosed population Stein AS, et al, *J Clin Oncol*, (2023) (suppl 16): 7005. All participants with R/R AML. ^Grade 3 pneumonia unrelated to SAR443579.
CR, complete remission; CRi, CR with incomplete hematological recovery; DL, dose level; IV, intravenous; Q4W, once every 4 weeks.

Safety and Efficacy Update*

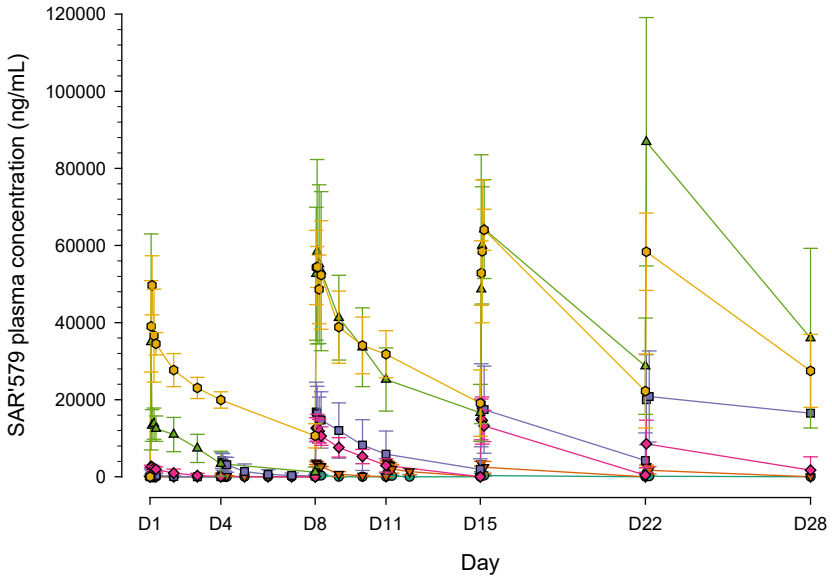
- **Most common treatment related adverse events remain consistent with previous report[1]**
- **CR/CRi achieved in 3 of 8 (37.5%) participants treated at a maximal target dose of 1000 µg/kg/infusion (DL3-DL4)[1,2]**
- **Two responders remain in remission after 8.8 and 12.2 months of treatment**



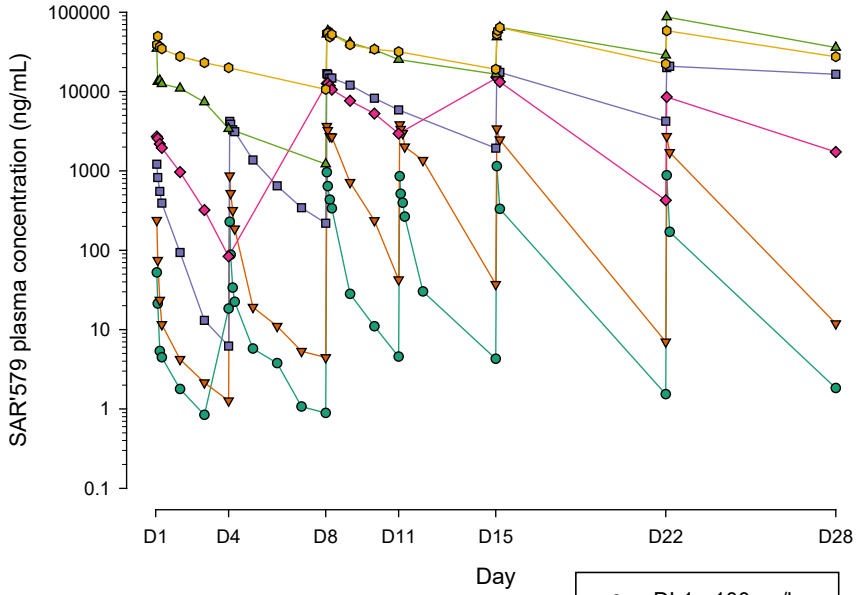
*Data cut-off; August 07, 2023 for included participants. 1. Stein AS, et al, *J Clin Oncol*, (2023) (suppl 16): 7005; All treatment-related adverse events were grade 1 or 2 with most common being infusion-related reaction (56.5%), decreased appetite (8.7%), headache (8.7%), diarrhea (8.7%), and nausea (8.7%). 2. Response assessments occur at the end of each induction cycle and as clinically indicated during maintenance. All responding patients in this presentation declined or were ineligible for stem cell transplant.

