

Lifileucel TIL Cell Therapy in Patients With Advanced Melanoma After Progression on Immune Checkpoint Inhibitors (ICI) and Targeted Therapy: Tumor Tissue Procurement Data From the C-144-01 Study

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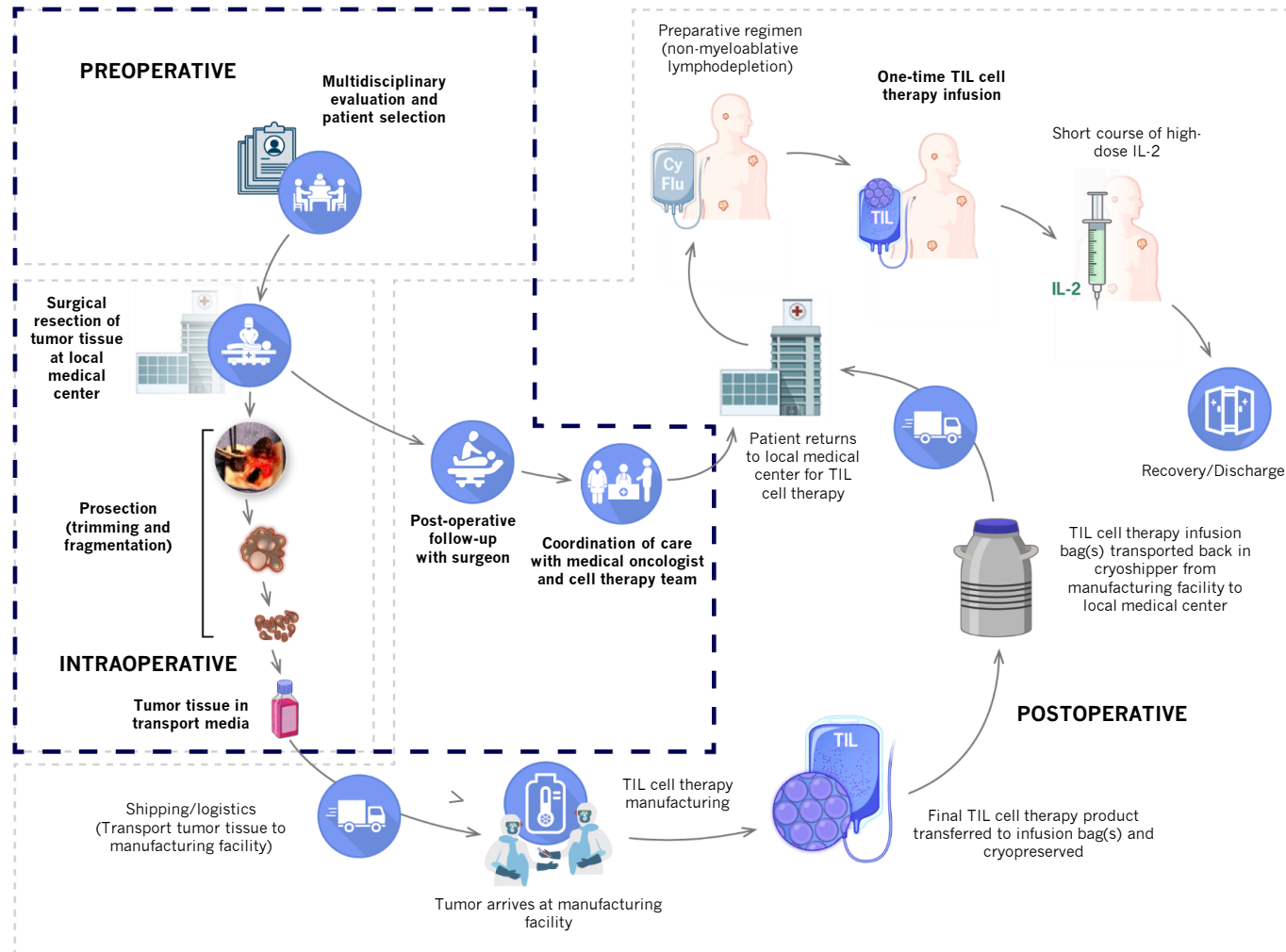
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Background

- Treatment options for advanced (unresectable or metastatic) melanoma are limited after progression on or after ICI and targeted therapy¹⁻⁵
- One promising treatment option is autologous TIL cell therapy, in which surgeons play a critical role by collecting tumor tissue for TIL cell therapy manufacturing
- Lifileucel, an investigational adoptive cell therapy using cryopreserved autologous TIL, has demonstrated encouraging activity in patients with advanced melanoma who progressed after ICI and targeted therapy (if indicated) in a multicenter phase 2 study (C-144-01, NCT02360579)⁶
- **We now report outcomes of lifileucel in a large cohort of patients, with a focus on surgical aspects of the treatment**

1. Cybulska-Stopa B et al. *Adv Med Sci.* 2020;65:316–323. 2. Olson DJ et al. *J Clin Oncol.* 2021;39:2647–2655. 3. VanderWalde A et al. Presented at 2022 AACR Annual Meeting. April 8–13, 2022: New Orleans, LA. Abstract CT013. 4. Weber JS et al. *Lancet Oncol.* 2015;16:375–84. 5. Goldinger SM et al. *Eur J Cancer.* 2022;162:22–33. 6. Chesney J et al. *J ImmunoTher Cancer* 2022;10:e005755.
ICI, immune checkpoint inhibitor; TIL, tumor-infiltrating lymphocytes.

