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Obsidian Therapeutics

FEBRUARY 2025

OBX-115: Patient-centric TIL Cell Therapy

- **Differentiated safety** profile
- 44% ORR[1]: **Deep responses** without IL2
- **Outpatient ACZ re-dosing** safe and well-tolerated
- **Convenient TTP**: Core needle biopsy feasible
- Compatible with **cryopreservation**
- Potential for **low-dose LD**

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1. Amaria RN et al. ASCO 2024 (Abstract 9515).
ACZ, acetazolamide. LD, lymphodepletion. TTP, tumor tissue procurement.

OBX-115 is a Differentiated TIL Cell Therapy Product

Critical manufacturing attributes drive superior TIL cell therapy product with distinct patient advantages

Engineered TIL / Proprietary Manufacturing

Engineered with regulatable mbIL15

Optimized, proprietary pre-REP and REP

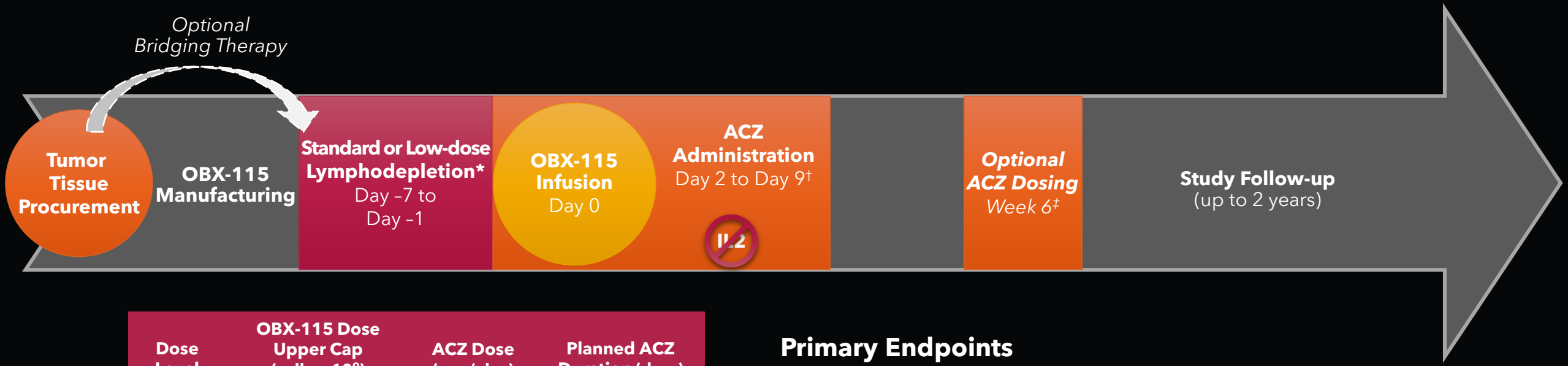
REP: ACZ (no IL2) & iFeeder cells (expressing IL21 & 4-1BBL)

Product and Patient-centric Advantages

- mbIL15 enables potential for **reduced-dose lymphodepletion**
- ACZ-driven mbIL15 expression eliminates need for IL2, thus **improving safety profile**
- ACZ-driven pulsatile redosing allows for **reactivation** of persistent, antigen-exposed OBX-115 TIL
- Skews product toward CD8+ **cytotoxic**, **stem-like** T cells with **memory phenotype** for greater efficacy
- Flexible tumor tissue procurement procedure, compatible with **core needle biopsy**

First-in-human Study Design (NCT05470283)

Advanced melanoma relapsed and/or refractory to ICI therapy



Dose Level	OBX-115 Dose Upper Cap (cells × 10^9)	ACZ Dose (mg / day)	Planned ACZ Duration (days)
1	150	500	365
Dose de-escalation implemented based on Patient 1 OBX-115 cell expansion and transient AEs			
–1	30	125	7
2	100	125	7
2	100	125	10

Primary Endpoints

- Safety, tolerability, and dose identification
  - Incidence and severity of AEs, SAEs, and DLTs

Key Secondary Endpoints

- Investigator-assessed ORR, DOR, and PFS

*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.

Amaria RN et al. ASCO 2024 (Abstract 9515).

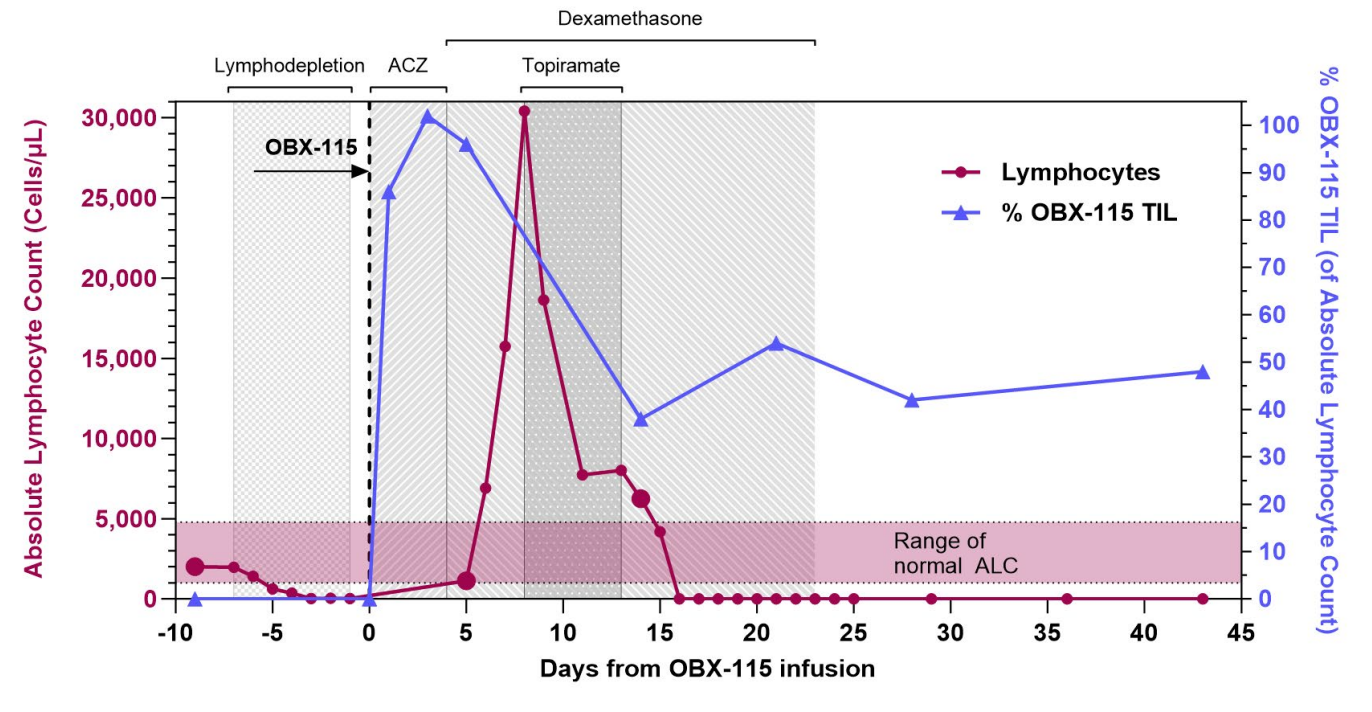
Case Study: Patient Experience Validates cytoDRiVE Platform

