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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

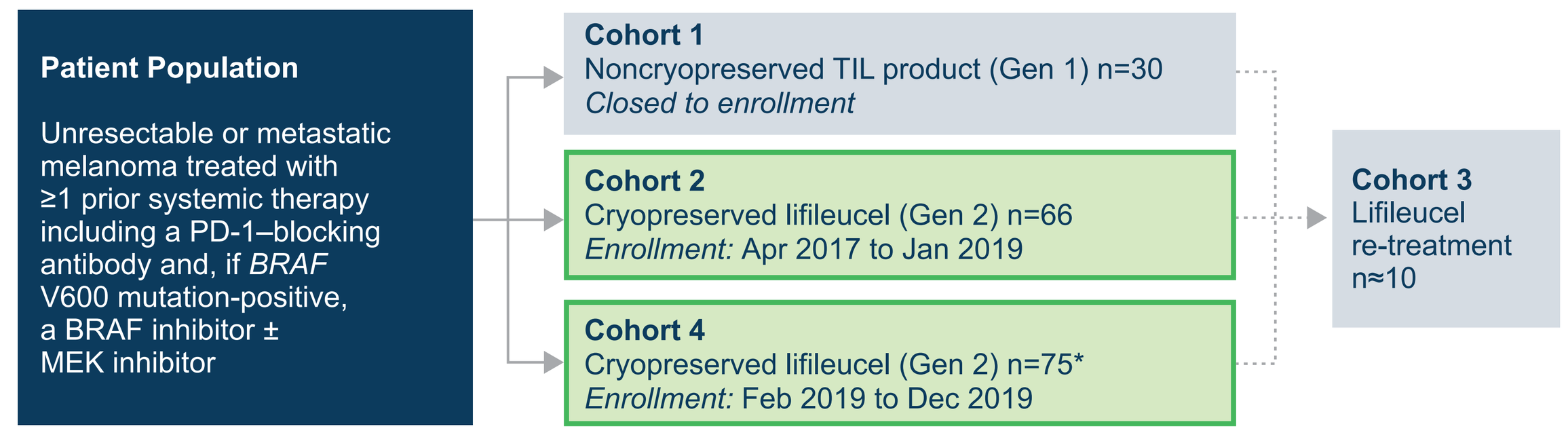
- Treatment options for advanced (unresectable or metastatic) melanoma are limited after non-response or progression on or after ICI and targeted therapy[1-5]
- Autologous TIL cell therapy recognizes and targets a multitude of patient-specific neoantigens to mediate tumor cell death
- Prior data from single-center experiences in ICI-naïve 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%) in patients with a median of 1 prior line of therapy (86% with prior anti–PD-1 therapy)[8]
- Lifileucel, an investigational adoptive cell therapy using cryopreserved autologous TIL, has demonstrated encouraging antitumor activity 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]

Objective

- To report outcomes of lifileucel across Cohorts 2 and 4, representing the largest cell therapy study in advanced melanoma in the post-ICI setting

