

How Tumor-Infiltrating Lymphocytes are Transforming Cancer Treatment

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Disclosures

Consulting

Adaptimmune, Bristol Myers Squibb, cTRL Therapeutics, Genmab, Immatics, IO Biotech, Iovance Biotherapeutics, Novartis, Merck, Pfizer, Replimune, Resolute Bio

Research Funding (Institutional)

Bristol Myers Squibb, Immatics, Immunocore, Iovance Biotherapeutics, Lyell Immunopharma, Obsidian Therapeutics, Replimune



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Learning Objectives

1. Understand the fundamental principles of TIL cell therapy including the rationale, methodology, and clinical evidence
2. Summarize the renal risk points and management strategies for nephrotoxicity associated with TIL cell therapy
3. Describe emerging strategies in the TIL field

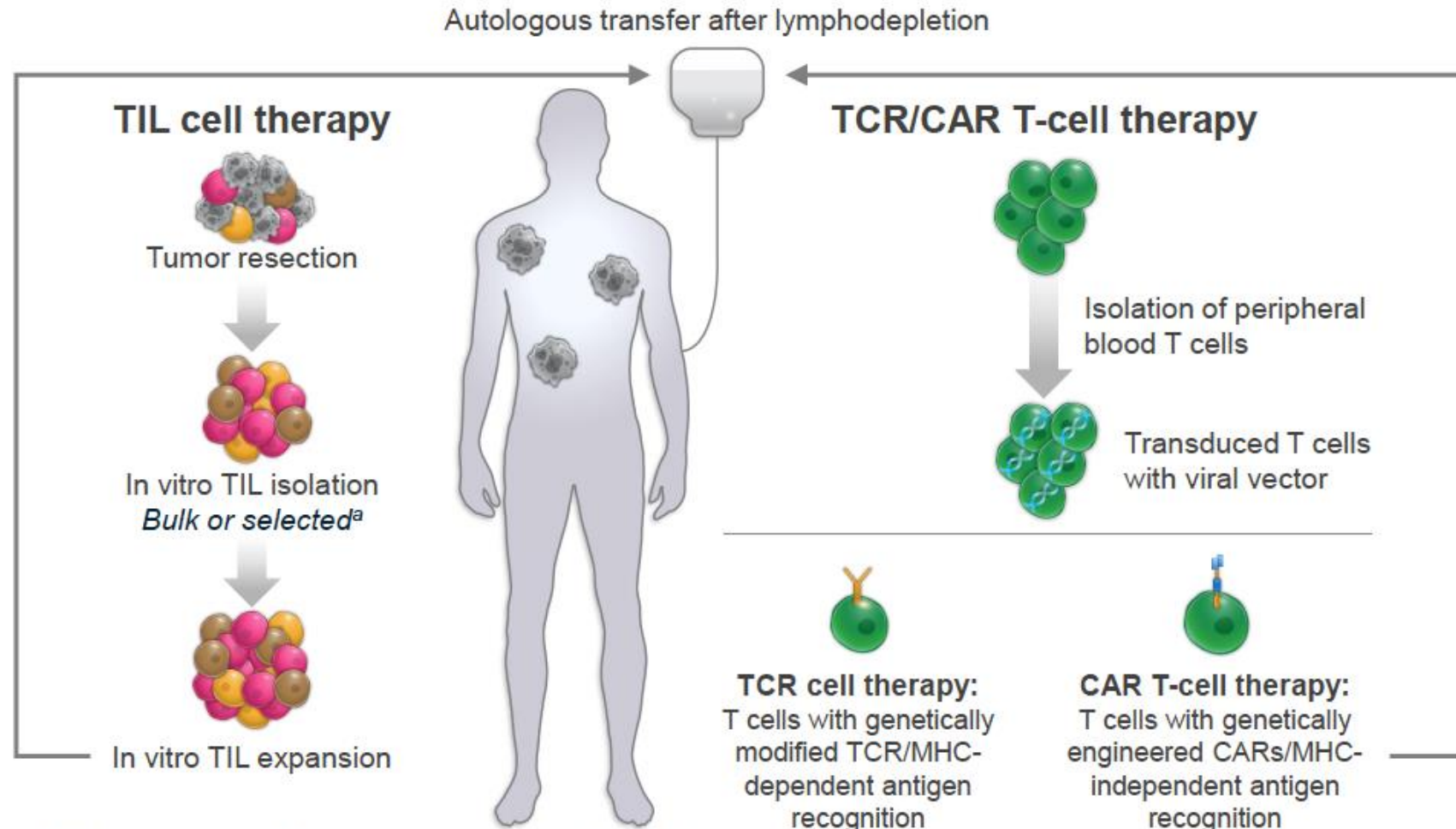


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Clinical Potential of Adoptive Cell Therapy



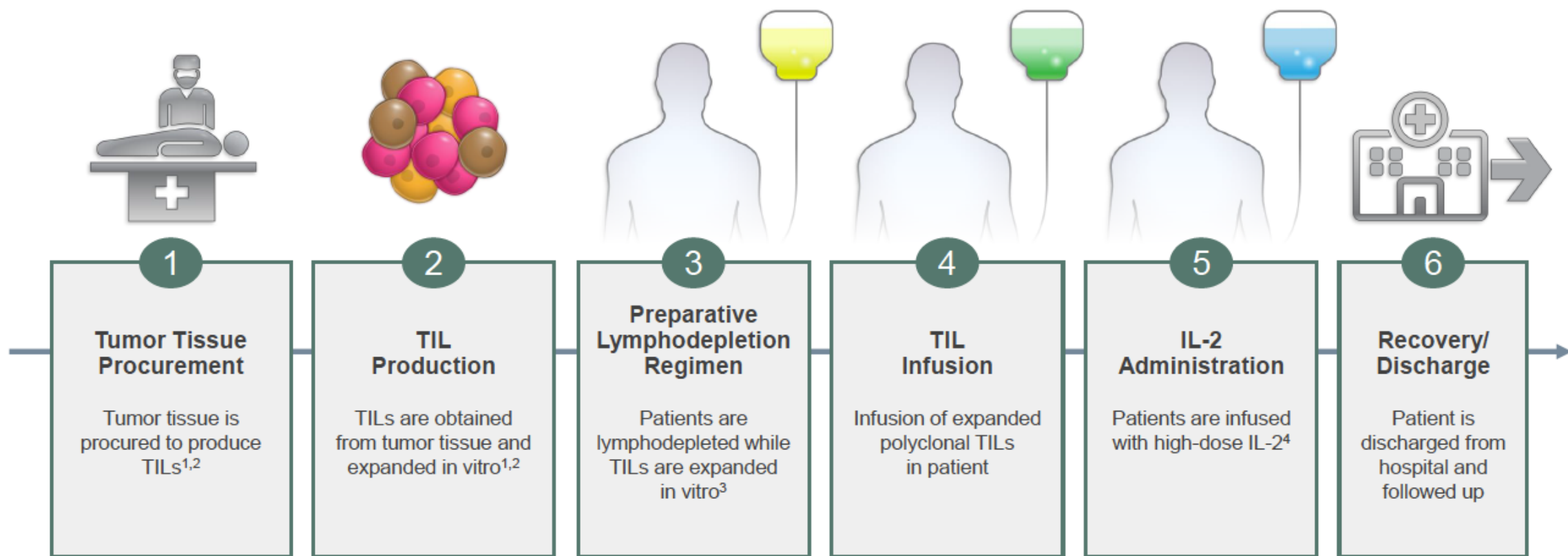
CAR, chimeric antigen receptor; MHC, major histocompatibility complex; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.

^a Bulk TIL refers to non-selected TILs; selected TILs refers to TILs selected against specific antigens.

Rohaani MW, et al. *Virchows Arch.* 2019;474:449.