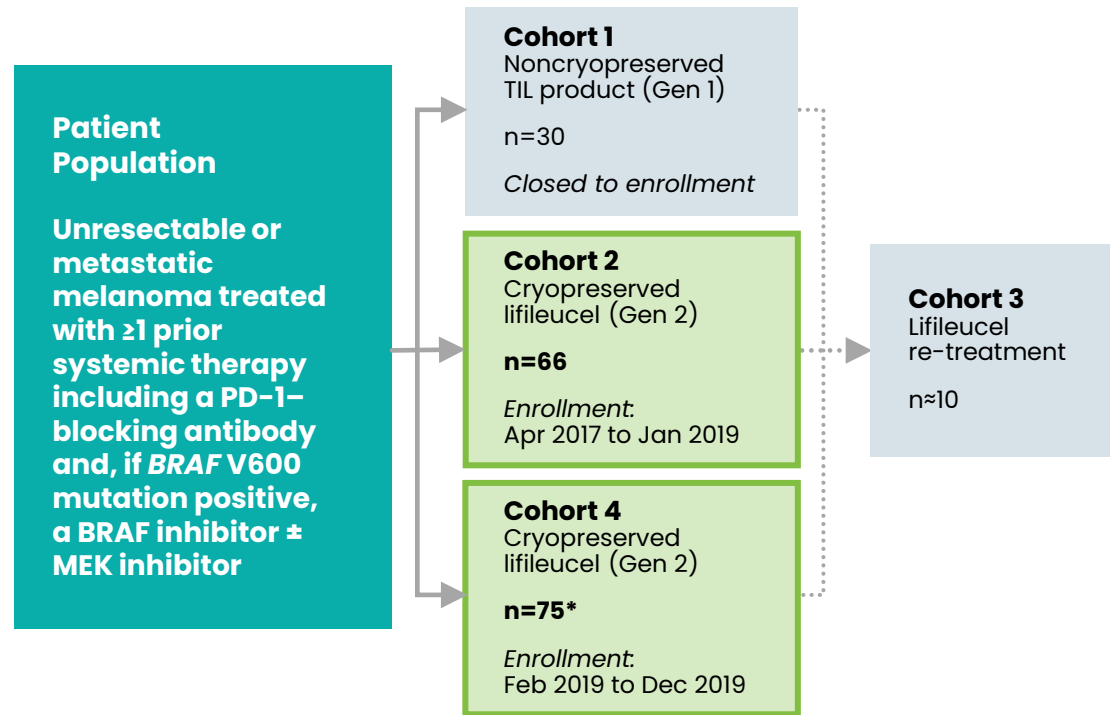
Role of the Surgeon in the Lifileucel TIL Cell Therapy Process



- Surgeons are key contributors in the patient care journey
- Pre-operative
 - Multidisciplinary discussion
 - Lesion selection
 - Operative approach
- Intraoperative
 - Resection, prosection, maintaining COI/COC
- Postoperative
 - Recovery prior to NMA-LD
 - Coordination of care

COC, Chain of Custody; COI, Chain of Identity; IL-2, interleukin-2; NMA-LD, non-myeloablative lymphodepletion; TIL, tumor-infiltrating lymphocytes.

C-144-01 Study Design



Eligibility and treatment were identical for consecutively enrolled Cohorts 2 and 4

Key Endpoints

- Primary: ORR (IRC-assessed using RECIST v1.1)
- Secondary: DOR, PFS, OS, TEAE incidence and severity

Key Eligibility Criteria

- ≥1 tumor lesion resectable for TIL generation (≥1.5 cm in diameter) and ≥1 target tumor lesion for response assessment
- Age ≥18 years at time of consent
- ECOG performance status 0–1
- No limit on number of prior therapies

Treatment Regimen

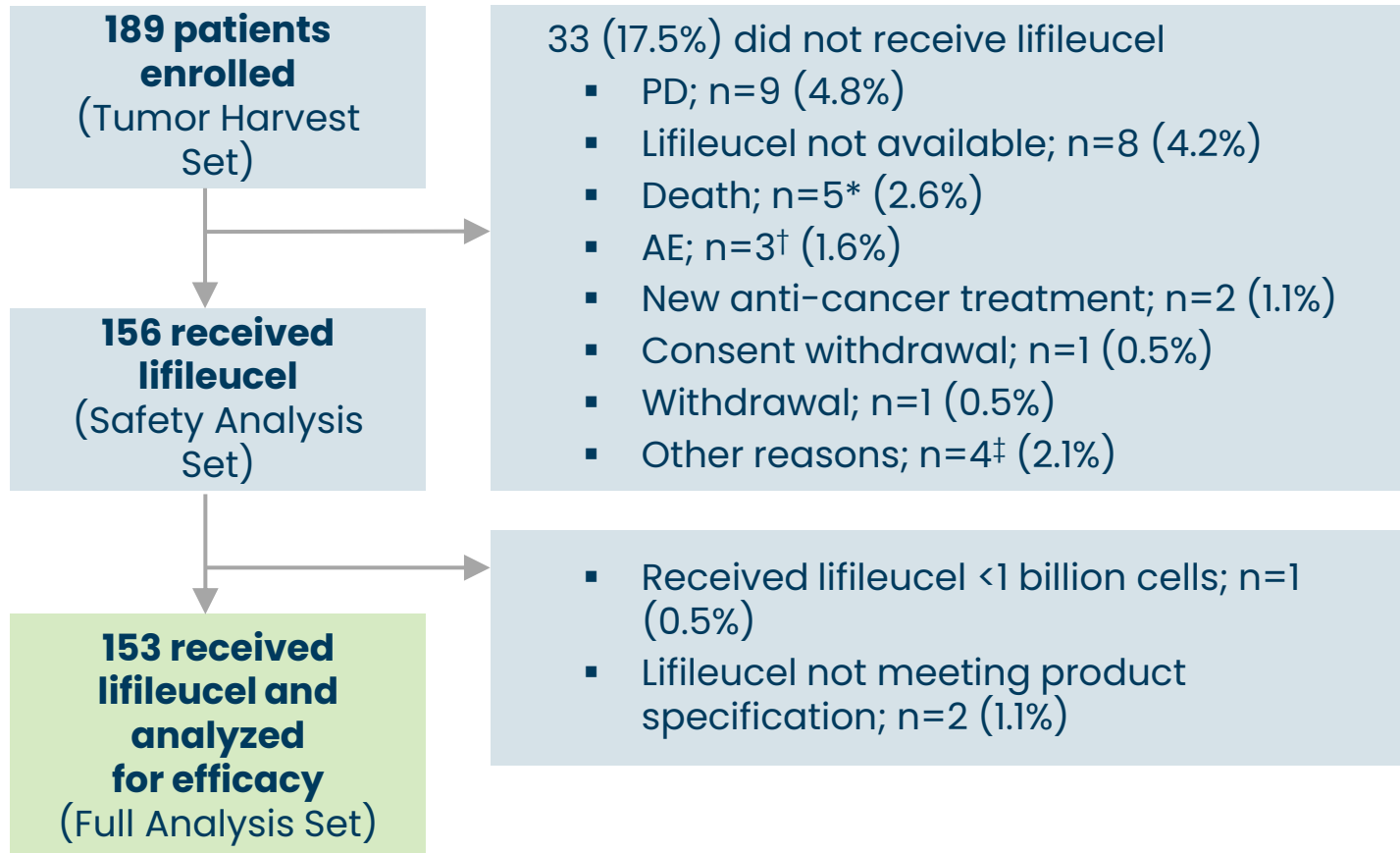
- Lifileucel, a cryopreserved TIL cell therapy product, was used in Cohorts 2 and 4 and manufactured using the same 22-day Gen 2 process
- All patients received NMA-LD, a single lifileucel infusion, and up to 6 doses of high-dose IL-2