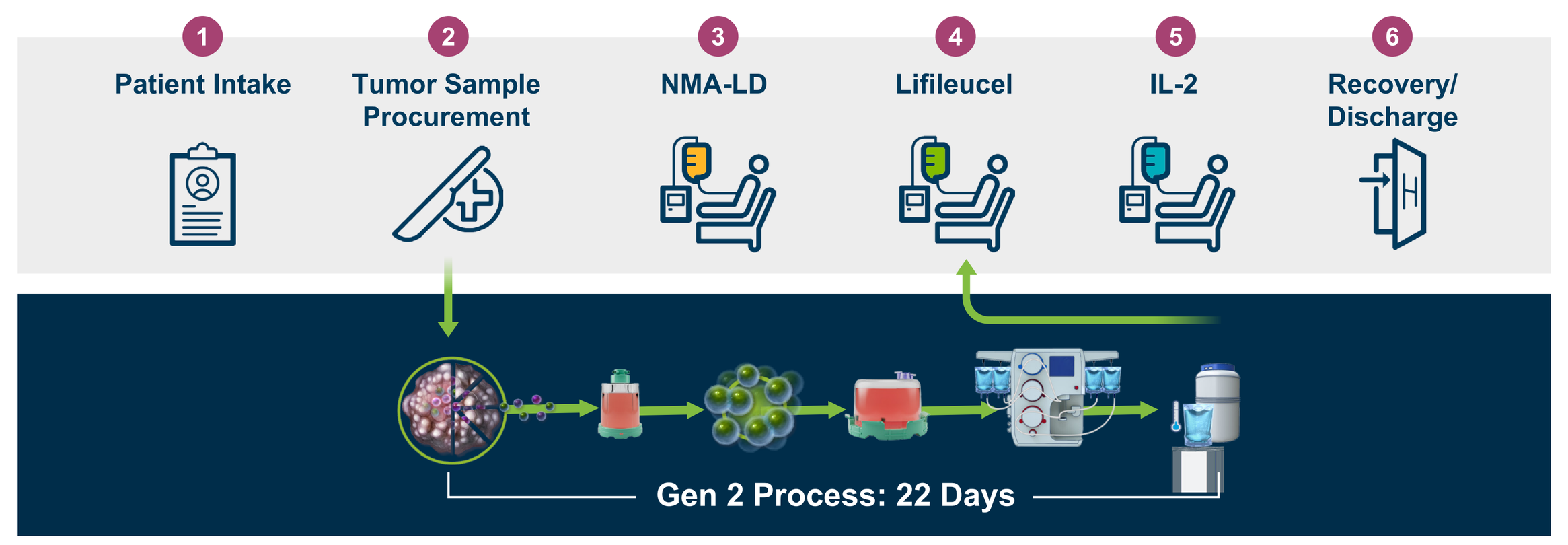
Methods

Figure 1. C-144-01 (NCT02360579) Study Design



*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.

Figure 2. Lifileucel Manufacturing and Patient Journey



Key Endpoints

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

Key Eligibility Criteria

- Documented radiologic disease progression
- ≥1 tumor lesion resectable for TIL generation (≥1.5 cm in diameter) and ≥1 target tumor lesion for RECIST 1.1 response assessment
- Age ≥18 years at time of consent
- ECOG performance status of 0–1
- No limit on number of prior therapies

