OBX-115 engineered tumor-infiltrating lymphocyte (TIL) cell therapy with regulatable membrane-bound IL15 (mbIL15) in patients with immune checkpoint inhibitor (ICI)-resistant advanced melanoma

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Key Takeaway Points/Conclusions

1

OBX-115 TIL are engineered to express mbIL15 regulated by acetazolamide via a drug-responsive domain, abrogating the need for IL2

2

OBX-115 is compatible with low-dose lymphodepletion and has a positively differentiated safety profile

3

At RP2D, OBX-115 can induce deep and durable responses in patients with ICI-resistant advanced melanoma

ICI, immune checkpoint inhibitors; IL2, interleukin 2; mbIL15, membrane-bound interleukin 15; RP2D, recommended phase 2 dose; TIL, tumor-infiltrating lymphocytes.

Background

Non-engineered TIL cell therapy is approved in the unmet-need post-ICI advanced melanoma setting,[1] but requires high-dose IL2 and standard-dose lymphodepletion

- High-dose IL2 has well-described toxicity limiting patient eligibility
- The regimen is associated with a treatment-related mortality rate of 7.5%[1]

OBX-115 TIL are engineered to express regulatable mbIL15 to support TIL expansion and persistence, abrogating the need for IL2

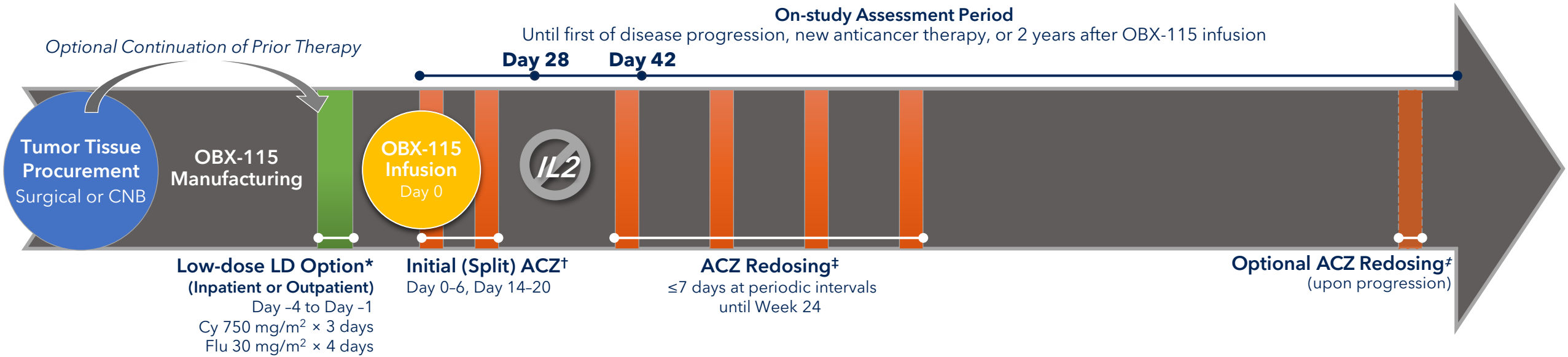
- mbIL15 expression is regulated via a drug-responsive domain (DRD) using the FDA-approved small-molecule drug acetazolamide (ACZ)
- ACZ is well-tolerated and can be redosed to re-activate and re-expand persistent OBX-115 TIL[2]

Single-center phase 1 data of predominantly fresh OBX-115 in patients with ICI-resistant advanced melanoma demonstrated differentiated early safety and promising efficacy (NCT05470283)[3]

We report the initial safety and efficacy data from the multicenter phase 1/2 Agni-01 trial evaluating cryopreserved OBX-115 in patients with ICI-resistant advanced melanoma

1. AMTAGVI Prescribing Information (n=73). Accessed April 1, 2025. 2. Burga R et al, *Molecular Therapy* 2025. DOI: 10.1016/j.ymthe.2025.04.031. 3. Amaria RN et al, ASCO 2024 (Abstract 9515).
ACZ, acetazolamide; DRD, drug-responsive domain; ICI, immune checkpoint inhibitor; IL2, interleukin 2; mbIL15, membrane-bound interleukin 15; TIL, tumor-infiltrating lymphocytes.