Overview of the TIL Process

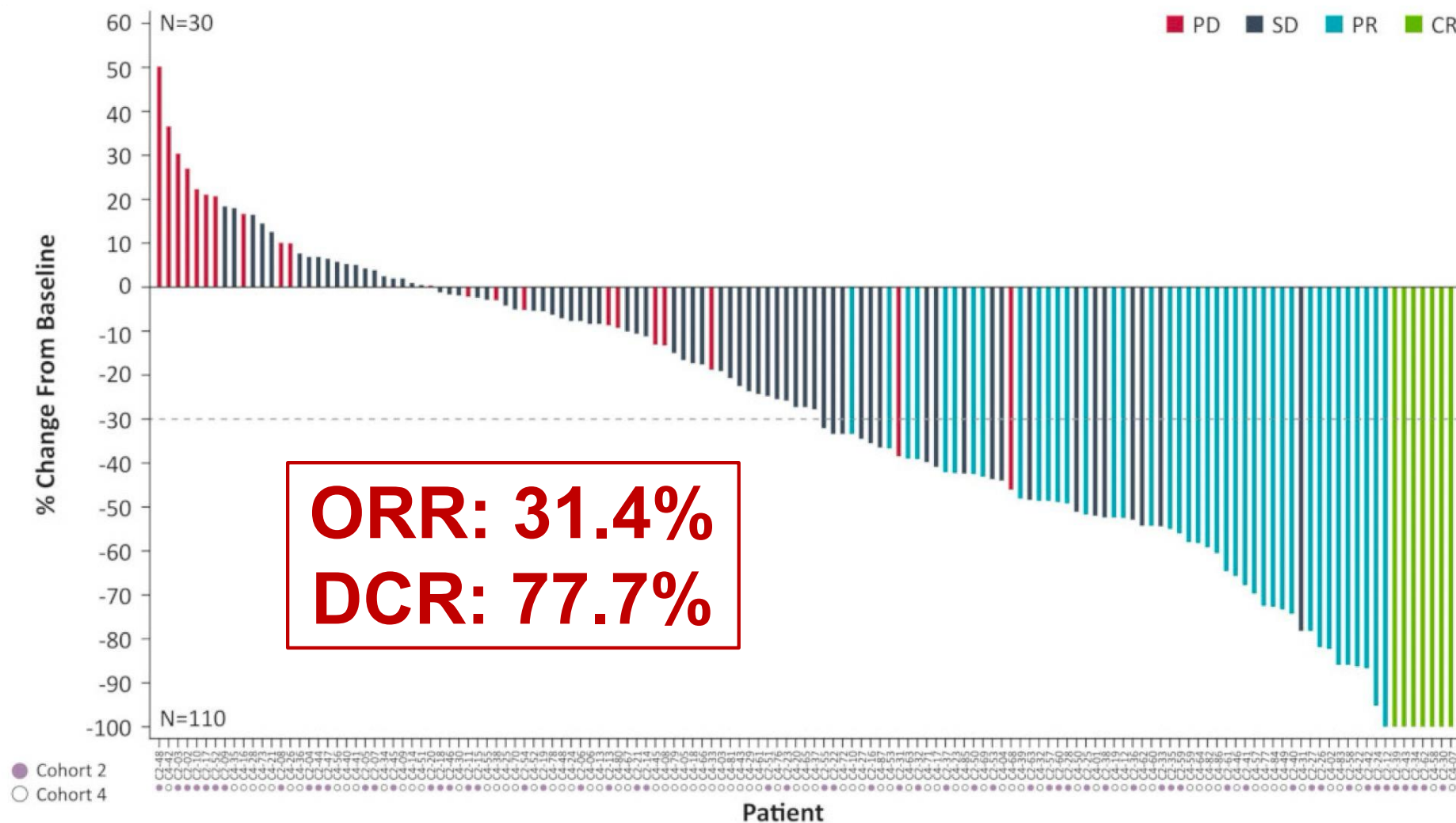


IL, interleukin; TIL, tumor-infiltrating lymphocyte.

1. Itzhaki O, et al. *J Immunother*. 2011;34:212. 2. Dudley ME, et al. *J Immunother*. 2003;26:332. 3. Dudley ME, et al. *J Clin Oncol*. 2008;26:5233. 4. Atkins MB, et al. *J Clin Oncol*. 1999;17:2105.

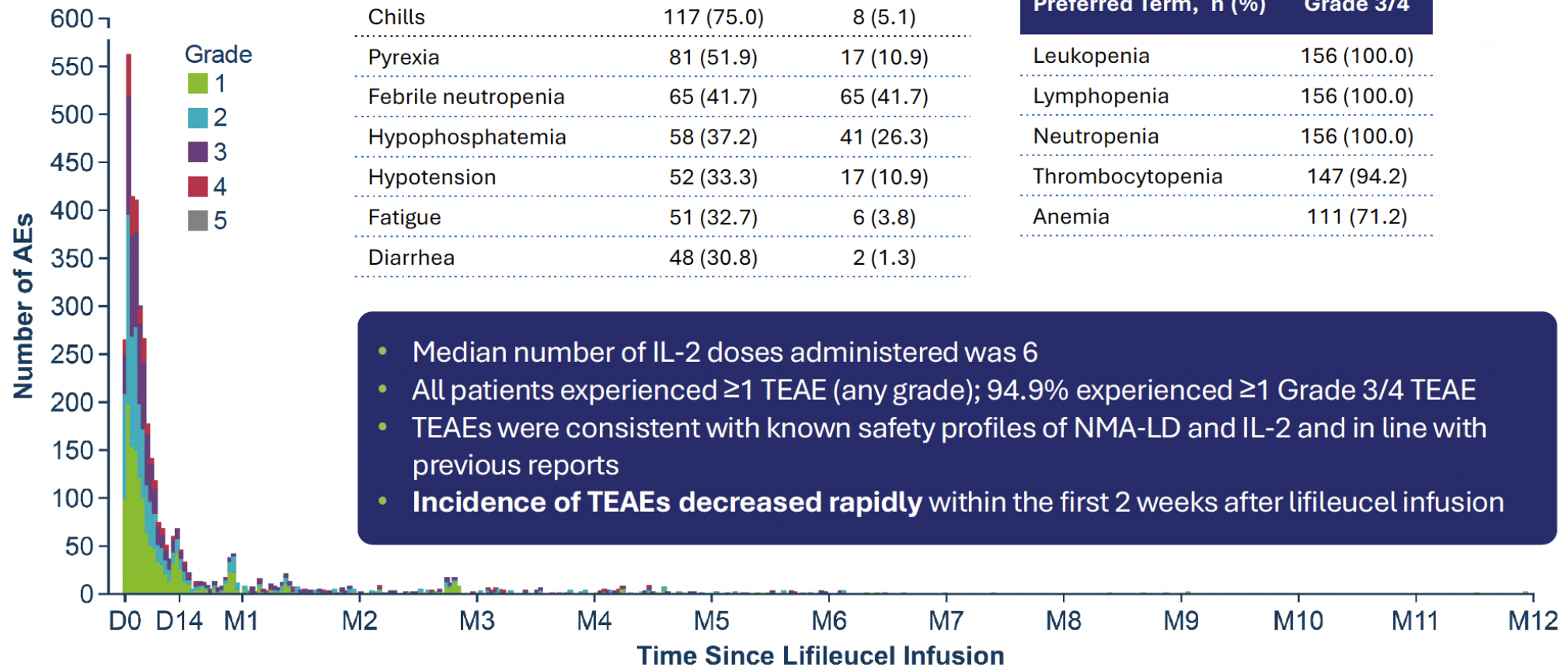


Lifileucel for PD-1 Refractory Melanoma

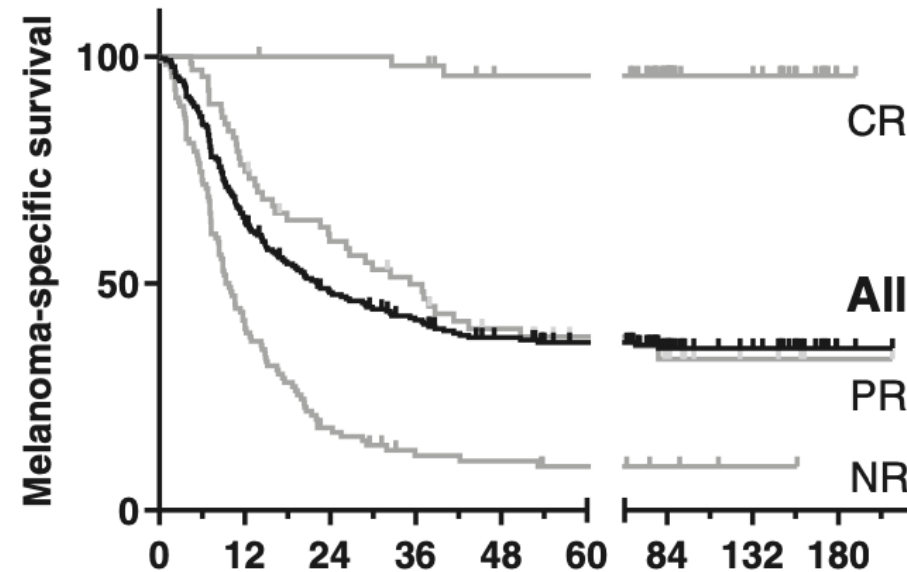


Lifileucel for PD-1 Refractory Melanoma

Safety



TIL: Potential for CURE in Metastatic Melanoma



10 year Melanoma-Specific Survival: 96%

# At risk	Months since cell transfer							
All: 226	146	105	88	74	65	43	21	
CR: 49	49	48	47	42	42	30	16	
PR: 67	51	38	31	23	18	10	4	
NR: 110	46	19	10	9	5	3	1	

40ish Years in the Making, the Era of TIL Therapy is FINALLY Here!

FDA U.S. FOOD & DRUG ADMINISTRATION

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FDA NEWS RELEASE

FDA Approves First Cellular Therapy to Treat Patients with Unresectable or Metastatic Melanoma

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For Immediate Release: February 16, 2024

Today, the U.S. Food and Drug Administration approved Amtagvi (lifileucel), the first cellular therapy indicated for the treatment of adult patients with a type of skin cancer (melanoma) that is unable to be removed with surgery (unresectable) or has spread to other parts of the body (metastatic) that previously has been treated with other therapies (a PD-1 blocking antibody, and if *BRAF* V600 mutation positive, a *BRAF* inhibitor with or without a MEK inhibitor).