Pharmacokinetics: Mean Plasma Concentration

Cycle 1: Mean Plasma Concentration (DL1-6)



Cycle 1: Mean Plasma Concentration (DL1-6)

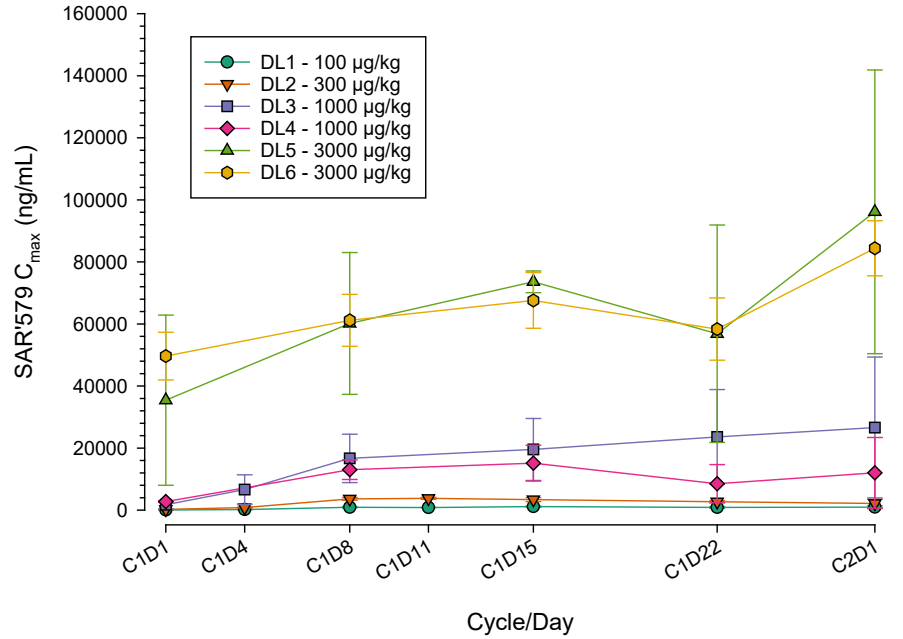


- **TMDD: PK linearity achieved from Cycle 1 at 3000 µg/kg QW (DL5/DL6)**
- **ADA: Anti-SAR'579 antibodies observed in 26% of analyzed patients (DL1-5) with no apparent impact on activity.**

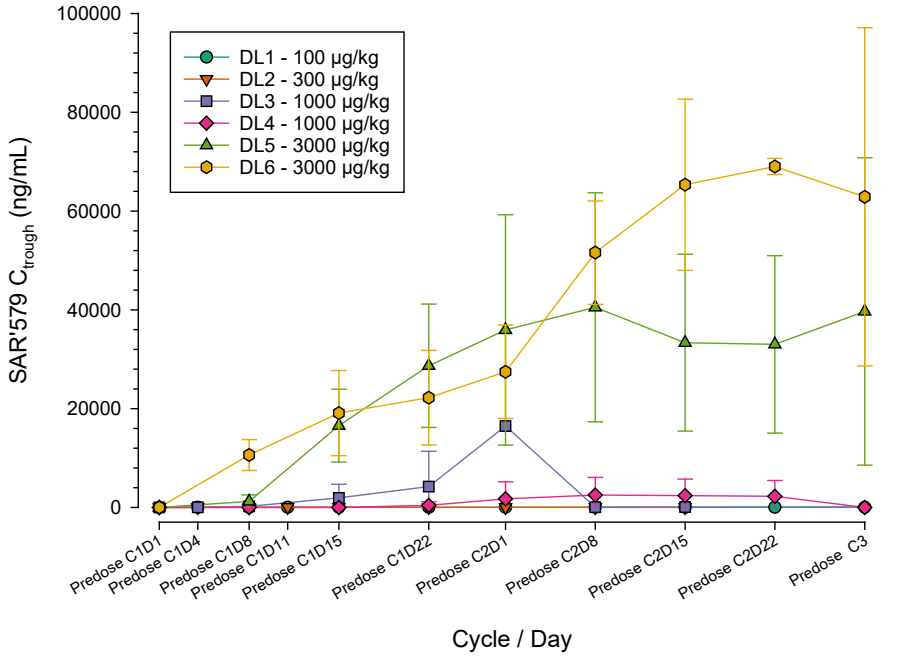
D, day; ADA, anti-drug antibodies; TMDD, target mediated drug disposition.

