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Lifileucel TIL Cell Monotherapy in Patients With Advanced Melanoma After Progression on Immune Checkpoint Inhibitors and Targeted Therapy: Pooled Analysis of Consecutive Cohorts (C-144-01 Study)

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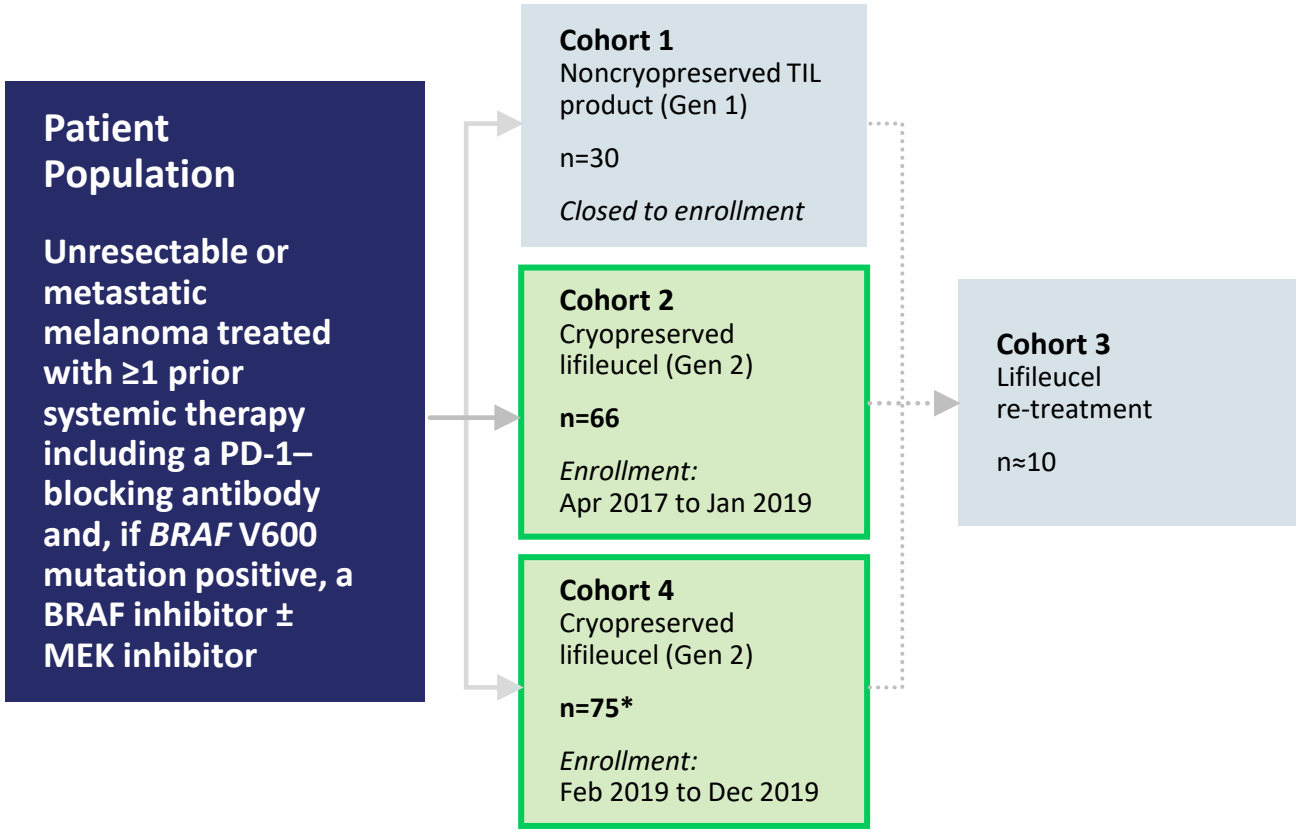
Background

- Treatment options for advanced (unresectable or metastatic) melanoma are limited after non-response or progression on or after ICI and targeted therapy[1-5]
- Autologous TIL cell therapy recognizes and targets a multitude of patient-specific neoantigens to mediate tumor cell death
- Prior data from single-center experiences in ICI-naive melanoma patients over 3 decades[6,7] provide evidence for the potential efficacy of TIL cell therapy
- More recently, a phase 3 study conducted at 2 centers in Europe has shown superior ORR with noncryopreserved TIL cell therapy (49%) versus ipilimumab (21%) (median 1 prior line of therapy; 86% with prior anti–PD-1)[8]
- Lifileucel, an investigational adoptive cell therapy using cryopreserved autologous TIL, has demonstrated encouraging potential efficacy in Cohort 2 of the C-144-01 study (NCT02360579), a multicenter phase 2 study in advanced melanoma
  - Investigator-assessed ORR of 36.4%; median follow-up 33.1 months[9]
- We now report outcomes of lifileucel across Cohorts 2 and 4, representing the largest cell therapy study in advanced melanoma in the post-ICI setting

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. Rosenberg SA et al. *Clin Cancer Res* 2011;17:4550-4557. 7. Seitter SJ et al. *Clin Cancer Res* 2021;27:5289-5298. 8. Haanen JBAG et al. *Ann Oncol.* 2022;33(suppl_7):S808-S869. 9. Larkin J et al. *J Clin Oncol.* 2021;39(suppl_14):9505-9505.
ICI, immune checkpoint inhibitor; ORR, objective response rate; PD-1, programmed cell death protein 1; TIL, tumor-infiltrating lymphocytes.

