CD127 is expressed by acute lymphoblastic leukemias and is efficiently targeted by Lusvertikimab (OSE-127) through IL-7Rα blockade and antibody dependent phagocytosis

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most frequent childhood cancer and arises from the uncontrolled proliferation of precursor B or T cells (B- or T-ALL). Current treatment protocols achieve cure rates of up to 90% in children, yet they are based on profound polychemotherapy which harbor a significant toxicity profile. Furthermore, some subgroups such as MLLr and Philadelphia-like B-ALL, as well as high-risk (HR) T-ALL and adult ALL are still associated with adverse outcomes. Novel targeted immunotherapy options are urgently needed to substitute unspecific chemotherapy and improve survival chances after relapse, especially in the case of T-ALL for which immunotherapies remain scarce.

The Interleukin 7 receptor (IL-7R) plays a pivotal role in the development of B- and T-ALL. This may occur by gain of function (GoF) mutations predominantly affecting exon 6 which are present in a small fraction of B-ALLs and ~10% of T-ALL cases. Such GoF-mutations can initiate a preleukemic stage in B-cell precursors and alone or in conjunction with MYC were shown to promote T-ALL[1-4]. Moreover, overexpression of wt CD127 was sufficient to induce malignant transformation and IL-7-independency in ALL[5-7]. Moreover, other mutational events such as NOTCH1 and RAS alterations may fuel IL-7R-mediated tumor progression[8].

We and others have previously shown that CD127 (the IL-7Rα chain) can directly be targeted using research grade IgG1 monoclonal antibodies (mAbs) leading to significantly reduced leukemic burden in patient derived xenograft (PDX) models of B- and T-ALL[8-10]. Despite promising efficacies of this strategy, no clinically available IL-7R-immunotherapy has to date been translated into ALL-treatment.

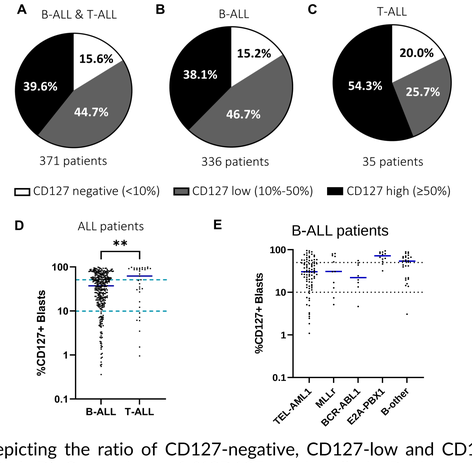
OSE-127 (Lusvertikimab, LUSV) is a humanized IgG4 mAb which, through its binding to site-1 and site-2b of CD127, prevents the heterodimerization and subsequent activation of the IL-7R. It demonstrated an excellent safety profile during a phase I clinical trial (NCT03980080)[11] conducted in a cohort of 63 healthy volunteers where no peripheral cytokine release nor significant lymphopenia or significant peripheral T-cell subtype modifications were observed. Based on its safety profile and IL-7R-antagonistic properties, OSE-127 is currently evaluated in phase 2 trials in ulcerative colitis (CoTikiS study: NCT04882007, OSE Immunotherapeutics) and in Primary Sjögren's syndrome (NCT04605978, Servier).

The aim of this study was to evaluate the preclinical efficacy of OSE-127 treatment in ALL.

RESULTS

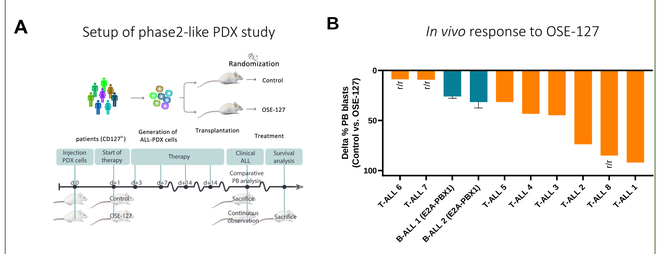
1. CD127 (IL-7Rα) surface protein is expressed in more than 80% of ALL cases

CD127 surface expression was prospectively measured via flow cytometry in 371 diagnostic blood or bone marrow samples of pediatric ALL patients in accordance with iBFM-FLOW standards[12]. Blasts were identified within the CD45dim/CD19+ (B-ALL) or CD45dim/CD7+ (T-ALL) cell populations.

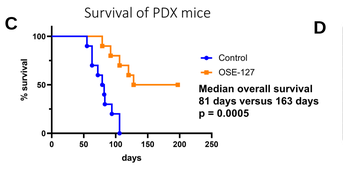


A-C) Pie charts depicting the ratio of CD127-negative, CD127-low and CD127-high ALL patients, as indicated. **D)** Comparison of %CD127+ ALL cells in B-ALL vs T-ALL cases, **P=0.0023, unpaired two-sided t-test. **E)** Ratio of CD127+ ALL cells in different B-ALL subgroups.