Pharmacokinetics: Mean C_{max} and C_{trough} Concentrations

C_{max}: Cycle 1 (DL1-6)



C_{trough}: Cycle 1 (DL1-6)

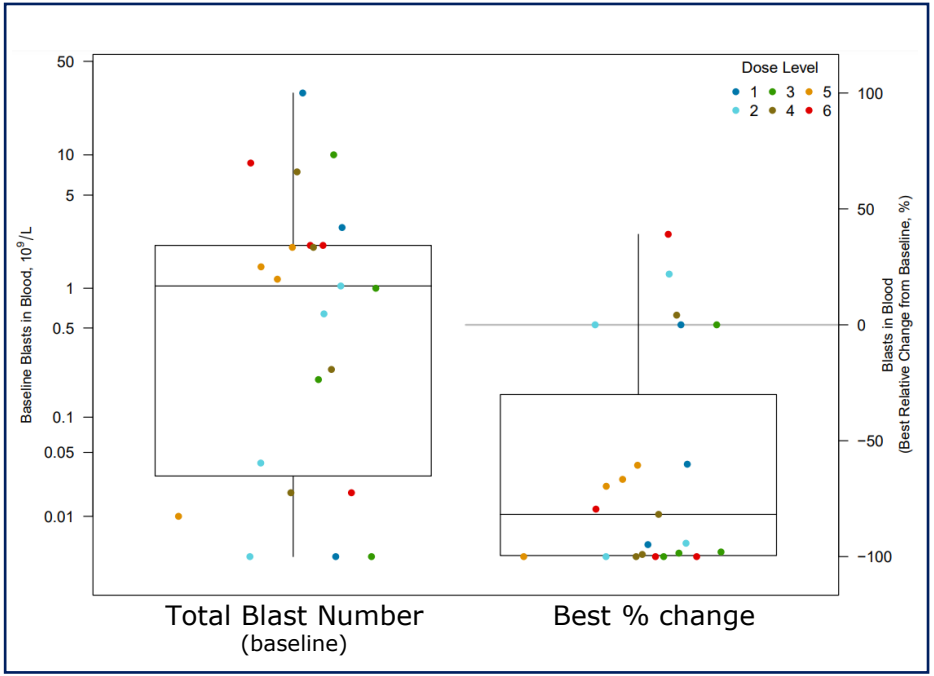


C_{max} and C_{trough} increased with dose level increases

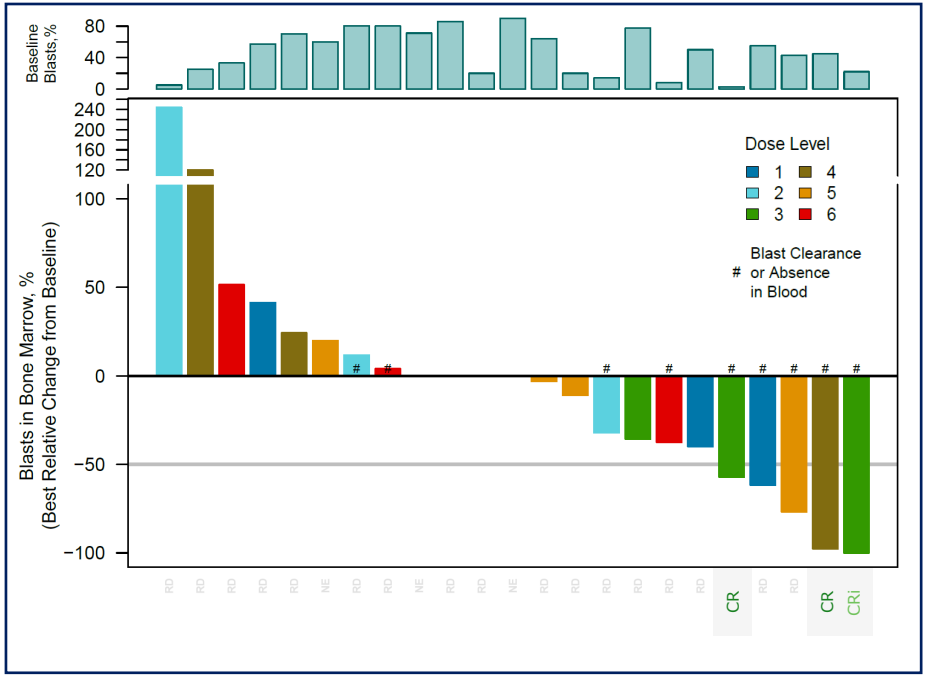
CxDx, cycle number day number.

