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OBX-115 engineered tumor-infiltrating lymphocytes (TIL) with regulatable membrane-bound IL15 (mbIL15): Translational data from a single-center phase 1 trial in patients with immune checkpoint inhibitor (ICI)-resistant advanced melanoma

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Introduction

- Non-engineered TIL cell therapy requires systemic high-dose IL2 to activate and expand infused T cells
- High-dose IL2 has well-described toxicity limiting patient eligibility and contributes to treatment-related morbidity and mortality
- OBX-115 TIL are engineered to express mbIL15 regulated by the FDA-approved small-molecule drug acetazolamide (ACZ) via a drug-responsive domain (DRD), abrogating the need for toxic high-dose IL2 after TIL infusion
  - mbIL15 provides cytokine support for TIL expansion and persistence
  - ACZ is well-tolerated and can be redosed to re-activate and re-expand persisting OBX-115 TIL[1]
- Single-center phase 1 data (NCT05470283) demonstrated differentiated early safety and promising efficacy[2]
- We present translational data from the first-in-human phase 1 study supporting OBX-115 mechanism of action

Methods

- Trial design and clinical results were previously described[2] (NCT05470283)
  - Briefly, patients received lymphodepletion (standard- or low-dose options) followed by OBX-115 infusion (Day 0) and ≤10 days of orally administered ACZ (Day 0 or 2 to Day 9) or until absolute lymphocyte count was ≥5000 cells/µL, whichever was earlier; some patients received additional ACZ dosing at Week 6
- Translational Analyses
  - Peripheral blood (PB) and tumor tissue samples were collected at Baseline (pre-lymphodepletion) and subsequent timepoints for longitudinal analysis
  - OBX-115 drug product and PB samples were assessed for phenotype using spectral flow cytometry
  - Post-infusion PB and tumor tissue samples were assessed for OBX-115 DNA using droplet digital polymerase chain reaction (ddPCR)
  - Serum cytokines were assessed by median fluorescence intensity of the analyte using multiplex bead-based immunoassay Luminex
  - PB samples were assessed for T-cell receptor (TCR) repertoire (Clonotype, Adaptive Biotechnologies)

Results (ASCO 2024[2] Recap)

Table 1. Baseline Characteristics

Baseline Patient and Disease Characteristics	All Patients (N=10)
Age, median (range), years	48.5 (28–74)
Sex, n (%)	
Female	7 (70.0)
Mutation status, n (%)	
BRAF-mutant	3 (30.0)
NRAS-mutant	2 (20.0)
GNA11-mutant (non-uveal *GNA11* subtype)*	1 (10.0)
Target lesion SOD, median (range), mm	39.9 (11.7–82.8)
LDH >ULN, n (%)	5 (50.0)
Treatment Characteristics	
Lines of prior systemic therapy, median (range)	3.5 (1–6)
Lines of prior ICI therapy	2.0 (1–3)
Prior systemic therapy, n (%)	
Anti–PD-1	**10 (100)**
Anti–CTLA-4	**10 (100)**
Anti–PD-1 + anti–CTLA-4 combination	9 (90.0)
Anti–PD-1 + anti-LAG3 combination	2 (20.0)
BRAF ± MEK TKI	2 (20.0)
Primary-resistant (SITC criteria), n (%)	
Anti–PD-1[3]	**8 (80.0)**
Anti–PD-1 + anti–CTLA-4 or anti-LAG3 combination[4]	**8 (80.0)**

*Efficacy assessed as a separate cohort per protocol.

- In data presented at ASCO 2024[2]
  - Patients had advanced and substantially pre-treated disease (**Table 1**)
  - ORR was 44.4% (4/9), with 2 CRs (22.2%) in 9 protocol-specified efficacy-evaluable patients
    - Disease control rate was 100% (no best response of PD)
    - 24-week progression-free survival was 75%
  - At a median study follow up of 29.5 weeks, OBX-115 demonstrated a differentiated safety profile
    - No dose-limiting toxicity; no Grade 4+ non-hematologic event
    - No TRM; all patients were alive at data cutoff
- The 10 patients included in the ASCO 2024 analysis[2] are included in this analysis (OBX-115: fresh, n=8; cryopreserved, n=2)

References

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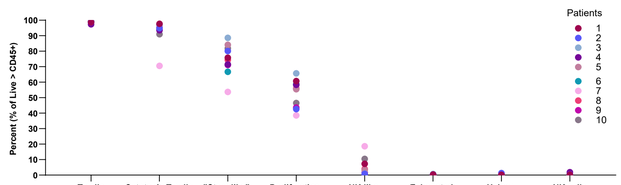
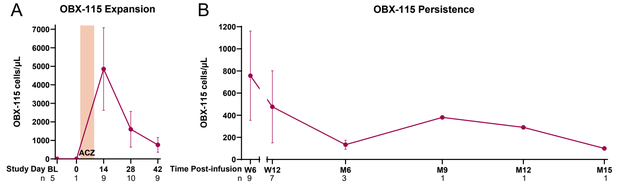
Results

