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Minimally Invasive Tumor Tissue Procurement is Feasible for Clinical Manufacturing of OBX-115 Engineered Tumor-infiltrating Lymphocytes (TIL)

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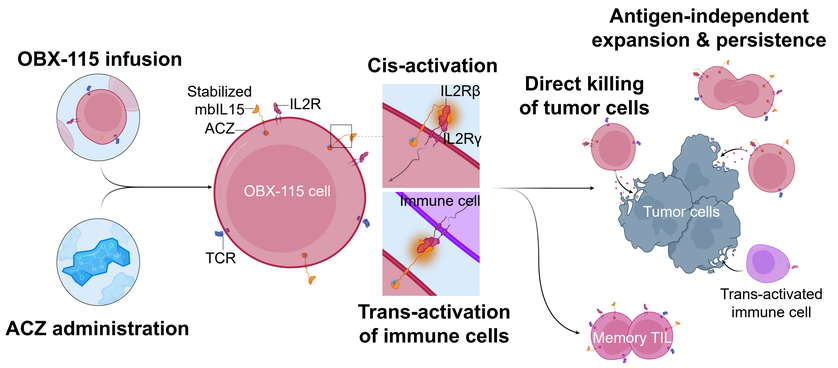
Introduction

- TIL cell therapy is a promising treatment for patients with advanced solid tumors resistant to immune checkpoint inhibitors (ICI)
- As an autologous adoptive T-cell therapy, a portion of the patient's tumor tissue is used as the starting material to manufacture the TIL infusion product
- Although tumor tissue procurement (TTP) is typically done by surgical excision, minimally invasive TTP using an outpatient core needle biopsy (CNB) procedure may avoid surgical morbidity, reduce cost, and alleviate scheduling challenges
- Herein we describe manufacturing success, phenotype, and clinical outcomes of OBX-115 engineered TIL expressing regulatable membrane-bound IL15 (mbIL15; **Figure 1**), manufactured using tissue obtained by minimally invasive and surgical TTP in a Phase 1 first-in-human study

Figure 1. OBX-115 Mechanism of Action

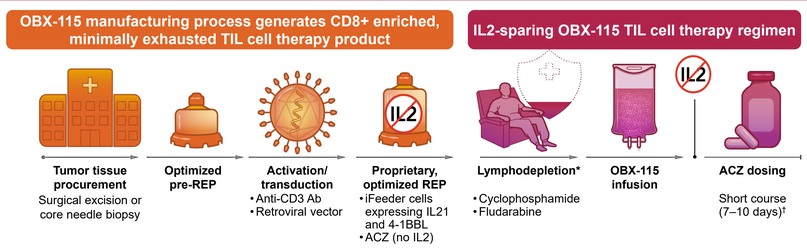


Methods

Phase 1 First-in-human Study (NCT05470283)

- Eligible patients had:
  - Pathologically confirmed diagnosis of metastatic melanoma (unresectable Stage III or Stage IV)
  - Disease that was relapsed and/or refractory to ICI therapy, including anti–PD-1 with or without anti–CTLA-4 or anti–LAG3 antibody
  - ≥1 lesion suitable for OBX-115 manufacturing
  - ≥1 lesion remaining after TTP for RECIST v1.1 response assessment
  - ECOG PS 0–1
- Eligible patients underwent TTP by either surgical excision or CNB to provide starting material for OBX-115 manufacturing (≥1.5-cm total length CNBs or ≥1.5-cm diameter surgical tissue)
- Tumor tissue was fragmented and TIL were expanded ex vivo after transduction with retroviral vector to express mbIL15 as a fusion protein with a drug-responsive domain that allows pharmacologic regulation of mbIL15 cell-surface expression using the FDA-approved small-molecule drug acetazolamide (ACZ)
- Fresh (non-cryopreserved) OBX-115 was infused intravenously following standard- or low-dose lymphodepletion (based on clinical eligibility) with cyclophosphamide and fludarabine, followed by ACZ administration (**Figure 2**)
- Data cutoff date: January 2, 2024

Figure 2. OBX-115 Manufacturing and Treatment Regimen



*Standard-dose LD consisted of cyclophosphamide 60 mg/kg on Days –7 and –6, fludarabine 25 mg/m^2 on Days –5 to –1; option to reduce or omit doses (low-dose LD).
†ACZ redosing (Week 6, up to 7 days) permitted for patients without radiographic response at Week 6.

Results

- All CNBs were performed without general anesthesia
- Regardless of TTP method, OBX-115 met cell dose and phenotype requirements for infusion (**Table 1**)
- The infusion products were predominantly CD3+ and CD8+, with minimal CD4+ and NK cells
- A median of 72% of cells in the infusion product were IL15+

Table 1. OBX-115 Infusion Product Characteristics

Characteristic	N=6
Tumor tissue procurement method, n (%)	
Surgical excision*	1 (16.7)
Core needle biopsy	5 (83.3)
Number of cores, range	3–9
Tumor tissue procurement sites, n (%)	
Abdominal soft tissue	1 (16.7)
Chest wall soft tissue	1 (16.7)
Liver	1 (16.7)
Lymph node	3 (50.0)
OBX-115 infusion product†	
Manufactured dose, median (range),‡ × 10^9 cells	85.4 (9.6–183)
Viability, median (range), %	96 (95–98)
CD3+ cells, median (range),§ %	99 (97–100)
CD8+ cells, median (range),§ %	97.5 (95.9–99.5)
CD4+ cells, median (range),§ %	0.2 (0.1–1.3)
IL15+ viable cells, median (range),§ %	72 (48–78)
NK cells, range,§ %	Not detected–1.0

*Patient 5 had surgical excision of tumor tissue.
†All OBX-115 infusion products were fresh (not cryopreserved).
‡Infused dose was capped at protocol-specified maximums.
§Of all live cells.

