The anti-CD19 antibody-drug conjugate SAR3419 prevents hematolymphoid relapse post-induction therapy in preclinical models of pediatric acute lymphoblastic leukemia.

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Abstract C107

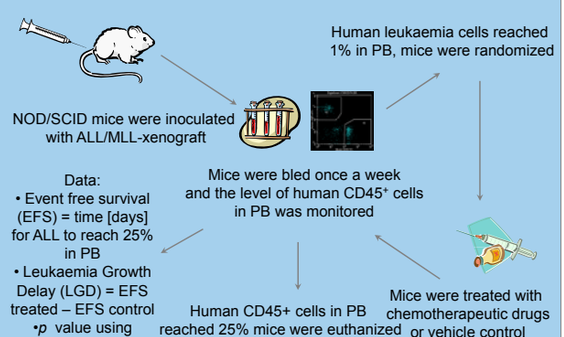
INTRODUCTION

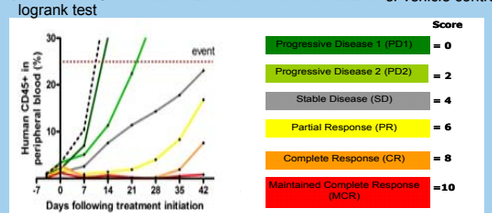
SAR3419 is an antibody-drug conjugate (ADC) of a humanized anti-CD19 antibody and the maytansinoid DM4 currently in clinical trials for relapsed or refractory B cell non-Hodgkin's lymphoma and adult acute lymphoblastic leukemia. SAR3419 was previously shown by the Pediatric Preclinical Testing Program (PPTP) to be highly effective in delaying the progression of CD19$^+$ B cell precursor ALL (BCP-ALL) xenografts in NOD/SCID mice, while being ineffective against CD19$^-$ T-lineage ALL. In the current study we evaluated the efficacy of SAR3419 against additional BCP-ALL and infant mixed lineage leukemia (MLL) xenografts, assessed its therapeutic range, and studied its efficacy in combination with an induction-type regimen of vincristine/dexamethasone/L-asparaginase (VXL).

METHODS

Engraftment and responses of xenografts to drug treatments were assessed by enumeration of the proportion of human versus mouse CD45$^+$ cells in the peripheral blood (PB) of NOD/SCID mice. Mice with established systemic disease received vehicle, SAR3419 (2.5-10 mg/kg, weekly x 3, i.p.), or VXL (0.15 mg/kg V weekly; 5 mg/kg X daily x 5; 1,000 IU/kg L daily x 5; i.p. x 2 weeks) followed by SAR3419 (10 mg/kg) either for 3 weeks or continuous treatment in an attempt to eradicate residual disease. Three measures of anti-leukemic activity were used: (1) an objective response measure (ORM) modeled after the clinical setting; (2) time to event based on the median event-free survival (EFS) of treated or control groups; and (3) a leukemia growth delay (LGD) measure comparing the EFS of treated and control groups.

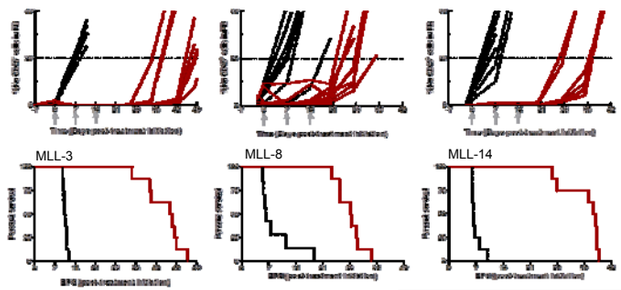
ALL/MLL xenograft model. Top: Monitoring of disease progression in xenografted mice and LGD estimation. **Bottom:** Assignment of OMR scores.





RESULTS

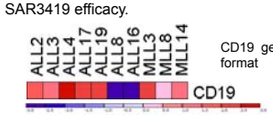
SAR3419 exerts significant *in vivo* single-agent efficacy against MLL xenografts.
SAR3419 as a single agent significantly delayed the progression of three MLL xenografts by 22.1 to 36.5 days and induced objective responses in all three.



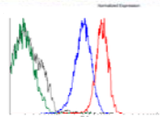
Following establishment of disease mice were randomized and treated with vehicle (dashed lines) or 10 mg/kg SAR3419 (solid red lines) once a week for 3 weeks.

Xenograft	Median EFS [days] Control	Median EFS [days] SAR3419	T-C/D [days]	Significance [p value]*	Median ORM
MLL-3	22.5	47	36.5	<0.0001	CR
MLL-8	9.1	19.2	22.1	<0.0001	PR
MLL-14	8.2	57.6	49.4	<0.0001	CR

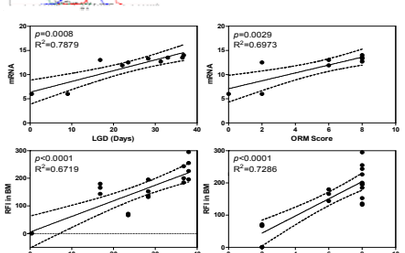
CD19 expression correlates with *in vivo* response to SAR3419.
Relative surface CD19 expression across the BCP-ALL xenograft panel significantly correlated with both LGD and ORM scores, indicating that CD19 density is an important determinant of SAR3419 efficacy.