Figure 1. OBX-115 Has Positively Differentiated Phenotypic Attributes



- OBX-115 was successfully manufactured from core needle biopsy (n=5) and surgical excision (n=5) of tumor tissue[2]
  - OBX-115 was enriched for beneficial phenotypic attributes for antitumor activity, including cytotoxic T cells (CD8+) with "stem-like" memory progenitor phenotype (CD39-CD69-)[5] and proliferating T cells (Ki67+; **Figure 1**)
  - A minimal number of exhausted (PD1+) CD8+ T cells,[6,7] helper T cells (CD4+), and NK cells (CD3-CD56+; **Figure 1**) were detected

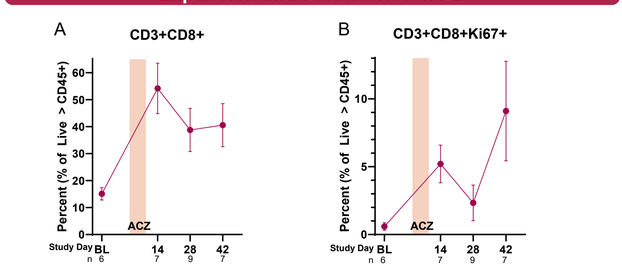
Figure 2. OBX-115 Expands and Persists in Peripheral Blood



Mean (SEM) value presented.

- PB samples demonstrated ACZ-driven OBX-115 TIL expansion, reaching a mean of ~4800 cells/µL at Day 14 (approximate day of OBX-115 expansion peak; median number of days of ACZ was 7 [range, 5-10]; **Figure 2A**)
- In patients with ≥6-week follow-up, OBX-115 remained detectable through 15 months (**Figure 2B**)

Figure 3. OBX-115 Demonstrates ACZ-dependent Expansion and Persistence in PB



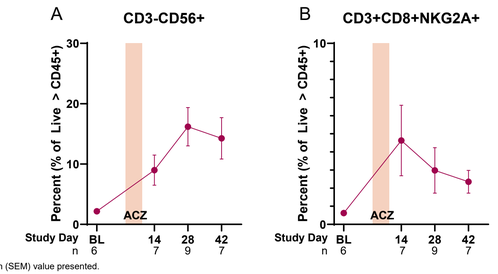
Mean (SEM) value presented.

- In the immediate post-infusion phase (up to Day 14), PB flow cytometry indicated expansion of product-derived CD3+CD8+ cells (**Figure 3A**), including proliferating CD8+ cells expressing Ki67 (during ACZ exposure; **Figure 3B**)
- After Day 28, CD3+CD8+ and CD3+CD8+Ki67+ increase was related to normal immune reconstitution given the drop in OBX-115 absolute cell count between Day 28 and Day 42 as shown in **Figure 2**

Abbreviations

ACZ, acetazolamide; BL, Baseline; CTLA-4, cytotoxic T-lymphocyte antigen-4; ddPCR, droplet digital polymerase chain reaction; D, Day; DOR, duration of response; DRD, drug-responsive domain; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; IL2, interleukin 2; IL6, interleukin 6; IL7, interleukin 7; IL15, interleukin 15; LAG3, lymphocyte activation gene 3; LDH, lactate dehydrogenase; mbIL15, membrane-bound interleukin 15; M, Month; mOS, median overall survival; mPFS, median progression-free survival; NK, natural killer; ORR, objective response rate; PB, peripheral blood; PD-1, programmed cell death protein-1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SITC, Society for Immunotherapy of Cancer; SOD, sum of diameters; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; TKI, tyrosine kinase inhibitor; TTP, tumor tissue procurement; ULN, upper limit of normal; W, Week.

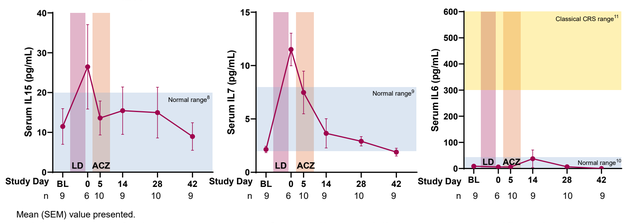
Figure 4. Endogenous Immune Cell Populations Respond to IL15 Signal



Mean (SEM) value presented.