Content current as of: 02/16/2024

Regulated Product(s)
Biologics

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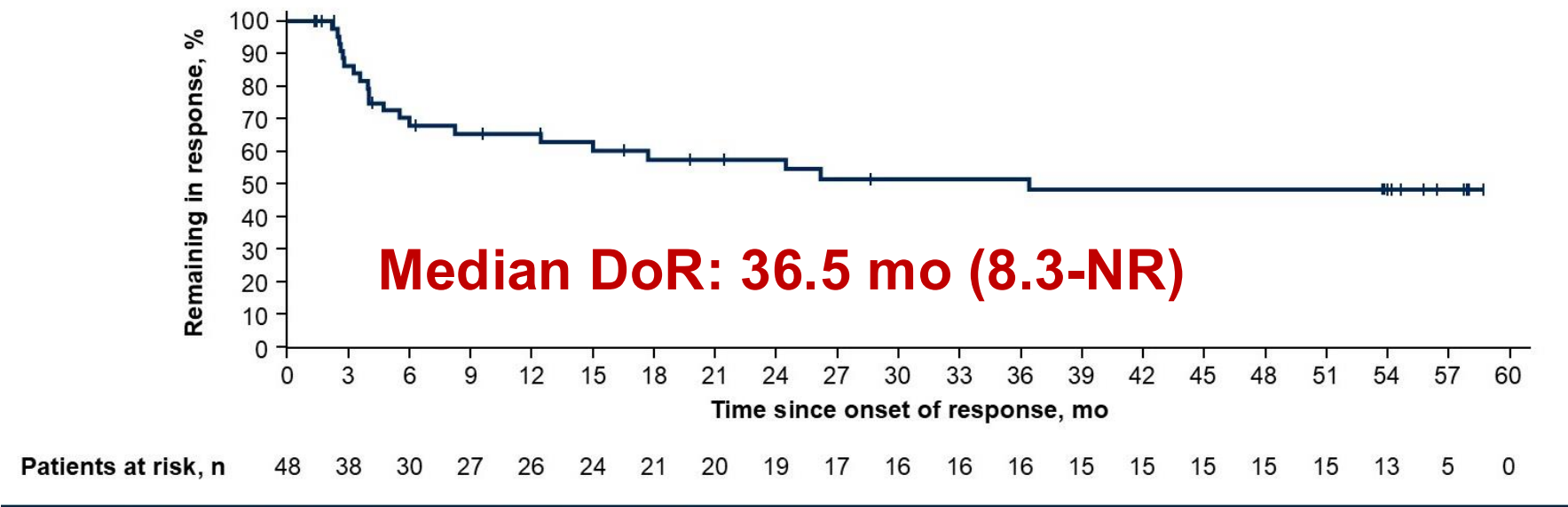
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Lifileucel 5-Year Data: Durable Responses

Duration of Response

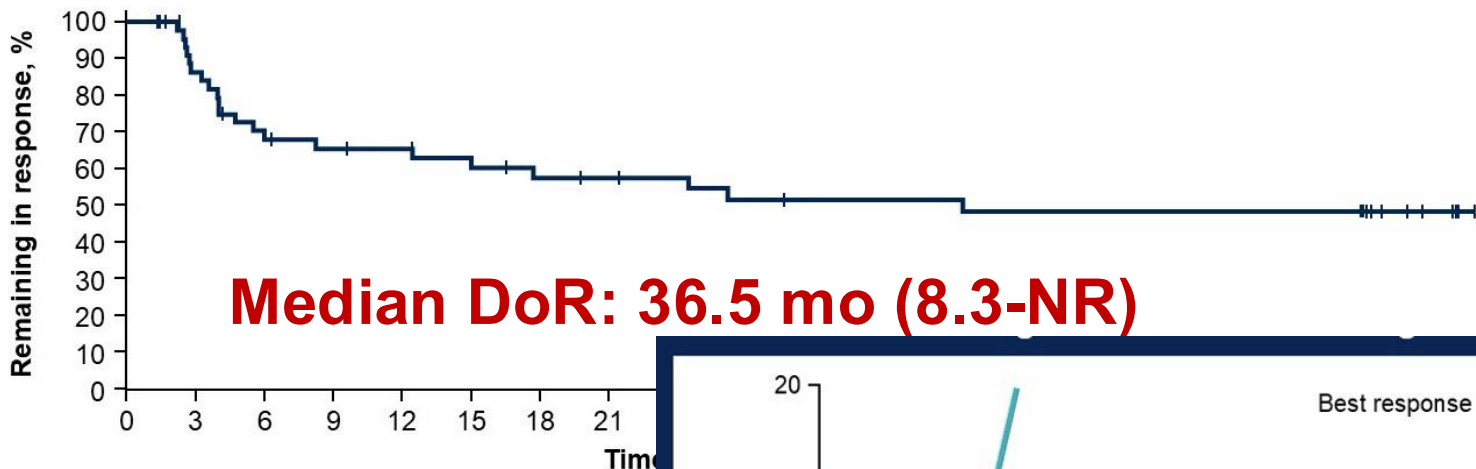


(Medina et al. ASCO 2025)

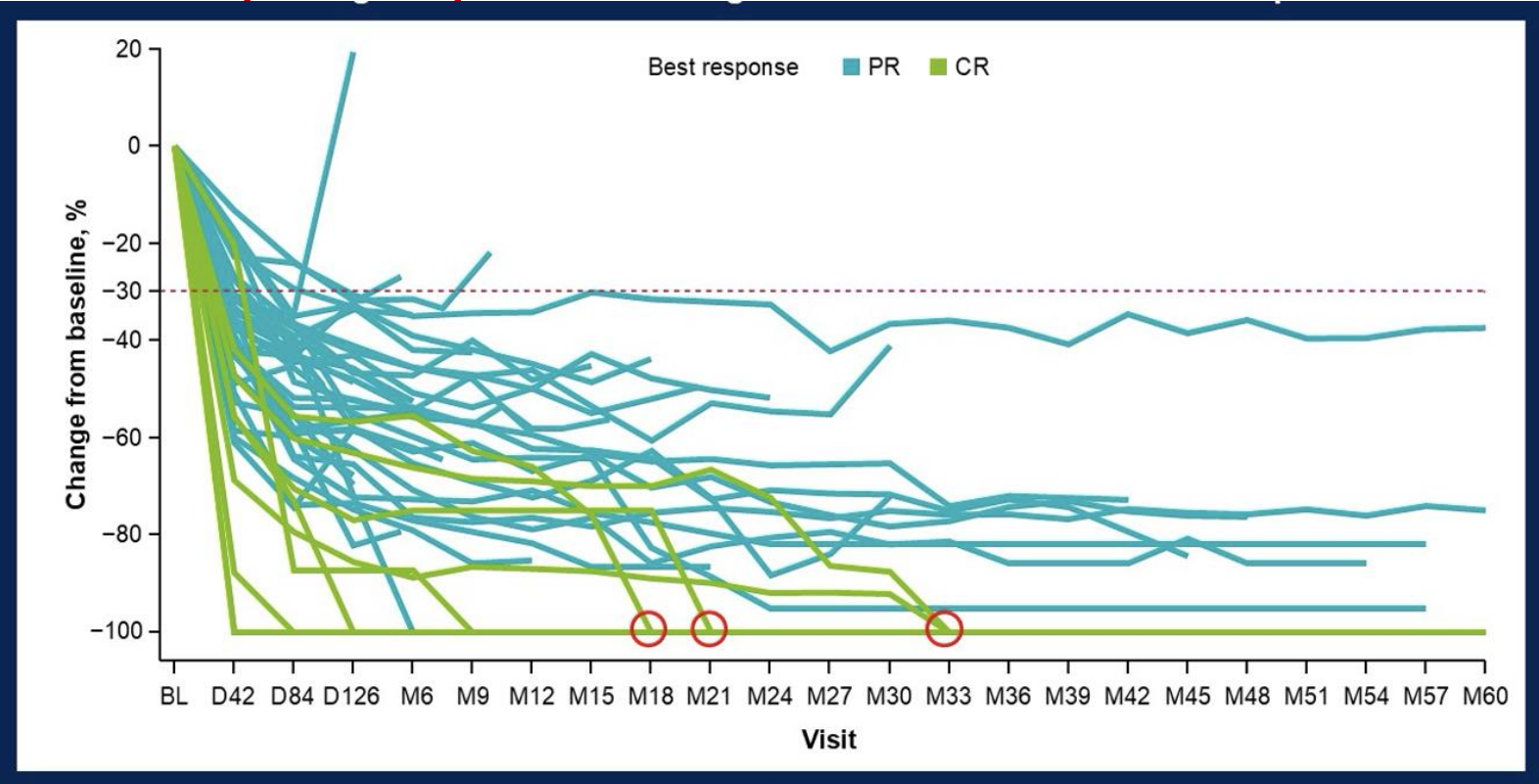


Lifileucel 5-Year Data: Durable Responses

Duration of Response



Patients at risk, n 48 38 30 27 26 24 21 20



So How Do We Actually Give TILs Safely?

