ABSTRACT 9515

OBX-115, an interleukin 2 (IL2)-sparing engineered tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with immune checkpoint inhibitor (ICI)-resistant unresectable or metastatic melanoma

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Learning Outcomes

Patients with advanced (unresectable or metastatic) melanoma refractory to both anti–PD-1 and anti–CTLA-4 agents have a particularly poor prognosis and new treatments are needed

Lifileucel, a non-engineered tumor-infiltrating lymphocyte (TIL) cell therapy, was recently approved for patients with immune checkpoint inhibitor (ICI)-exposed advanced melanoma, but requires systemic high-dose IL2, which has well-described high-grade toxicity limiting patient eligibility, and had a treatment-related mortality rate of 7.5%

OBX-115 engineered TIL cell therapy does not require IL2 due to regulatable expression of membrane-bound IL15 (mbIL15), driven by the FDA-approved small-molecule drug acetazolamide (ACZ)

We describe a first-in-human dose-finding study of OBX-115 engineered TIL cell therapy demonstrating a **positively differentiated safety profile** with **sustained responses without IL2 administration**

ACZ, acetazolamide; CTLA-4, cytotoxic T-lymphocyte antigen-4; ICI, immune checkpoint inhibitor; IL2, interleukin 2; mbIL15, membrane-bound interleukin 15; PD-1, programmed cell death protein-1; TIL, tumor-infiltrating lymphocyte.

Background

- Patients with melanoma refractory to both anti–PD-1 and anti–CTLA-4 agents have a particularly poor prognosis
  - Subsequent chemotherapy or ICI retreatment results in 0%–10% ORR, 2–3 mo mPFS, and 7–8 mo mOS[1–4]
  - Patients with prior BRAF tyrosine kinase inhibitor (TKI) exposure,[5,6] anti–CTLA-4 exposure,[5] and brain metastasis have limited benefit from current non-engineered TIL cell therapy[7,8]

- Lifileucel, a non-engineered TIL cell therapy requiring systemic IL2, was recently approved[9] in the post-anti–PD-1 setting
  - The pivotal cohort had an ORR of 31.5%,[10] mPFS of 4.1 mo,[8] and mOS of 12.7 mo at a median 8.4-mo follow up[10]
  - High-dose IL2 has well-described high-grade toxicity limiting patient eligibility, and the regimen had an overall treatment-related mortality rate of 7.5%[9]

- OBX-115 autologous engineered TIL cell therapy does not require co-administration of IL2 due to inducible and regulatable expression of mbIL15 using a carbonic anhydrase-2 drug-responsive domain (DRD), making its expression inducible with the FDA-approved small-molecule drug ACZ
  - 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[11]

- We present data from a first-in-human phase 1 dose-finding study of OBX-115 in patients with ICI-resistant advanced melanoma*

1. Vanderwalde AM et al. *Cancer Res* 2022:82(12_supplement (Abstract CT013). 2. Pires da Silva I et al. *Lancet Oncol* 2021:22(6):836-847. 3. Ascierto PA et al. *J Clin Oncol* 2023:41(15):2724-2735. 4. Kirchberger et al. *Eur J Cancer* 2016; 65. 5. Forget M et al. *Clin Cancer Res* 2018; 24(18): 4416. 6. Seitter SJ et al. *Clin Cancer Res* 2021;27:5289–98. 7. Mehta GU et al. *J Immunother*. 2018; 41(5): 241–247. 8. Chesney JA et al. *J Immunother Cancer* 2022;10:e005755. 9. AMTAGVI Prescribing Information (n=73). Accessed April 1, 2024. 10. BLA Clinical Review and Evaluation BLA 125773: Approval History, Letters, Reviews, and Related Documents – AMTAGVI. Accessed April 29, 2024. 11. Burga R et al, SITC 2023 (Abstract 348).
*Data cutoff April 4, 2024; 10 patients who had started study treatment by December 31, 2023, are included.
ACZ, acetazolamide; CTLA-4, cytotoxic T-lymphocyte antigen-4; DRD, drug-responsive domain; ICI, immune checkpoint inhibitor; IL2, interleukin 2; mbIL15, membrane-bound interleukin 15; mo, month; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; PD-1, programmed cell death protein-1; TIL, tumor-infiltrating lymphocyte; TKI, tyrosine kinase inhibitor.

