An investigator-initiated phase I study to assess safety and tolerability of ex vivo next-generation neoantigen-selected tumor-infiltrating lymphocyte (TIL) therapy in advanced immune checkpoint blockade (ICB) resistant solid tumors (NEXTGEN-TIL-ACT)

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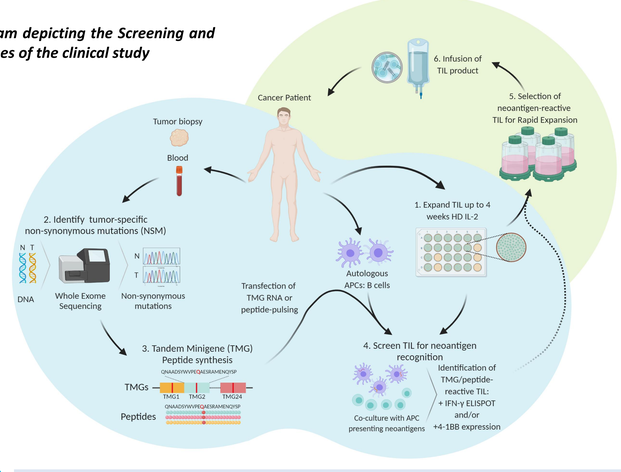
Background

Lymphocytes play a crucial role in cancer immunity and patient survival, representing an attractive treatment option for melanoma and diverse epithelial tumors. Neoantigen-reactive TILs can recognize and kill cancer cells, inducing tumor regression and potentially increasing the efficacy of adoptive cell therapies (ACT). NEXTGEN-TIL-ACT consists of TIL selected based on identifying somatic non-synonymous mutations or viral neoantigens encoded in tandem minigenes and presented by autologous peripheral B cells.

Methods

This is an investigator-initiated phase 1, single-center, open-label study assessing safety, tolerability, and anti-tumor activity of single-dose NEXTGENTIL with high-dose IL-2 (720.000 IU/kg) following non-myeloablative lymphodepleting chemotherapy in adults with confirmed metastatic or unresectable advanced ICB-resistant solid tumors. The NEXTGENTIL product contains a polyclonal autologous lymphocyte population of TILs ranging from 5x108 to 1.11x1011 cells expanded from core tumor biopsies and selected based on neoantigen recognition using a high-throughput personalized screening approach.

Figure 1. Diagram depicting the Screening and Treatment phases of the clinical study



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Study Design

This study is a single-center, open-label, phase I trial of neoantigen-reactive *ex vivo* expanded TILs (NEXTGEN-TIL) in patients with metastatic or unresectable epithelial tumors refractory to standard therapy or with ICB resistant solid tumors.
The first safety evaluation will be carried out with the 6 first patients. If there is a maximum of one TLT the study will continue recruiting patients for up to a total of 10 patients.

The TILs obtained from the patients who satisfied all the inclusion and none of the exclusion criteria of the Pre-treatment Phase and underwent biopsy/resection will be screened for neoantigen-recognition. The immuno-oncology team will evaluate this population and will offer NEXTGEN-TIL-ACT treatment only to those having at least one intermediate product (TIL pre-REP) with neoantigen-reactivity that can be used for the REP.
While the TIL product is going through the manufacturing process, the patients can receive Standard of Care (SOC) treatment as per standard guidelines.

Table 1. Treatment Schedule

Day	-5	-4	-3	-2	-1	0	1	2
Therapy								
Cyclophosphamide 60 mg/kg	X	X						
Mesna (continuous infusion)	X	X						
Fludarabine 25 mg/m2	X	X	X	X	X			
NEXTGEN-TIL Cells						X		
IL-2 (720.000 IU/kg every 8h)						X	X	X

Endpoints

Primary:
- Safety, tolerability

Secondary:
- Rate of successful neoantigen-selected TIL (NEXTGEN-TIL) generation from biopsied patients and frequency of neoantigen-specific TILs in all TILs produced from biopsied patients included in this trial.
- The initial clinical activity measured using best response per RECIST 1.1, as well as objective response rate, duration of objective response, and progression-free survival

Assessments

Treatment-Limiting Toxicity (TLT)
- TLT period: within 30 days starting at the first date of the chemotherapy (day -5)
- Grading will be carried out per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Safety and tolerability
- Weekly until week 4, weeks 6, 9, 12, 18, 24, 30, 36, at 1 year, 1,5 and 2 years after NEXTGEN-TIL infusion.

Exploratory assessments
- Peripheral blood evaluation for exploratory assessments at week 3 and 6 after NEXTGEN-TIL infusion, and at every safety analysis follow-up visit thereafter, and upon progression.

Efficacy
- Response will be measured using radiographic tumor evaluation on weeks 6, 12, and then every 3 months during 2 years from NEXTGEN-TIL infusion.
- Assessment of antitumor activity will be conducted according to RECIST 1.1.

Key Eligibility Criteria

- Patients must be at least 18 years old, have ECOG 0-1, and have received standard therapy (including ICB when indicated).
- One target lesion must be accessible for a biopsy/resection that allows TIL generation, and another must meet RECIST v1.1 criteria.
- Patients must be medically fit enough to undergo all study procedures and interventions and have adequate cardiovascular and pulmonary functions.
- Patients with an autoimmune disease requiring immunosuppressive treatments will be excluded.

Conflicts of Interest

The first author has no conflict of interest

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