Open access

Position article and guidelines



Expert consensus guidelines on management and best practices for tumor-infiltrating lymphocyte cell therapy

Allison Betof Warner ,¹ Omid Hamid,² Krishna Komanduri,³ Rodabe Amaria,⁴ Marcus O Butler,⁵ John Haanen ,⁶ Sarah Nikiforow,⁷ Igor Puzanov ,^{8,9} Amod Sarnaik ,¹⁰ Michael R Bishop,¹¹ Adam J Schoenfeld ¹²

To cite: Betof Warner A, Hamid O, Komanduri K, et al. Expert consensus guidelines on management and best practices for tumor-infiltrating lymphocyte cell therapy. *Journal for ImmunoTherapy of Cancer* 2024;12:e008735. doi:10.1136/jitc-2023-008735

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/jitc-2023-008735>).

ABW and AIS contributed equally.

Accepted 08 February 2024

ABSTRACT

Adoptive cell therapy with autologous, ex vivo-expanded, tumor-infiltrating lymphocytes (TILs) is being investigated for treatment of solid tumors and has shown robust responses in clinical trials. Based on the encouraging efficacy, tolerable safety profile, and advancements in a central manufacturing process, lifileucel is now the first US Food and Drug Administration (FDA)-approved TIL cell therapy product. To this end, treatment management and delivery practice guidance is needed to ensure successful integration of this modality into clinical care. This review includes clinical and toxicity management guidelines pertaining to the TIL cell therapy regimen prepared by the TIL Working Group, composed of internationally recognized hematologists and oncologists with expertise in TIL cell therapy, and relates to patient care and operational aspects. Expert consensus recommendations for patient management, including patient eligibility, screening tests, and clinical and toxicity management with TIL cell therapy, including tumor tissue procurement surgery, non-myeloablative lymphodepletion, TIL infusion, and IL-2 administration, are discussed in the context of potential standard of care TIL use. These recommendations provide practical guidelines for optimal clinical management during administration of the TIL cell therapy regimen, and recognition of subsequent management of toxicities. These guidelines are focused on multidisciplinary teams of physicians, nurses, and stakeholders involved in the care of these patients.

their polyclonality and ability to recognize and target a multitude of patient-specific tumor neoantigens to mediate tumor cell lysis.³

The Surgery Branch at the National Cancer Institute (NCI) began the pioneering research efforts in TIL cell therapy in the 1980s. Studies in patients with metastatic melanoma treated with non-myeloablative lymphodepletion (NMA-LMD), TIL, and interleukin-2 (IL-2) confirmed clinical safety and demonstrated significant efficacy, with objective tumor regression in up to 55% of patients.^{4,5}

Since then, several studies from the NCI and other groups have aimed to optimize the regimen in patients with metastatic melanoma.^{6–10} Access to TIL has increased with the adoption of centralized manufacturing, increasing the number of sites available to offer this therapy. Current trials accrue multiple tumor types. Lifileucel, the first US Food and Drug Administration (FDA)-approved autologous, cryopreserved TIL cell therapy product, showed clinically meaningful activity (independent review committee-assessed objective response rate (ORR) of 31.4% and



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TIL Therapy: What Does the Onconeurologist Need to Know?

- **Pretreatment:**

- FDA boxed warning for renal impairment!
- Creatinine-based GFR overestimates true GFR in cancer patients due to sarcoma (use cystatin C-creatinine combined equations)

- **Lymphodepletion:**

- Fludarabine is renally cleared and neurotoxic at high exposures--> Dose Reduce! (20 mg/m² if CrCl 50-79; 15 mg/m² if CrCl 40-49)
- Cyclophosphamide: watch for hemorrhagic cystitis (give with mesna) and electrolyte shifts



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TIL Therapy: What Does the Onconeurologist Need to Know?

- *****IL-2***:**
 - **Highest renal risk**
 - Induces capillary leak syndrome (CLS) via cytokine release (TNF- α , etc) complement activation, and increased endothelial permeability
 - Volume status: Extravascularly wet, intravascularly dry
 - NSAIDs need to be used with caution
 - Hold antihypertensives PRIOR to starting IL-2
 - UA with IL-2: Proteinuria, hematuria, pyuria, granular casts are common
 - Typically reversible with fluids and holding/stopping IL-2
 - Renally and hepatically cleared quickly! **No established role for dialysis in IL-2 management!!**



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40ish Years in the Making, the Era of TIL Therapy is **FINALLY** Here!



...so where
do we go
from here?



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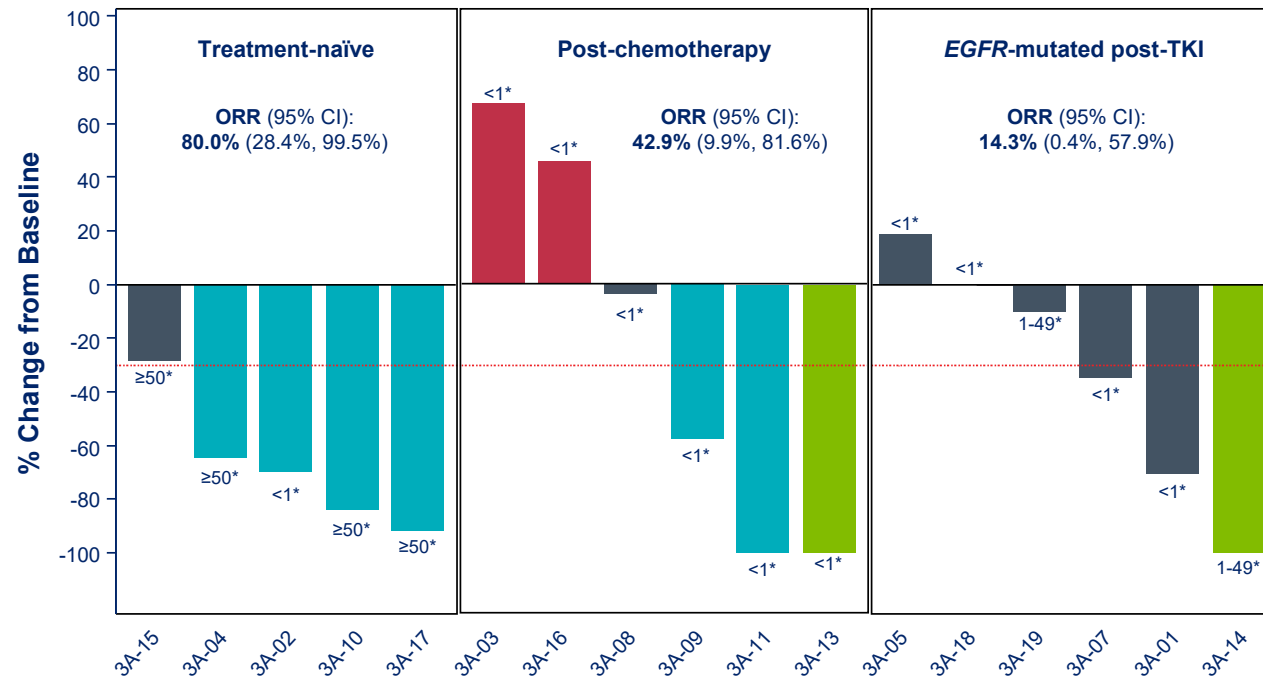


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TIL Therapy: Beyond Melanoma

Results: Clinical Efficacy in ICI-naïve mNSCLC Responses (RECIST v1.1) Observed Independent of PD-L1 Status

Best Percentage Change from Baseline in Target Lesion SOD for Evaluable Patients



- 76.5% of patients experienced reduction in tumor burden
- Treatment-naïve or post-chemotherapy: 58.3% (7/12)
- Treatment-naïve: 80.0% (4/5)
- Post-chemotherapy: 42.9% (3/7)
- **PD-L1-negative disease: 50.0% (4/8)**
- EGFR-mutated post-TKI: 14.3% (1/7)

*PD-L1 status (%) as adjudicated between site-reported and central-laboratory data.

CR, complete response; DCR, disease control rate; ICI, immune checkpoint inhibitor; mNSCLC, metastatic non-small cell lung cancer; NE, non-evaluable; ORR, objective response rate; PD-L1, programmed death ligand-1; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters; TKI, tyrosine kinase inhibitor.



