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OBX-115 engineered tumor-infiltrating lymphocyte (TIL) cell therapy induced deepening and durable responses without interleukin 2 (IL2) in patients with immune checkpoint inhibitor (ICI)-resistant unresectable or metastatic melanoma

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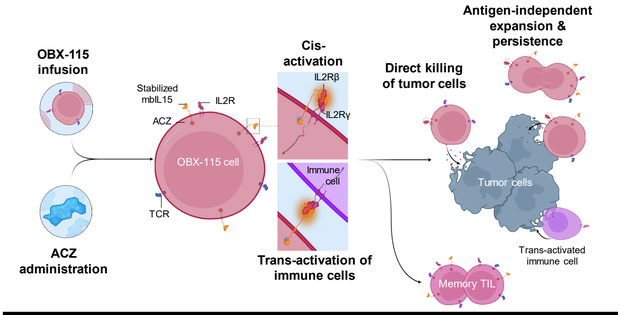
Introduction

- Treatment options are limited for patients with immune checkpoint inhibitor (ICI)-resistant advanced (unresectable or metastatic) melanoma
- 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 advanced melanoma[1] and has shown promising activity in this setting (objective response rate [ORR], 31.5%; median duration of response [mDOR], not reached), but is associated with a treatment-related mortality rate of 7.5%[2]
- All non-engineered TIL cell therapies require high-dose interleukin 2 (IL2), which has well-described high-grade toxicity,[2–4] limiting patient eligibility and frequently requiring specialized management
- OBX-115 TIL are engineered with a transgene to express membrane-bound human IL15 (mbIL15). The transgene encodes a fusion protein that couples mbIL15 with a drug-responsive domain (DRD) derived from the carbonic anhydrase 2 protein. The FDA-approved small-molecule drug, acetazolamide (ACZ), when administered, binds to the DRD, stabilizes the fusion protein, and allows for expression of mbIL15 on the cell surface of OBX-115 (**Figure 1**)
- mbIL15 drives the in vivo expansion and persistence of OBX-115, promoting elimination of tumor cells without co-administration of IL2
- We report results from the first 6 patients treated with OBX-115 in a first-in-human single-center study in patients with ICI-resistant advanced melanoma (NCT05470283)

Figure 1. OBX-115 Mechanism of Action



Methods

Primary Endpoints
- Safety: Incidence and severity of adverse events (AEs) and serious AEs (SAEs)
- Tolerability: Dose interruptions, reductions, and discontinuations
- Identification of recommended dose: Incidence and nature of dose-limiting toxicities (DLTs)

Key Secondary Endpoints
- Efficacy: Investigator-assessed ORR, DOR, and PFS per RECIST v1.1

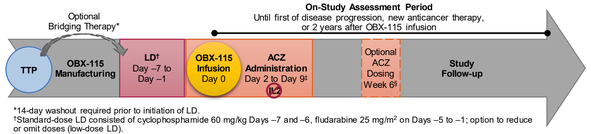
Dose-escalation
- Cohort 1 (n=3)
  - OBX-115 30 × 10^9 cells maximum (Patient 1 received 150 × 10^9 cells and ACZ 500 mg/day per earlier version of the protocol)
  - ACZ 125 mg/day from Day 2 to Day 9
- Cohort 2b (n=3–6)
  - OBX-115 100 × 10^9 cells maximum
  - ACZ 125 mg/day from Day 2 to Day 9
- Additional escalation/de-escalation cohorts will be enrolled as needed

Key Eligibility Criteria
- Pathologically confirmed diagnosis of metastatic melanoma (unresectable Stage III or Stage IV)
- 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 tumor tissue procurement (TTP) for RECIST v1.1 response assessment
- ECOG PS 0–1

Treatment Regimen
- Fresh (non-cryopreserved) OBX-115 is manufactured using the patient's own tumor tissue, procured by either excisional or core needle biopsy (CNB), and is infused intravenously following standard- or low-dose lymphodepletion (based on clinical eligibility) with cyclophosphamide and fludarabine (**Figure 2**)
- ACZ is administered orally at cohort-defined doses once daily for up to 7 days, with optional additional ACZ at Week 6–8 if initial tumor response is less than partial response (PR)
- No systemic high-dose IL2 is administered

Data cutoff date: January 2, 2024

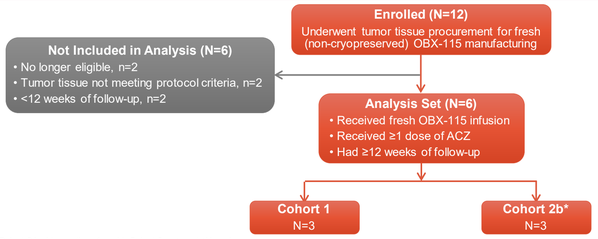
Figure 2. OBX-115 Treatment Regimen



*14-day washout required prior to initiation of LD.
†Standard-dose LD consisted of cyclophosphamide 60 mg/kg Days –7 and –6, fludarabine 25 mg/m² on Days –5 to –1; option to reduce or omit doses (low-dose LD).
‡Or until absolute lymphocyte count ≥5000 cells/μL, whichever is earlier.
§Patients may receive additional ACZ dosing at Week 6–8 for up to 7 days if the initial observed tumor response is less than PR.