ALC Kinetics

Lymphodepletion:
ALC decreases to nearly 0, as expected

Expansion:
Rapid rise in ALC reflects ACZ-driven expansion of OBX-115

Contraction:
Withdrawal of ACZ leads to ALC contraction



OBX-115 TIL Frequency

Pre-infusion, mbIL15 transgene **not detected** in peripheral blood

During lymphopenic phase, OBX-115 represented **86%** of PBMCs (Day 1), peaking at **~100%** (Day 3)

During lymphocyte recovery and proliferation, OBX-115 TIL persisted at **>38%** of PBMCs through Day 42

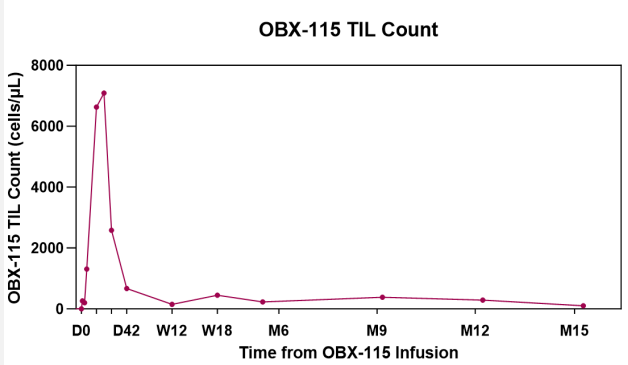
ACZ, acetazolamide; ALC, absolute lymphocyte count; CAR, chimeric antigen receptor; D, day; ddPCR, droplet digital PCR; mbIL15, membrane-bound IL15; PBMC, peripheral blood mononuclear cell; TIL, tumor-infiltrating lymphocytes.

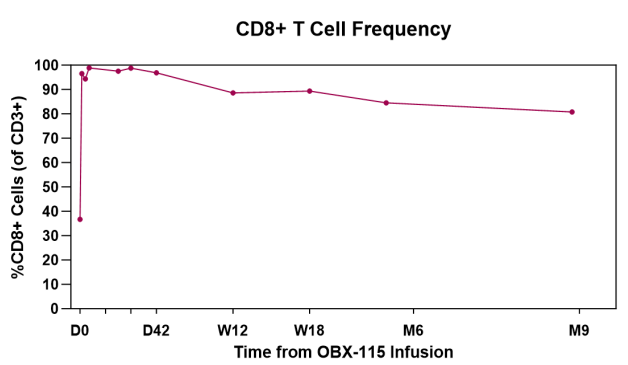
Hari P. SITC 2024 (TIL Symposium Presentation).

Case Study: Patient Experience Validates cytoDRiVE Platform

Peripheral Blood Analysis

OBX-115 TIL Count:
OBX-115 TIL **persisted** in peripheral blood through Month 15 (100 cells/µL)



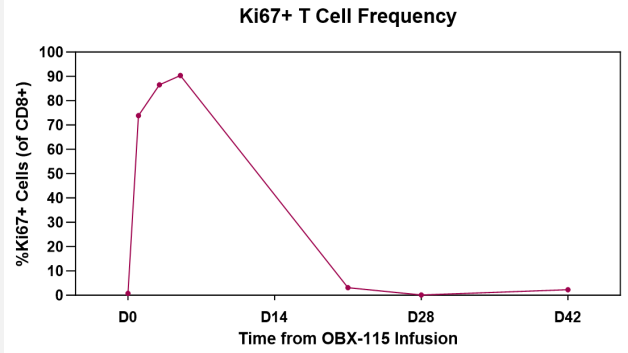


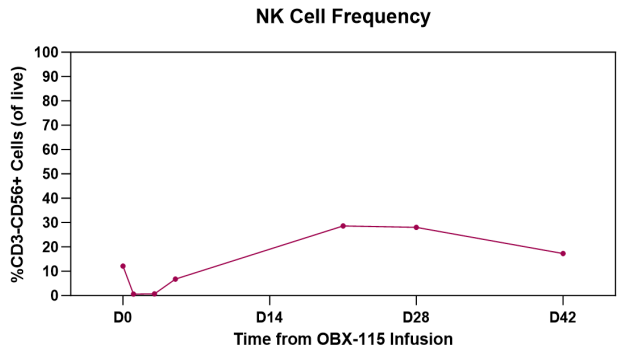
CD8+ T Cell Frequency:
Peripheral blood was **enriched for CD8+** T cells post-infusion

- ✓ **Day 0: ~37%**
- ✓ Through Day 42: >90%
- ✓ **Through Month 9: >80%**

Ki67+ T Cell Frequency:
OBX-115 TIL **proliferated** during ACZ administration period

- ✓ **Day 0: <1%**
- ✓ **Day 5: 90%**
- ✓ Day 21: 3%
- ✓ Month 9: 1%





NK Cell Frequency:
NK cells increased post-infusion, consistent with **trans-activation of endogenous immune cells**

ACZ, acetazolamide; NK, natural killer; TIL, tumor-infiltrating lymphocytes.