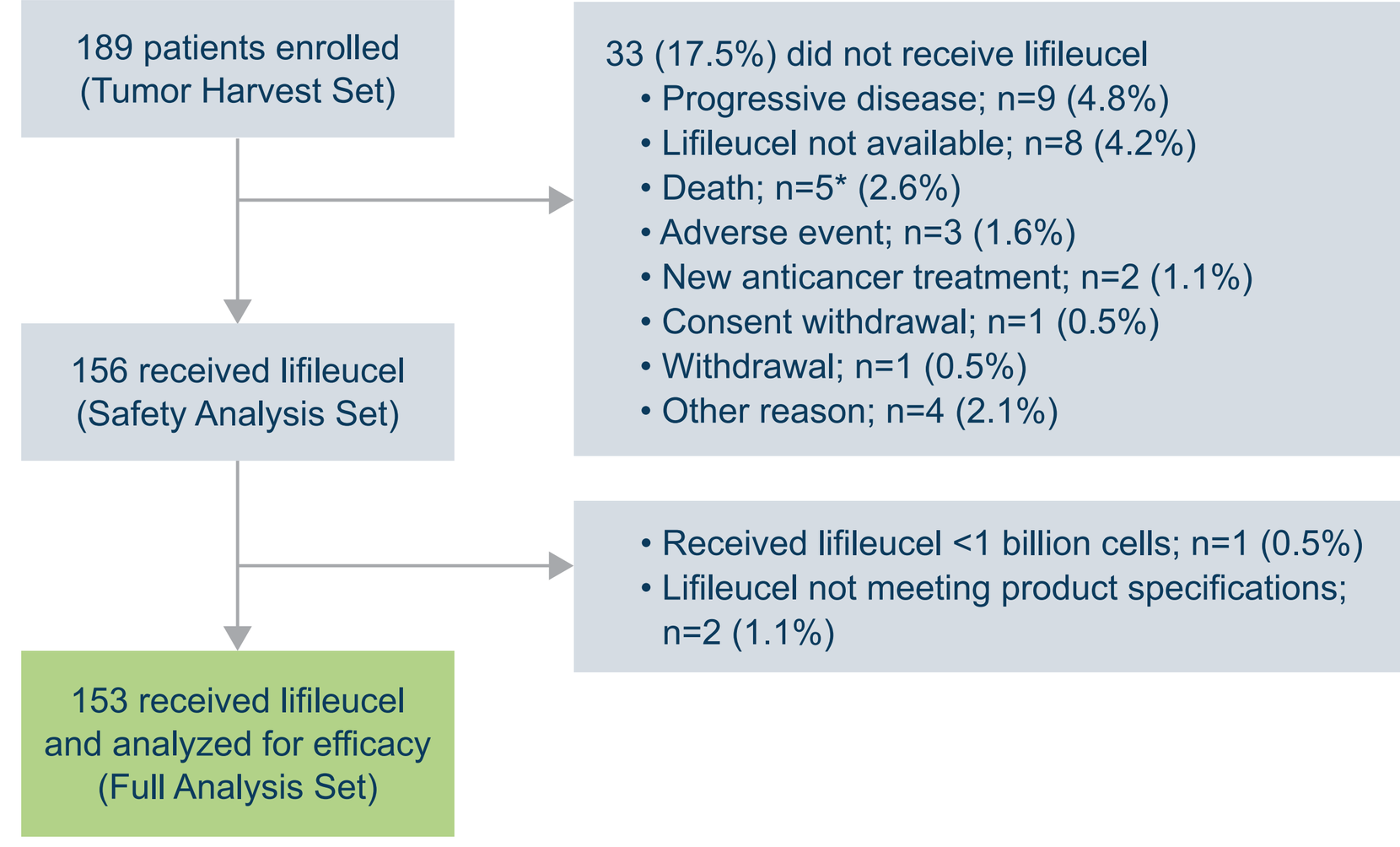
Treatment Regimen

- Lifileucel, a cryopreserved TIL cell therapy product, was used in both Cohorts 2 and 4 and manufactured using the same Gen 2 process (**Figure 2**)
- All patients received NMA-LD, a single lifileucel infusion, and up to 6 doses of high-dose IL-2 (**Figure 2**)
- **Data cutoff date:** 15 July 2022

Eligibility and treatment were identical for Cohorts 2 and 4

Results

Figure 3. CONSORT Diagram for Cohorts 2 and 4



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

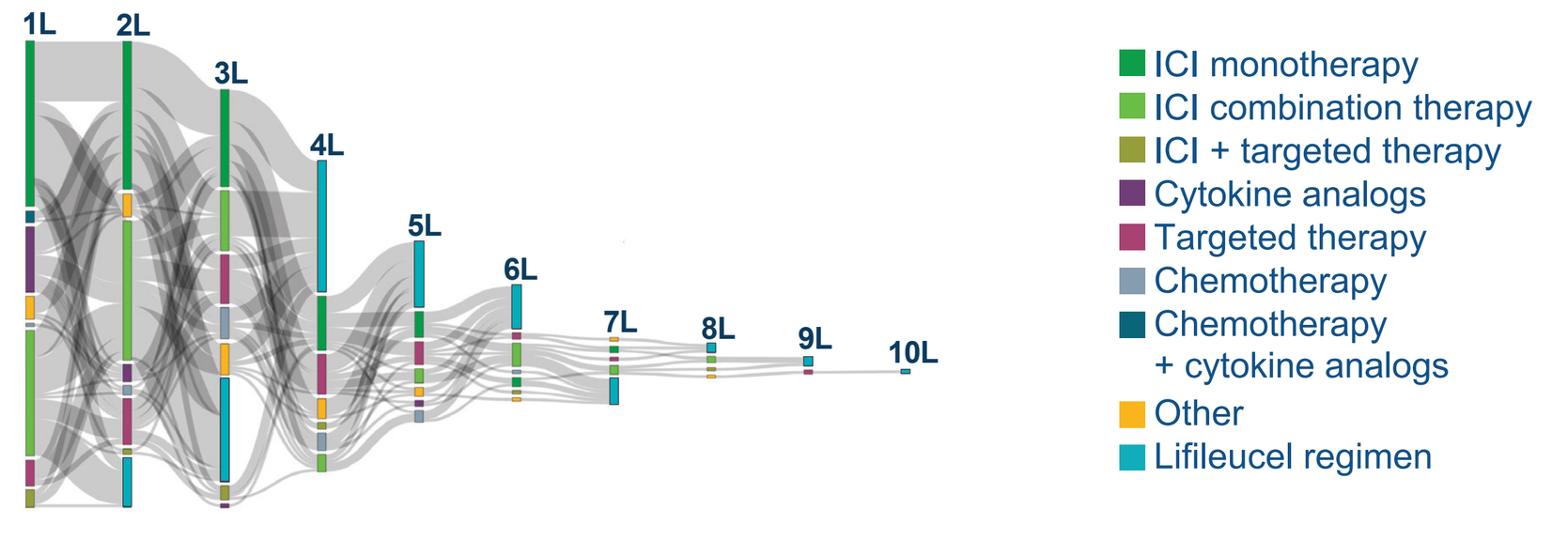
- Median number of TIL cells infused was 21.1 × 10^9 (range 1.2 × 10^9 to 99.5 × 10^9)
- Lifileucel was manufactured within specification in 94.7% of patients
- Median time from resection to lifileucel infusion was 33 days