C-144-01 Study Design

Phase 2, multicenter study to assess the efficacy and safety of autologous TIL (lifileucel) for treatment of patients with metastatic melanoma (NCT02360579)



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

Eligibility and treatment were identical for Cohorts 2 and 4

*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, interleukin 2; IRC, Independent Review Committee; NMA-LD, nonmyeloablative 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.

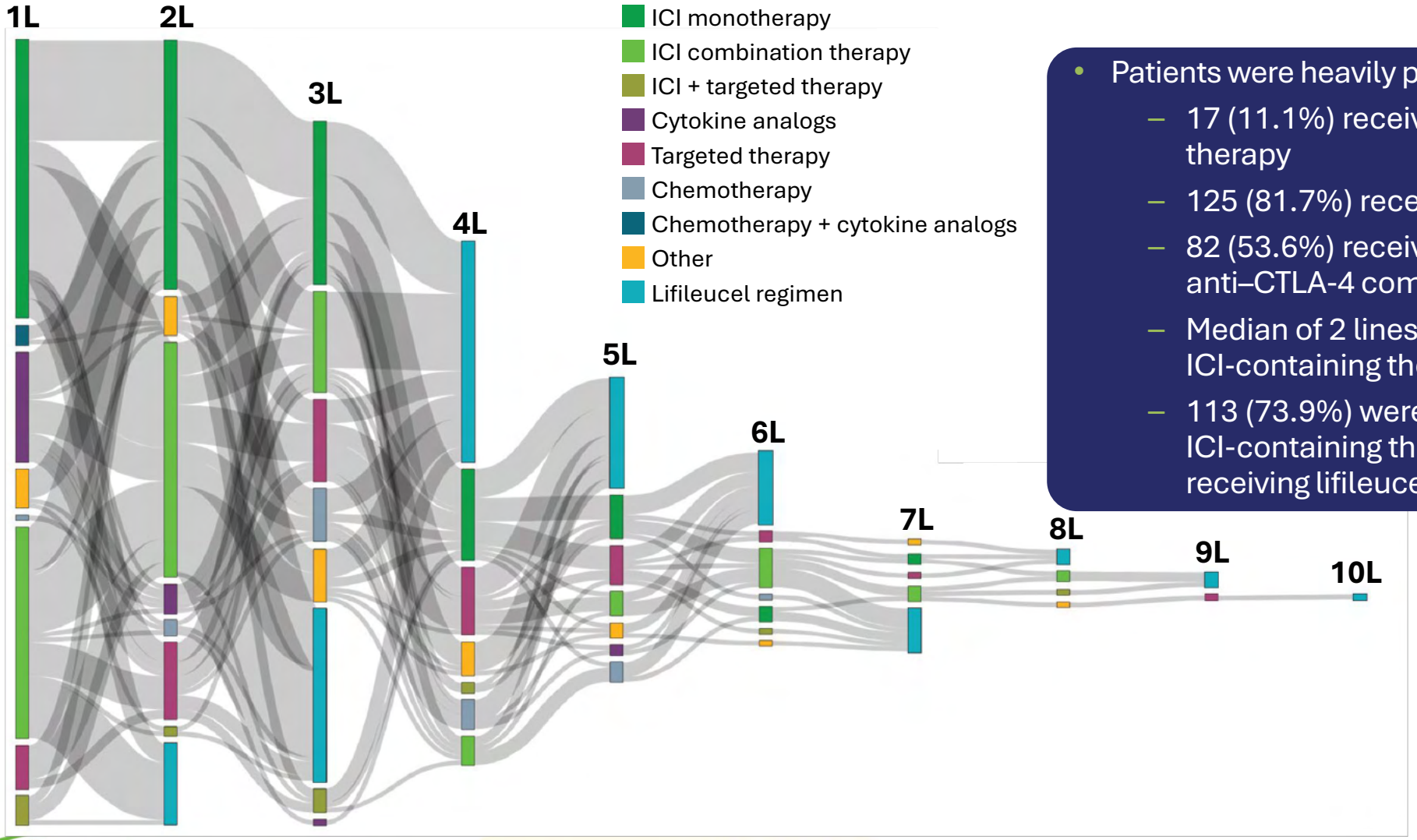
Baseline Patient and Disease Characteristics

Characteristic	Cohort 2 (n=66)	Cohort 4 (n=87)	Cohort 2+4 (N=153)
Median age (range), years	55.0 (20, 79)	58.0 (25, 74)	**56.0 (20, 79)**
Sex, n (%)			
Male	39 (59.1)	44 (50.6)	**83 (54.2)**
Female	27 (40.9)	43 (49.4)	**70 (45.8)**
Screening ECOG performance status, n (%)			
0	42 (63.6)	62 (71.3)	**104 (68.0)**
1	24 (36.4)	25 (28.7)	**49 (32.0)**
Melanoma subtype,* n (%)			
Cutaneous	39 (59.1)	44 (50.6)	**83 (54.2)**
Mucosal	4 (6.1)	8 (9.2)	**12 (7.8)**
Acral	4 (6.1)	6 (6.9)	**10 (6.5)**
BRAF V600-mutated, n (%)	17 (25.8)	24 (27.6)	**41 (26.8)**
PD-L1 status,† n (%)			
TPS ≥1%	37 (56.1)	39 (44.8)	**76 (49.7)**
TPS <1%	12 (18.2)	20 (23.0)	**32 (20.9)**
Liver and/or brain lesions by IRC, n (%)	28 (42.4)	44 (50.6)	**72 (47.1)**
Median target lesion SOD (range), mm	95.8 (13.5, 271.3)	99.5 (15.7, 552.9)	**97.8 (13.5, 552.9)**