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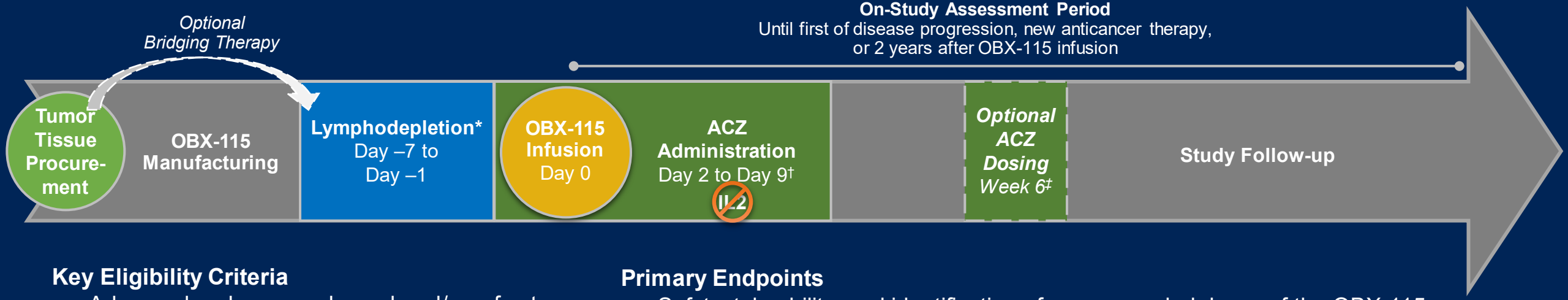
First-in-human Study Design (NCT05470283)



Key Eligibility Criteria

- Advanced melanoma relapsed and/or refractory to ICI therapy
- ≥1 lesion suitable for tumor tissue procurement (TTP) for manufacturing and ≥1 remaining lesion amenable to RECIST v1.1 response assessment
- Protocol-defined high-risk patients (e.g. mucosal and uveal or genomically equivalent mutations) may be enrolled after initial safety established

Primary Endpoints

- Safety, tolerability, and identification of recommended doses of the OBX-115 regimen: all treated patients
  - Incidence and severity of adverse events (AEs), serious AEs (SAEs), and dose-limiting toxicities (DLTs)

Key Secondary Endpoints

- Investigator-assessed ORR, DOR, and PFS: by dose level for full efficacy set
  - Protocol-defined high-risk patients assessed separately

Data cutoff: April 4, 2024 (10 patients who had started study treatment by December 31, 2023 are included).
*Standard- or low-dose lymphodepletion options. †Or until absolute lymphocyte count ≥5000 cells/μL, whichever is earlier. ‡Patients may receive additional ACZ dosing at Week 6.
ACZ, acetazolamide; AE, adverse event; DLT, dose-limiting toxicity; DOR, duration of response; ICI, immune checkpoint inhibitor; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TTP, tumor tissue procurement.

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All Patients Had ICI-resistant Disease

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 (rare uveal-equivalent subtype)*	1 (10.0)
Target lesion SOD, median (range), mm	39.9 (11.7–82.8)
Brain lesions with prior treatment, n (%)	2 (20.0)
Target lesion site(s), n (%)	
Liver	3 (30.0)
Lymph node	3 (30.0)
Other†	6 (60.0)
ECOG PS, n (%)	
0	7 (70.0)
1	3 (30.0)
LDH >ULN, n (%)	5 (50.0)

Treatment Characteristics	All Patients (N=10)
Lines of prior systemic therapy, median (range)	3.5 (1–6)
Lines of prior ICI therapy	2.0 (1–3)
Prior adjuvant therapy, n (%)	5 (50.0)
Anti–CTLA-4	1 (10.0)
Anti–PD-1	3 (30.0)
Chemotherapy	1 (10.0)
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[1]	**8 (80.0)**
Anti–PD-1 + anti–CTLA-4 or anti-LAG3 combination[2]	**8 (80.0)**
Systemic bridging therapy, n (%)	1 (10.0)
Chemotherapy	1 (10.0)