Table 1. 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)
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,[10] 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 Cohorts 2+4 had missing PD-L1 status.
‡1 patient in Cohort 2 had missing data on number of baseline target and nontarget lesions.

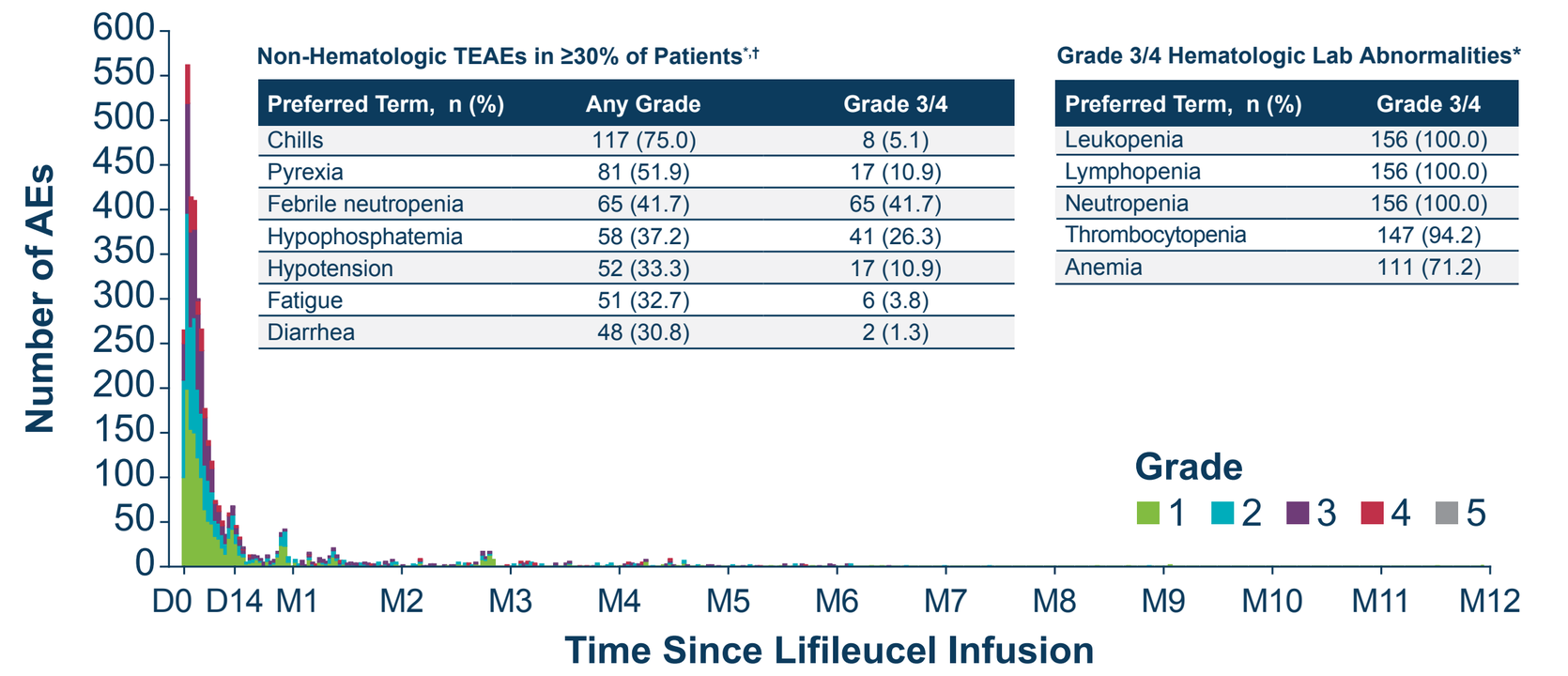
Figure 4. Patient Treatment Patterns



The Sankey plot depicts the therapies that each individual patient received prior to lifileucel and shows the complexity of treatment patterns in each patient's journey.
The first line of therapy is depicted graphically as color-coded bars at the left of the figure with each subsequent line shown on the right.