Data cutoff date: 15 July 2022

*The planned sample size for Cohort 4 was 75 per statistical plan, but the Full Analysis Set, defined as patients who received lifileucel that met specification, consisted of 87 patients due to rapid enrollment.

DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IL-2, Gen, generation, IL-2, interleukin-2; IRC, Independent Review Committee; NMA-LD, non-myeloablative lymphodepletion; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; RECIST, Response evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse events; TIL, tumor-infiltrating lymphocytes.

Patient Disposition and Treatment



- Lifileucel was manufactured within specification in 94.7% of patients
- Of the 33 (17.5%) patients who did not receive lifileucel, 25 had patient-related reasons, whereas lifileucel was not available for infusion for 8 patients

*Reasons for death included PD (n=4) and AE (acute kidney injury [n=1]).

†AEs included gastrointestinal bleeding, septic shock, and pleural effusion.

‡Other reasons include study discontinuation (n=2), investigator decision (n=1), and chronic systemic steroid (n=1).

AE, adverse event; PD, progressive disease; TIL, tumor-infiltrating lymphocyte.

Baseline Patient and Disease Characteristics

Characteristic	Cohort 2+4 (N=153)
Median age (range), y	56.0 (20, 79)
Sex, n (%)	
Male	83 (54.2)
Screening ECOG performance status, n (%)	
0	104 (68.0)
1	49 (32.0)
Melanoma subtype,* n (%)	
Cutaneous	83 (54.2)
Mucosal	12 (7.8)
Acral	10 (6.5)
BRAF V600-mutated, n (%)	41 (26.8)
PD-L1 status,† n (%)	
TPS ≥1%	76 (49.7)
TPS <1%	32 (20.9)

Characteristic	Cohort 2+4 (N=153)
Liver and/or brain lesions by IRC, n (%)	72 (47.1)
Median target lesion SOD (range), mm	97.8 (13.5, 552.9)
Baseline lesions in ≥3 anatomic sites, n (%)	109 (71.2)
Baseline target and nontarget lesions,‡ n (%)	
≤3	36 (23.5)
>3	116 (75.8)
LDH, n (%)	
≤ULN	70 (45.8)
>1–2 × ULN	54 (35.3)
>2 × ULN	29 (19.0)
Median number of prior therapies (range)	3.0 (1, 9)
Primary resistance to anti-PD-1/PD-L1 per SITC criteria,¹ n (%)	109 (71.2)

*47 patients (31%) had melanoma of other subtype (including unknown primary subtype or insufficient information).

†45 patients in the Cohorts 2+4 had missing PD-L1 status.

‡One patient in Cohort 2 had missing data on number of baseline target and nontarget lesions.

¹. Kluger HM et al. *J Immunother Cancer*. 2020;8:e000398.

ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; SITC, Society for Immunotherapy of Cancer; SOD, sum of diameters; TPS, tumor proportion score; ULN, upper limit of normal.

Distribution of Anatomic Sites of Resection

Anatomic site of resection, n (%)	Cohort 2+4 (N=153)
Visceral organ	42 (27.5)
Lymph node/skin/subcutaneous	71 (46.4)
Other*	40 (26.1)

- 94.9% of patients had a single site of tumor resection
- In the 8 patients (5.1%) with multiple resection sites, all sites were in the same category (eg, 3 skin sites, 2 subcutaneous sites)

*Other sites of resection included muscle, soft tissue, bone, limb/extremity, and others.

Adverse Events

Tumor-Resection AEs* Related to Surgery Occurring in >1 Patient (Any Grade), n (%)	Tumor Harvest Set (N=189)	
	Any Grade	Grade 3/4
Number of patients reporting >1 tumor-resection AE related to surgery	60 (31.7)	6 (3.2)
Procedural pain	22 (11.6)	0
Nausea	5 (2.6)	1 (0.5)
Vomiting	4 (2.1)	0
Abdominal pain	3 (1.6)	1 (0.5)
Cellulitis	3 (1.6)	2 (1.1)
Flank pain	3 (1.6)	0
Incision site erythema	3 (1.6)	0
Seroma	3 (1.6)	0
Decreased appetite	2 (1.1)	0
Erythema	2 (1.1)	0
Incision site pain	2 (1.1)	0
Localized edema	2 (1.1)	0
Lymphocele	2 (1.1)	0
Postoperative wound infection	2 (1.1)	0
Wound dehiscence	2 (1.1)	0

1. Sarnaik AA, et al. *J Clin Oncol*. 2021;39(24):2656–2666.

*Tumor-resection AEs refer to AEs that started after tumor resection and before the start of NMA-LD.

AE, adverse event; IL-2, interleukin-2; NMA-LD, non-myeloablative lymphodepletion; TEAE, treatment-emergent adverse event.

