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Trial in Progress: A Phase 1/2 Study to Investigate the Safety and Efficacy of OBX-115 Engineered Tumor-infiltrating Lymphocyte (TIL) Cell Therapy in Patients with Advanced Solid Tumors (Agni-01)

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INTRODUCTION

- Immune checkpoint inhibitors (ICI) have improved treatment outcomes for patients with melanoma and non-small cell lung cancer (NSCLC); however, most patients do not achieve long-term survival
- Lifileucel, a non-engineered tumor-derived autologous T-cell immunotherapy (tumor-infiltrating lymphocyte [TIL] cell therapy), was recently FDA-approved for anti–PD-1–experienced unresectable or metastatic melanoma[1] and has shown promising activity in this setting (ORR, 31.5%; mDOR, NR), but is associated with a treatment-related mortality rate of 7.5%[2]
- Lifileucel is also being investigated in patients with ICI-resistant advanced NSCLC, and a response rate of 21% has been reported[3]
- Non-engineered TIL cell therapies require high-dose interleukin 2 (IL2), which has well-described high-grade toxicity,[2,4,5] limiting patient eligibility and frequently requiring specialized management
- OBX-115 TIL are engineered to express mbIL15 fused to a drug-responsive domain, which allows for a dose-dependent increase in functional mbIL15 levels in the presence of an FDA-approved stabilizing drug (acetazolamide [ACZ]), avoiding the need for IL2 (**Figure 1**)
- In preclinical studies, cytoTIL15™ TIL (OBX-115) in the presence of ACZ demonstrated enhanced proliferation, persistence, and antitumor activity compared with non-engineered TIL + IL2[6,7] (**Figure 2**)
- OBX-115 TIL have favorable characteristics for response, with a high proportion of CD8+ T cells, an effector-memory and stem-like–progenitor phenotype, with low levels of immune checkpoint markers[8]
- In the first-in-human clinical experience, OBX-115 has demonstrated promising activity (ORR, 44%; 6-mo PFS, 75%) and a differentiated safety profile[9]
- The current study (Agni-01 [NCT06060613]) is enrolling at multiple US sites using centralized manufacturing

Figure 1. OBX-115 Mechanism of Action

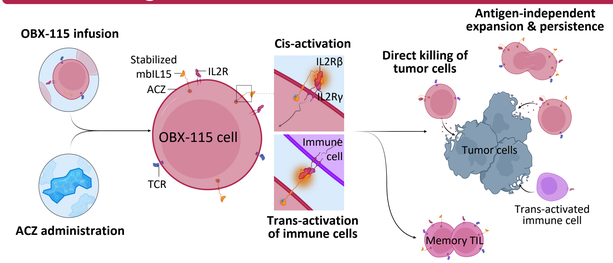
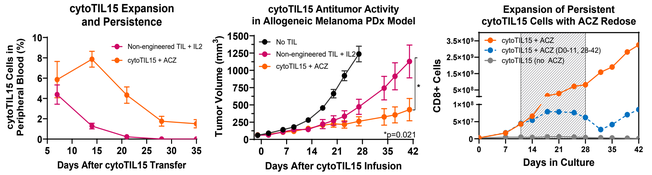


Figure 2. Preclinical Data



STUDY DESIGN

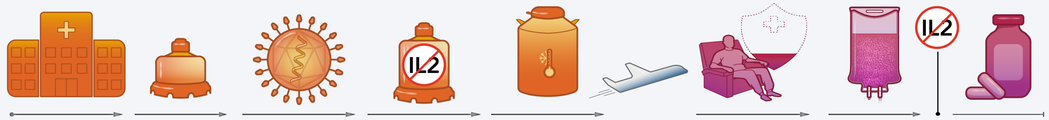
This single-arm, open-label, nonrandomized, multicenter study will assess the safety, tolerability, and efficacy of the autologous OBX-115 engineered TIL cell therapy regimen in patients with advanced solid tumors

- Cryopreserved OBX-115 is manufactured using the patient's own tumor tissue, procured by either surgical excision or core needle biopsy, and is infused intravenously following standard- or low-dose (based on clinical eligibility) lymphodepletion with cyclophosphamide and fludarabine (**Figure 3**)
- ACZ is administered orally at cohort-defined doses and durations. Additional ACZ is dosed as specified in the protocol, and upon progression (all patients) when new anticancer therapy is not immediately warranted (**Figures 4–5**)
- No IL2 is administered

Figure 3. Centralized OBX-115 Manufacturing and Patient Journey

OBX-115 manufacturing process generates CD8+ enriched, minimally exhausted TIL cell therapy product

IL2-free OBX-115 TIL cell therapy regimen



Tumor tissue procurement
Surgical excision or core needle biopsy

Optimized pre-REP

Activation/ transduction
- Anti-CD3 Ab
- Retroviral vector

Proprietary, optimized REP
- iFeeder cells expressing IL21 and 4-1BBL
- ACZ (no IL2)

Cryopreservation

Lymphodepletion*
- Cyclophosphamide
- Fludarabine

OBX-115 infusion

ACZ dosing

*May be standard-dose (5-day regimen) or low-dose (4-day regimen).