Green hues represent ICI, either as monotherapy or in combination with other therapies.
Lifileucel is shown in turquoise blue.
The R package networkD3 was used to generate the Sankey plot.

- Patients were heavily pretreated (**Figure 4**)
  - 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 (74%) patients were re-treated with ICI-containing therapy prior to receiving lifileucel

Figure 5. 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)

*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).

- 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 (**Figure 5**)

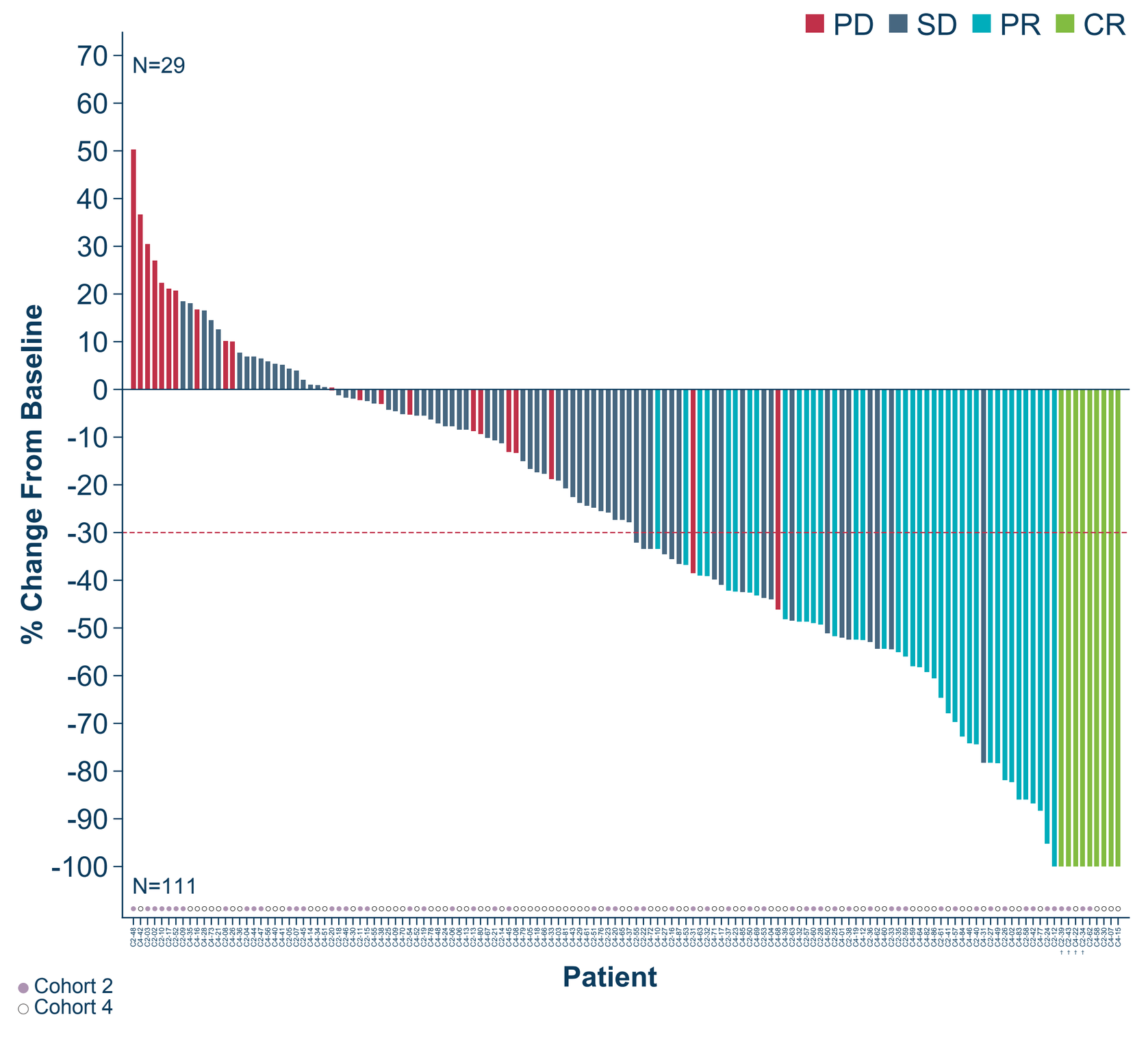
Table 2. Efficacy Outcomes by IRC per RECIST v1.1