- 6 patients were infused with fresh (non-cryopreserved) OBX-115, had ≥1 dose of ACZ, and had ≥12 weeks of follow-up (**Figure 3**)
  - All patients had disease that was primary-resistant to and had progressed on anti–PD-1 therapy (**Table 1**)
  - All patients had received and progressed on prior anti–CTLA-4 therapy
  - 5 (83.3%) patients received combination anti–CTLA-4 and anti–PD-1 therapy
  - OBX-115 was successfully manufactured for all 6 patients, including from core needle biopsy tumor tissue (**Table 2**)

Figure 3. Patient Disposition



*Cohort 2 had two options (a or b); Cohort 2a was not skipped.

Table 1. Baseline Patient and Disease Characteristics (N=6)

Age, median (range), years	47.5 (28–64)
Sex, n (%) Male Female	 1 (16.7) 5 (83.3)
Mutational status, n (%) *BRAF*-mutant *NRAS*-mutant	 2 (33.3) 2 (33.3)
Target lesion SOD, median (range), mm	39.4 (11.7–81.5)
Brain lesions, n (%)	1 (16.7)
Liver lesions, n (%)	2 (33.3)
ECOG PS, n (%) 0 1	 4 (66.7) 2 (33.3)
LDH, n (%) ≤ULN >ULN	 4 (66.7) 2 (33.3)
Lines of prior systemic therapy, median (range) Lines of prior ICI therapy	2.5 (1–5) 2.5 (1–3)
Prior systemic therapy, n (%) Prior anti–PD-1 therapy Prior anti–CTLA-4 therapy Prior anti–PD-1 + anti–CTLA-4 combination	 6 (100) 6 (100) 5 (83.3)
Anti–PD-1 primary resistant, n (%)	6 (100)
Systemic bridging therapy, n (%)	0 (0)

Table 2. Treatment Characteristics (N=6)

Tumor tissue procurement method, n (%) Surgical excision Core needle biopsy	 1 (16.7) 5 (83.3)
Lymphodepletion regimen, n (%) Standard-dose Low-dose*	 5 (83.3) 1 (16.7)
OBX-115 infusion, median (range)† Infused cells,‡ × 10^9 CD3+ cells, % CD8+ cells, % IL15+ viable cells, %	 54.5 (9.6–150) 99 (97–100) 97.5 (95.9–99.5) 71.5 (48–78)
Initial ACZ doses,§ median (range)	7 (5–7)
ACZ redosed at Week 6,¶ n (%)	4 (80.0)

*~50% dose of standard-dose cyclophosphamide. †All OBX-115 infusion products were fresh (not cryopreserved). ‡Cohort 1 dose capped at 30 × 10^9; Cohort 2 capped at 100 × 10^9 cells. §Does not include Week 6 redosing. ¶5 patients were eligible for ACZ redosing.

- Median study follow-up was 24.9 weeks (range, 15.7–56.0)
- No DLTs were reported
- Hematologic AEs were consistent with known safety profile of lymphodepletion
- 3 Grade 3 (n=2 patients) and no Grade 4 non-hematologic AEs were reported within 30 days after OBX-115 infusion (**Table 3**)
- No confirmed ICANS, capillary leak syndrome, or cytokine release syndrome
- 5 patients experienced rash and pruritus; 3 patients experienced uveitis (all Grade 1 or 2)
- No patient died during the study or received care in the ICU

Table 3. Safety (N=6)

Nonhematologic AE,* n (%)	All Grades	Grade 3	Grade 4
Abdominal pain	1 (16.7)	1 (16.7)	0
ALT elevation	3 (50.0)	1 (16.7)	0
Syncope	1 (16.7)	1 (16.7)	0

*Grade ≥3 events reported within 30 days after OBX-115 infusion.

Results

- Objective responses were observed in 3 of 6 patients (50% ORR; **Table 4**)
- All patients experienced disease control
- All patients were alive at the time of the data cut-off

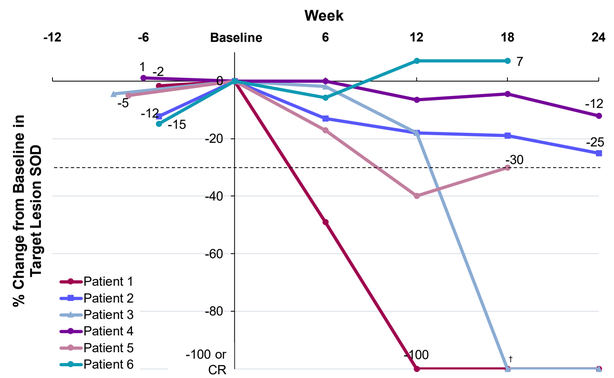
Table 4. Efficacy (RECIST v1.1 [N=6])

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 complete response, partial response, or stable disease for ≥12 weeks (confirmed with emerging data).