Pharmacodynamics: AML Blast Assessment

Whole Blood



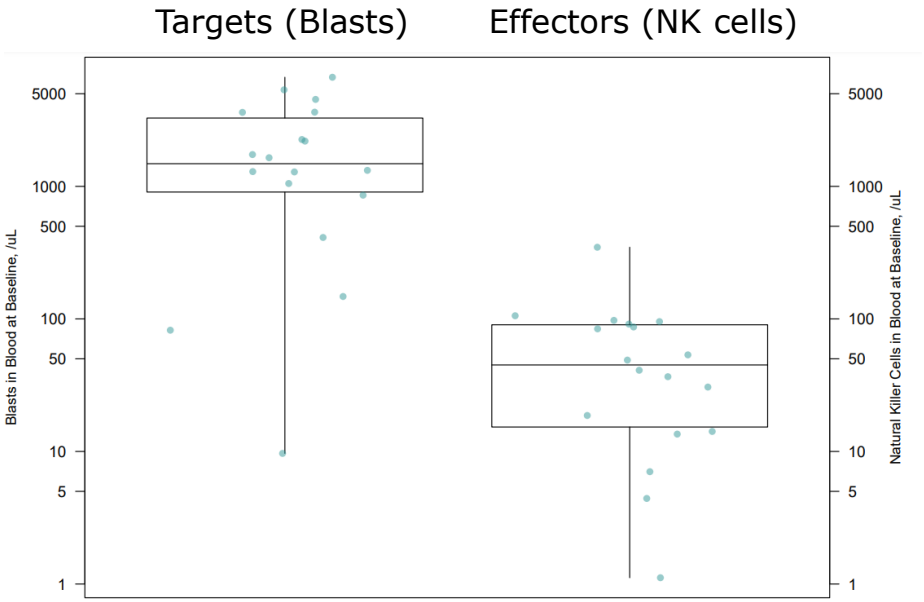
Bone Marrow

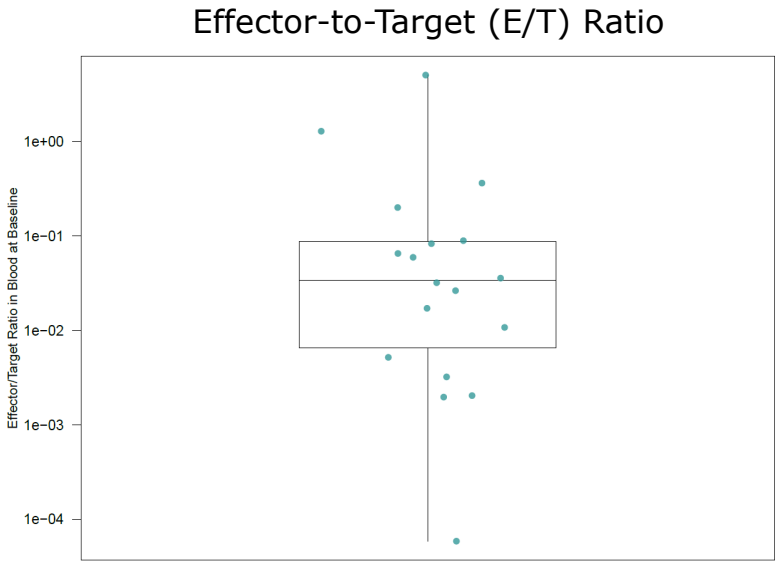


- **High variability in baseline AML blasts (marrow and peripheral blood)**
- **AML blast reductions observed across all SAR'579 dose levels**

NE, non-evaluable; RD, resistant disease.