- Tumors were resected from diverse sites with minimal surgical morbidity
- Grade 3/4 tumor-resection AEs related to surgery were seen in 6 (3.2%) patients
- No patient had surgery-related AEs that prevented lifileucel infusion or required blood transfusion

Treatment-Emergent Adverse Events

- Most TEAEs were expected and manageable, and the incidence decreased rapidly over the first 2 weeks after lifileucel infusion
- As previously described, TEAEs were consistent with known safety profiles of NMA-LD (cyclophosphamide, fludarabine) and IL-2¹

Objective Response Rate (IRC-assessed)

	Cohort 2+4 (N=153)
ORR, n (%)	48 (31.4)
(95% CI)	(24.1, 39.4)
Best overall response, n (%)	
CR	9 (5.9)
PR	39 (25.5)
SD	71 (46.4)
Non-CR/Non-PD*	1 (0.7)
PD	27 (17.6)
Nonevaluable†	6 (3.9)

- **IRC-assessed ORR was 31.4%**
- Median number of TIL cells infused was 21.1×10^9 (range, 1.2×10^9 to 99.5×10^9)
- Median time from resection to lifileucel infusion was 33 days
- Response to lifileucel was observed across all subgroups analyzed
 - In multivariate analyses, ORR was correlated with baseline target lesion sum of diameters and LDH^{1,2}

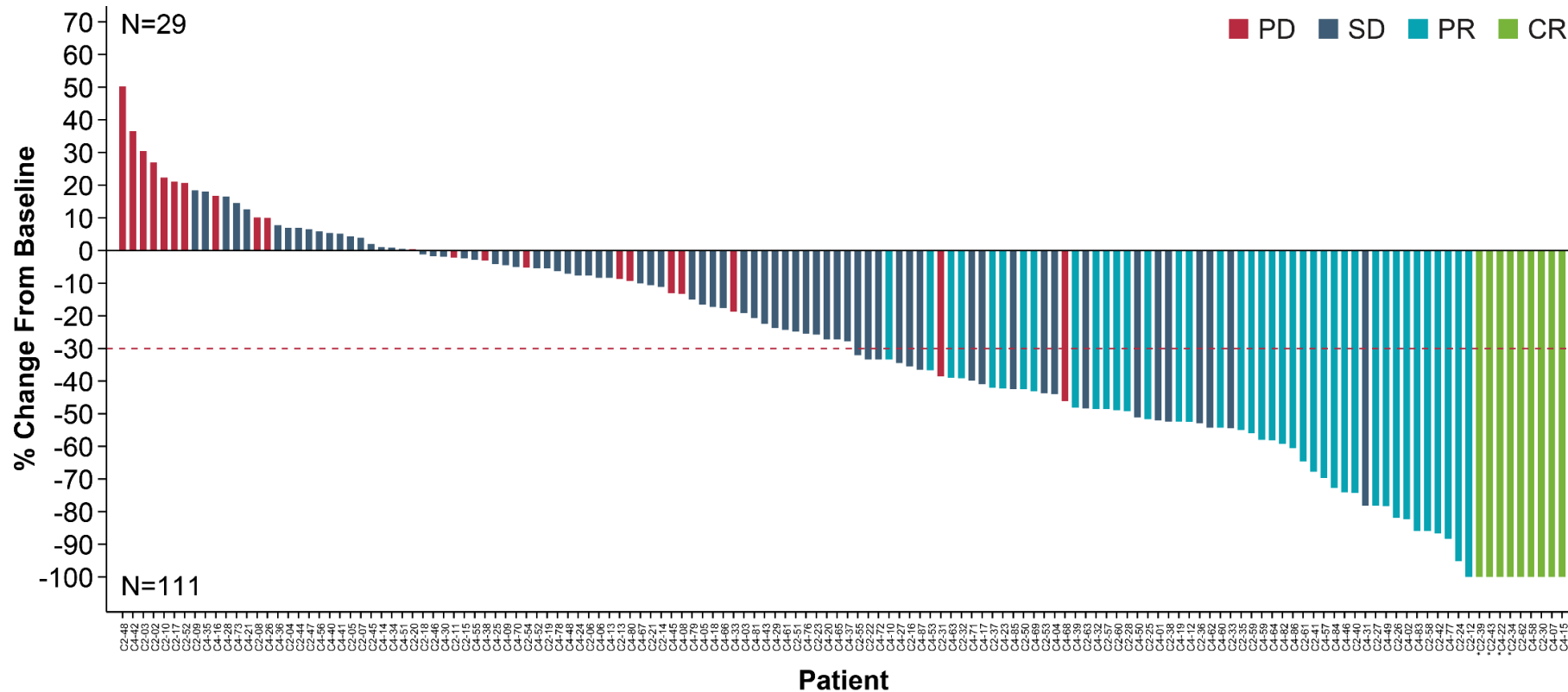
*Patient did not have measurable target lesions by IRC and had best overall response of non-CR/non-PD per IRC assessment.

†Six patients were nonevaluable for response (5 due to early death; 1 due to new anticancer therapy).

1. Sarnaik et al. Presented at 2022 SITC Annual Meeting, November 8-12, 2022: Boston, MA. Abstract 789. 2. Chesney et al. *J Immunother Cancer*. 2022;10:e005755.

CR, complete response; IRC, independent review committee; LDH, lactate dehydrogenase; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TIL, tumor-infiltrating lymphocytes.