TIL Therapy: Beyond Melanoma

ICI-Refractory NSCLC (NCT03645928)

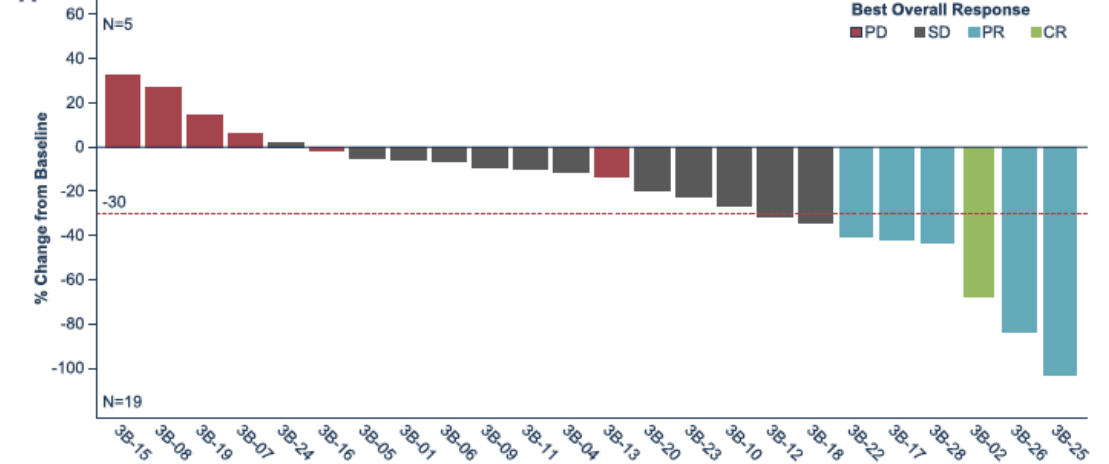
IOV-COM-202 (NCT03645928)

A Phase 2,
multicenter study of
autologous TIL in
patients with solid
tumors

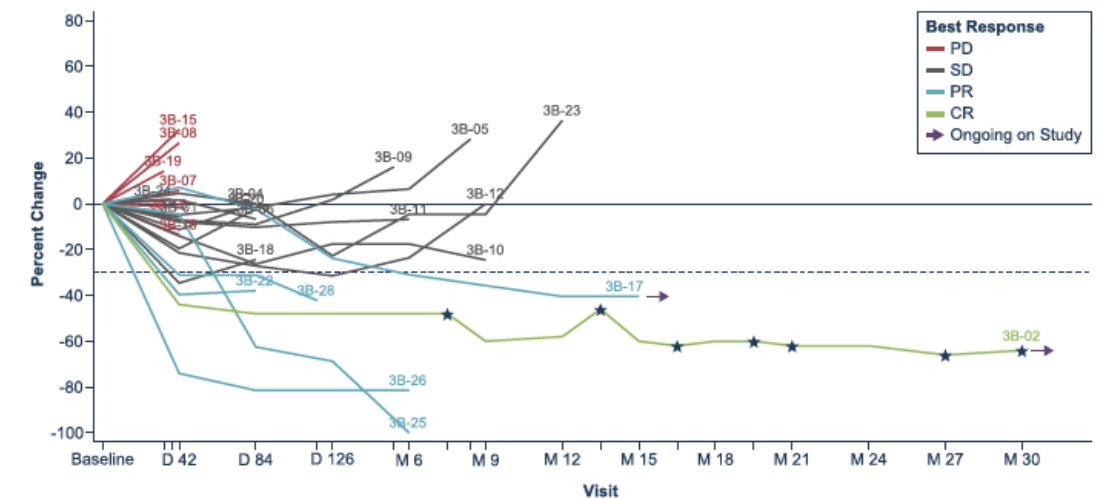
Cohort 3B
Metastatic lung cancer with
progression on 1-3 lines of
prior therapy receive LN-145
monotherapy



Figure 1



B



TIL Therapy: Beyond Melanoma

HNSCC: LN-145 ± Pembrolizumab (NCT03645928)

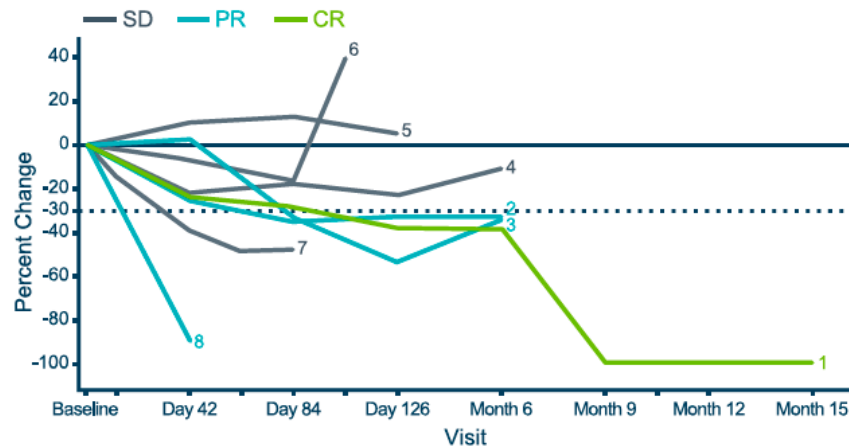
Cervical Cancer: LN-145 (NCT03108495)

RESPONSE (RECIST v1.1)	PATIENTS, N=9 n (%)
Objective Response Rate (ORR)	4 (44.4)
Complete Response (CR)	1 (11.1)
Partial Response (PR)	3 (33.3)
Stable Disease (SD)	4 (44.4)
Progressive Disease (PD)	0 (0)
Non-Evaluable	1 (11.1)
Disease Control Rate (DCR)	8 (88.9)
Median Duration of Response (DOR)	Not Reached
Min, Max	1.0+, 10.9+

Median study follow up: 8.6 month

RESPONSE (RECIST v1.1)	PATIENTS, N=27 n (%)
Objective Response Rate (ORR)	12 (44.4%)
Complete Response (CR)	3 (11.1%)
Partial Response (PR)	9 (33.3%)
Stable Disease (SD)	11 (40.7%)
Progressive Disease (PD)	4 (14.8%)
Non-Evaluable	0
Disease Control Rate (DCR)	23 (85.2%)
Median Duration of Response (DOR)	Not Reached
Min, Max (range)	2.6+ to 9.2+ months

Figure 6. Percent Change from Baseline in Sum of Target Lesion Diameters over Time



(Jimeno et al. SITC 2020)



(Jazeri et al. ESMO 2020)

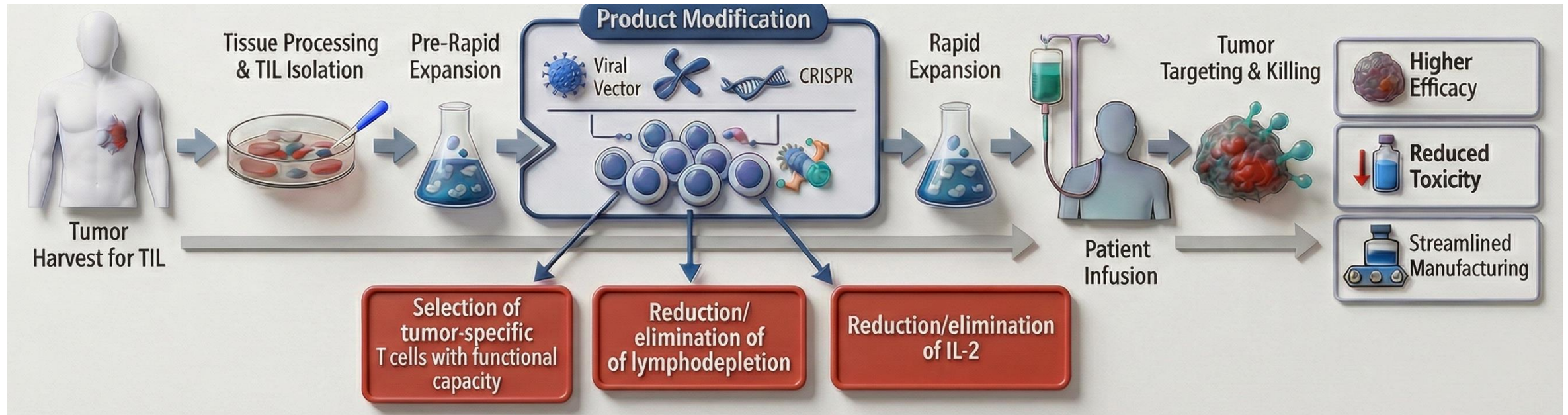


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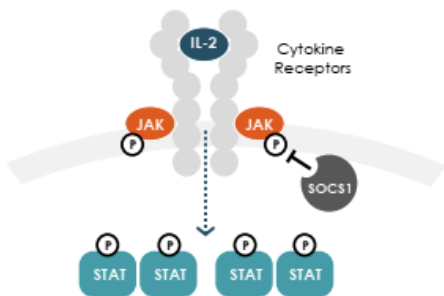
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Strategies for Modified TIL Therapy