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Hari P. SITC 2024 (TIL Symposium Presentation).

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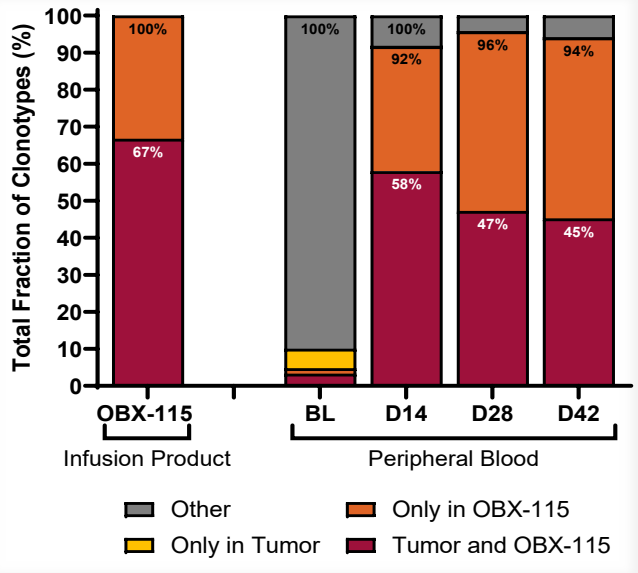
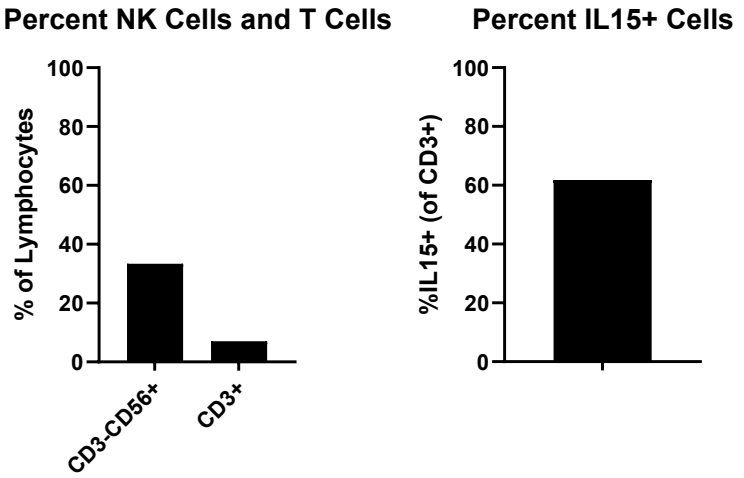
Case Study: OBX-115 TIL Remodel the TCR Clonotype Repertoire, Infiltrate Tumors, and Enrich for Tumor-specific TCR Clones

Tumor-derived, **antigen-specific T cells** in the OBX-115 infusion product **infiltrate, expand**, and **enrich** in the post-treatment peripheral blood

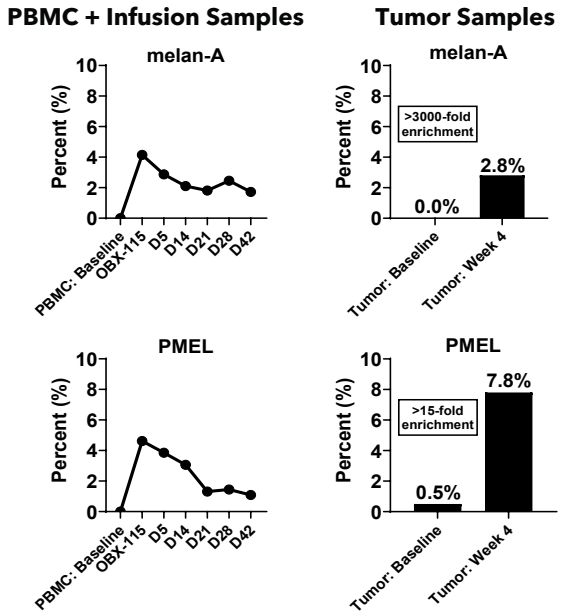


Week 4 Tumor Biopsy

- **NK cells**: 33% of lymphocytes were CD3-CD56+
- **OBX-115**: 62% of CD3+ cells were IL15+



OBX-115 Tumor-specific TCR Clones Expand in PBMC and are Enriched in Tumor Post-infusion



BL, Baseline; D, Day; PBMC, peripheral blood mononuclear cell; NK, natural killer; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocytes.

Hari P. SITC 2024 (TIL Symposium Presentation).