Best Percentage Change From Baseline in Target Lesion Sum of Diameters



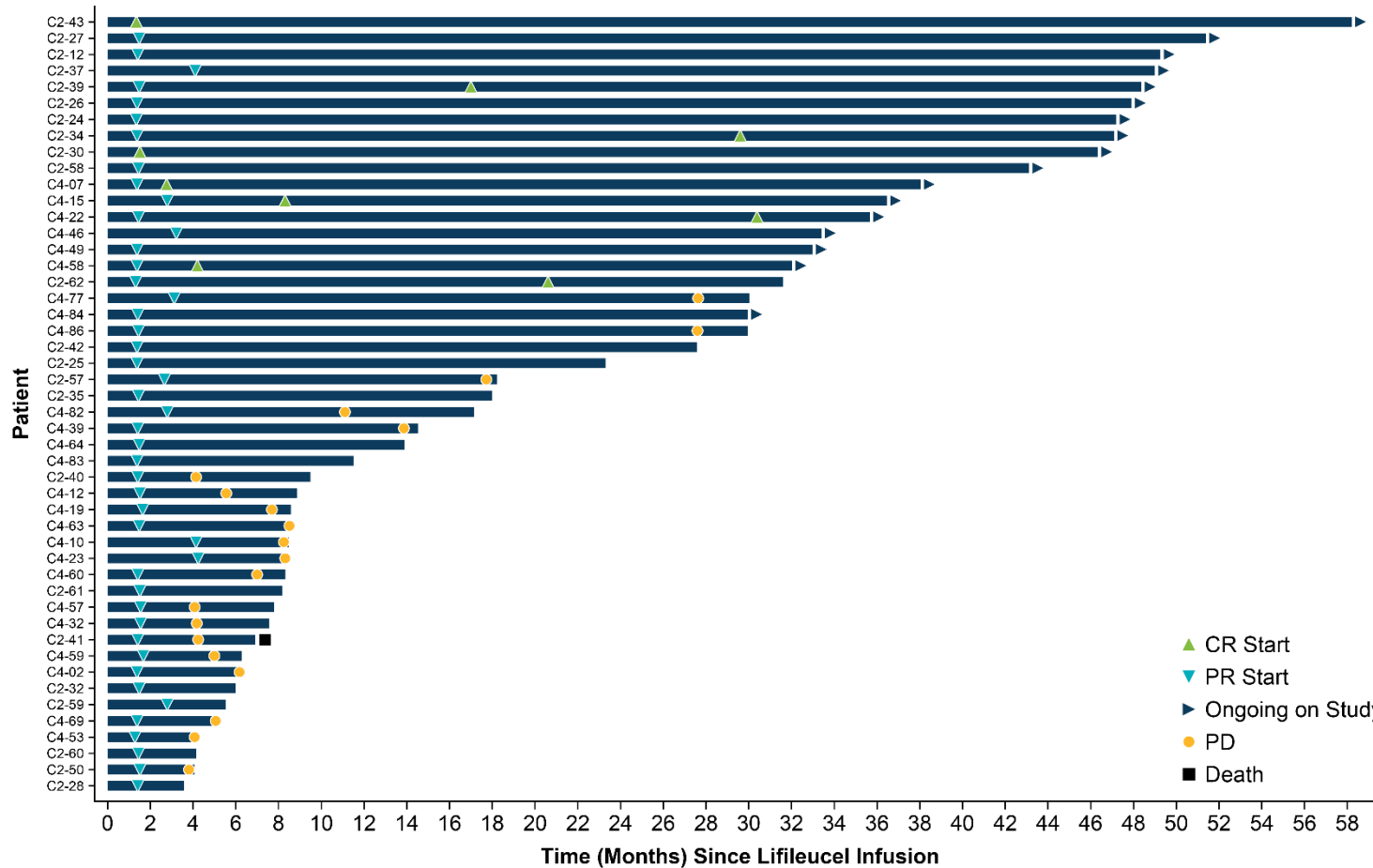
■ 79.3% (111/140) of patients had a reduction in tumor burden

13 patients in the Full Analysis Set are not included (best overall responses included NE [n=6], non-CR/non-PD [n=1], and PD [n=6]) for reasons including having no measurable lesions at baseline or no post-lifileucel target lesion SOD measurements.

*-100% change from baseline is presented for CR assessment that includes lymph node lesions.

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters.

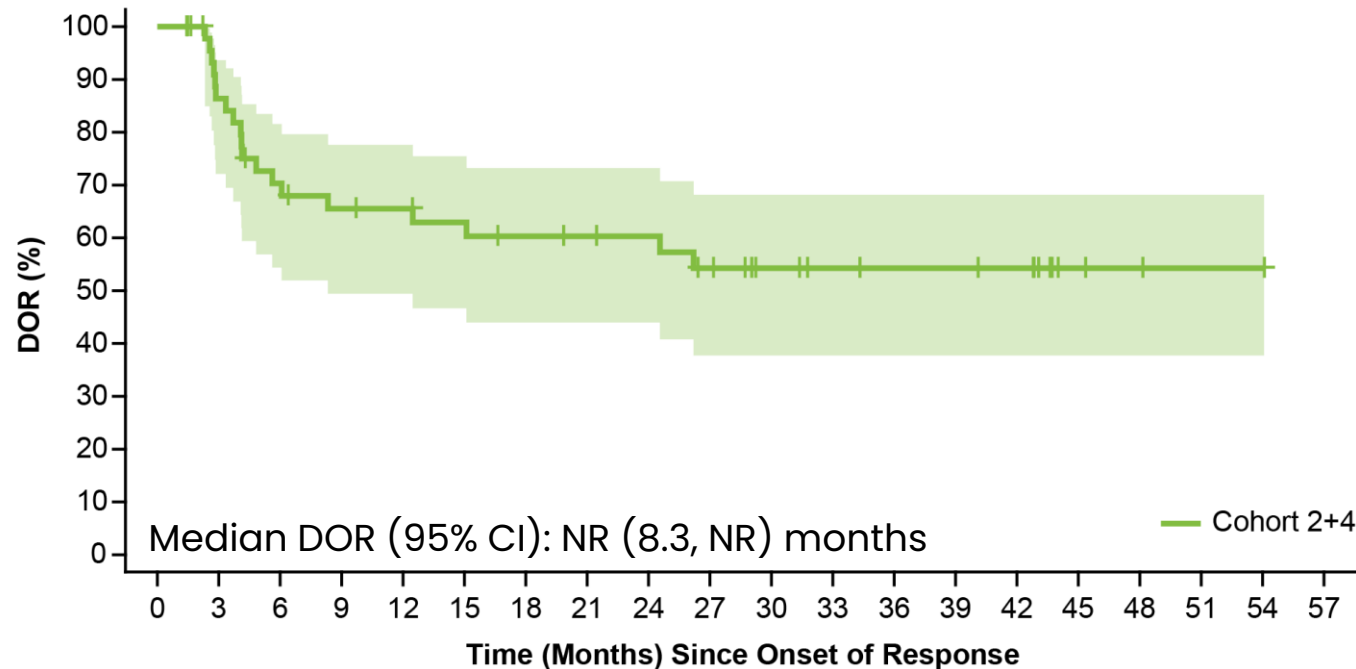
Time to First Response, Duration of Response, and Time on Efficacy Assessment for Confirmed Responders