Characteristic	Cohort 2 (n=66)	Cohort 4 (n=87)	Cohort 2+4 (N=153)
Baseline lesions in ≥3 anatomic sites, n (%)	44 (66.7)	65 (74.7)	**109 (71.2)**
Baseline target and nontarget lesions,‡ n (%)			
>3	43 (65.2)	73 (83.9)	**116 (75.8)**
LDH, n (%)			
≤ULN	39 (59.1)	31 (35.6)	**70 (45.8)**
>1–2 × ULN	19 (28.8)	35 (40.2)	**54 (35.3)**
>2 × ULN	8 (12.1)	21 (24.1)	**29 (19.0)**
Median number of prior therapies (range)	3.0 (1, 9)	3.0 (1, 8)	**3.0 (1, 9)**
Primary resistance to anti–PD-1/PD-L1 per SITC criteria,[1] n (%)	52 (78.8)	57 (65.5)	**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.
BOR, best overall response; 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; TIL, tumor-infiltrating lymphocytes; TPS, tumor proportion score; ULN, upper limit of normal.

Patient Treatment Patterns



- Patients were heavily pretreated
  - 17 (11.1%) received only 1 line of prior therapy
  - 125 (81.7%) received anti–CTLA-4
  - 82 (53.6%) received anti–PD-1 + anti–CTLA-4 combination
  - Median of 2 lines (range, 1-7) of ICI-containing therapy
  - 113 (73.9%) were retreated with ICI-containing therapy prior to receiving lifileucel

The R package networkD3 was used to generate the Sankey plot.
ICI, immune checkpoint inhibitors; L, line of therapy.

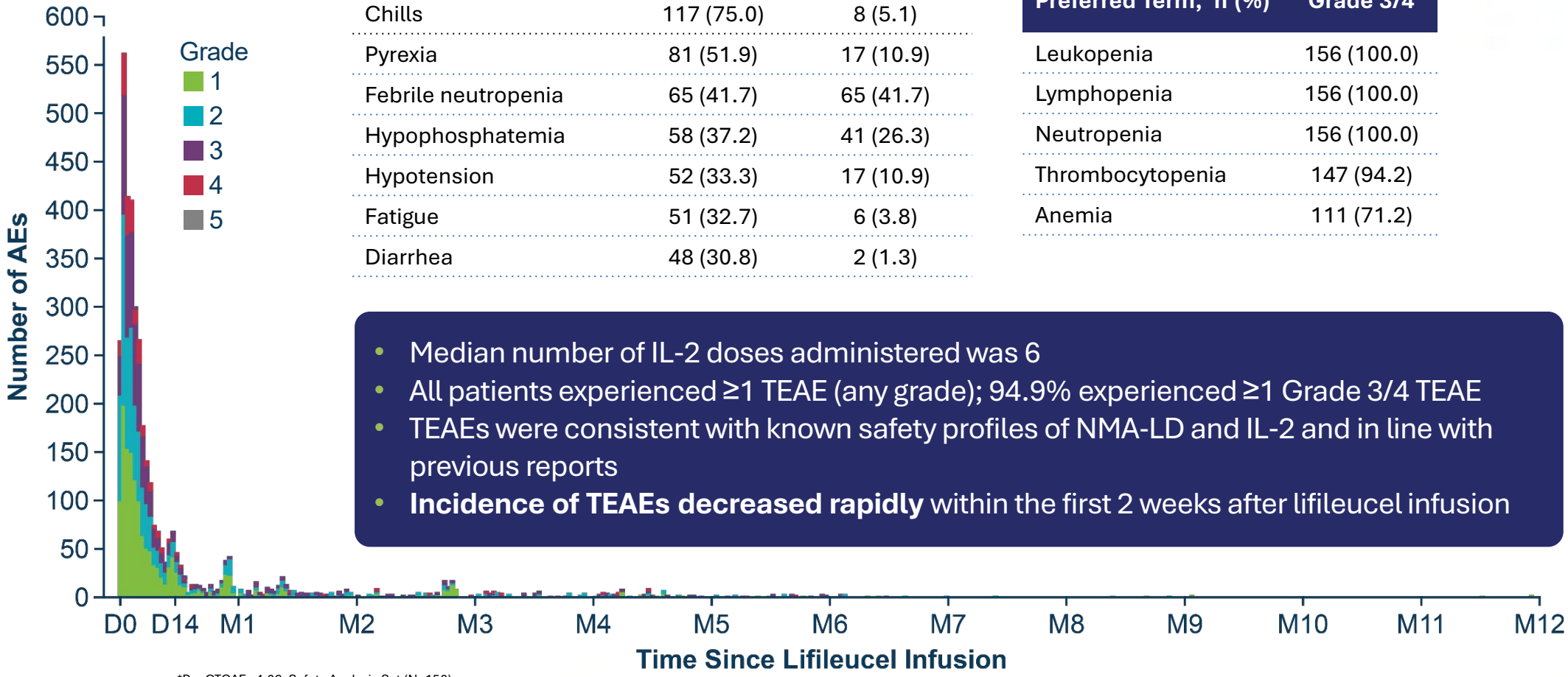
Safety

Non-Hematologic TEAEs in ≥30% of Patients*†

Preferred Term, n (%)	Any Grade	Grade 3/4
Chills	117 (75.0)	8 (5.1)
Pyrexia	81 (51.9)	17 (10.9)
Febrile neutropenia	65 (41.7)	65 (41.7)
Hypophosphatemia	58 (37.2)	41 (26.3)
Hypotension	52 (33.3)	17 (10.9)
Fatigue	51 (32.7)	6 (3.8)
Diarrhea	48 (30.8)	2 (1.3)