- Day 14 post-infusion peripheral blood showed endogenous NK cell expansion (CD3-CD56+; **Figure 4A**), and increase in NK-like cytotoxic T cells (CD3+CD8+NKG2A+; **Figure 4B**)
- NK cell expansion was likely due to trans-presentation of mbIL15 on OBX-115 TIL

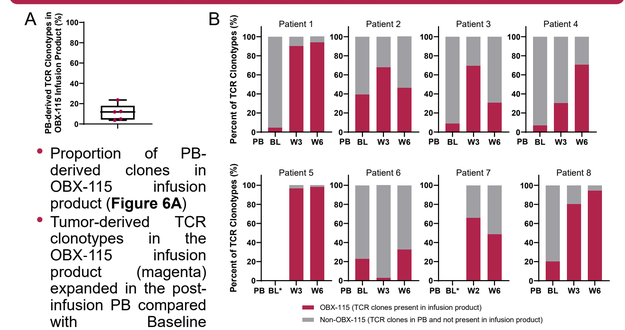
Figure 5. Key Pro-inflammatory Cytokine Levels Are Not Elevated Post-infusion



Mean (SEM) value presented.

- Mean post-infusion serum levels of IL15, IL7, and IL6 were not significantly elevated above Baseline through Day 42 ($p > 0.05$; paired one-tailed t-test adjusted for multiple comparisons [Bonferroni correction]; **Figure 5**)
  - As expected, serum IL15 concentration increased as a result of lymphodepletion (Day 0), but remained at or below Baseline level thereafter, suggesting IL15 from OBX-115 did not enter systemic circulation (**Figure 5A**)
  - Similarly, serum IL7 levels increased as an expected consequence of lymphodepletion (Day 0) and rapidly returned to Baseline level (**Figure 5B**)
  - Notably, serum IL6 levels were well below levels typically associated for CRS (300–600 pg/mL[11]; **Figure 5C**), even in patients with fever

Figure 6. PB TCR Clonotype Repertoire Remodels to Reflect the OBX-115 Infusion Product



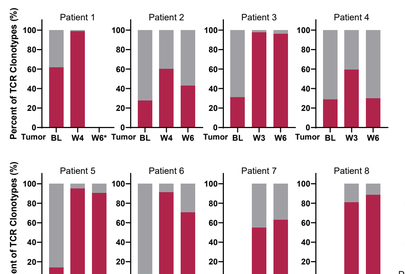
- Proportion of PB-derived clones in OBX-115 infusion product (**Figure 6A**)
- Tumor-derived TCR clonotypes in the OBX-115 infusion product (magenta) expanded in the post-infusion PB compared with Baseline (**Figure 6B**)

Data available for 8 patients.
*Baseline data not available for Patients 5 and 7.

Disclosures

Rodabe N Amaria has received research funding and honoraria for Advisory Board participation from Obsidian Therapeutics.

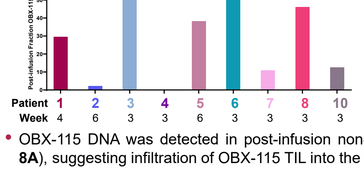
Figure 7. Tumor TCR Clonotype Repertoire Remodels to Reflect the OBX-115 Infusion Product



- Tumor-derived TCR clonotypes in the OBX-115 infusion product (magenta) infiltrated, expanded, and enriched in the post-infusion tumor compared with Baseline (**Figure 7**)

Data available for 8 patients.
*Baseline data not available for Patients 7 and 8. Week 6 data not available for Patient 1, due to CR.

Figure 8. Post-infusion Non-target Tumor and Brain Metastases Demonstrate OBX-115 Infiltration



- OBX-115 DNA was detected in post-infusion non-target lesion tumor tissue (**Figure 8A**), suggesting infiltration of OBX-115 TIL into the tumor microenvironment
- Pathologic assessment of a resected residual brain metastasis at Week 40 indicated tumor necrosis (**Figure 8B**); OBX-115 TIL were detected by PCR (not shown)
  - No new brain metastases have developed
  - Patient remains in complete response after nearly 2.5 years

Conclusions

- **OBX-115 is a highly differentiated TIL cell therapy** with optimized characteristics for response and persistence
- These data confirm **successful platform validation**, supporting the proposed OBX-115 mechanism of action
  - ACZ-driven OBX-115 TIL **expansion, persistence,** and **tumor infiltration**
  - **Endogenous immune cell expansion**, presumably driven by transactivation via mbIL15 on OBX-115
  - **No significant elevation of key pro-inflammatory cytokines**
  - **PB and tumor TCR repertoire remodeling** with tumor-derived TCR clonotypes
- ACZ-driven regulatable mbIL15 expression on OBX-115 enables **elimination of IL2** from the regimen and the potential for a **safer, more effective TIL cell therapy**
- Investigation of the OBX-115 regimen is ongoing in the **Phase 1/2 Agni-01 multicenter study** in patients with advanced melanoma and metastatic non-small cell lung cancer (NCT06060613)
  - See **Abstract 9517**: Mon Jun 2, 9:45–11:15 AM CDT (Rapid Oral Abstract – Melanoma/Skin Cancers)

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