Agni-01 Study Design (NCT06060613)



Key Eligibility Criteria

- Advanced melanoma relapsed and/or refractory to ICI therapy
- No upper age limit
- ≥1 lesion suitable for tumor tissue procurement (TTP) for manufacturing and ≥1 remaining lesion amenable to RECIST v1.1 response assessment
- Tumor tissue procurement by core needle biopsy (CNB) feasible

Primary Endpoints

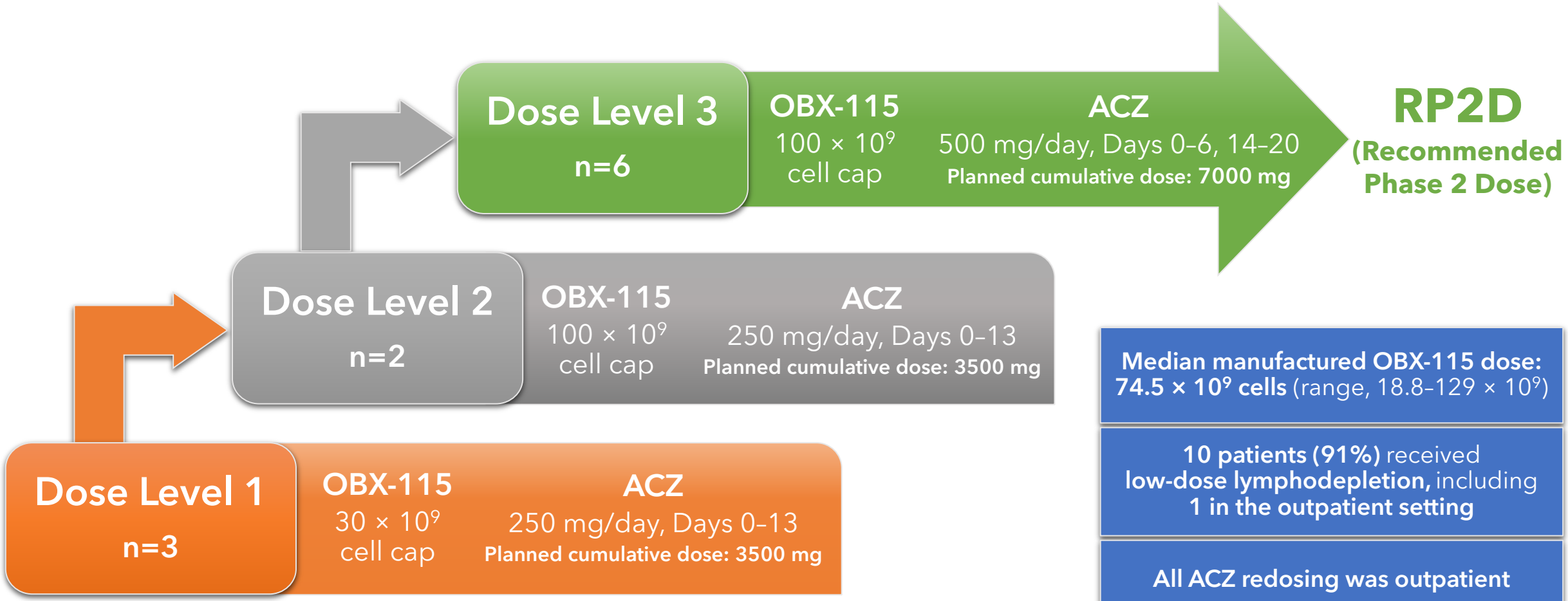
- Safety, tolerability, and identification of recommended dose of the OBX-115 regimen
  - Incidence and severity of AEs, SAEs, and DLTs