Pharmacodynamics: NK and AML Blasts in Peripheral Blood at Baseline

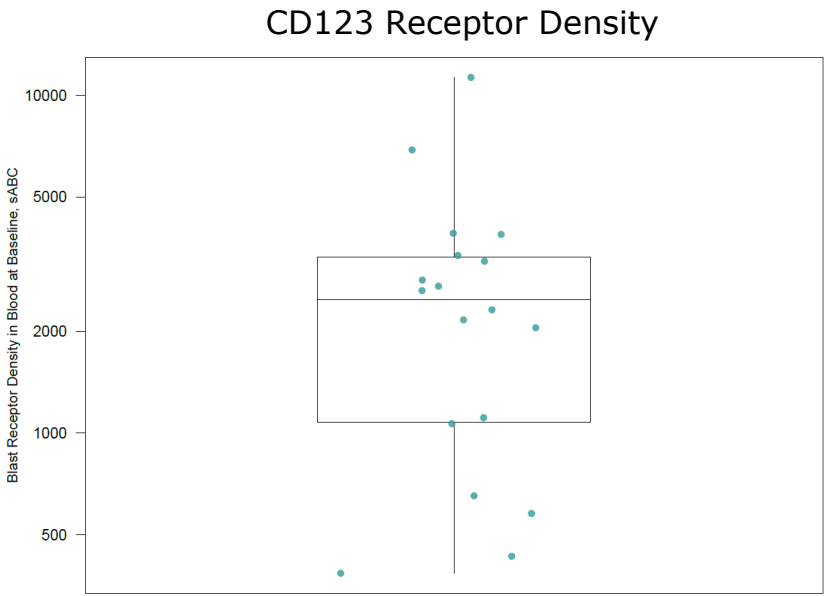


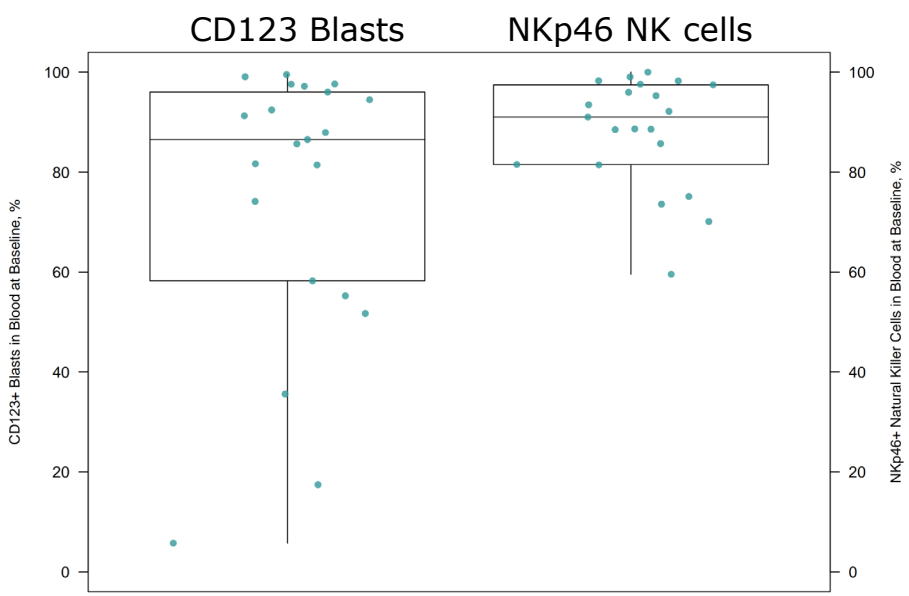


- **High variability in baseline NK cell counts and E:T ratio**
- **Insufficient data to correlate with response**

Whole blood characterized by Flow Cytometry