Summary: Positive Initial Clinical Data for OBX-115 in Advanced or Metastatic Melanoma Post-anti–PD-1 Therapy[1]

Efficacy (RECIST v1.1 [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%

- ✓ Patients with advanced and substantially pre-treated disease
  - All had received prior anti–PD-1 and anti–CTLA-4 therapy‡
  - 80% had anti–PD-1 primary-resistant disease
- ✓ Median study follow up = 29.5 weeks
- ✓ **Differentiated safety**§: No dose-limiting toxicities or Grade 4+ non-hematologic events have been observed
- ✓ 75% 6-month PFS: all patients alive at data cutoff
- ✓ Translational data confirm successful **platform validation**

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1. Amaria RN et al. ASCO 2024 (Abstract 9515). *Data cutoff: April 4, 2024; per-protocol efficacy analysis set (n=9). One patient in 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. ‡ 9 (90.0%) patients received combination anti–CTLA-4 and anti–PD-1 therapy. § Positively differentiated safety compared with non-engineered TIL cell therapy.
CTLA-4, cytotoxic T-lymphocyte–associated protein 4; PD-1, programmed cell death protein-1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Patients with Heavily Pre-treated Recalcitrant Disease

Baseline Patient and Disease Characteristics	All Patients (N=10)
Mutation status, n (%)	
BRAF-mutant	3 (30.0)
NRAS-mutant	2 (20.0)
GNA11-mutant*	1 (10.0)
Target lesion SOD, median (range), mm	39.9 (11.7–82.8)
Brain lesions with prior treatment, n (%)	2 (20.0)
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 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)**
Unknown	1 (10.0)
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).
*Rare uveal-equivalent subtype; 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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Amaria RN et al. ASCO 2024 (Abstract 9515).

OBX-115 Has a 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
- Grade 1-2 uveitis / iritis in 4 patients consistent with on-target, off-tumor effect

*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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Amaria RN et al. ASCO 2024 (Abstract 9515).

Safety: OBX-115 Has a Differentiated Safety Profile Compared to High-dose IL2-dependent Non-engineered TIL Cell Therapy

Event	Lifileucel (N=156)[1]*	OBX-115 N=10[2†]
Treatment-related mortality (TRM)	7.5%	0
Reported Grade ≥3 Non-hematologic TEAEs		
Febrile neutropenia	47%	0
Infections / Infestations	14%	0
Hypoxia	12%	0
Hypotension	11%	0
Pyrexia	10%	0
Rash	10%	0
Chills	5%	0
Capillary leak	5%	0
Abdominal pain	Not reported	10%
Increased alanine aminotransferase	Not reported	10%
Syncope	Not reported	10%

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*Grade ≥3 reported in >10% of patients. †No Grade 4 events were observed.
1. AMTAGVI Prescribing Information. 2. Amaria RN et al. ASCO 2024 (Abstract 9515).
Abbreviations: TEAE, treatment-emergent adverse event. SAE, serious adverse event. ICU, intensive care unit. DLT, dose-limiting toxicity.

OBX-115: Promising Efficacy Profile Without IL2 Administration

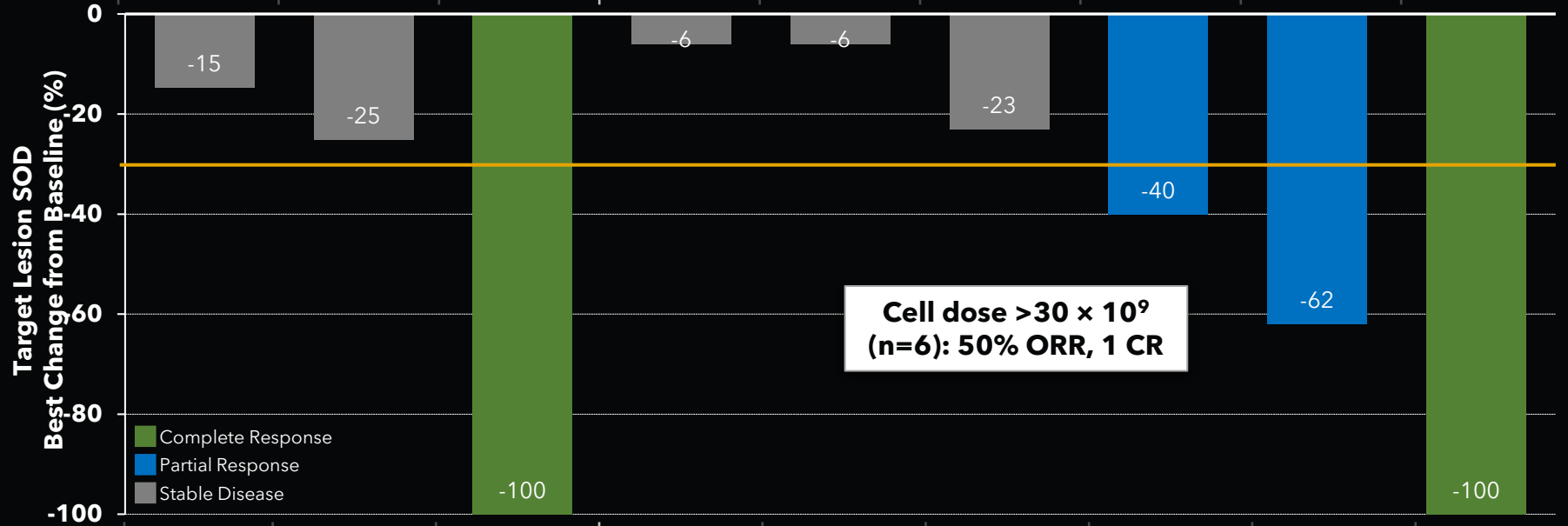
	Per-protocol Efficacy Cohort (n=9) †
Objective response rate, n (%)	**4 (44.4)**
Complete response	**2 (22.2)**
Partial response	2 (22.2)
Stable disease ≥12 weeks	5 (55.6)
Progressive disease	0
Disease control rate,* n (%)	9 (100)
Progression-free survival at 24 weeks	75%

*Defined as stable disease (or better) for ≥12 weeks post-infusion. † Per-protocol high-risk cohort (n=1, *GNA11*-mutated rare uveal-equivalent subtype): best response of progressive disease
CR, complete response; IL2, interleukin 2; ORR, objective response rate.

Amaria RN et al. ASCO 2024 (Abstract 9515).