Grade 3/4 Hematologic Lab Abnormalities*

Preferred Term, n (%)	Grade 3/4
Leukopenia	156 (100.0)
Lymphopenia	156 (100.0)
Neutropenia	156 (100.0)
Thrombocytopenia	147 (94.2)
Anemia	111 (71.2)



- Median number of IL-2 doses administered was 6
- All patients experienced ≥1 TEAE (any grade); 94.9% experienced ≥1 Grade 3/4 TEAE
- TEAEs were consistent with known safety profiles of NMA-LD and IL-2 and in line with previous reports
- **Incidence of TEAEs decreased rapidly** within the first 2 weeks after lifileucel infusion

*Per CTCAE v4.03; Safety Analysis Set (N=156).
†Grade 5 TEAEs included pneumonia (n=1), acute respiratory failure (n=1), arrhythmia (n=1), and intra-abdominal hemorrhage (n=1).
All occurrences of AEs were counted if a patient experienced a new onset of the same AE at different timepoints. If multiple records were reported on the electronic case report form because of toxicity grade decrease of the same AE that had not resolved, then the event was counted once with the highest grade reported.
15 events were reported after Month 12 (Grade 1, n=7; Grade 2, n=6; Grade 3, n=1; Grade 5, n=1).
AE, adverse event; D, day; IL-2, interleukin 2; M, month; NMA-LD, nonmyeloablative lymphodepletion; TEAE, treatment-emergent adverse event.

Objective Response Rate (IRC-assessed)

	Cohort 2 (n=66)	Cohort 4 (n=87)	Cohort 2+4 (N=153)
ORR, n (%)	**23 (34.8)**	**25 (28.7)**	**48 (31.4)**
(95% CI)	(23.5, 47.6)	(19.5, 39.4)	**(24.1, 39.4)**
Best overall response, n (%)			
CR	5 (7.6)	4 (4.6)	**9 (5.9)**
PR	18 (27.3)	21 (24.1)	**39 (25.5)**
SD	24 (36.4)	47 (54.0)	**71 (46.4)**
Non-CR/Non-PD*	1 (1.5)	0	**1 (0.7)**
PD	15 (22.7)	12 (13.8)	**27 (17.6)**
Nonevaluable†	3 (4.5)	3 (3.4)	**6 (3.9)**

- **IRC-assessed ORR** was **31.4%**
- The concordance rate between IRC- and investigator-assessed ORR was 91%
- Median number of TIL cells infused was 21.1×10^9 (range, 1.2×10^9 to 99.5×10^9)
- Lifileucel was manufactured within specification in 94.7% of patients
- Median time from resection to lifileucel infusion was 33 days

*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).
CR, complete response; IRC, independent review committee; ORR, objective response rate;
PD, progressive disease; PR, partial response; SD, stable disease.

Tumor Burden Reduction and Best Response to Lifileucel

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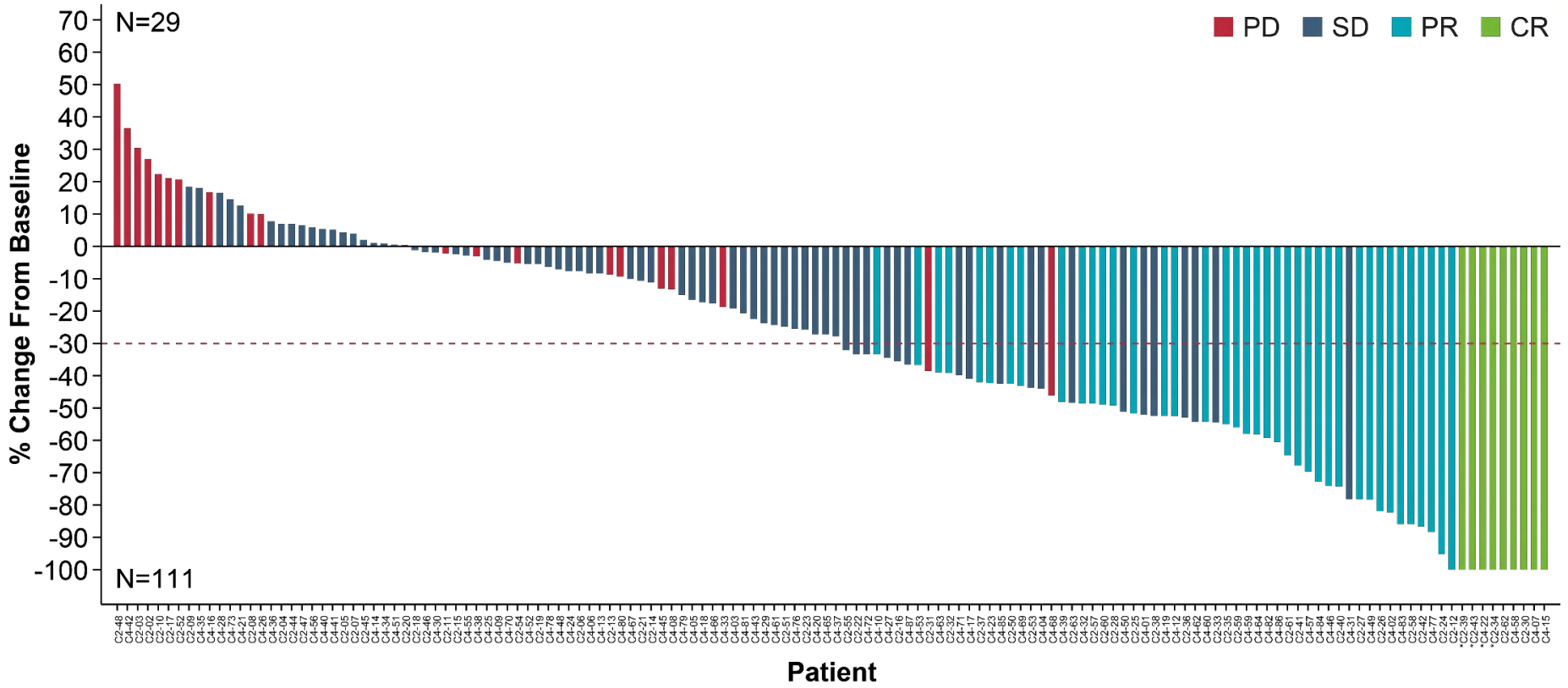
Best Percentage Change From Baseline in Target Lesion SOD (Cohort 2+4)