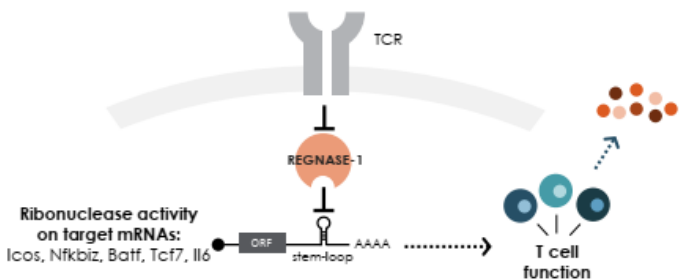


Novel TIL Approaches: SOCS1/Regnase-1 Deletion (KSQ-004EX)

SOCS1

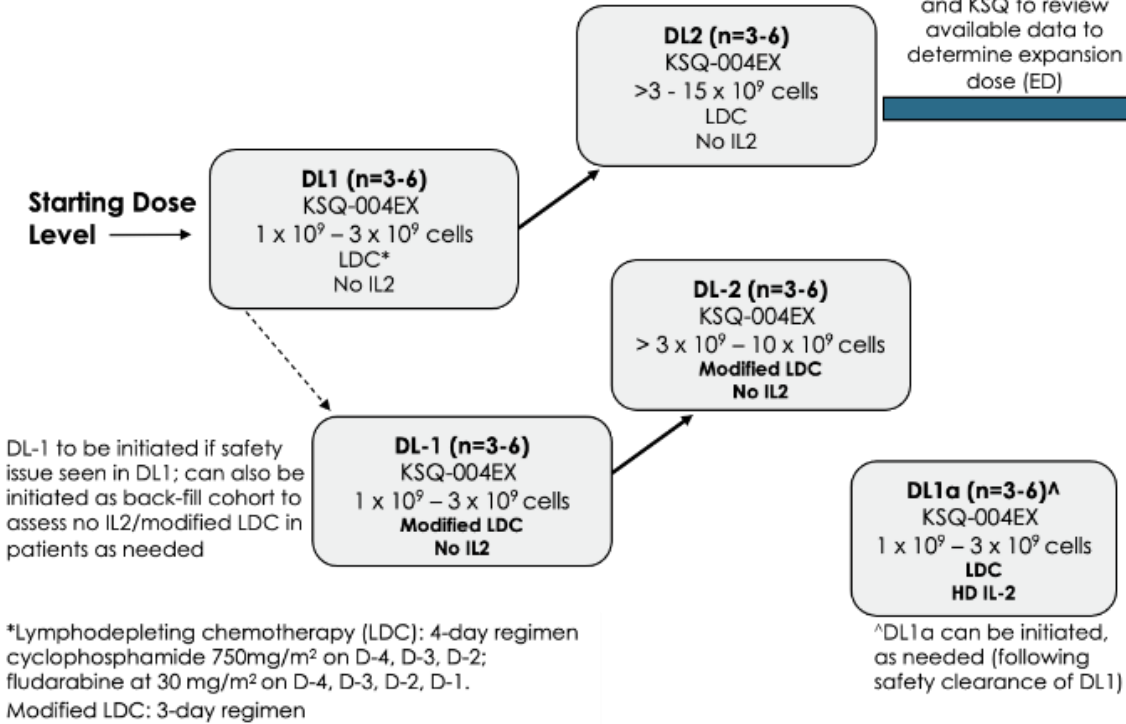


Regnase-1



Phase 1: Dose Escalation

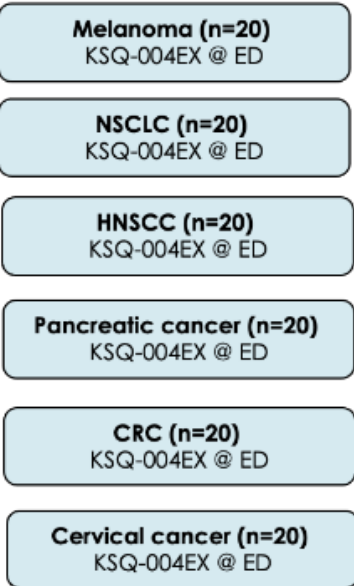
Starting Dose Level



DL-1 to be initiated if safety issue seen in DL1; can also be initiated as back-fill cohort to assess no IL2/modified LDC in patients as needed

*Lymphodepleting chemotherapy (LDC): 4-day regimen cyclophosphamide 750mg/m² on D-4, D-3, D-2; fludarabine at 30 mg/m² on D-4, D-3, D-2, D-1. Modified LDC: 3-day regimen

Phase 2: Expansion



Note: Indication-specific futility assessment (FA) after 10 pts/indication in Expansion

CRC: colorectal cancer; ED: expansion dose; HNSCC: head and neck squamous cell carcinoma; MDACC: MD Anderson Cancer Center; NSCLC: Non-small cell lung cancer

ClinicalTrials.gov ID: NCT06598371

(Halpin-Veszeleiova et al. SITC 2024)

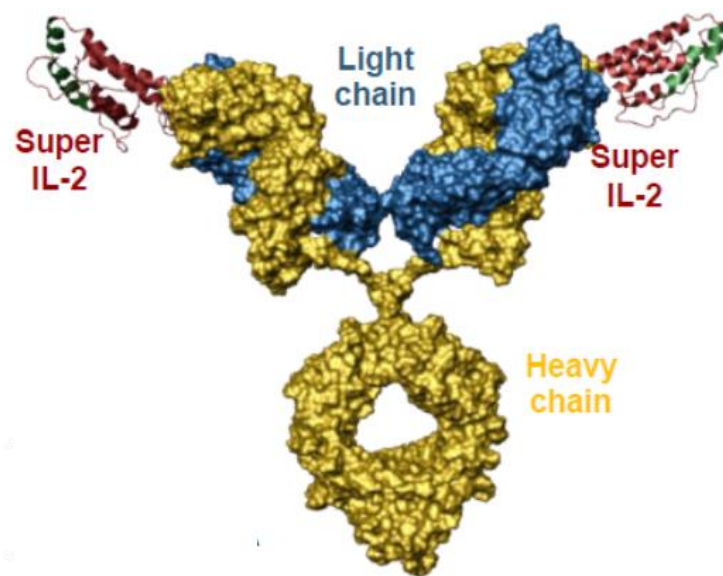


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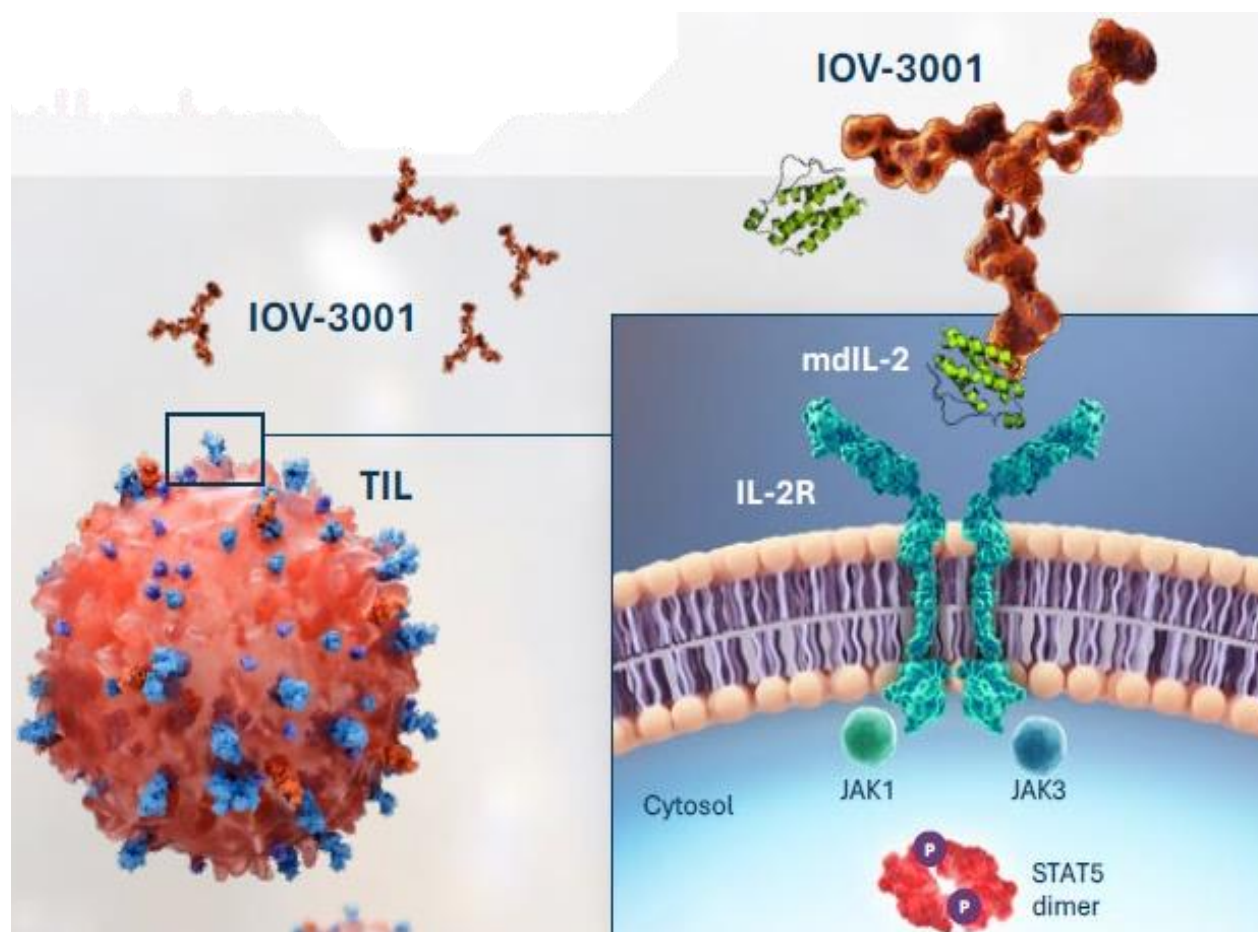