CD19 gene expression in heat map format

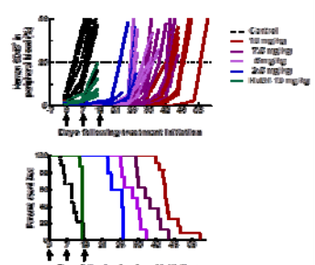


CD19 surface expression (by flow cytometry, isotype control, gray; ALL-16, green; ALL-3, blue; ALL-19, red).



Regression curves and 95% confidence intervals of CD19 mRNA and protein expression correlated with median ORMs (right panels) or LGDs (left panels).

SAR3419 is effective against ALL-4 *in vivo* over a broad dose range.
SAR3419 was highly effective against a chemoresistant BCR-ABL1$^+$ xenograft (ALL-4), inducing complete responses (CRs) over a wide range of doses (2.5-10 mg/kg), while the unconjugated antibody (huB4) had limited efficacy, indicating that DM4 is critical for the high efficacy of this ADC.

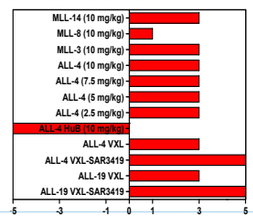


Response to treatment and disease progression were monitored by weekly enumeration of the proportion of %huCD45$^+$ cells in the PB of individual mice (top), and Kaplan-Meier analysis of EFS (bottom). Arrows indicate treatment time points.

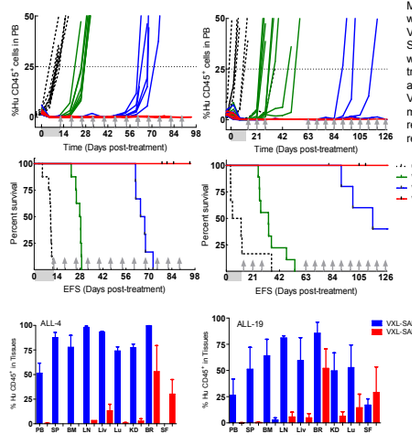
Summary of SAR3419 dose response and VXL combination efficacy studies.
SAR3419 extended the LGD induced by VXL treatment of ALL-4 and another chemoresistant BCP-ALL xenograft (ALL-19) by an additional 38.1 and 82.3 days, respectively, and improved the ORM from CRs to maintained CRs for both xenografts.

	Xenograft/ Treatment	Median EFS [days]	LGD [days]	Significance [p value]*	Median ORM
ALL-4	Control (Vehicle)	8.9			
	SAR3419 10 mg/kg	45.7	36.8	<0.0001	CR
	SAR3419 7.5 mg/kg	38.3	29.4	<0.0001	CR
	SAR3419 5 mg/kg	33.6	24.7	<0.0001	CR
	SAR3419 2.5 mg/kg	28.2	19.3	0.007	CR
	HuB4 10 mg/kg	13	4.1	0.0393	PD1
	Control (Vehicle)	10.1			
	VXL	28.1	18	<0.0001	CR
	VXL-SAR3419 x 3	66.2	56.1	<0.0001	MCR
	VXL-SAR3419 x 12	84	73.9	0.0008	MCR
ALL-19	Control (Vehicle)	8.3			
	VXL	33.4	25.1	<0.0001	CR
	VXL-SAR3419 x 3	115.7	107.4	0.0005	MCR
	VXL-SAR3419 x 13	107.5	99.2	0.0038	MCR

"COMPARE-like" plot of the midpoint difference representing the median ORM of xenografts. A score of -5 to 0 indicates that an objective response was not achieved for a particular xenograft, whereas a score of >0 to 5 indicates an objective response. Red bars indicate that the EFS was significantly different between control and treated mice.



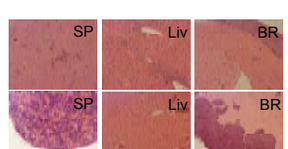
SAR3419 prevents hematolymphoid relapse of BCP-ALL xenografts following remission induction with VXL therapy.
Mice receiving VXL followed by 3 weekly doses of SAR3419 eventually relapsed with dissemination of leukemia into hematolymphoid organs. However, mice that received continuous weekly SAR3419 treatment post-VXL eventually relapsed with leukemia infiltration to the central nervous system (brain and spinal fluid), but without evidence of infiltration of major organs (bone marrow, spleen, liver, kidney, lung, PB).



Mice engrafted with ALL-4 (left) or ALL-19 (right), were treated with vehicle (black dashed lines); VXL (green); VXL followed by 3 weekly doses of SAR3419 (blue) or VXL followed by up to 13 weekly doses of SAR3419 (red). The VXL treatment period is indicated by the shaded area, and SAR3419 treatments by gray arrows. For the VXL/SAR3419 extended treatment events due to morbidity in the absence of hematolymphoid relapse are shown as vertical black lines on the red lines in the middle panels.

%huCD45$^+$ cells in various tissues at necropsy: PB, peripheral blood; SP, spleen; BM, bone marrow; LN, lymph node; Liv, liver; Lu, lung; KD, kidney; BR, brain; SF, spinal fluid.

H&E staining of tissues collected from mice engrafted with ALL-19 and treated with VXL/SAR3419 three times (top panel) or VXL/SAR3419 on a protracted treatment (bottom panel).



CONCLUSIONS

- **SAR3419 was highly effective against aggressive and chemoresistant CD19$^+$ pediatric ALL xenografts over a wide range of doses.**
- **When used as maintenance therapy following VXL, SAR3419 prevented hematolymphoid relapse.**
- **These findings suggest that SAR3419 may be effective for high-risk CD19$^+$ ALL in both the remission induction and the post-remission settings.**

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