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+



- **6-month PFS: 75%**
- **100% survival**
- **All patients derived benefit**

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

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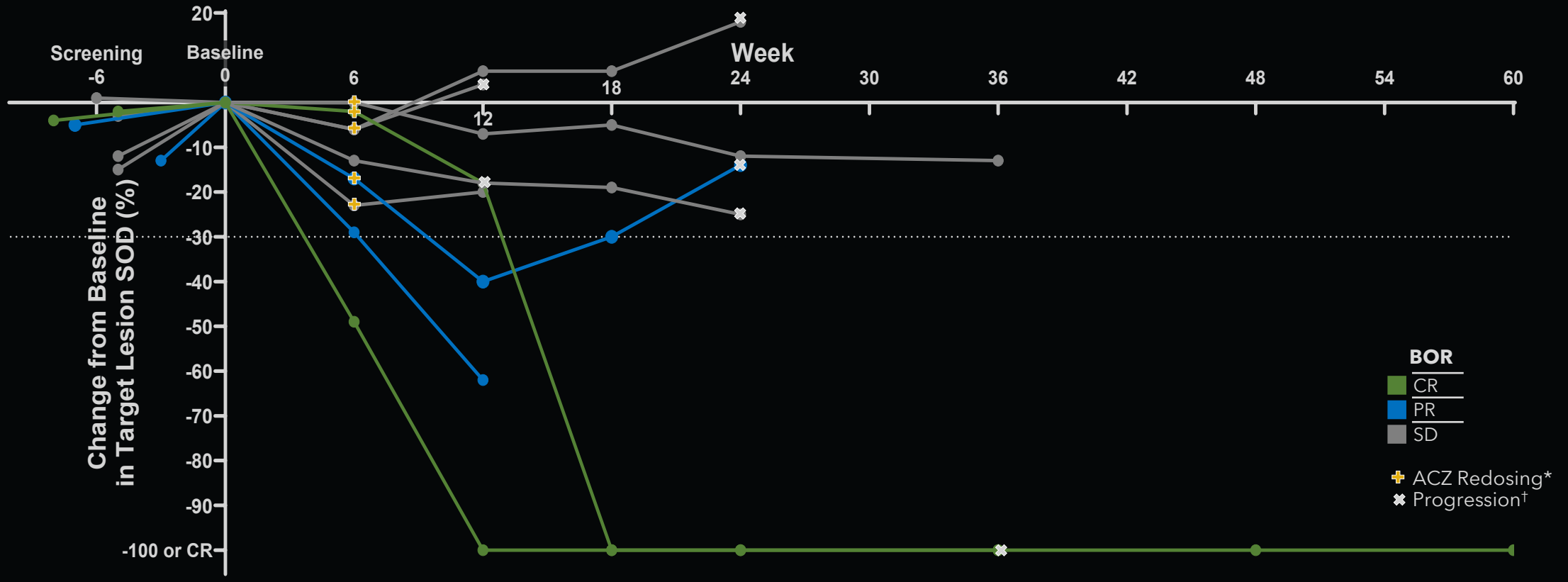
*Patient received cryopreserved OBX-115. † Patients with isolated brain progression did not receive systemic treatment post-progression.
‡"+" indicates no progression at latest follow-up.
CR, complete response; ORR, objective response rate; SOD, sum of diameters; TKI, tyrosine kinase inhibitor; wks,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

Amaria RN et al. ASCO 2024 (Abstract 9515).

OBX-115: Deepening, Durable Benefit Without IL2 in Patients with Substantially Advanced and Pre-treated Disease

% Change from Baseline in Target Lesion SOD (n=9)



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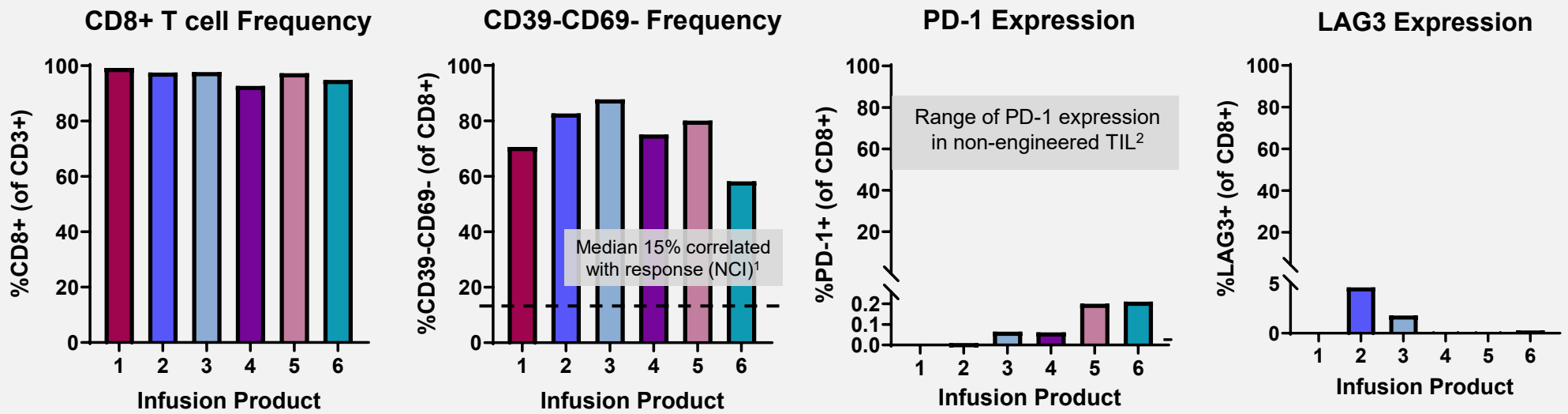
*ACZ redosing in Patients 3, 4, 5, 6, 7, 9. †Progression in Patients 2 (Wk 24), 3 (Wk 36, 5 (Wk 24), 6 (Wk 24), 7 (Wk 12), 9 (Wk 12).
ACZ, acetazolamide; BOR, best overall response; CR, complete response; IL2, interleukin 2; PR, partial response; SD, stable disease; SOD, sum of diameters.