2. OSE-127 reduces the leukemic burden of MRD PDX models of B- and T-ALL, including r/r cases, leading to curative effects in some instances



A) CD127[hi] ALL PDX mice were treated with OSE-127 (5mg/kg) or a control (n= 1 to 10 mice/patient) starting the day after leukemia injection, modelling an MRD-situation. **B)** Difference of frequencies of PB blasts (delta % PB blasts) between control and OSE-127 treated animals was evaluated via flow cytometry upon signs of overt leukemia.



D

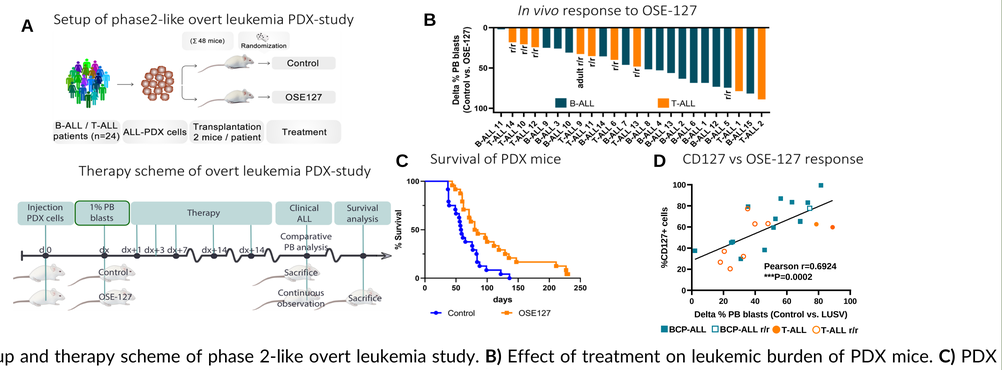
MRD detection after sacrifrice

Mouse No.	Control	OSE-127	Mouse No.	Control	OSE-127
M1	pos (10^{-1})	neg (10^{-6})	M1	pos (10^{-1})	neg (10^{-6})
M2	pos (10^{-1})	neg (10^{-6})	M2	neg (10^{-6})	neg (10^{-6})
M3		neg (10^{-6})	M3	pos (10^{-1})	neg (10^{-6})
M4		neg (10^{-6})	M4		neg (10^{-6})
M5		neg (10^{-6})	M5		neg (10^{-6})
M6		neg (10^{-6})	M6		neg (10^{-6})
M7		neg (10^{-6})	M7		pos (10^{-1})
M8		neg (10^{-6})	M8		neg (10^{-6})
M9		neg (10^{-6})	M9		neg (10^{-6})
M10		neg (10^{-6})	M10		pos (10^{-1})

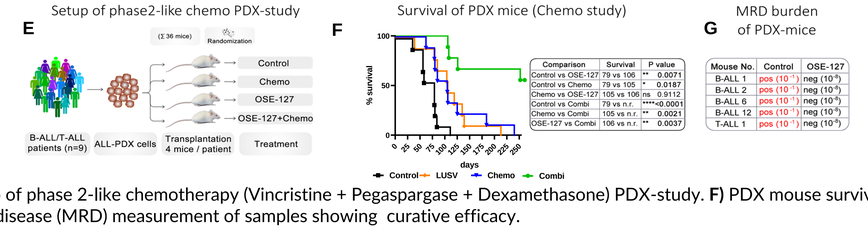
Mouse No.	Control	OSE-127
T-ALL 2	pos (10^{-1})	neg (10^{-6})
T-ALL 5	n/a	n/a
T-ALL 8	pos (10^{-1})	neg (10^{-6})

C) Kaplan-Meier log-rank statistical analysis of PDX mouse survival. **D)** Minimal residual disease (MRD) measurement by PCR for patient-specific immunoglobulin/T-cell receptor rearrangements in mice of samples showing curative efficacy.

3. OSE-127 reduces the leukemic burden of overt leukemia in vivo models of B- and T-ALL and synergizes with polychemotherapy



A) Setup and therapy scheme of phase 2-like overt leukemia study. **B)** Effect of treatment on leukemic burden of PDX mice. **C)** PDX mouse survival. **D)** Correlation between CD127 blast expression level and delta % PB blasts (Delta PBB).