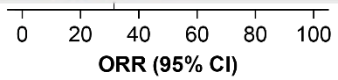
- 79.3% (111/140) of patients had a reduction in tumor burden

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.

Univariable and Multivariable Analyses of ORR

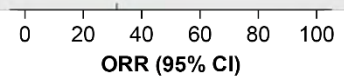
ORR by Patient and Disease Characteristics

Subgroup	n/N	ORR	95% CI
Overall	48/153	31.4	(24.1, 39.4)
Age Group, years			
<65	39/117	33.3	(24.9, 42.6)
≥65	9/36	25.0	(12.1, 42.2)
Baseline ECOG Performance Status			
0	32/84	38.1	(27.7, 49.3)
≥1	16/69	23.2	(13.9, 34.9)
BRAF Mutation Status			
V600E or V600K Mutated	13/41	31.7	(18.1, 48.1)
Non-Mutated	35/112	31.3	(22.8, 40.7)
PD-L1 Status			
TPS ≥1%	28/76	36.8	(26.1, 48.7)
TPS <1%	11/32	34.4	(18.6, 53.2)
Patients with Baseline Liver Lesions	17/59	28.8	(17.8, 42.1)
Patients with Baseline Liver and/or Brain Lesions	19/72	26.4	(16.7, 38.1)
Baseline Target Lesion Sum of Diameters			
<Median (98 mm)	34/74	45.9	(34.3, 57.9)
≥Median (98 mm)	14/75	18.7	(10.6, 29.3)



ORR by Disease and Prior Therapy Characteristics

Subgroup	n/N	ORR	95% CI
Baseline LDH			
≤ULN	27/70	38.6	(27.2, 51.0)
>ULN	21/83	25.3	(16.4, 36.0)
>2×ULN	3/29	10.3	(2.2, 27.4)
Prior Lines of Therapy			
1-3	32/99	32.3	(23.3, 42.5)
≥4	16/54	29.6	(18.0, 43.6)
Prior Anti–CTLA-4 Use			
Yes	41/125	32.8	(24.7, 41.8)
No	7/28	25.0	(10.7, 44.9)
Prior Anti–PD-1 + Anti–CTLA-4 Combination Use			
Yes	22/82	26.8	(17.6, 37.8)
No	26/71	36.6	(25.5, 48.9)
Primary Resistance to Prior Anti–PD-1 or PD-L1 by SITC Definition[1]	36/109	33.0	(24.3, 42.7)



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

95% CI is calculated using the Clopper-Pearson Exact test.