OBX-115 Infusion Product: Cytotoxic CD8+ T Cells, "Stem-like" Phenotype and Minimally Exhausted

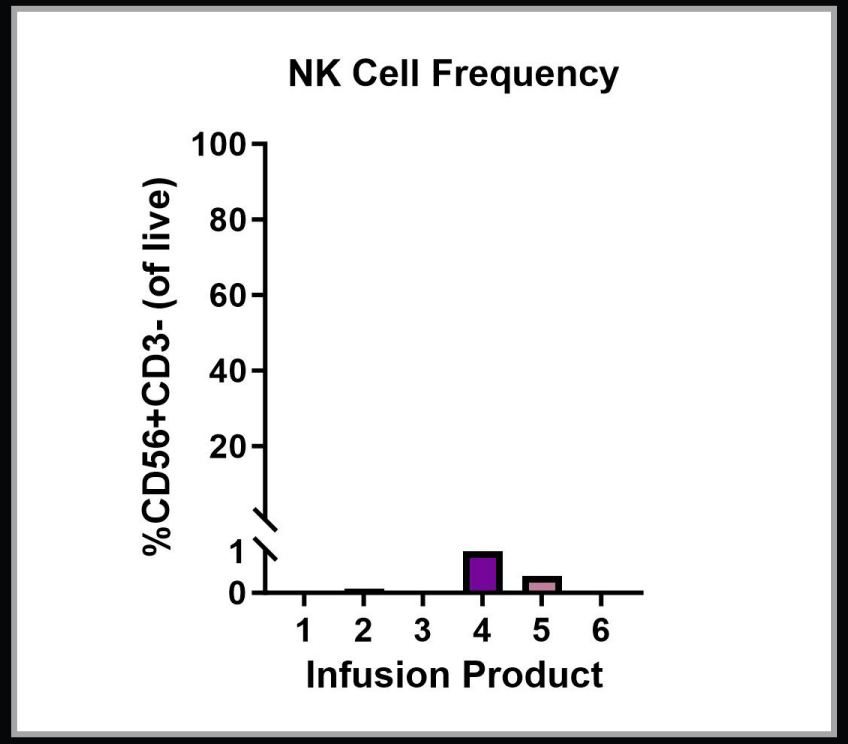


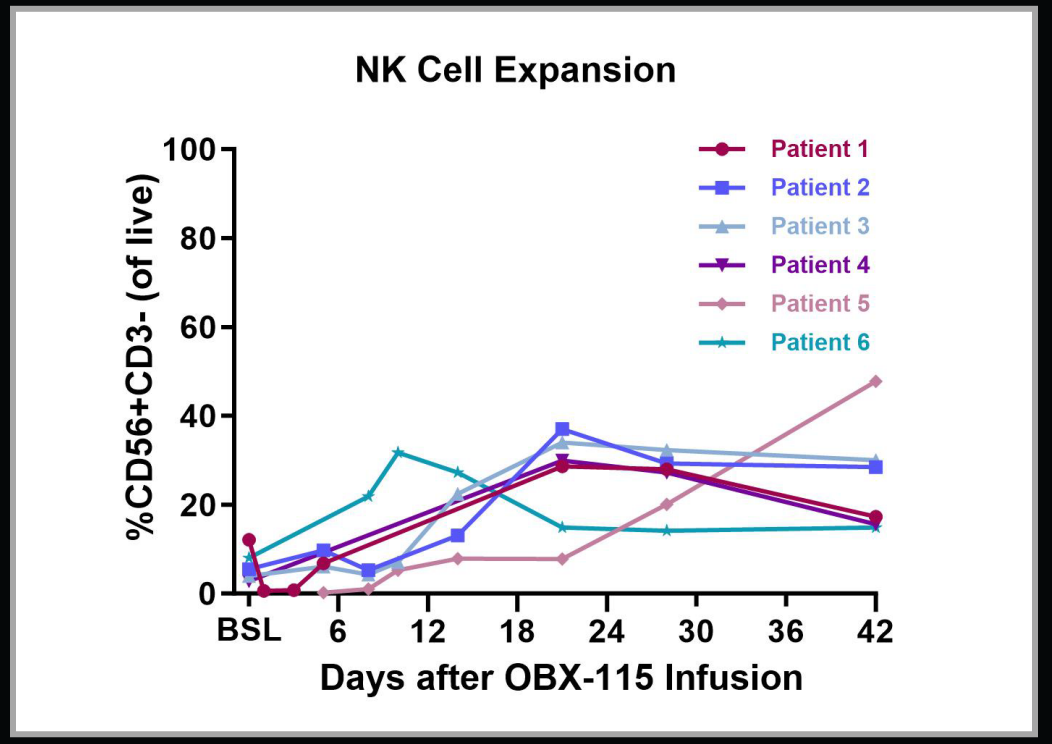
mbIL15 engineering paired with proprietary manufacturing process yields positively differentiated infusion product

Translational data available from first 6 infused patients (1–6).
1 Krishna et al Science. 2020 Dec 11;370(6522).
2. https://www.iovance.com/uploads/Onimus-et-al_Fresh-vs-Frozen-ASTCT2022_Poster_15April22_FINAL.pdf.
LAG-3, lymphocyte-activation gene 3; PD-1, programmed cell death protein-1.

Bernatchez C et al. ISCT 2024 (Abstract 909).

OBX-115 Promotes Expansion of Endogenous Immune Cells





Despite low levels of NK cells in OBX-115 infusion product (≤1%),
NK cells expanded in peripheral blood post-infusion

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Translational data available from first 6 infused patients #1-6.
PBMC, peripheral blood mononuclear cells.

Amaria RN et al. ASCO 2024 (Abstract 9515).

OBX-115: Favorable 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.

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Bernatchez C et al. ISCT 2024 (Abstract 909).

