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Trial in progress: Phase 1/2 study of OBX-115 engineered tumor-infiltrating lymphocyte (TIL) cell therapy in patients with advanced solid tumors

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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] as well as the ability to re-expand upon ACZ redosing (**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

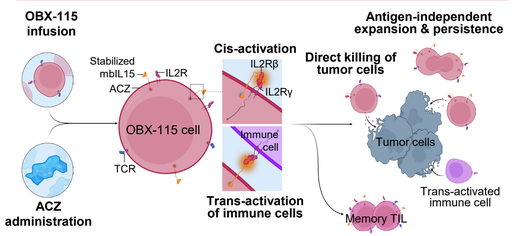
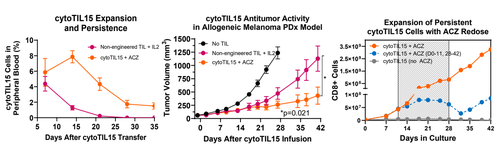


Figure 2. Preclinical Data



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 at cohort-defined doses once daily starting day of OBX-115 infusion for ≤14 days (split into two ≤7-day periods within 28 days), with additional ACZ dosing for ≤7 days at periodic intervals until Week 24, and upon progression 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 (7-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

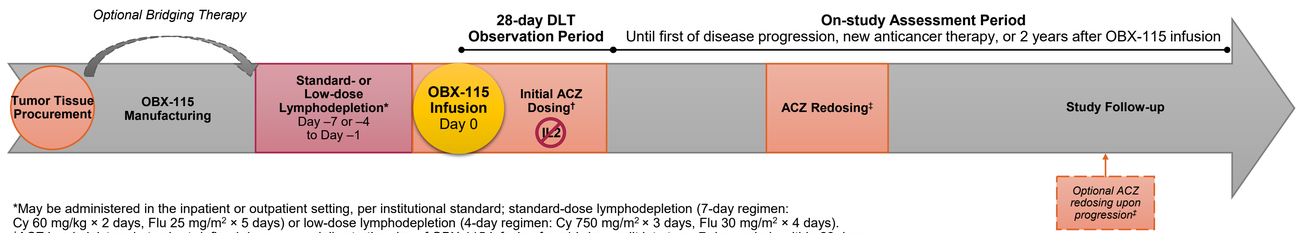
Melanoma Cohort / **NSCLC Cohort**: Up to 20 patients may be initially enrolled in each Phase 2 cohort, with a total of up to 40 patients enrolled in each cohort

*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 (7-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).
†ACZ is administered at cohort-defined doses once daily starting day of OBX-115 infusion for ≤14 days split into two ≤7-day periods within 28 days (Day 0–6 or until absolute lymphocyte count ≥5000 cells/μL whichever is earlier, and restarting between Day 14 and 21).
‡Additional ACZ dosing for ≤7 days at periodic intervals until Week 24, and upon progression when new anticancer therapy is not immediately warranted.

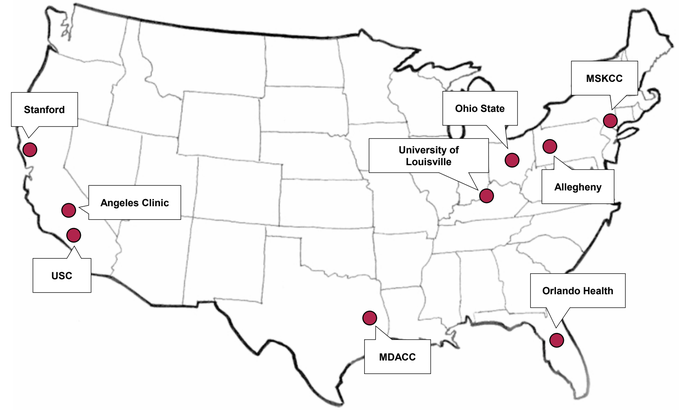
Key Inclusion Criteria

- 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 (≤2 prior lines; if [neo]adjuvant setting, progression during or within 12 weeks after the last dose)
  - Metastatic NSCLC previously treated with an approved systemic therapy for metastatic disease (including an ICI-based regimen and/or targeted therapy where applicable; prior exposure to both taxane and gemcitabine in the metastatic setting is not permitted) 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 ≤4 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

Figure 6. Activated Study Locations



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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.

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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