1. Kluger HM et al. *J Immunother Cancer* 2020;8(1). 2. Kluger H et al. *J Immunother Cancer* 2023;11(3).
*Efficacy assessed as a separate cohort per protocol. †"Other" includes abdominal wall (n=2) and pancreas, flank, retroperitoneum, sacrum, thigh muscle, and lateral hemithorax (n=1 each).
CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; LAG3, lymphocyte activation gene 3; LDH, lactate dehydrogenase; PD-1, programmed cell death protein-1; SITC, Society for Immunotherapy of Cancer; SOD, sum of diameters; TKI, tyrosine kinase inhibitor; ULN, upper limit of normal.

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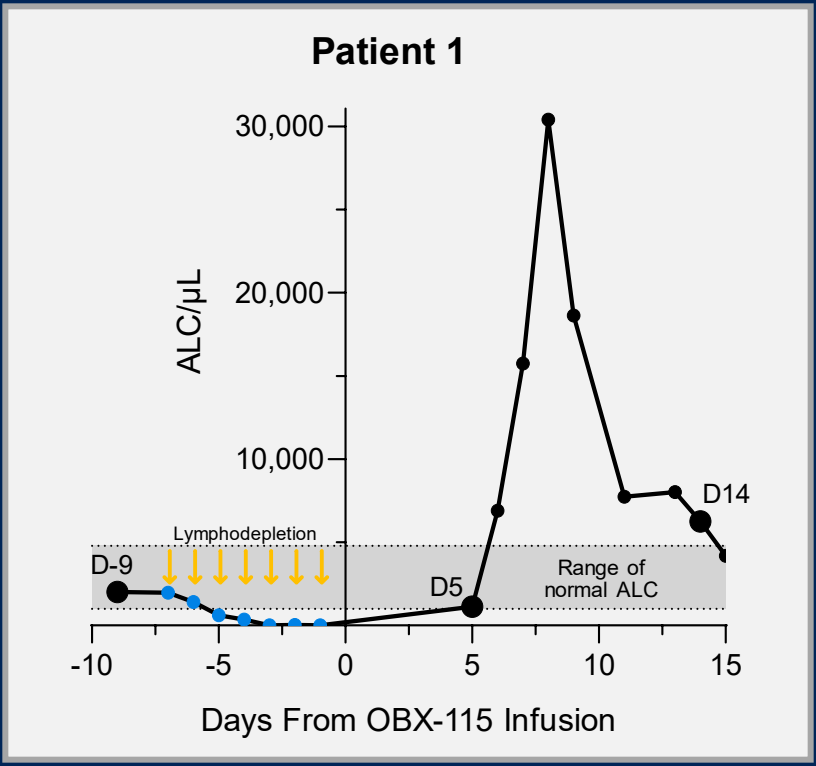
Patient 1 Key Learnings Informed Subsequent Dose-level Schema



- OBX-115: 150 × 10^9 cells
- ACZ: 500 mg/day (5 doses starting Day –1)
- Peak ALC: 30,400 cells/µL (Day 8)
- No DLTs
- PR achieved by Week 6, deepened to CR by Week 12

Dose de-escalation based on Patient 1 lymphocytosis and OBX-115 cell expansion

Dose Level	Fresh / Cryo	OBX-115 Dose Upper Cap (cells × 10^9)	ACZ Dose (mg / day)	Planned ACZ Duration (days)
1	Fresh	150	500	365
Dose de-escalation implemented				
–1	Fresh	30	125	7
2	Fresh	100	125	7
2	Cryo	100	125	10

Median (range) manufactured OBX-115 dose: 100 (9–190) × 10^9 cells

1. Dudley ME et al. *J Clin Oncol* 2005 Apr 1;23(10)2346-57. 2. Dudley ME et al. *J Immunother* 2002 May-Jun;25(3):243-51. 3. Fehse B et al. *Ther Methods Clin Dev* 2020 Jan 15;16:172-178.
ACZ, acetazolamide; ALC, absolute lymphocyte count; CR, complete response; Cryo, cryopreserved; D, day; DLT, dose-limiting toxicity; PR, partial response.