Pharmacodynamics: Expression of CD123 and NKp46

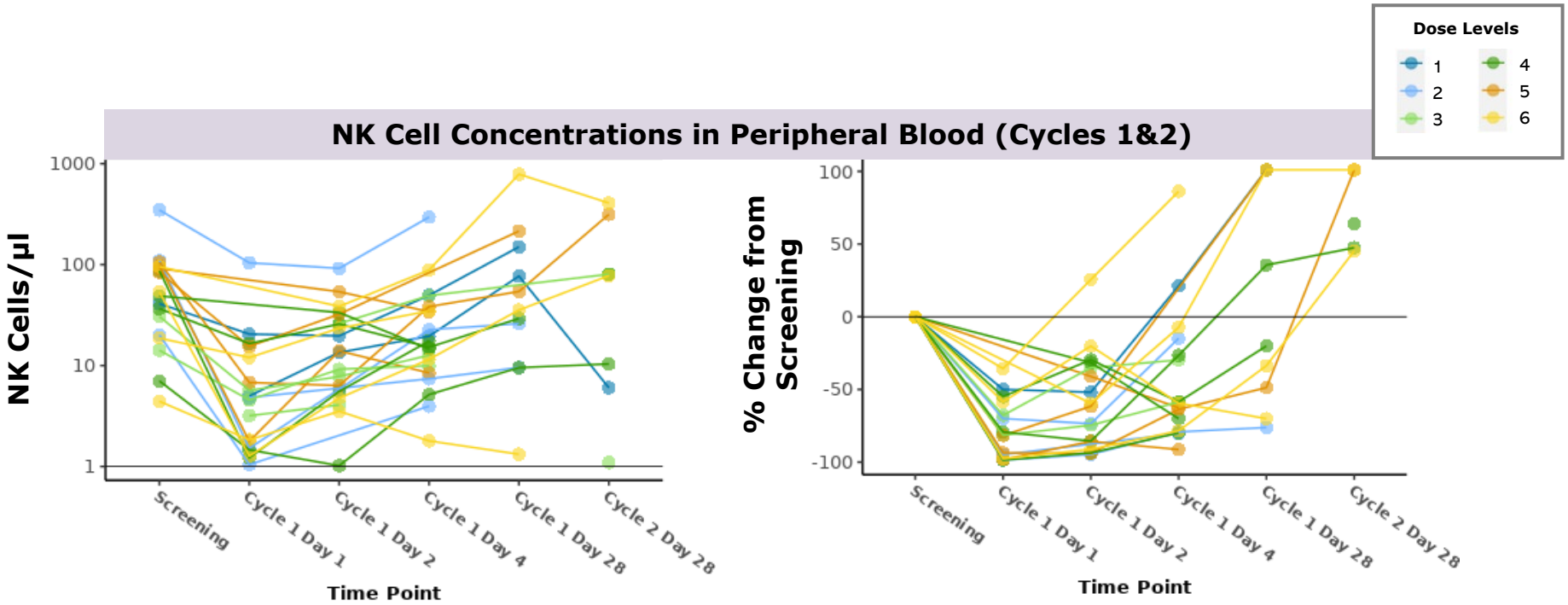




- **CD123 expression measured in all patients**
- **High variability in density of CD123 expression**
- **Robust expression (>60%) of NKp46 in all patients**

sABC, specific antibody binding capacity. Whole blood characterized by Flow Cytometry