Ongoing Multicenter Trial is Expanding OBX-115 into More Centers and NSCLC Indication

Agni-01 Phase 1/2 Study (NCT06060613)

Adult patients with **advanced, post-ICI melanoma**

OR

r/r metastatic NSCLC*

Phase 1: Identify Recommended Phase 2 Dose (RP2D) of OBX-115 + ACZ

- Three dose levels evaluated
- Regimen optimized across 3 components:

Melanoma RP2D declared Sep 2024
NSCLC RP2D expected early 2025

Phase 2: Evaluate clinical profile of OBX-115 + ACZ at RP2D in homogeneous populations

- Separate cohorts for melanoma & NSCLC
- ~20–40 patients per cohort

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*Prior treatment should include an approved ICI-based regimen and/or an approved targeted therapy in appropriate patients.
ACZ, acetazolamide; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; RP2D, recommended phase 2 dose.

Hari P. SITC 2024 (TIL Symposium Presentation).

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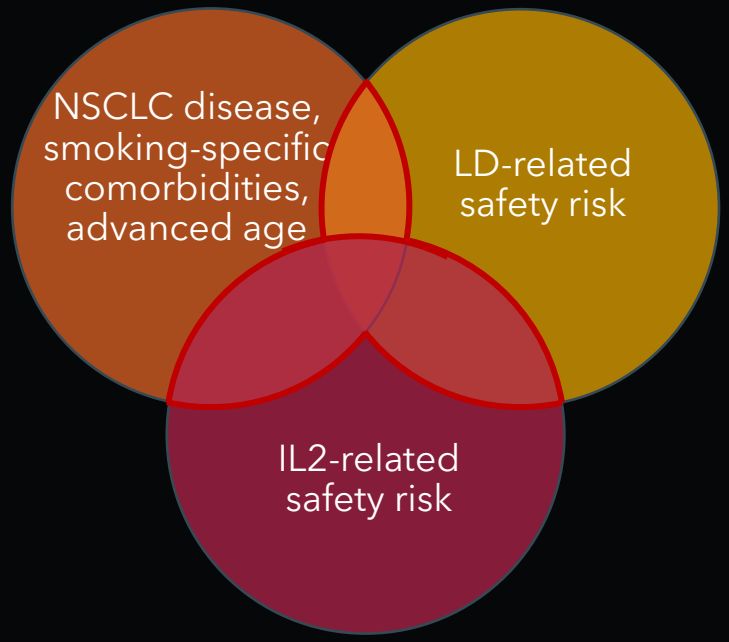
OBX-115 Solution Has Potential to Overcome Key Barriers Facing Non-engineered TIL Cell Therapy in NSCLC

Significant Toxicity Risk for Non-engineered TIL + High-dose IL2 [1,2]



OBX-115 Solution

Designed to Improve Safety Profile

- ✓**IL2-free** regimen
- ✓**Core needle biopsy** available
- ✓**Low-dose lymphodepletion**

Product & Biological Advantages

- ✓**Wide TCR repertoire, CD8+ enriched** product
- ✓**ACZ redosing** opportunity to extend TIL functionality
- ✓**mbIL15** drives memory phenotype and enhanced persistence
- ✓**NK cell** expansion could prevent tumor escape from MHC loss
- ✓**IL15** has activity in ICI-resistant NSCLC[3]

1. Gr 5 (7.1%) and Gr 3/4 (96.4%) TEAE reported (Schoenfeld et al., SITC 2021 Abstract 458). 2. Clinical hold attributed to lymphodepletion regimen using high-dose cyclophosphamide 60 mg/kg × 2 (Iovance Press Release dated Dec 12, 2023). 3. Wrangle JM et al. J Clin Oncol 2021 39:15_suppl 2596.
ACZ, acetazolamide; ICI, immune checkpoint inhibitor; IL2, interleukin 2; LD, lymphodepletion; mbIL15, membrane-bound interleukin 15; MHC, major histocompatibility complex; NK, natural killer; NSCLC, non-small cell lung cancer; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocytes.

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Hari P. SITC 2024 (TIL Symposium Presentation).