Figure 4. Study Overview

Adult patients with **advanced (unresectable or metastatic) melanoma resistant to ICI*** OR **relapsed or refractory metastatic NSCLC†**

NCT06060613

Phase 1: Identify Recommended Phase 2 Dose (RP2D) of OBX-115 + ACZ
- Dose-escalation and de-escalation will occur per protocol criteria
- Each dose-level cohort will contain 3–6 DLT-evaluable patients

Phase 2: Evaluate Efficacy and Safety of OBX-115 + ACZ at RP2D

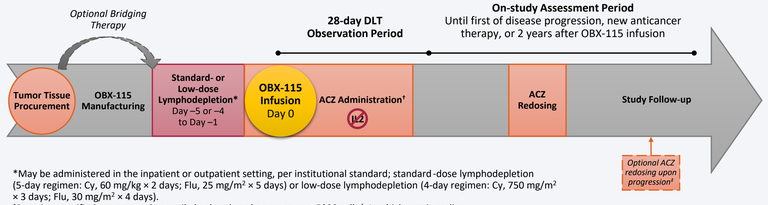
Melanoma Cohort
NSCLC Cohort
- Up to 20 patients may be initially enrolled in each Phase 2 cohort, with a total of up to 40 patients enrolled in each cohort

*Patients with *BRAF*-mutated disease must have received BRAF inhibitor ± MEK inhibitor therapy.
†Prior treatment should include an approved ICI-based regimen and/or an approved targeted therapy in appropriate patients.

Primary Endpoints
- Phase 1
  - Safety and tolerability (incidence and severity of adverse events [AEs] and serious AEs)
  - Incidence and nature of DLTs
- Phase 2
  - Efficacy (ORR per investigator/local assessment using RECIST v1.1)

Secondary Endpoints
- Phase 1
  - Efficacy (ORR, duration of response [DOR], disease control rate [DCR], progression-free survival [PFS], and overall survival [OS])
  - Manufacturing feasibility
  - OBX-115 cellular kinetics
- Phase 2
  - Safety and tolerability
  - Efficacy (DOR, DCR, PFS, and OS)
  - Manufacturing feasibility
  - OBX-115 cellular kinetics

Figure 5. Study Treatment Schema



*May be administered in the inpatient or outpatient setting, per institutional standard; standard-dose lymphodepletion (5-day regimen: Cy, 60 mg/kg × 2 days; Flu, 25 mg/m² × 5 days) or low-dose lymphodepletion (4-day regimen: Cy, 750 mg/m² × 3 days; Flu, 30 mg/m² × 4 days).
†Duration specified per protocol or until absolute lymphocyte count ≥5000 cells/µL, whichever is earlier.
‡ACZ may be redosed (melanoma or NSCLC) upon progression when new anticancer therapy is not immediately warranted.

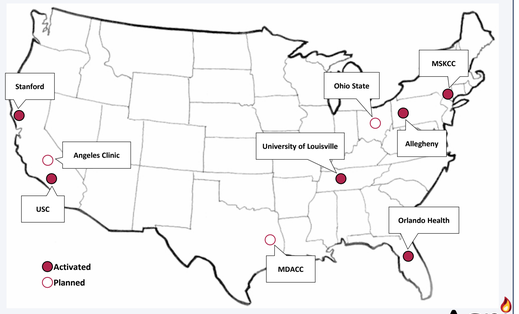
Key Inclusion Criteria

- Age ≥18 years
- Histologically confirmed diagnosis of melanoma or NSCLC:
  - Unresectable Stage IIIC, IIID, or Stage IV metastatic melanoma with documented radiographic disease progression after systemic therapy containing a PD-1– or PD-L1–blocking antibody (if adjuvant setting, progression during or within 12 weeks after the last dose) and received a BRAF inhibitor ± MEK inhibitor if *BRAF* V600 mutation-positive
  - Metastatic NSCLC previously treated with an approved systemic therapy for metastatic disease (including an ICI-based regimen and/or targeted therapy where applicable) and progressed or is no longer deriving benefit, or is unable to continue due to treatment intolerance
- ≥1 lesion suitable for OBX-115 manufacturing with expected minimum of 1.5-cm diameter
- Minimally invasive tumor tissue procurement (core needle biopsy) may be considered on a case-by-case basis
- ≥1 RECIST v1.1-measurable lesion remaining after tumor tissue procurement
- ECOG performance status 0 or 1
- Estimated life expectancy >6 months

Key Exclusion Criteria

- Uveal melanoma
- Active autoimmune disease, including active uveitis or any other medical illness that would pose increased risks for study participation
- History of brain metastases or leptomeningeal disease; patients with brain metastases that are ≤1.5-cm diameter that have been treated and are asymptomatic may be eligible
- Prior allogeneic organ transplant, allogeneic cell therapy, or genetically engineered cell therapy (not including autologous stem cell or non-engineered TIL cell therapy)
- Systemic steroid therapy >10 mg/day of prednisone or equivalent

Study Locations



Abbreviations

Ab, antibody; ACZ, acetazolamide; AE, adverse event; DCR, disease control rate; DOR, duration of response; DLT, dose-limiting toxicity; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitors; IL2, interleukin 2; IL2R, interleukin 2 receptor; mbIL15, membrane-bound interleukin 15; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; QD, daily; RECIST, Response Evaluation Criteria in Solid Tumors; REP, rapid expansion protocol; RP2D, recommended phase 2 dose; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocytes.

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Disclosures

Adam J Schoenfeld reports consulting or advisory roles with Johnson & Johnson/Janssen, KSQ Therapeutics, Perceptive Advisors, Heat Biologics, Bristol-Myers Squibb, Enara Bio, Umoja Biopharma, Oppenheimer, Iovance Biotherapeutics, Lyell Immunopharma, Merck, Immunocore, Legend Biotech, Amgen, and Prelude Therapeutics; travel, accommodations, or expenses from Iovance Biotherapeutics and Instil Bio; research funding from GlaxoSmithKline, Merck, Bristol-Myers Squibb, Iovance Biotherapeutics, Achilles Therapeutics, Amgen, PACT Pharma, Harpoon Therapeutics, and Instil Bio; and other relationship with Merck, Bristol-Myers Squibb, Iovance Biotherapeutics, PACT Pharma, Achilles Therapeutics, GlaxoSmithKline, Harpoon Therapeutics, Amgen, and Instil Bio.

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