Trial in progress: A phase 1/2 study to investigate the safety and efficacy of OBX-115 tumor-infiltrating lymphocytes (TIL) expressing regulatable membrane-bound IL15 (mbIL15) in patients with advanced or metastatic melanoma resistant to immune checkpoint inhibitors (ICI)

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Background

- ICI have improved treatment outcomes for patients with melanoma; however, most patients (~60%) do not achieve long-term survival
- In clinical trials, unengineered bulk TIL cell therapy has shown an objective response rate (ORR) of 31–49% in patients with unresectable or metastatic melanoma,[1,2] but requires coadministration of systemic high-dose IL2, which is associated with considerable toxicity
- 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 a 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 unengineered TIL + IL2[3,4] (**Figure 2**)
- The current study (NCT06060613) is enrolling at multiple US sites using centralized manufacturing (**Figure 3**)

Figure 1. OBX-115 Mechanism of Action

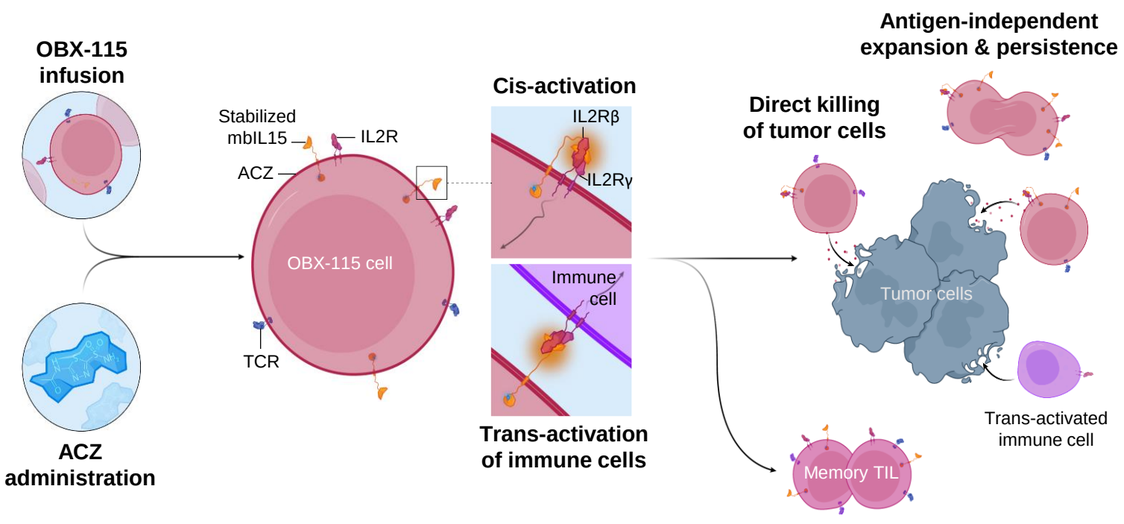
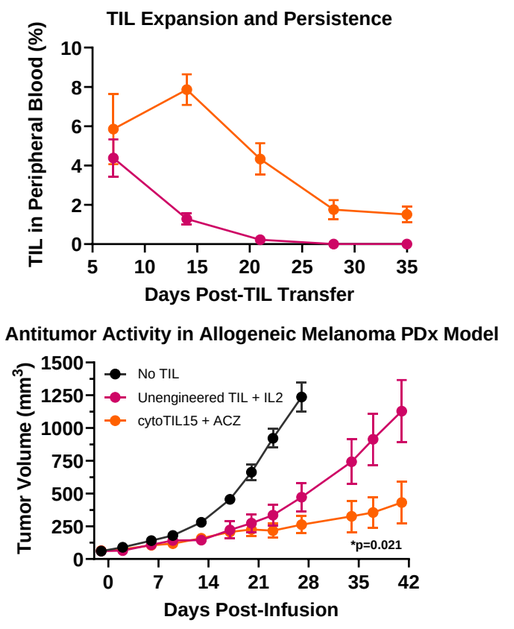


Figure 2. Preclinical Data



Study Design

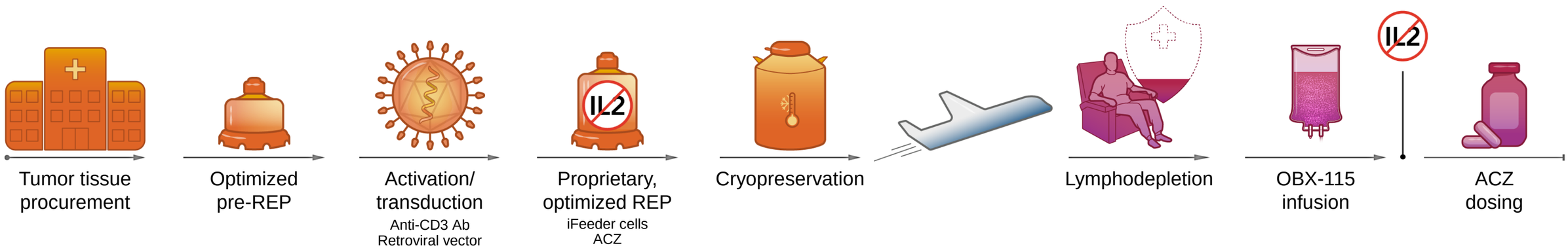
This single-arm, open-label, nonrandomized, multicenter study will assess the safety, tolerability, and efficacy of the autologous OBX-115 engineered TIL cell therapy regimen in patients with unresectable or metastatic melanoma resistant to ICI