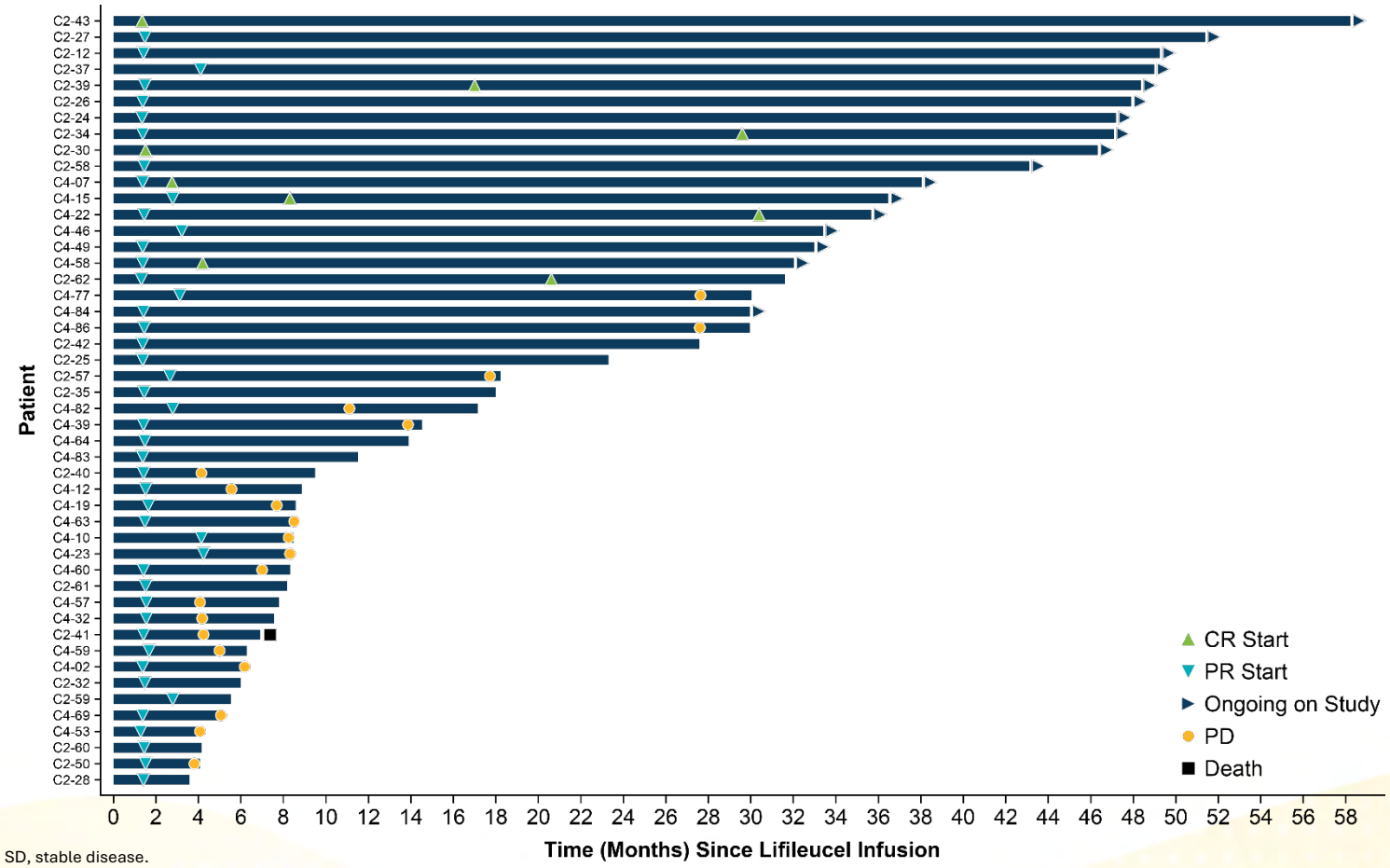
Vertical dotted line represents overall ORR (31.4%).

- Response to lifileucel was observed across all subgroups analyzed
- In adjusted (ECOG PS) multivariable analyses, **LDH** and **target lesion sum of diameters (SOD)** were correlated with ORR (*P*=0.008)
  - Patients with normal LDH and SOD <median had greater odds of response than patients with either (OR: 2.08) or both (OR: 4.42) risk factor(s)

CTLA-4, cytotoxic T lymphocyte-associated protein 4; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; OR, odds ratio; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PS, performance score; SOD, sum of diameters; TPS, tumor proportion score; ULN, upper limit of normal.

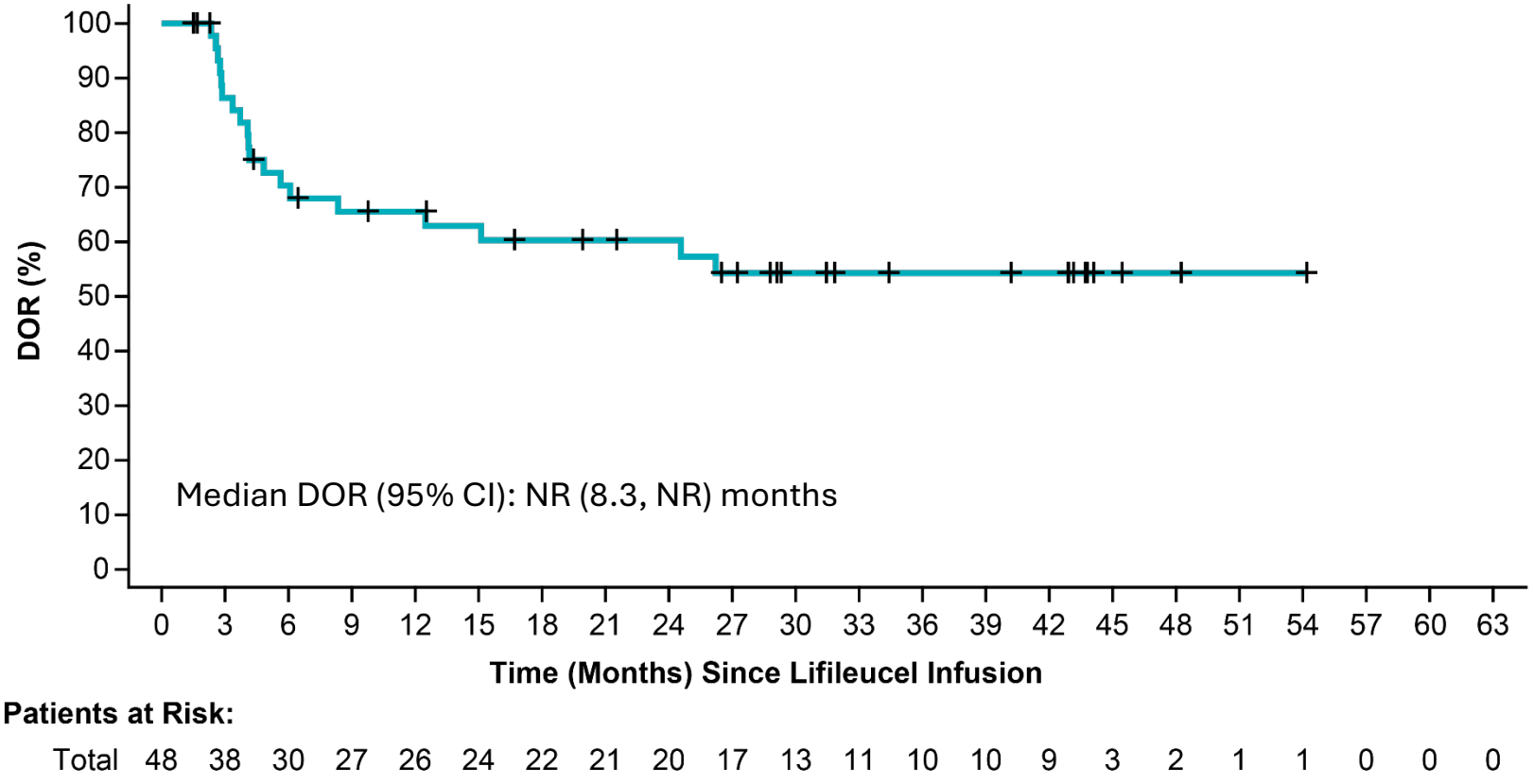
Time to Response, Duration of Response, and Time on Efficacy Assessment for Confirmed Responders (PR or Better)