- A decrease in target lesion sum of diameters (SOD) was observed in most patients (**Figure 5**)

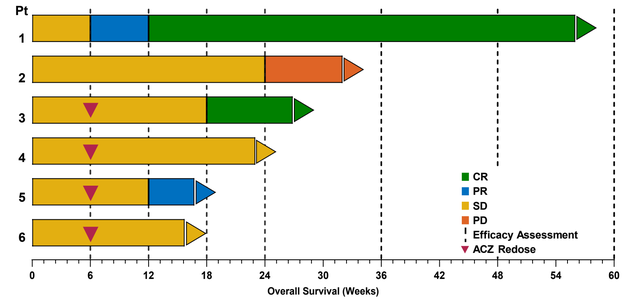
Figure 5. Target Lesion SOD Reduction from Baseline*



*Assessed by investigator (RECIST v1.1 per protocol), as of Jan 29, 2024. SOD increases normalized to baseline. †Includes resolution of lymph node to <10 mm.

- Responses were established between Week 6 and 18, and were ongoing as of the data cutoff date (**Figure 6**)
- Responses appear to be durable and to deepen over time and across OBX-115 doses
- One patient developed new metastatic disease (liver) and progressed at Week 24, despite continued target lesion reduction

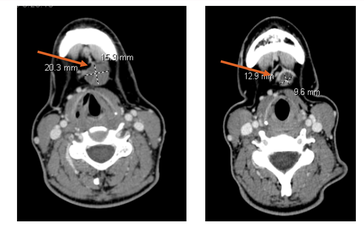
Figure 6. Onset and Duration of Response



Abbreviations

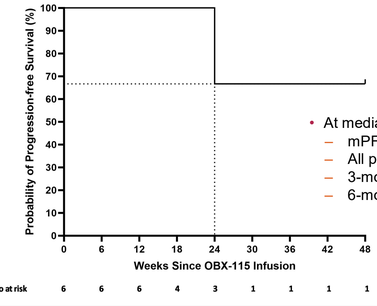
ACZ, acetazolamide; AE, adverse event; CNB, core needle biopsy; CR, complete response; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; DOR, duration of response; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; ICANS, immune effector cell-associated neurotoxicity syndrome; ICI, immune checkpoint inhibitors; ICU, intensive care unit; IL2, interleukin 2; IL2R, interleukin 2 receptor; LAG3, lymphocyte-activation gene 3; LD, lymphodepletion; LDH, lactate dehydrogenase; mbIL15, membrane-bound interleukin 15; mDOR, median duration of response; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein-1; PFS, progression-free survival; PR, partial response; Pt, patient; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; SD, stable disease; SOD, sum of diameters; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocytes; TTP, tumor tissue procurement; ULN, upper limit of normal.

Figure 7. Necrosis and Resolution of Target Submental Lymph Node



- Radiographic images from a patient with disease that responded to therapy show a baseline target submental lymph node (left, 20.3 × 15.9 mm), and complete resolution (<10mm in short axis) with necrosis and shrinkage at Week 18 (right, **Figure 7**)

Figure 8. Progression-free Survival



- At median 25-week study follow-up:
  - mPFS not reached (**Figure 8**)
  - All patients were alive
  - 3-month PFS: 100%
  - 6-month PFS: 67%

Conclusions

- OBX-115 engineered TIL cell therapy produced **durable antitumor responses** in patients with ICI-resistant advanced melanoma, **without IL2 administration**
  - Demonstrates the **successful clinical application of DRD technology** for **regulatable transgene expression** at the protein product level
  - **Clinically validates mbIL15** as a cytokine that supports TIL expansion and function
- OBX-115 was **well-tolerated**, with a **differentiated safety profile**
  - No DLTs or Grade 4 non-hematologic events, limited Grade 3 events, and no confirmed cytokine release syndrome, capillary leak syndrome, or ICANS
- OBX-115 induced consistently **deepening and durable responses**
  - Investigator-assessed **ORR was 50%**
  - Despite continued tumor growth in most patients prior to OBX-115 infusion, all patients experienced **tumor burden reduction** and meaningful **disease control for ≥12 weeks** after infusion
  - Durable responses were observed with OBX-115 manufactured from **CNB tumor tissue**
  - Initial **PFS data are encouraging**
- OBX-115 engineered TIL cell therapy has the **potential to fulfill the unmet need** in ICI-resistant advanced melanoma
- These results support **continued investigation of the OBX-115 regimen** in this and an ongoing Phase 1/2 multicenter study (NCT06060613)

References

1. US Food and Drug Administration Center for Biologics Evaluation and Research (CBER). AMTAGVI Accelerated BLA Approval. (https://www.fda.gov/media/176418/download?attachment).
2. US Food and Drug Administration Center for Biologics Evaluation and Research (CBER). AMTAGVI Prescribing Information. (https://www.fda.gov/media/176417/download).
3. Rohaan MW, et al. *N Engl J Med* 2022;387(23):2113–2125.
4. Chesney J, et al. *J Immunother Cancer* 2022;10(12).

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