Key Secondary Endpoints

- Investigator-assessed ORR, DOR, PFS, and OS

*May be administered in the inpatient or outpatient setting, per institutional standard. Low-dose LD administered to all but 1 patient, who received standard-dose LD (7-day regimen: Cy 60 mg/kg × 2 days, Flu 25 mg/m² × 5 days).
†ACZ is administered at cohort-defined doses once daily starting day of OBX-115 infusion for ≤14 days; at Dose Level 3, initial ACZ dosing was split into two ≤7-day periods within 28 days (Day 0–6 or until ALC ≥5000 cells/µL whichever is earlier, and restarting between Day 14 and 21).
‡Additional ACZ dosing for ≤7 days at periodic intervals until Week 24, and upon progression when new anticancer therapy is not immediately warranted.
ACZ, acetazolamide; AE, adverse event; CNB, core needle biopsy; Cy, cyclophosphamide; DLT, dose-limiting toxicity; DOR, duration of response; Flu, fludarabine; ICI, immune checkpoint inhibitor; LD, lymphodepletion; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TTP, tumor tissue procurement.

Protocol-defined Dose-escalation Strategy



Median manufactured OBX-115 dose: 74.5 × 10^9 cells (range, 18.8–129 × 10^9)

10 patients (91%) received **low-dose lymphodepletion,** including **1 in the outpatient setting**

All ACZ redosing was outpatient

ACZ, acetazolamide; RP2D, recommended phase 2 dose.

Patients Had Advanced ICI-resistant Disease

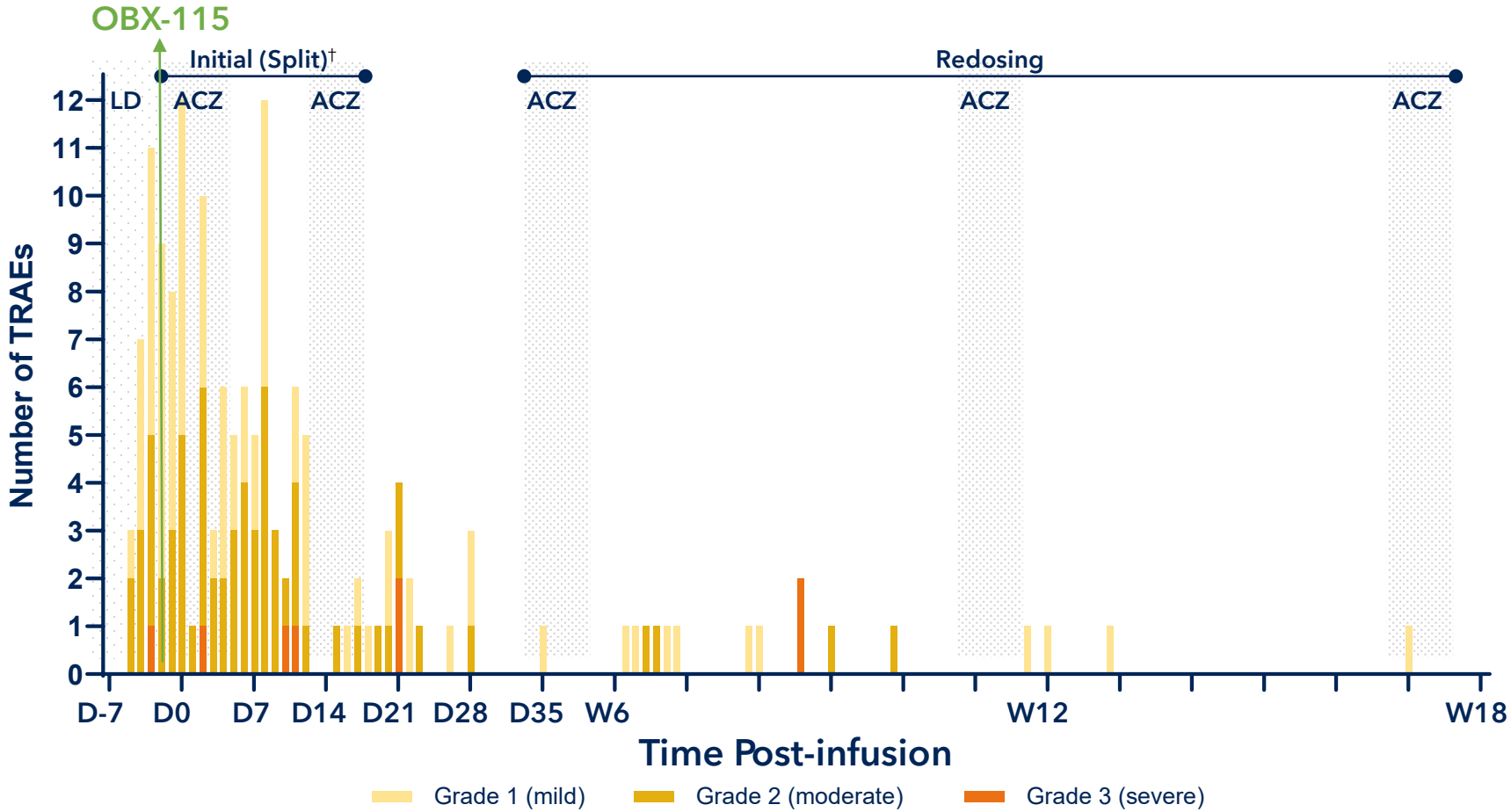
Baseline Patient and Disease Characteristics	All Patients (N=11)
Age, median (range), years	**52 (27–78)**
Sex, n (%)	
Female	4 (36)
Mutation status, n (%)	
BRAF V600-mutant	4 (36)
NRAS-mutant	3 (27)
GNA11-mutant (non-uveal *GNA11* subtype)	1 (9)
Target lesion SOD, mean (SD), mm	94.8 (57)
Brain metastases, n (%)	**3 (27)**
Target lesion site(s), n (%)	
Skin / subcutaneous	3 (27)
Lymph node	8 (73)
Visceral	5 (45)
Soft tissue	2 (18)
Other*	2 (18)
ECOG PS, n (%)	
0	8 (73)
1	3 (27)
LDH >ULN, n (%)	4 (36)