- Median time from lifileucel infusion to best response was 1.5 months
- Responses deepened over time;** 7 patients (14.6%) initially assessed as a PR achieved confirmed CR; 10 patients (20.8%) improved from SD to PR
- 35.4% of responses were ongoing at the time of data cutoff

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Duration of Response



Patients at Risk:

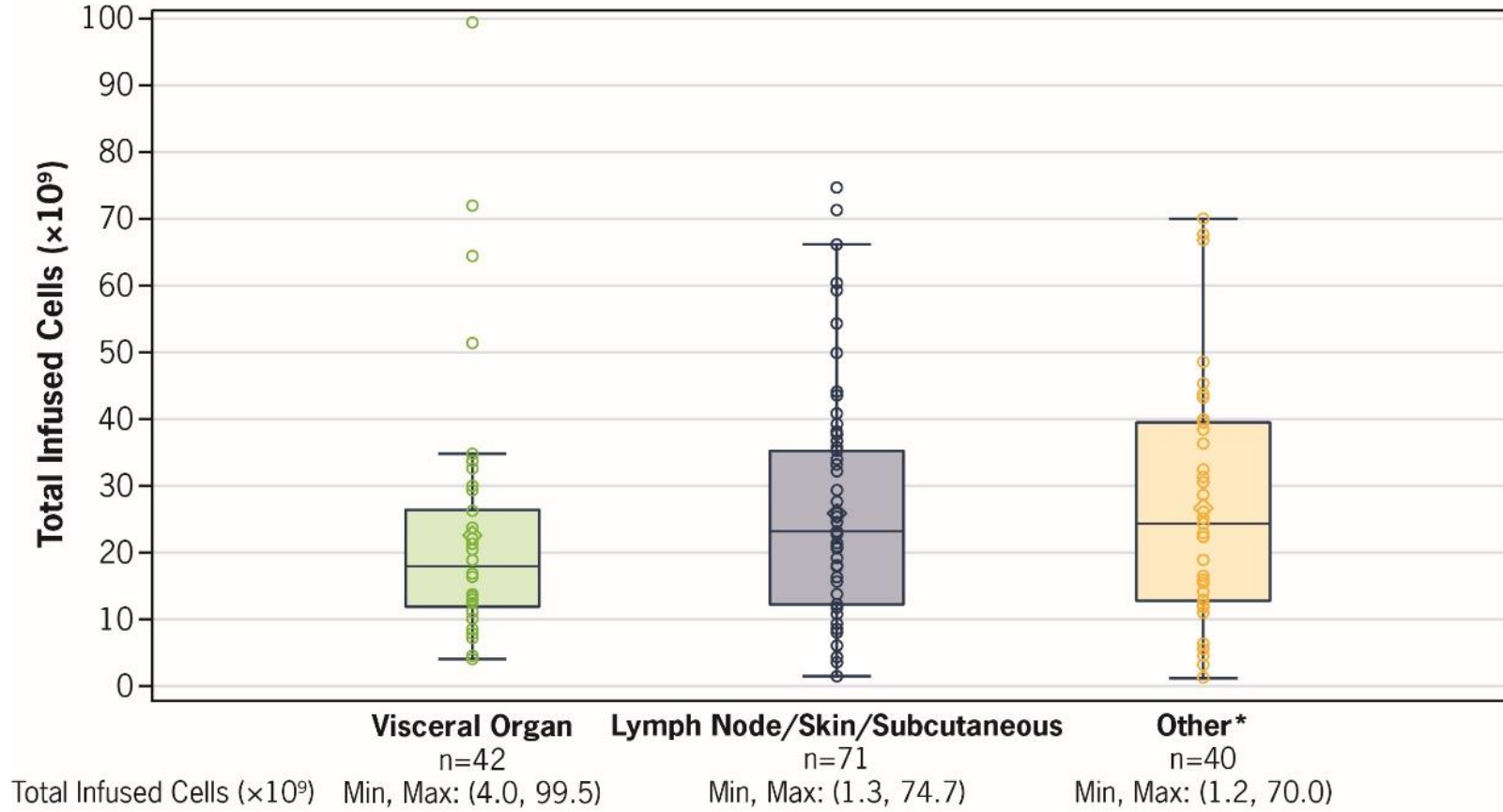
Cohort 2+4	48	38	30	27	26	24	22	21	20	17	13	11	10	10	9	3	2	1	1	0
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*Based on Kaplan-Meier estimate.
CI, confidence interval; DOR, duration of response; NR, not reached.

	Cohort 2+4 (N=48)
Median DOR*, months	NR
95% CI	(8.3, NR)
Min, max (months)	1.4+, 54.1+
DOR ≥12 months, n (%)	26 (54.2)
DOR ≥24 months, n (%)	20 (41.7)

- At a median study follow up of 36.5 months, **median DOR was not reached**
- 41.7% of responses were maintained ≥24 months