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OBX-115 Has a Positively Differentiated Safety Profile

No treatment- or disease-related mortality at median study follow-up of ~30 weeks
No ICU care needed in any patient

At a median study follow-up of 29.5 weeks (range, 13.0–69.3):

- ✓ No DLTs reported at any dose level
- ✓ No confirmed CRS, ICANS, or capillary leak syndrome
- ✓ No AEs related to outpatient ACZ redosing at Week 6 (n=7)
- ✓ No patient discontinued study due to AEs
- ✓ No Grade 4+ nonhematologic TEAEs (Grade 3 events, n=3 in 2 patients)*

	All Patients (N=10)		
Nonhematologic TEAE,* n (%)	All Grades	Grade 3	Grade 4+
Increased alanine aminotransferase	4 (40.0)	1 (10.0)	0
Abdominal pain†	1 (10.0)	1 (10.0)	0
Syncope	1 (10.0)	1 (10.0)	0

- Hematologic AEs were consistent with known lymphodepletion safety profile
- Eight patients experienced rash / pruritus (all Grade 1–2)
- Uveitis / iritis (all Grade 1–2) in 4 patients, 1 of whom reported optic neuritis (Grade 3) that has resolved

*Grade ≥3 events reported within 30 days after OBX-115 infusion. †Included increased alanine aminotransferase and required prolonged hospitalization (only patient with TEAE resulting in prolonged hospitalization).
ACZ, acetazolamide; AE, adverse event; DLT, dose-limiting toxicity; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICU, intensive care unit; TEAE, treatment-emergent adverse event.

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OBX-115: Promising Efficacy Profile Without IL2 Administration

	Efficacy Cohort (n=9)
Objective response rate, n (%)	**4 (44.4)**
Complete response	**2 (22.2)**
Partial response	2 (22.2)
Stable disease ≥12 weeks	5 (55.6)
Progressive disease	0
Disease control rate,* n (%)	9 (100)
Progression-free survival at 24 weeks	75%

- Per-protocol efficacy analysis set (n=9)
  - 44.4% ORR, including 2 CRs
- Per-protocol high-risk cohort (n=1, *GNA11*-mutated rare uveal-equivalent subtype)
  - Best response of progressive disease

*Defined as stable disease (or better) for ≥12 weeks post-infusion.
CR, complete response; IL2, interleukin 2; ORR, objective response rate.

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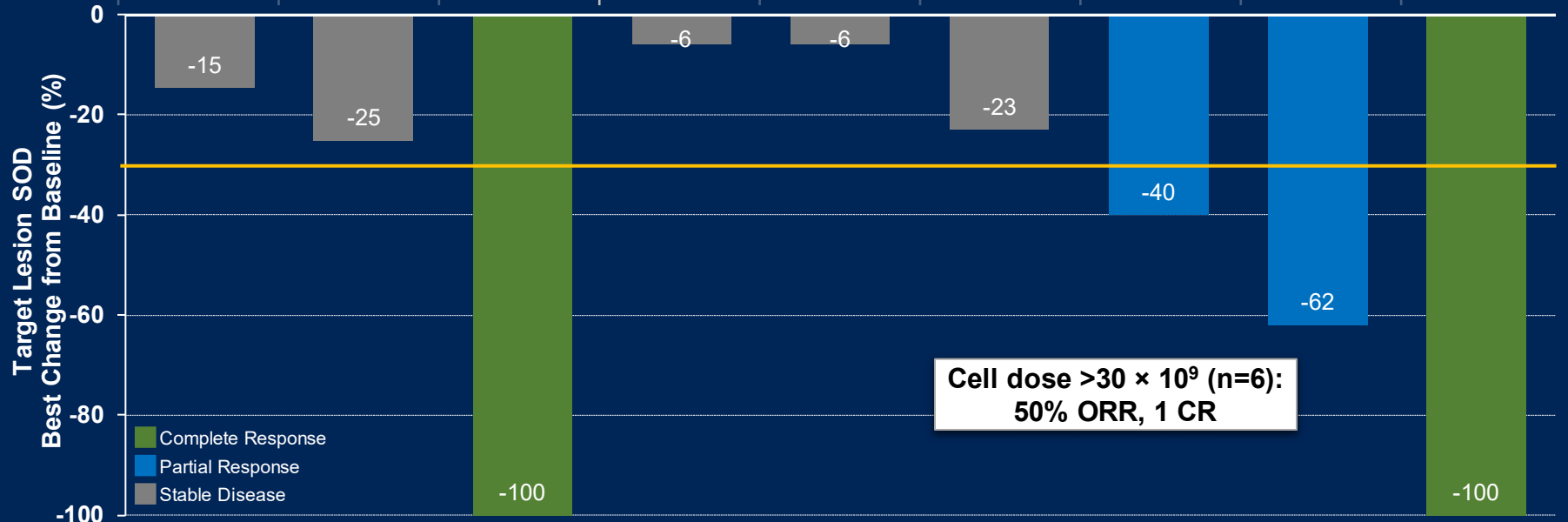
All Patients Experienced Tumor Burden Reduction