- Cryopreserved OBX-115 is manufactured using the patient's own tumor tissue, procured by either excisional or core biopsy, and is infused intravenously following standard or low-dose (based on clinical eligibility) lymphodepletion with cyclophosphamide and fludarabine (**Figures 3 and 4**)
- ACZ is administered orally at cohort-defined doses once daily for up to 10 days, with optional additional ACZ at Week 6–8 if the initial tumor response is less than PR
- **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



Study Overview

Adult patients with **unresectable Stage III or Stage IV metastatic melanoma** whose disease has **relapsed or progressed after ICI-based therapy** and after BRAF/MEK inhibitor therapy in patients with *BRAF*-mutated disease

NCT06060613

Phase 1

Identify Recommended Phase 2 Dose (RP2D) of OBX-115 + ACZ

- The first 3 patients will be enrolled in a staggered fashion with a 28-day dose-limiting toxicity (DLT) observation period
- Further dose-escalation cohorts will be added as indicated

Phase 2

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

- Up to 20 patients may be initially enrolled, with a total of up to 40 patients enrolled in Phase 2

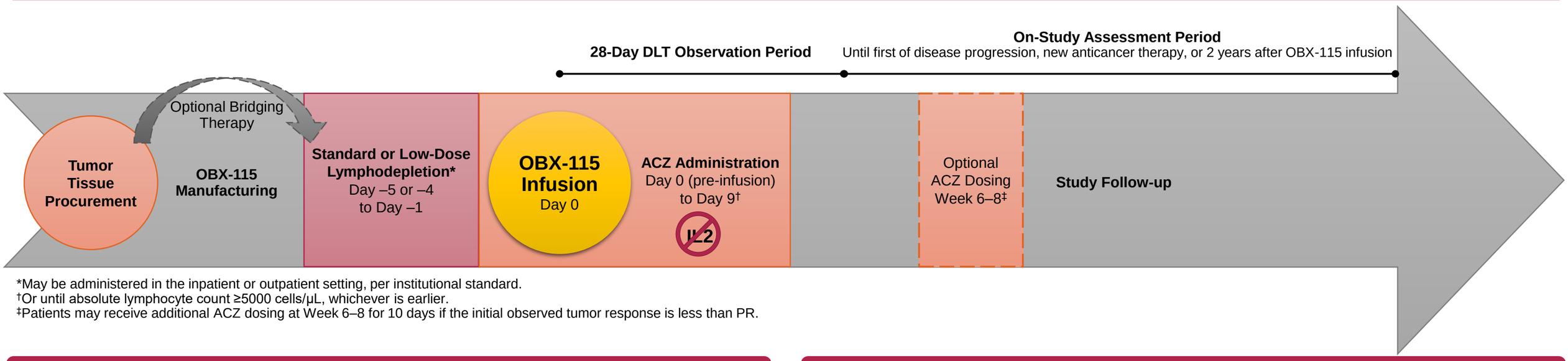
Primary Endpoints

- 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], and progression-free survival [PFS]; 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 4. 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.
‡Patients may receive additional ACZ dosing at Week 6–8 for 10 days if the initial observed tumor response is less than PR.

Key Inclusion Criteria

- Age ≥18 years
- Histologically confirmed diagnosis of unresectable Stage IIIC, IIID, or Stage IV metastatic melanoma
- 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)
- Received a BRAF inhibitor ± MEK inhibitor if *BRAF* V600 mutation-positive
- ≥1 lesion suitable for OBX-115 generation with expected minimum of 1.5-cm diameter
  - Minimally invasive tumor tissue procurement (core biopsy) may be considered on a case-by-case basis after discussion with the Medical Monitor
- ≥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
- Brain metastasis or leptomeningeal disease
- Active autoimmune disease, including active uveitis or any other medical illness that would pose increased risks for study participation
- Prior allogeneic organ transplant, allogeneic cell therapy, or genetically engineered cell therapy (not including autologous stem cell or unengineered TIL cell therapy)
- Systemic steroid therapy >10 mg/day of prednisone or equivalent

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; 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.

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