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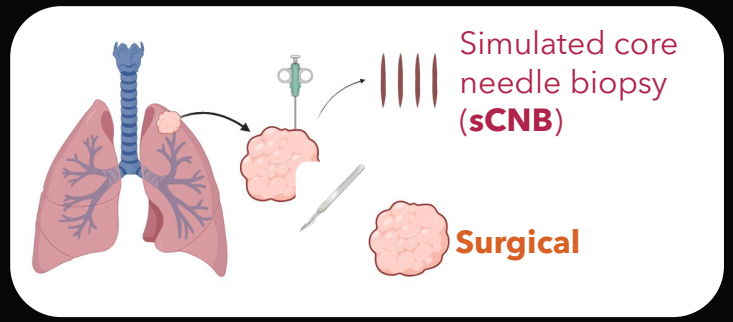
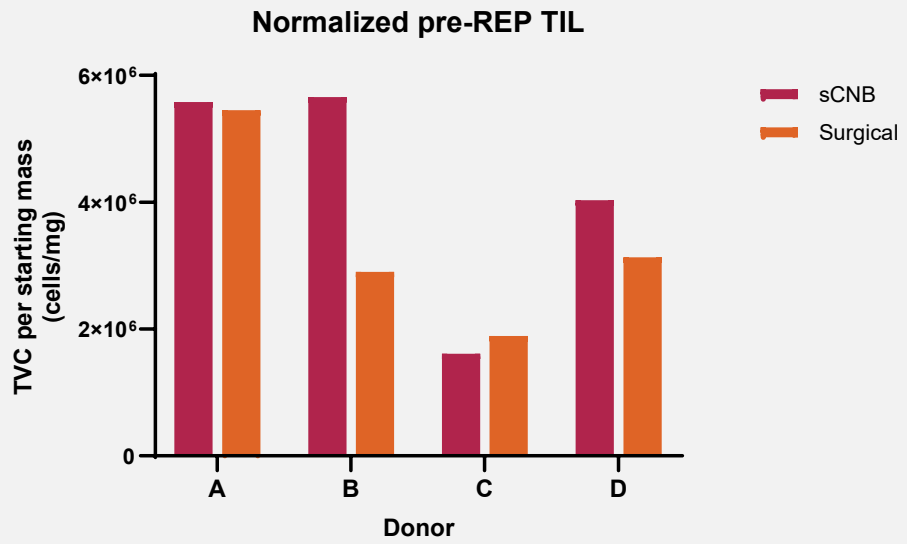
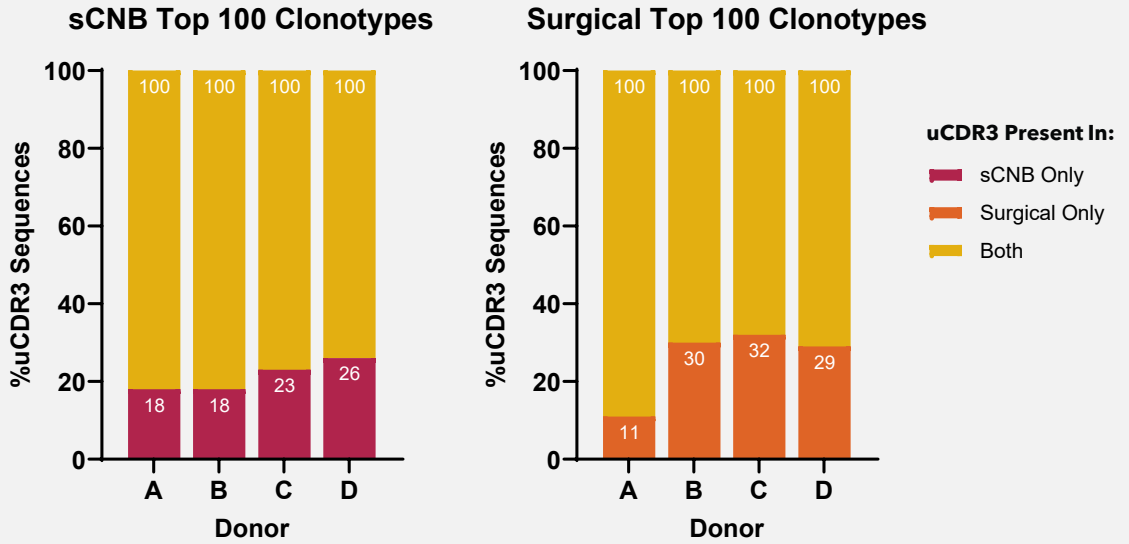
Core Needle Biopsy (CNB) Tumor Tissue Procurement in NSCLC



Similar OBX-115 Expansion During Manufacturing (pre-REP and REP)



Similar OBX-115 TCR Repertoire*



*Number of unique clonotypes detected in each sample group across all donors was within the expected range and was not statistically significant ($p < 0.385$; paired two-tail T test).
REP, rapid expansion protocol; sCNB, simulated core needle biopsy; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocytes; TVC, total viable cells; uCDR3, unique CDR3 sequences.

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Hari P. SITC 2024 (TIL Symposium Presentation).
Bott M, et al. SITC 2024 (Abstract 444).

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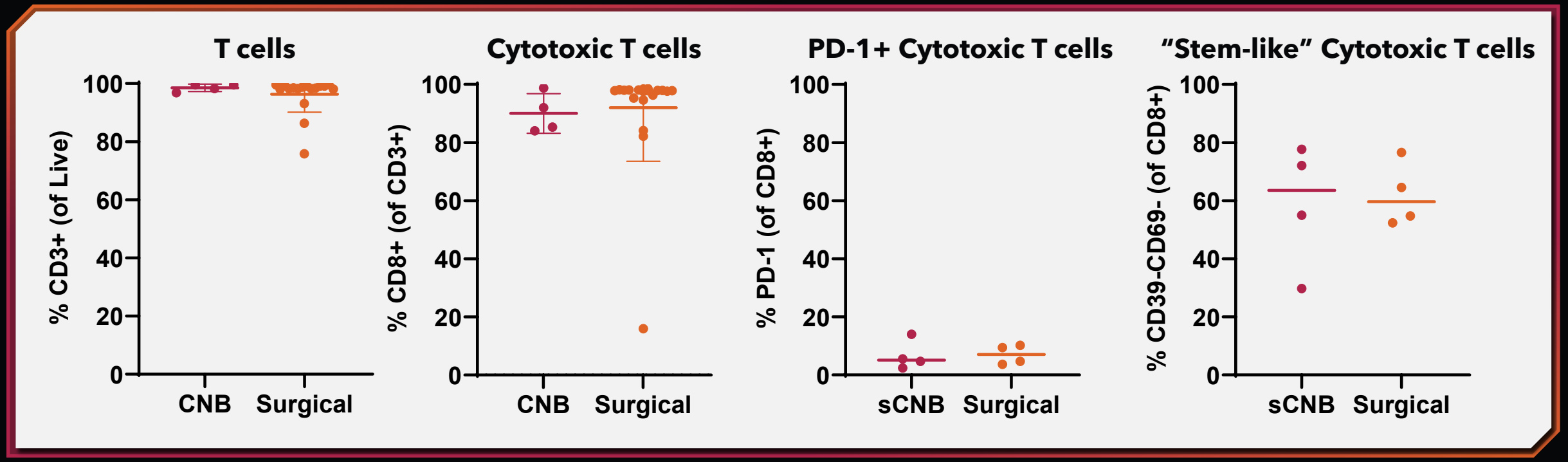
OBX-115 Drug Product Phenotypic Attributes

CNB/sCNB vs Surgical Tumor Tissue Procurement



OBX-115 drug product manufactured from surgical and CNB (or sCNB) tumor tissue had **similar positive phenotypic attributes***

CNB, core needle biopsy; PD-1, programmed cell death protein 1; sCNB, simulated core needle biopsy.

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Hari P. SITC 2024 (TIL Symposium Presentation).
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