Treatment Characteristics	All Patients (N=11)
Lines of prior systemic therapy, median (range)	3 (1–5)
Lines of prior ICI therapy	2 (1–5)
Prior (neo)adjuvant therapy, n (%)	
Anti–PD-1	5 (45)
BRAF± MEK TKI	1 (9)
Prior systemic therapy in metastatic setting, n (%)	
Anti–PD-1	**11 (100)**
Anti–CTLA-4	**9 (82)**
Anti–PD-1 + anti–CTLA-4 combination	9 (82)
Anti–PD-1 + anti-LAG3 combination	6 (55)
BRAF ± MEK TKI	5 (45)
Primary-resistant (SITC criteria), n (%)	
Anti–PD-1[1]	**9 (82)**
Anti–PD-1 + anti–CTLA-4 or anti-LAG3 combination[2]	**8 (73)**

Data cutoff March 26, 2025.
1. Kluger HM et al. *J Immunother Cancer* 2020;8(1). 2. Kluger H et al. *J Immunother Cancer* 2023;11(3).
*"Other" includes 1 patient with pelvic mass and 1 patient with abdominal wall and pleural wall.
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.

Agni-01 Safety

All-grade Nonhematologic TRAEs*



At median 34-week study follow-up:

- No Grade 5 events
- No Grade 4 nonhematologic TRAEs
- 5 patients had Grade 3 nonhematologic TRAEs:
  - Pain (n=1)
  - ALT/AST increase (n=2)
  - Hyponatremia (n=1)
  - Hypokalemia/dehydration (n=1)
- No DLT
- No Grade ≥3 CRS‡
- No ICANS
- No capillary leak syndrome
- No treatment-emergent ICU transfer

*TRAEs are any AEs attributed by investigator as "possibly," "probably," or "definitely" related to one or more component of the treatment regimen (LD, OBX-115, or ACZ)..
†ACZ dosing varied by dose level; DL3 / RP2D dosing shown.
‡Grade 2 CRS (n=2).
ACZ, acetazolamide; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRS, cytokine release syndrome; D, Day; DLT, dose-limiting toxicity; ICANS, immune effector cell-associated neurotoxicity syndrome; ICU, intensive care unit; LD, lymphodepletion; TRAE, treatment-related adverse event; W, Week.