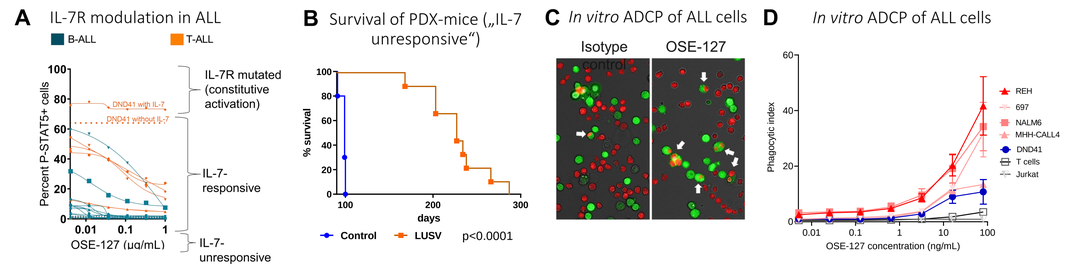
Comparison	Survival	P value
Control vs OSE-127	79 vs 106	** 0.0071
Control vs Chemo	79 vs 105	* 0.0187
Chemo vs OSE-127	105 vs 106	ns 0.9112
Control vs Combi	79 vs n.r.	**** <0.0001
Chemo vs Combi	105 vs n.r.	*** 0.0021
OSE-127 vs Combi	106 vs n.r.	** 0.0037

Mouse No.	Control	OSE-127
B-ALL 1	pos (10^{-1})	neg (10^{-6})
B-ALL 2	pos (10^{-1})	neg (10^{-6})
B-ALL 6	pos (10^{-1})	neg (10^{-6})
B-ALL 12	pos (10^{-1})	neg (10^{-6})
T-ALL 1	pos (10^{-1})	neg (10^{-6})

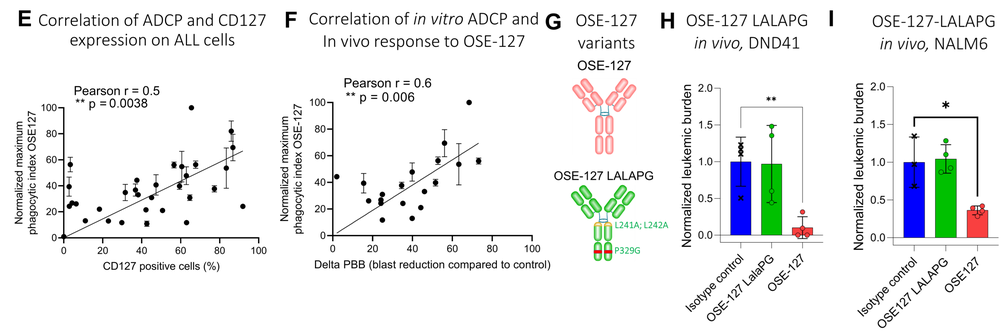
E) Set-up of phase 2-like chemotherapy (Vincristine + Pegaspargase + Dexamethasone) PDX-study. **F)** PDX mouse survival. **G)** Minimal residual disease (MRD) measurement of samples showing curative efficacy.

RESULTS

4. The anti-leukemic mechanism of action of OSE-127 is driven by its antagonist activity and by macrophage-mediated ADCP

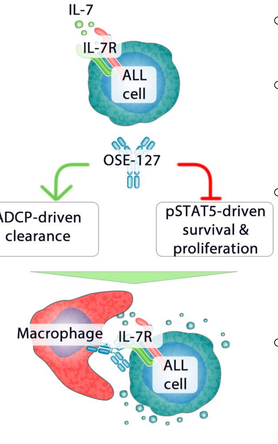


A) Level of phosphorylated STAT5 in leukemic cells after IL-7 stimulation +/- OSE-127 treatment. **B)** Survival of mice engrafted with an IL-7 unresponsive B-ALL treated with OSE-127 or vehicle (n=10, each) in an overt-leukemia PDX model. **C)** Representative image of human macrophages (labeled in green) engulfing T-ALL PDX cells (labeled in red) after isotype control or OSE-127 treatment. **D)** Dose response induction of phagocytosis induced by OSE-127 treatment.



E) Correlation between OSE-127 treatment induced ADCP levels and **E)** the level of CD127 expression on leukemic cells or with **F)** *in vivo* efficacy of OSE-127 treatment. *In vivo* leukemic burden following control, **G)** OSE-127 LALAPG or OSE-127 treatments in mice engrafted with **H)** DND41 or **I)** NALM6 cells.

CONCLUSIONS & OUTLOOK



- CD127 (IL-7Rα) **is expressed in more than 80%** of B- and T-ALL cases.
- OSE-127 immunotherapy efficiently targets B- and T-ALL *in vivo* in MRD and overt leukemia settings and **synergizes with standard of care polychemotherapy.**
- OSE-127 acts via a **dual mode of action**: full antagonist of the IL-7R oncogenic pathway and macrophage mediated ADCP ➔ the anti-leukemic activity of OSE-127 extends to **any CD127 expressing ALL cases**, even in IL-7R dysregulated leukemias.
- OSE-127 may be an **effective and safe immunotherapy option** in ALL as addition to SOC backbones or a bridge to stem cell transplantation in r/r patients.

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