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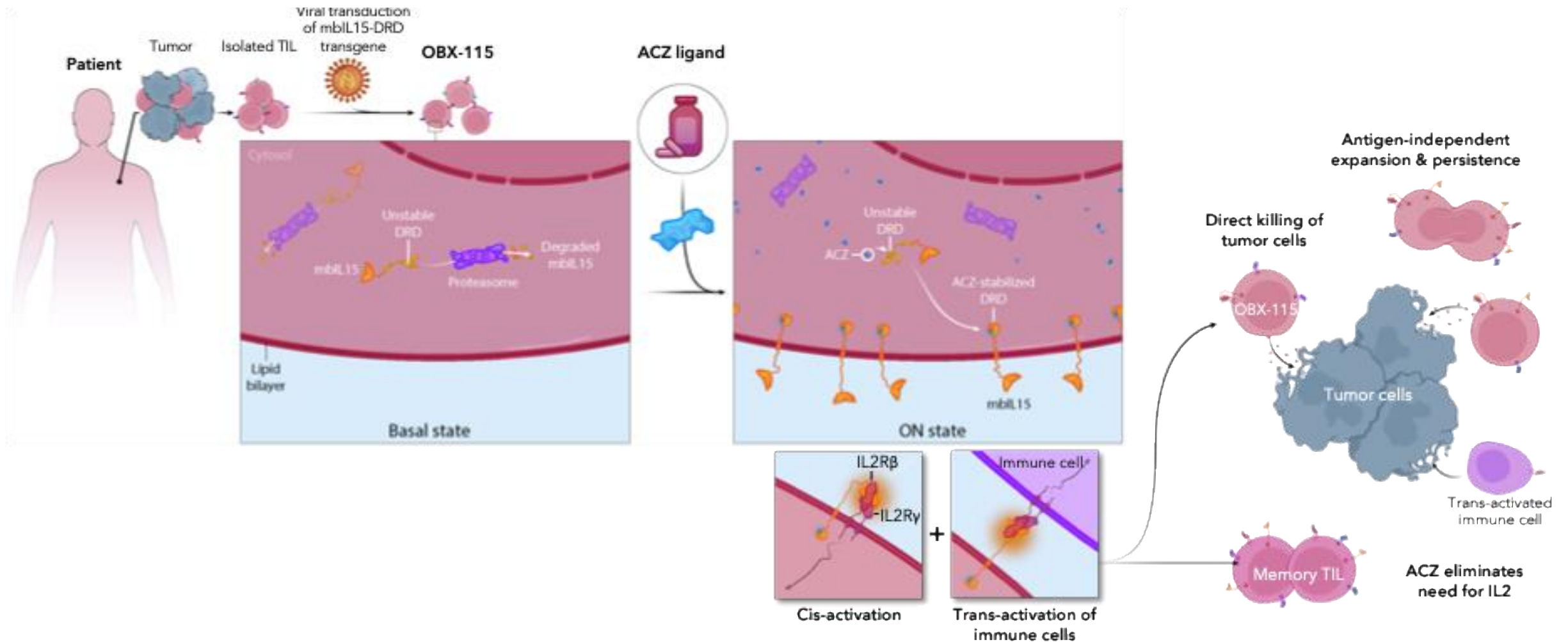
Novel TIL Approaches: IL-2 Analogue (IOV-3001)



Simpson-Abelson et al., ASCO 2024



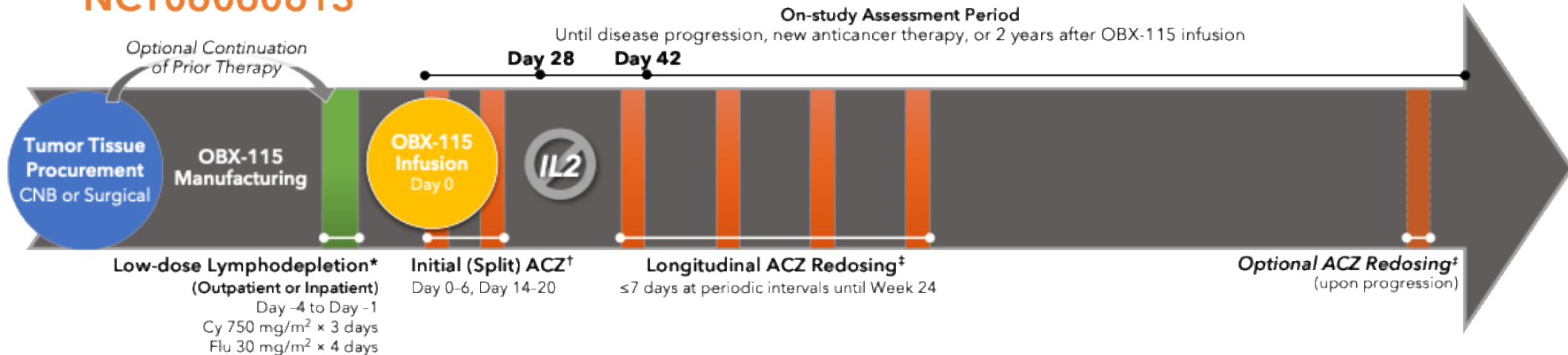
Novel TIL Approaches: Regulatable mbIL-15 OBX-115



Novel TIL Approaches: Regulatable mbIL-15 OBX-115

Agni-01 Single-arm Open-label Phase 1/2 Study

NCT06060613



Treatment Regimen

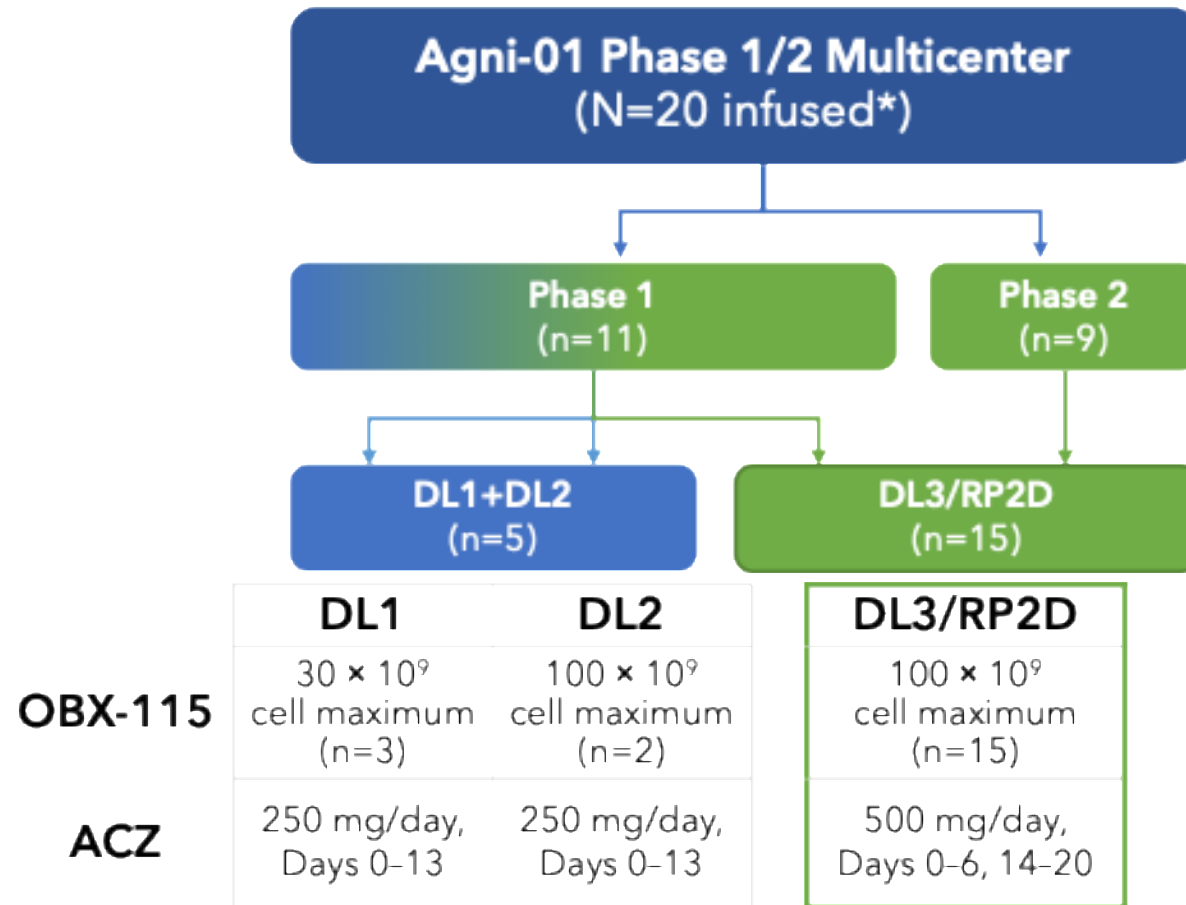
- Low-dose lymphodepletion
- OBX-115: $1-100 \times 10^9$ cells
- ACZ: 500 mg/day orally
 - Initial split-dose ACZ†
 - Longitudinal ACZ redosing‡ after recovery from lymphodepletion