- Median time from lifileucel infusion to best response was 1.5 months
- **Responses deepened over time**
  - 7 patients (14.6%) initially assessed as PR were later confirmed CR
  - 4 patients (8.3%) converted to CR >1 year post-lifileucel infusion; 2 (4.2%) of these 4 patients converted after 2 years
  - Best response of 10 patients (20.8%) improved from SD to PR
- 35.4% of responses were ongoing as of the data cutoff



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

Duration of Response

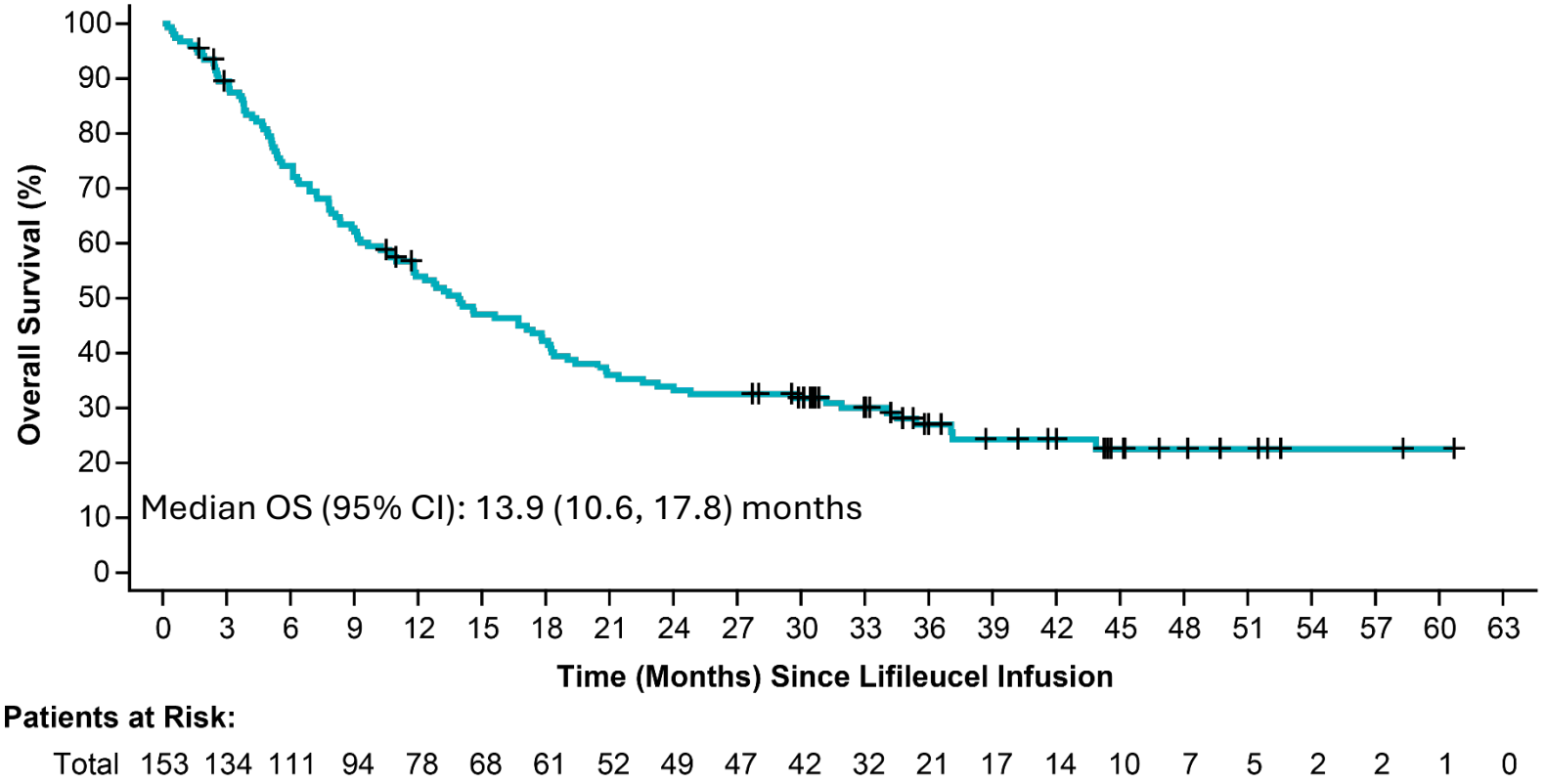


	Cohort 2 (n=23)	Cohort 4 (n=25)	Cohort 2+4 (N=48)
Median DOR*, months	NR	10.4	NR
95% CI	(NR, NR)	(4.1, NR)	(8.3, NR)
Min, max (months)	1.4+, 54.1+	1.4+, 34.3+	1.4+, 54.1+

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

*Based on Kaplan-Meier estimate.
DOR, duration of response; NR, not reached.