- The OBX-115 infusion product is dominated by an effector memory phenotype and has low levels of central memory and T_{EMRA} subsets (**Figure 3**)

Figure 3. OBX-115 TIL Have a Primarily Effector Memory Phenotype

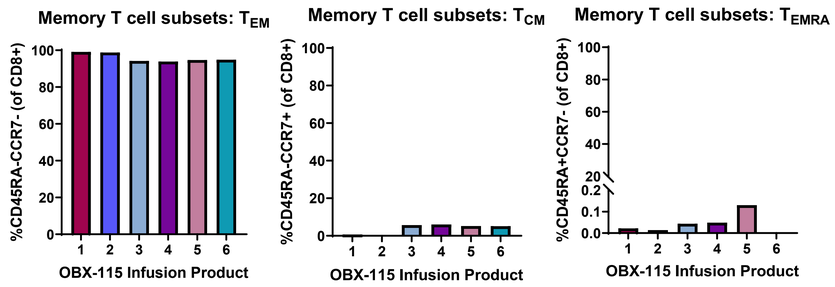
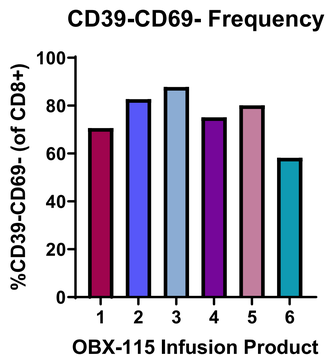


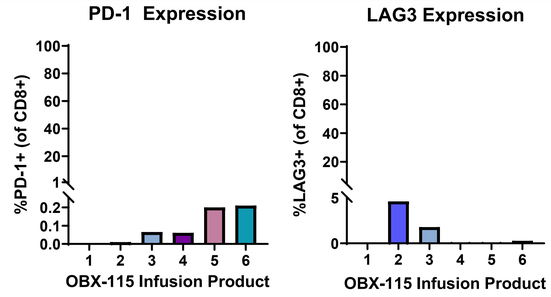
Figure 4. OBX-115 TIL Have a "Stem-like" Progenitor Phenotype

- The OBX-115 infusion product contains a high proportion of CD8+CD39-CD69- (double-negative) "stem-like" progenitor cells (58.2%–87.8%; **Figure 4**)
- Prior reports have associated higher levels of these double-negative TIL with complete cancer regression and TIL persistence (mean ~15% in responders vs <10% in non-responders)[1]



- OBX-115 TIL express very low levels of exhaustion markers, such as PD-1 (<0.25%) and LAG3 (<5%; **Figure 5**)
  - In non-engineered TIL, PD-1 expression (~20%–80%)[2,3] and LAG3 expression (~0%–20%)[2] are generally higher

Figure 5. OBX-115 TIL Express Low Levels of Immune Checkpoint Markers



- Objective responses were observed in 3 of 6 patients (50% ORR; **Table 2**)
  - Two of the patients treated with OBX-115 manufactured from CNB experienced durable complete remission (CR), ongoing at 56 and 27 weeks post-infusion
  - The patient who had OBX-115 manufactured from surgical tumor tissue experienced a partial response (PR), ongoing at 17 weeks post-infusion
- All patients experienced disease control
- All patients were alive at the time of the data cutoff

Table 2. Best Overall Response (RECIST v1.1)

	N=6
Objective response rate, n (%)	**3 (50.0)**
Complete response	**2 (33.3)**
Partial response*	1 (16.7)
Stable disease	3 (50.0)
Progressive disease	0
Disease control rate,† n (%)	**6 (100)**

*Confirmed after data cut-off date.
†Defined as best response of complete response, partial response, or stable disease for ≥12 weeks (confirmed with emerging data).

Conclusions

- OBX-115 engineered TIL infusion product was **successfully manufactured** from CNB and surgical tumor tissue
- Regardless of TTP method, OBX-115 cell dose met predetermined specification for infusion and had **positive phenotypic attributes**
  - OBX-115 infusion product consisted primarily of **CD8+ cells**, with a high proportion of **IL15+ cells** and low proportion of non-CD3+ cells
  - OBX-115 TIL were primarily **effector memory phenotype**, and had a significant proportion of CD8+CD39-CD69- **"stem-like" progenitor** cells
  - OBX-115 TIL expressed **low levels of immune checkpoint markers**
- Two patients who received OBX-115 manufactured by CNB tumor tissue achieved **durable CRs**
- These results support the potential **feasibility of outpatient CNB TTP** for OBX-115 manufacturing that may **increase the eligible patient population** and **address logistic challenges,** and support **continued investigation of the OBX-115 regimen** in this and an ongoing Phase 1/2 multicenter study (Agni-01 [NCT06060613])

References

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Abbreviations

Ab, antibody; ACZ, acetazolamide; CNB, core needle biopsy; CR, complete response; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; ECOG PS, Eastern Cooperative Oncology Group performance status; G, grade; ICI, immune checkpoint inhibitors; IL2, interleukin 2; IL15, interleukin 15; LAG3, lymphocyte-activation gene 3; LD, lymphodepletion; mbIL15, membrane-bound interleukin 15; PD-1, programmed cell death protein-1; RECIST, Response Evaluation Criteria in Solid Tumors; PR, partial response; REP, rapid expansion protocol; T_{CM}, central memory T cell; T_{EM}, effector-memory T cell; T_{EMRA}, terminal effector memory T cell; TIL, tumor-infiltrating lymphocytes; TTP, tumor tissue procurement.

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