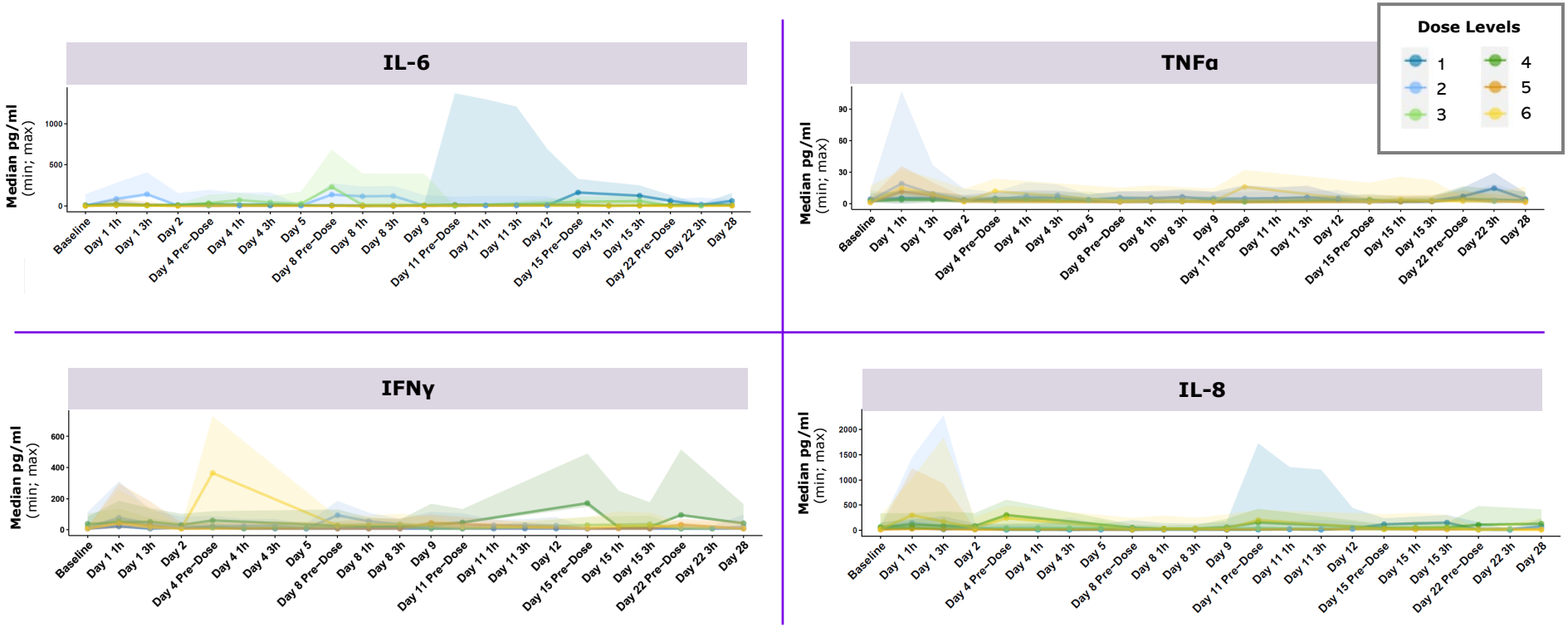
Pharmacodynamics: NK Cell Modulation in Peripheral Blood



- **Transient decrease in peripheral blood NK cells in all patients (peak between 4-24h)**

h, hours.