Overall Survival

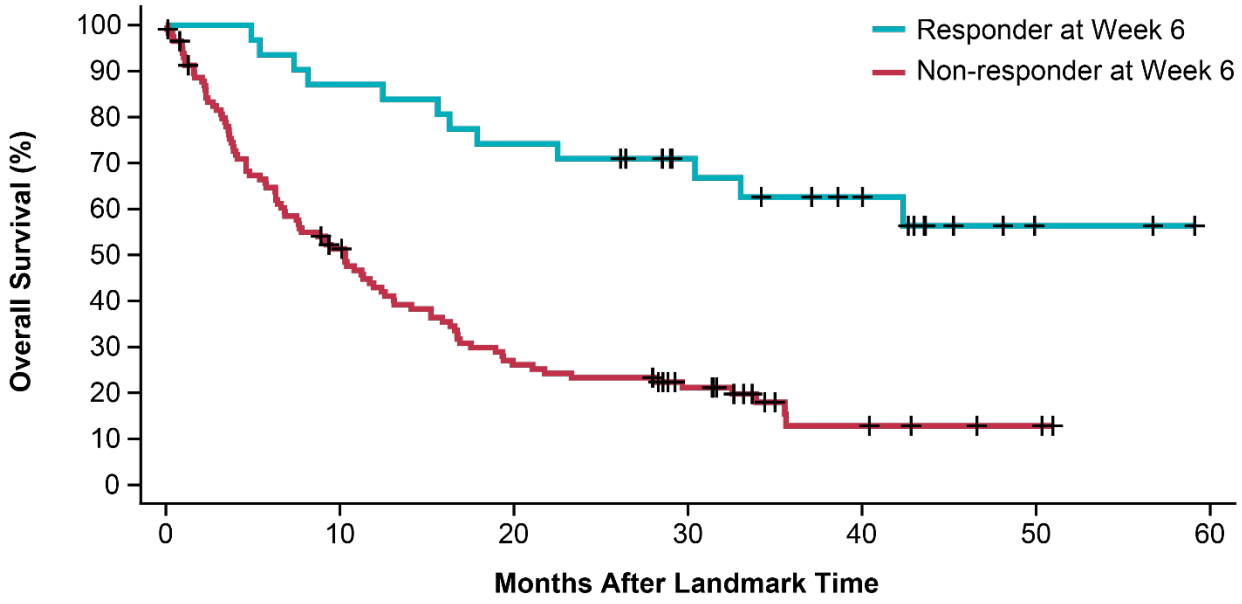


	Cohort 2 (n=66)	Cohort 4 (n=87)	Cohort 2+4 (N=153)
Median OS*, months	15.6	12.7	13.9
95% CI	(11.0, 23.3)	(8.3, 17.8)	(10.6, 17.8)

- The **median OS** was **13.9 months**
- The 12-month OS rate was 54.0% (95% CI: 45.6%, 61.6%)

*Based on Kaplan-Meier estimate.
OS, overall survival.

Overall Survival by Response at 6 Weeks After Lifileucel Infusion



Patients at Risk							
Responders	31	27	23	17	11	2	0
Non-responders	116	56	28	18	5	2	0

	Median OS* (months), by response at 6 weeks[1]	95% CI
Responders	NR	(30.4, NR)
Non-responders	10.3	(6.8, 13.1)
Log-rank *p*-value	<0.0001	

- In a landmark analysis in patients who achieved response at first assessment (6 weeks [~1.5 mo] post-lifileucel infusion), **median OS was not reached**

1. Buyse M, Piedbois P. On the relationship between response to treatment and survival. *Stat Med*. 1996;15:2797-2812.
*Based on Kaplan-Meier estimate.
NR, not reached; OS, overall survival.

Conclusions

- **Lifileucel TIL cell therapy addresses an important unmet need for patients with difficult-to-treat melanoma who lack effective treatment options in the post-ICI setting**
- In a large population of heavily pretreated patients with advanced melanoma who progressed on or after ICI and targeted therapy (where appropriate), lifileucel treatment demonstrated:
  - An expected and manageable safety profile
  - Clinically meaningful and durable efficacy
    - IRC-assessed **ORR was 31.4%**
    - **Median DOR was not reached** at a median follow-up of 36.5 months; 41.7% of responders had DOR ≥24 months
    - Responses were observed across subgroups, including in ICI primary-resistant disease

One-time lifileucel TIL cell therapy may be a viable option for patients with advanced melanoma after initial progression on ICI

CR, complete response; DOR, duration of response; ICI, immune checkpoint inhibitor; IRC, independent review committee; LDH, lactate dehydrogenase; ORR, objective response rate; PR, partial response; SD, stable disease; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes.

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