	Cohort 2 (n=66)	Cohort 4 (n=87)	Cohorts 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)
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+

*Patient did not have acceptable target lesions and had best overall response of non-CR/non-PD per IRC assessment.
†6 patients were nonevaluable for response (5 due to early death; 1 due to new anticancer therapy).
‡Median DOR was based on Kaplan-Meier estimate.

- The IRC-assessed ORR was 31.4% (**Table 2**)
- The concordance rate between IRC- and investigator-assessed ORR was 91%

Figure 6. Tumor Burden Reduction* and Best Response to Lifileucel

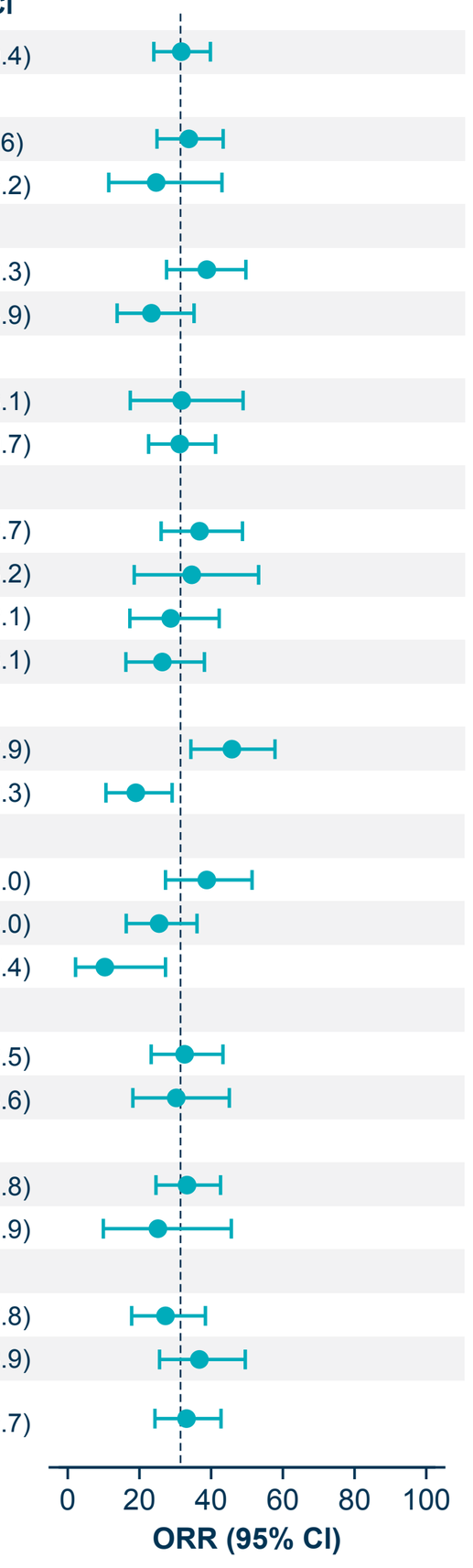


13 patients in the Full Analysis Set are not included (best overall responses included NE [n=6], non-CR/non-PD [n=1], and PD [n=6]) for reasons including having no measurable reassessment at baseline or no post-lifileucel target lesion SOD measurements.
*Best percentage change from baseline in target lesion SOD.
†-100% change from baseline is presented for CR assessment that includes lymph node lesions.

