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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]
- All 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 membrane-bound IL15 (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 high-dose 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**)
- The current study (Agni-01 [NCT06060613]) is enrolling at multiple US sites using centralized OBX-115 manufacturing

Figure 1. OBX-115 Mechanism of Action

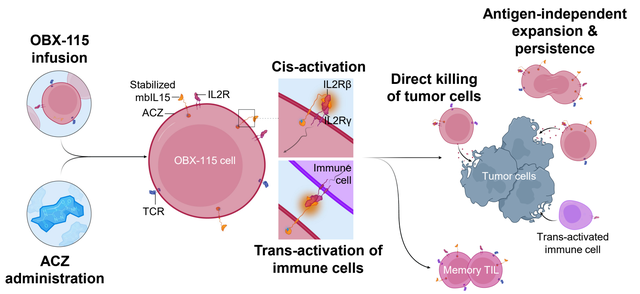
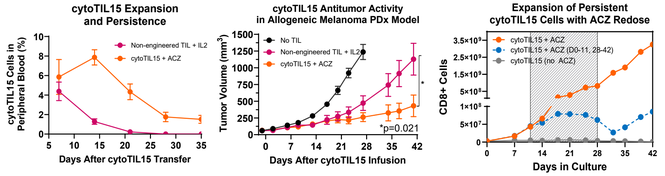


Figure 2. Preclinical Data



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 once daily for up to 14 days. Additional ACZ is dosed for up to 14 days at Week 6 (all patients), with optional redosing at Weeks 12 and 18 if an optimal response is not achieved (NSCLC only), and upon progression (all patients) when new anticancer therapy is not immediately warranted (**Figures 4–5**)
- No systemic high-dose 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 | **Optimized pre-REP** | **Activation/ transduction** Anti-CD3 Ab Retroviral vector | **Proprietary, optimized REP** iFeeder cells ACZ | **Cryopreservation** | **Lymphodepletion** | **OBX-115 infusion** | **ACZ dosing**

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-escalation cohort will contain 3–6 DLT-evaluable patients (maximum 15 patients per dose level)

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

Cohort 1: Unresectable/metastatic melanoma
Cohort 2: Metastatic NSCLC

- 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

Primary Endpoints

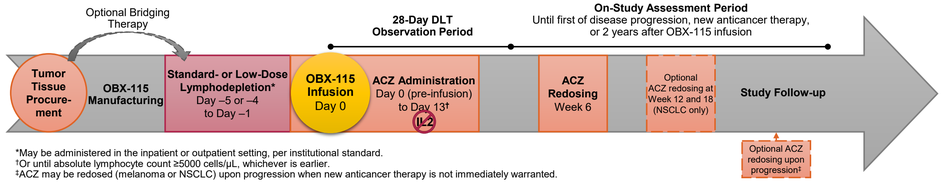
- Phase 1
  - Safety and tolerability (incidence and severity of adverse events [AEs] and serious AEs)
  - Incidence and nature of DLTs
- Phase 2
  - Efficacy (ORR per investigator/local assessment using RECIST v1.1)

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

*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.

Figure 5. Study Treatment Schema



*May be administered in the inpatient or outpatient setting, per institutional standard.
†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.

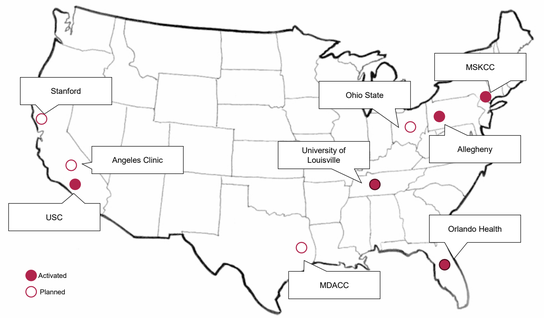
Key Inclusion Criteria

- 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, no longer deriving benefit, or unable to continue due to treatment intolerance
- ≥1 lesion suitable for OBX-115 generation 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 risk 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

Figure 6. 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 inhibitor; 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; 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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