Responses in Anti–PD-1–resistant Advanced Melanoma

	All Patients DL1, DL2, DL3 (N=11)	DL3 / RP2D (N=6)
Objective response rate, n (%)	**4 (36)**	**4 (67)**
Complete response	**1 (9)**	**1 (17)**
Partial response	3 (27)	3 (50)
Stable disease ≥12 weeks	5 (46)	2 (33)
Progressive disease	2 (18)	0
Disease control rate,* n (%)	9 (82)	6 (100)
Duration of response, months (median [95% CI])	**NR (2.6–NR)**	**NR (2.6–NR)**

Dose Level 3 / RP2D

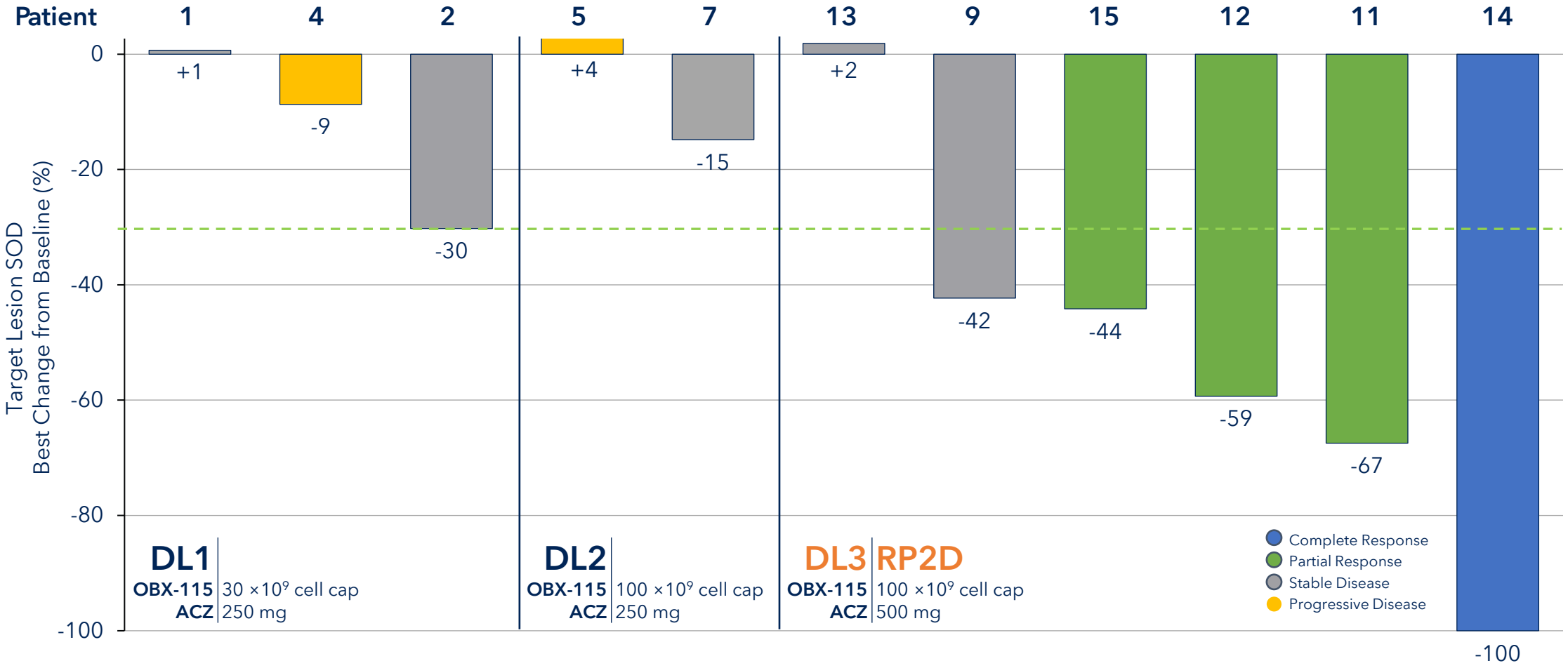
- ORR 67%
- 1 confirmed CR
- DCR 100%

Dose Level 3 / RP2D is being explored further in **Phase 2**

*Defined as stable disease (or better) for ≥12 weeks post-infusion.
CR, complete response; DCR, disease control rate; DL, dose level; NR, not reached; ORR, objective response rate; PD-1, programmed cell death protein-1; RP2D, recommended phase 2 dose.

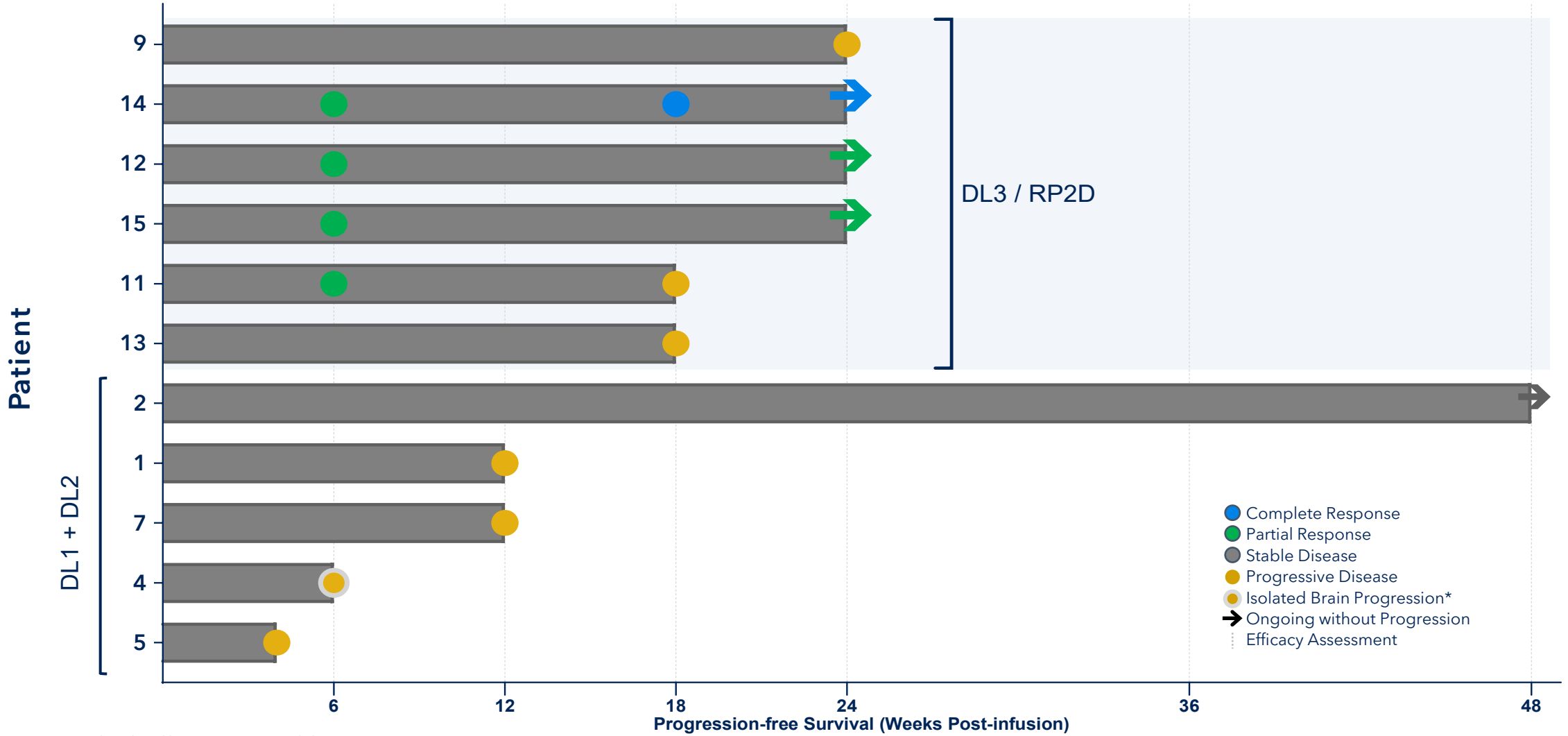
Tumor Burden Reduction in 73% of Patients