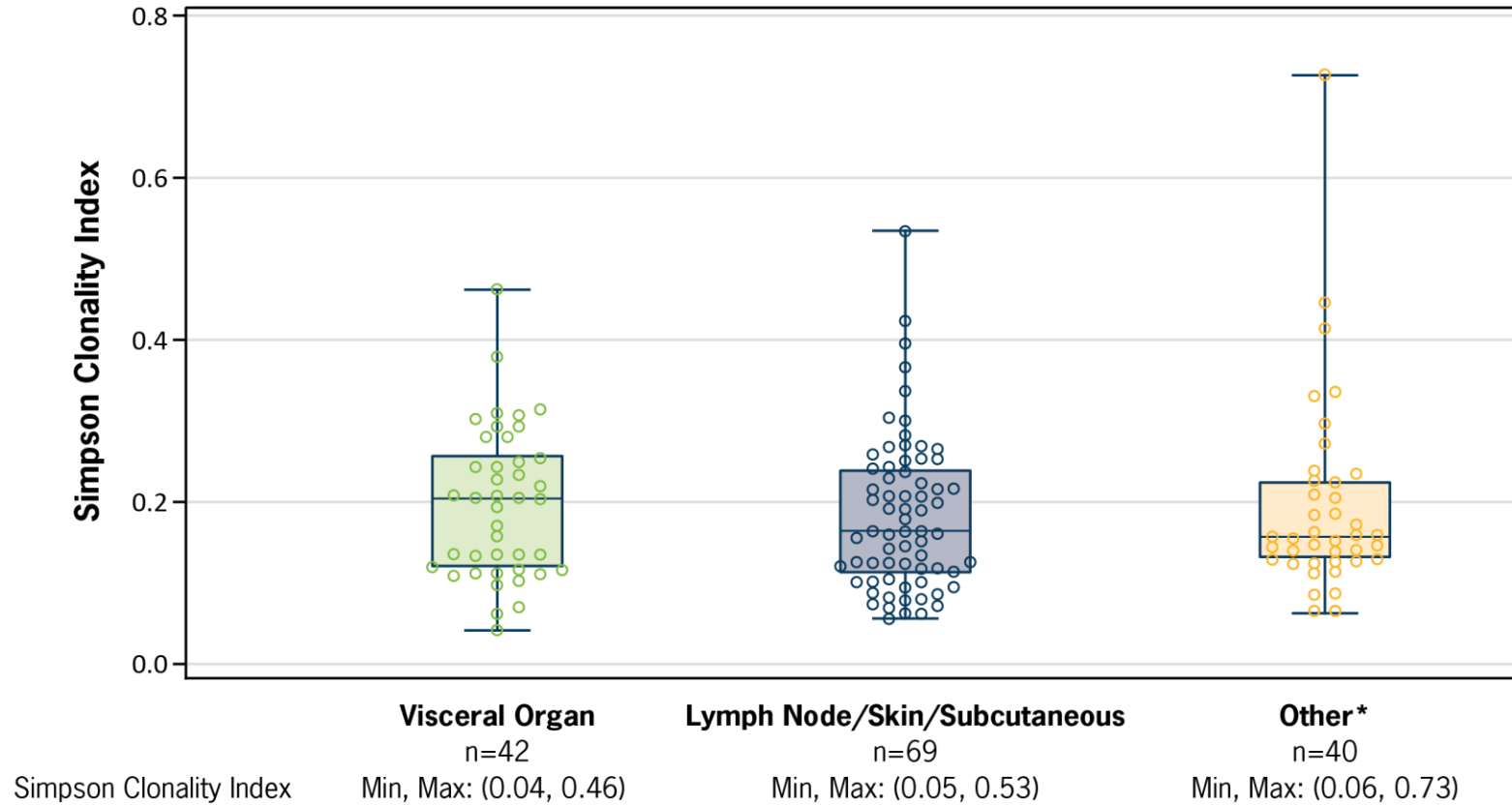
TIL Dose Was Similar Across Anatomic Sites of Resection



▪ TIL dose was similar across anatomic sites of resection

*Other sites of resection included muscle, soft tissue, bone, limb/extremity, and others.
TIL, tumor-infiltrating lymphocyte.

TCR Repertoire Clonality Was Similar Across Anatomic Sites of Resection



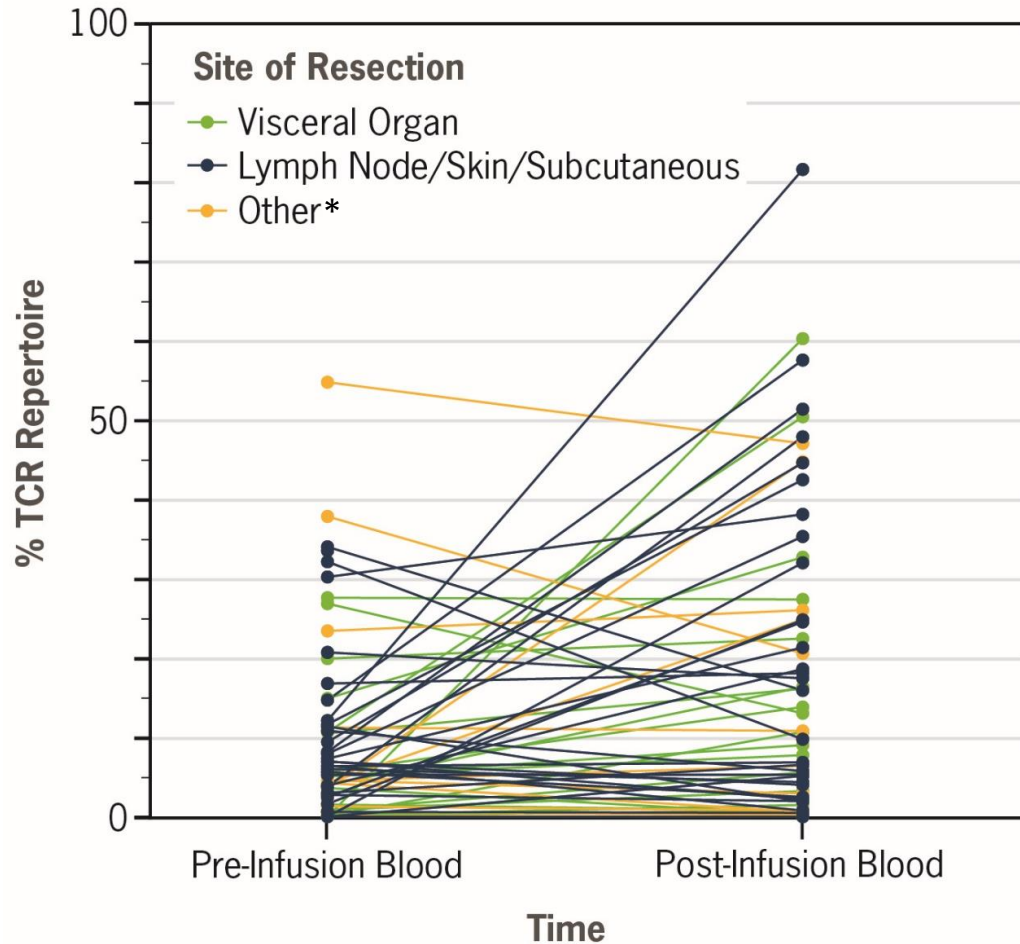
▪ The clonality[†] of the TCR repertoire was similar across tumor resection sites

*Other sites of resection included muscle, soft tissue, bone, limb/extremity, and others.