	Infused OBX-115 Dose ≤30 × 10^9 Cells			Infused OBX-115 Dose >30 × 10^9 Cells					
BRAF Mutation / TKI Exposure		+ / -		+ / +	+ / +				
Prior Lines of Systemic Therapy	1	2	2	4	6	6	3	3	3
Prior Brain Metastasis Therapy				+					+
Patient	4	2	3	9*	6	7	5	10*	1



Isolated Brain Progression†			+	+					
Progression Requiring Subsequent Systemic Therapy		+			+	+	+		
Time to Progression‡	36 wks+	24 wks	36 wks	13 wks	25 wks	12 wks	25 wks	12 wks+	60 wks+

*Patient received cryopreserved OBX-115. † Patients with isolated brain progression did not receive systemic treatment post-progression. ‡"+" indicates no progression at latest follow-up.
CR, complete response; ORR, objective response rate; SOD, sum of diameters; TKI, tyrosine kinase inhibitor; wks, weeks.

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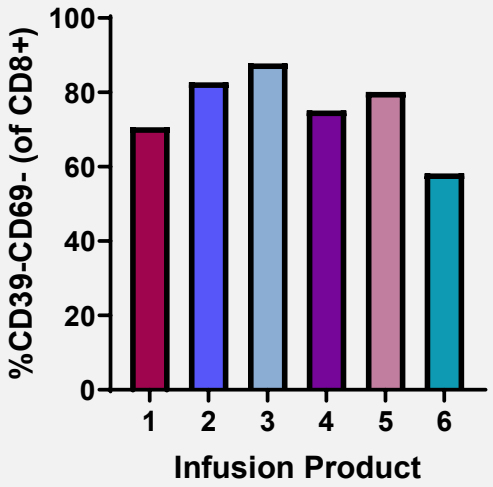
OBX-115 Has Positively Differentiated Phenotypic Attributes and Promotes Expansion of Endogenous Immune Cells*