83% of Patients Receiving DL3 / RP2D Experienced Tumor Burden Reduction



ACZ, acetazolamide; DL, dose level; RP2D, recommended phase 2 dose; SOD, sum of diameters.

Onset and Duration of Responses with DL3 / RP2D



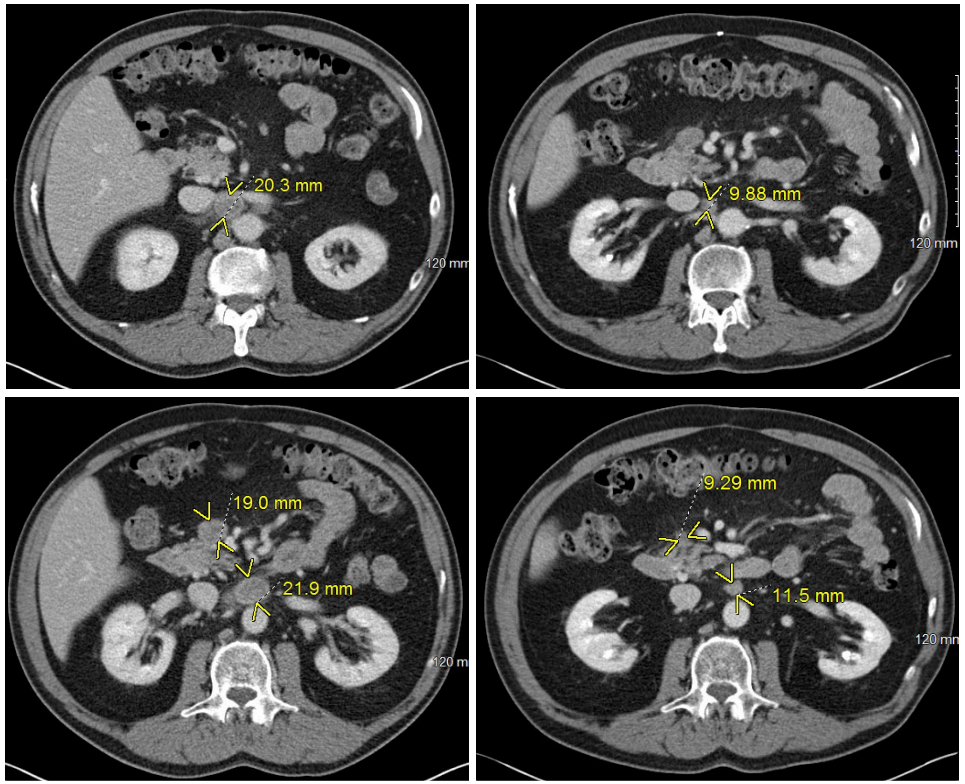
*Patients with isolated brain progression did not receive systemic treatment post-progression.
ACZ was redosed at Week 6 ± 1 week, except patients 2 and 5; redosing beyond Week 6 was introduced with PV 4.0.
ACZ, acetazolamide; DL, dose level; PV, protocol version; RP2D, recommended phase 2 dose.