†The Simpson Clonality Index reflects the mono- or poly-clonality of a sample; values can range from 0 (evenly distributed, polyclonal sample) to 1 (monoclonal sample).

TCR, T cell receptor.

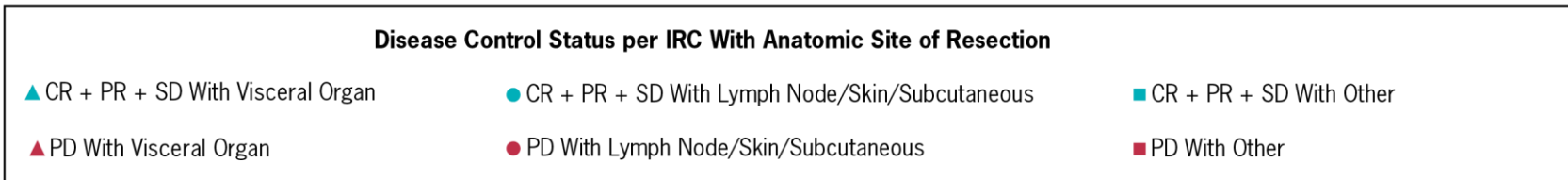
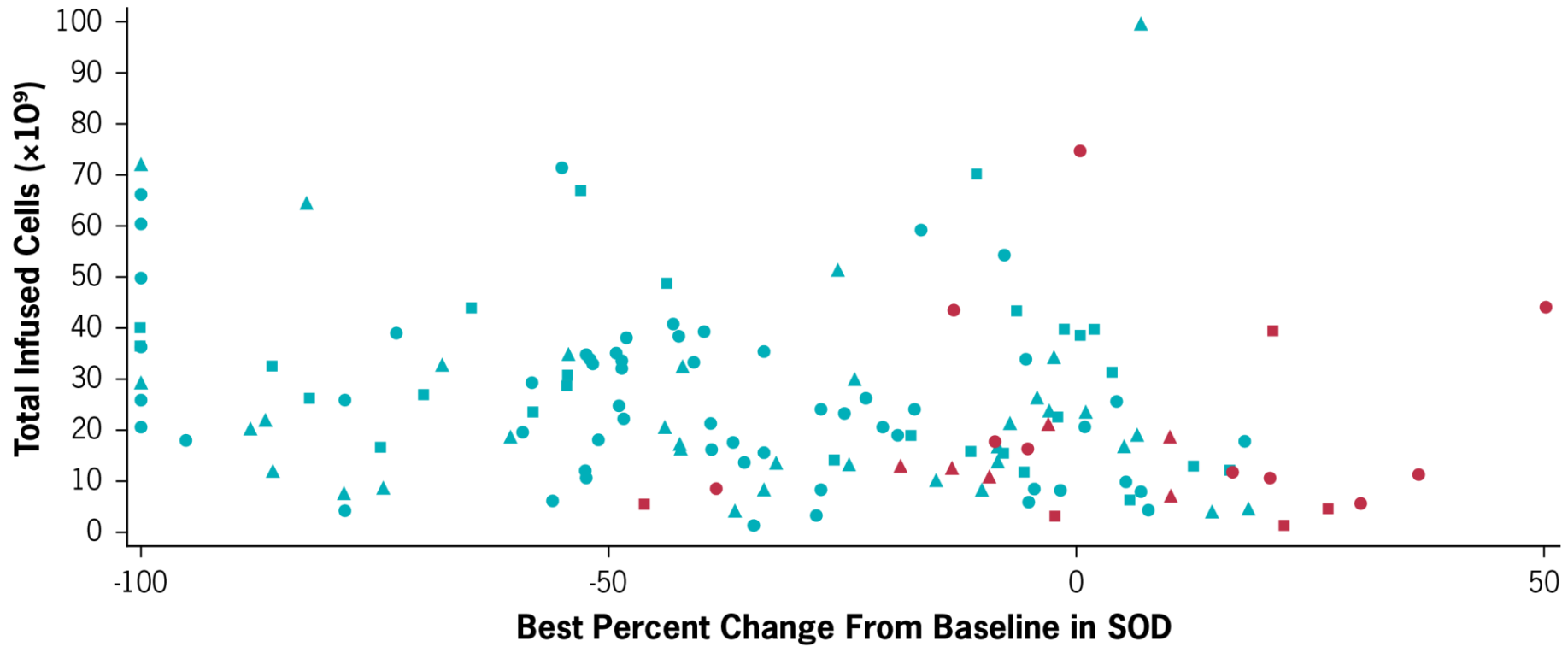
TCR Clonotypes Present in Tumor and TIL Infusion Product Increased in Relative Abundance Across Resection Sites



- The percentage of the TCR repertoire consisting of clonotypes (unique CDR3 sequences) shared between the tumor and TIL infusion product was measured in the patient's peripheral blood
- The relative abundance of these clones increased at Day 42 compared with pre-infusion regardless of the tumor resection site

*Other sites of resection included muscle, soft tissue, bone, limb/extremity, and others.
TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.

Target Lesion Sum of Diameters Reductions Were Seen Across Range of Infused Cell Doses and Resection Sites



CR, complete response; IRC, Independent Review Committee; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters.

Conclusions

■ **Clinical Outcomes:**

- In a large population of heavily pretreated patients with advanced melanoma who progressed on or after ICI and targeted therapy (where appropriate), lifileucel demonstrated clinically meaningful and durable efficacy, and may address an unmet need
- Anatomic sites of tumor resection did not correlate with:
 - Infused TIL cell dose
 - Target lesion SOD reductions
 - Relative abundance of tumor/TIL TCR clonotypes

➤ **Key Takeaways for the Surgical Community:**

- TIL cell therapy is a new paradigm leveraging existing surgical techniques to provide the starting material for TIL cell therapy manufacturing
- Multidisciplinary care involving the surgeon is integral to optimal patient outcomes
- Continued education of surgeons and other stakeholders is necessary to allow for broadened patient access

ICI, immune checkpoint inhibitor; SOD, sum of diameters TCR, T cell receptor; TIL, tumor-infiltrating lymphocytes.

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