Pharmacodynamics: Plasma Cytokine Levels (Cycle 1)



- **Transient increases in pro-inflammatory cytokines (IFNγ, TNFα, IL-8) after 1-3h after first dose**
  - **Increases consistent across all dose levels;**
- **No clinically significant increases in IL-6 levels**

CRS, cytokine release syndrome; IFN-γ, interferon gamma; IL, interleukin; max, maximum; min, minimum; TNF-α, tumor necrosis factor alpha.

Summary and Conclusions

Safety/Efficacy

- SAR'579 was well tolerated up to dose of 3000 µg/kg QW with clinical benefit in patients with R/R AML and additional dose levels are being investigated

Pharmacokinetics/ADA

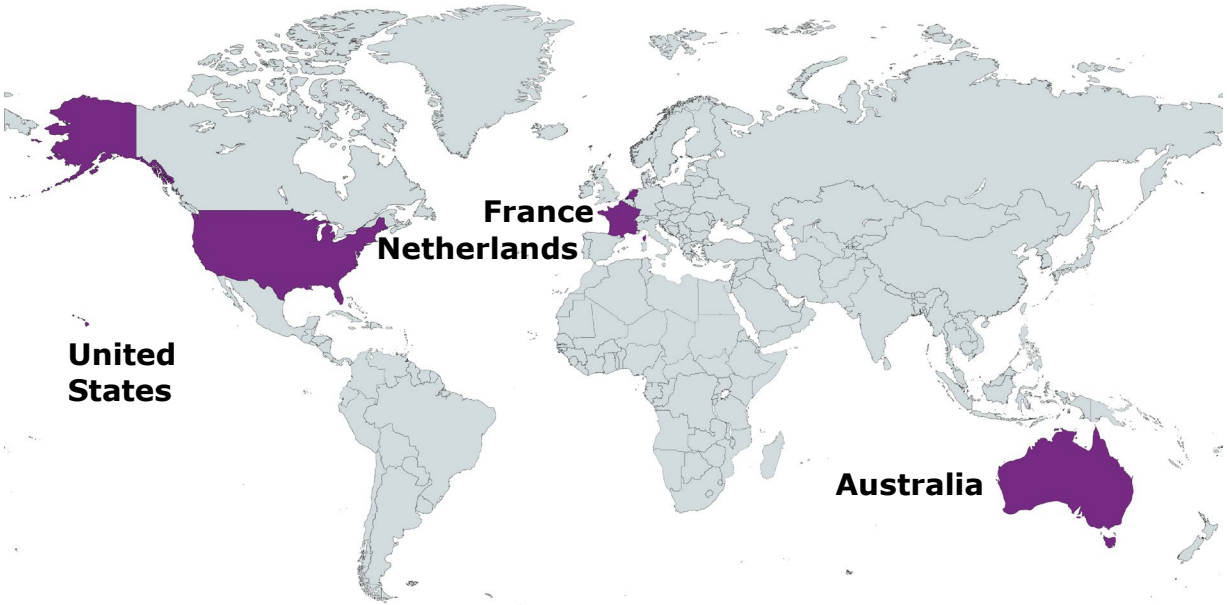
- PK linearity was achieved from Cycle 1 at 3000 µg/kg QW (TMDD)
- Preliminary incidence of immunogenicity was 26% with no identified impact on safety/efficacy to date

Pharmacodynamics

- SAR'579 induced reduction of leukemic blasts in whole blood and bone marrow
- Considerable variations in patient expression of CD123 were observed
- Heterogenous E/T ratio was observed from variable patient blasts and NK cell counts
- Modulation of peripheral NK cells was observed at all doses tested
- Peak cytokine levels demonstrated no significant dose-related increase or association with responses

SAR443579 continues to be investigated in hematological malignancies and was granted FDA Fast Track designation in May 2023

Acknowledgments



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For questions, please contact Dr. Mojca Jongen-Lavrencic at m.lavrencic@erasmusmc.nl