Deepening and Sustained Reduction in Lesions

67 yr-old (Patient 2)
Low-dose LD
DL1

Stage IV cutaneous melanoma; no driver mutations

Prior: Ipi-Nivo



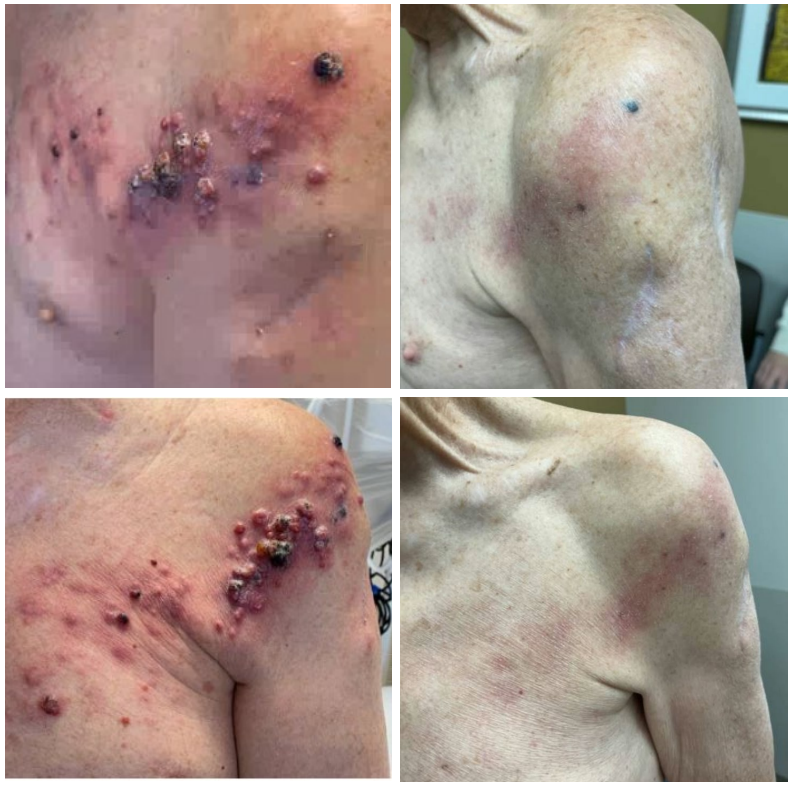
Day -6
Baseline

Week 48
Ongoing SD

74 yr-old (Patient 14)
Low-dose LD
DL3 / RP2D

Stage IV BRAF-mut cutaneous melanoma

Prior: Rela-Nivo BRAFi/MEKi



Day -6
Baseline

Week 18
PR converted to CR
Ongoing at Week 24

Patient 2 Week 48 visit occurred on March 28, 2025 (2 days after data cut).
CR, complete response; DL, dose level; LD, lymphodepletion; PR, partial response; RP2D, recommended phase 2 dose.

Conclusions

- ACZ-driven **regulatable mbIL15 expression** on OBX-115 TIL enables a potentially safer alternative to non-engineered TIL cell therapy and may **broaden the eligible patient population** by:
  - **Elimination of IL2** after cell infusion
  - Enabling a **low-dose lymphodepletion regimen**
- In this particularly **high unmet-need population** of patients with ICI-resistant melanoma, the OBX-115 regimen resulted in a **promising efficacy** profile, including:
  - **67% ORR (1 CR) in 6 patients receiving DL3 / RP2D**
  - **Median DOR not reached** (median 25 weeks follow-up since initial response)
- This ongoing Phase 1/2 multicenter study is **currently enrolling patients** with advanced melanoma and metastatic non-small cell lung cancer (NCT06060613)

See Abstract 9519: Translational data from the single-center first-in-human study

ACZ, acetazolamide; CR, complete response; DL, dose level; DOR, duration of response; IL2, interleukin 2; mbIL15, membrane-bound interleukin 15; ORR, objective response rate; RP2D, recommended phase 2 dose; TIL, tumor-infiltrating lymphocyte.

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