Key Eligibility Criteria

- Advanced non-uvéal melanoma progressing after ICI therapy
- No upper age limit
- Not restricted by LDH, HLA, or melanoma subtype
- ≥ 1 lesion suitable for TTP for manufacturing and ≥ 1 remaining lesion amenable to RECIST v1.1 response assessment
 - Minimally invasive TTP (core needle biopsy) feasible



Novel TIL Approaches: Regulatable mblL-15 OBX-115



At DL3/RP2D:

4 outpatient lymphodepletion

100% of ACZ redosing in outpatient setting[†]



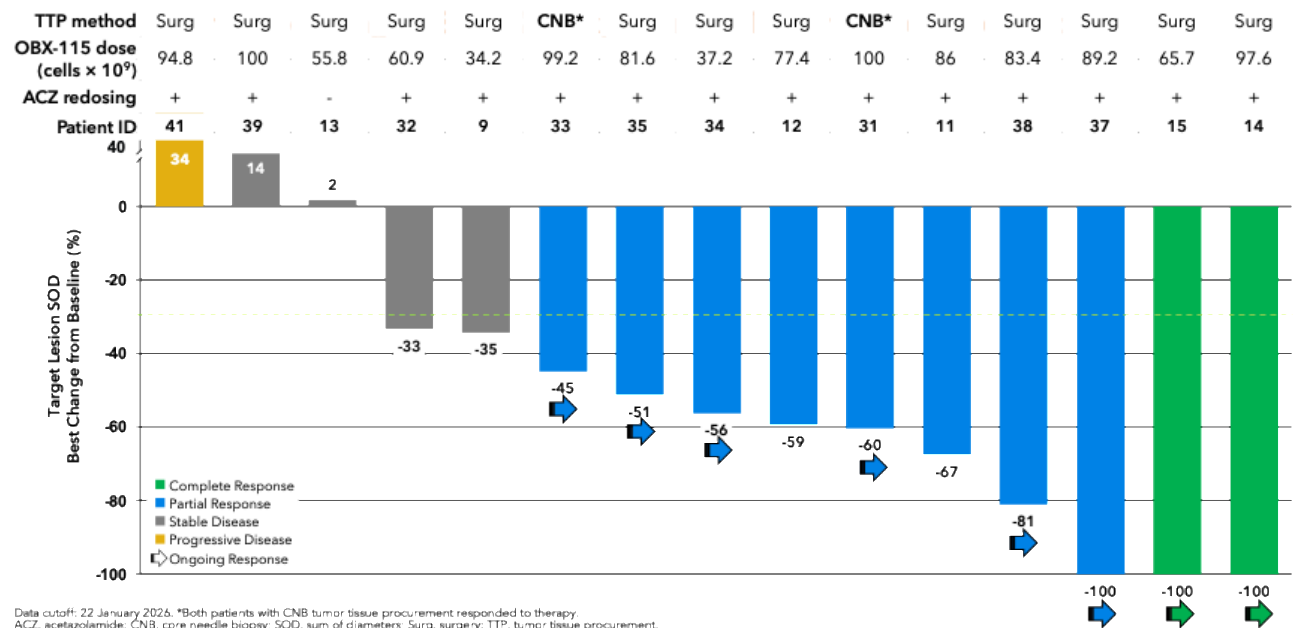
Data cutoff: 22 January 2026. *3 additional patients were enrolled and not infused: n=2 discontinued prior to treatment due to disease progression during DLT stagger phase; n=1 manufacturing failure. 114 patients received ACZ redosing, all of which were done in the outpatient setting.
ACZ, acetazolamide; DL, dose level; RP2D, recommended phase 2 dose.



Novel TIL Approaches: Regulatable mblL-15 OBX-115

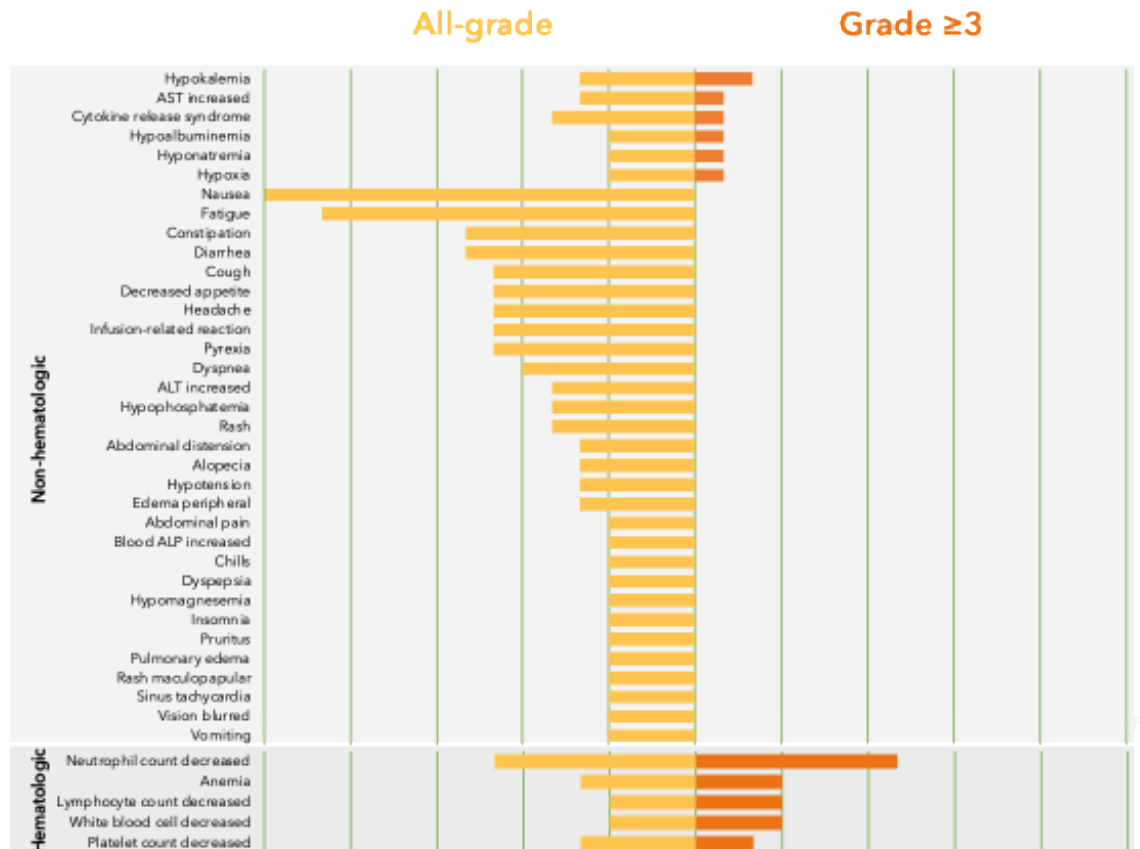
	OBX-115 (N=15)
Objective response rate, n (%)	10 (67)*
Complete response	2 (13)
Partial response	8 (53)
Stable disease	4 (27)
Progressive disease	1 (7)
Disease control rate, [†] n (%)	13 (93)
Duration of response, months (median [range])	NR (1.1+, 14.9+)

67% ORR, with SOD Reduction in 80% of Patients



Novel TIL Approaches: Regulatable mblL-15 OBX-115

TEAEs in $\geq 20\%$ of Patients



- Grade ≥ 3 non-hematologic toxicity was uncommon
- CRS was reported for 5 patients (33%)
 - 1 event (7%) was Grade 3
- Hematologic toxicity was favorable
 - 1 event (7%) of febrile neutropenia (Grade 3)
- No DLTs
- No ICANS
- No ICU transfer



Conclusions

- **Unmodified TILs have set a new bar for the treatment of PD-1 refractory melanoma**
- **There are significant risks and toxicities associated with TIL therapy by they tend to be transient and management strategies are improving**
- **More IL-2 is NOT better! When in doubt, stop IL-2!**
- **Engineering next-generation cell therapies provides opportunities to enhance both safety and efficacy**



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Thank You!



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Melanoma & Cutaneous
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