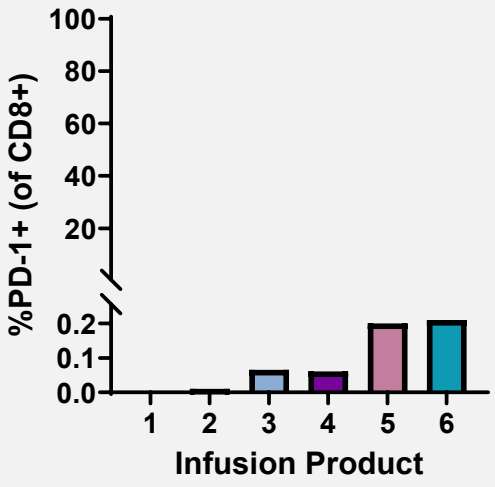
OBX-115 Infusion Product

CD39-CD69- Frequency



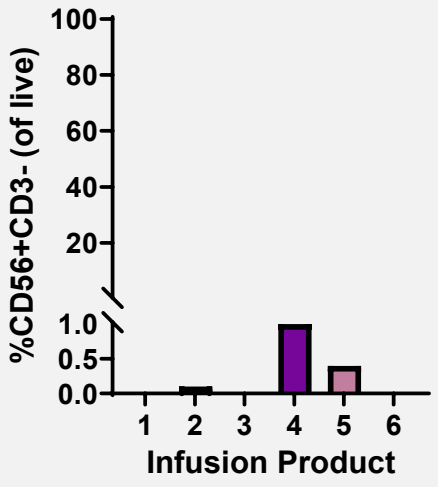
High proportion CD8+CD39-CD69- (double-negative) "stem-like" progenitor cells[1]

PD-1 Expression Frequency



Low proportion PD-1 expression on CD8+ cells[2]

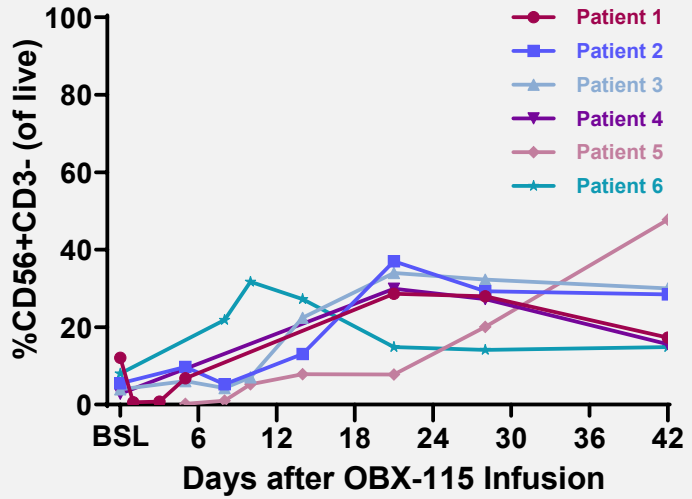
NK Cell Frequency



Low proportion NK cells

Peripheral Blood

NK Cell Expansion



Endogenous NK cell expansion consistent with **trans-activation of NK cells by mbIL15**[3]

OBX-115 was successfully manufactured from **core needle biopsy** (n=5) and surgical excision (n=5) of tumor tissue

* Translational data available from first 6 infused patients (1–6).

1. Double-negativity associated with response (Krishna S et al. *Science* 2020 Dec 11;370(6522):1328-1334). 2. PD-1 expression is generally higher in non-engineered TIL (~20%–80%) (Simpson-Abelson M et al. ESMO Virtual Congress 2020 (Abstract 1035P); Cubas R et al. Tandem Meetings of ASTCT & CIBMTR 2022 (Abstract 270). 3. Burga R et al, AACR 2024 (Abstract LB072).

mbIL15, membrane-bound interleukin 15; NK, natural killer; PD-1, programmed cell death protein-1; TIL, tumor-infiltrating lymphocytes.

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Conclusions

- OBX-115 is a highly differentiated TIL cell therapy product with optimized characteristics for response and persistence, which can be manufactured using tumor tissue obtained via core needle biopsy
  - ACZ-driven regulatable mbIL15 expression enables **elimination of IL2 from the regimen**
- In this Phase 1 first-in-human study exploring optimal dosing of OBX-115 + ACZ in this particularly **high unmet need population**, the OBX-115 regimen resulted in:
  - **Positively differentiated safety** from IL2-dependent non-engineered TIL cell therapy
  - **Promising efficacy profile without IL2 administration, including a 44% ORR across all dose-level cohorts (n=9)**
    - 50% ORR in patients receiving OBX-115 dose >30 × 10^9 cells
    - 100% disease control rate
    - Tumor burden reduction in all patients
    - 75% PFS at 24 weeks

Planned regimen optimization is **ongoing in a Phase 1/2 multicenter study**, currently enrolling patients with advanced melanoma and metastatic non-small cell lung cancer (NCT06060613 [Agni-01]; **Poster TPS9599**)

ACZ, acetazolamide; IL2, interleukin 2; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; TIL, tumor-infiltrating lymphocyte; TKI, tyrosine kinase inhibitor.

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