- 79.3% (111/140) of patients had a reduction in tumor burden (**Figure 6**)

Figure 7. Univariable Analysis of ORR

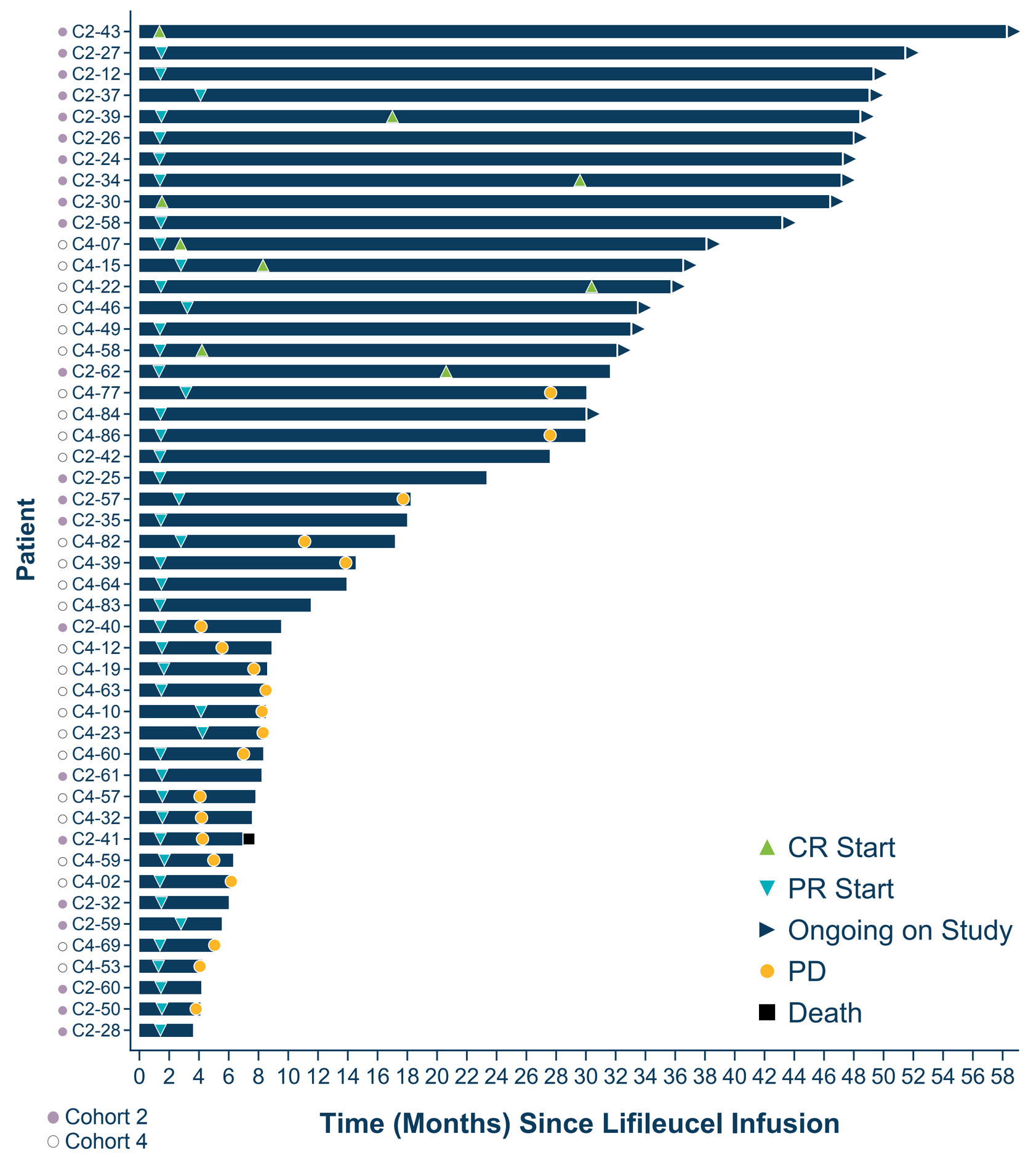
Subgroup	n/N	ORR	95% CI
Overall	48/153	31.4	(24.1, 39.4)
Age Group, years			
<65	39/117	33.3	(24.9, 42.6)
≥65	9/36	25.0	(12.1, 42.2)
Baseline ECOG Performance Status			
0	32/84	38.1	(27.7, 49.3)
≥1	16/69	23.2	(13.9, 34.9)
BRAF Mutation Status			
V600E or V600K Mutated	13/41	31.7	(18.1, 48.1)
Non-Mutated	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)
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[10]	36/109	33.0	(24.3, 42.7)



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

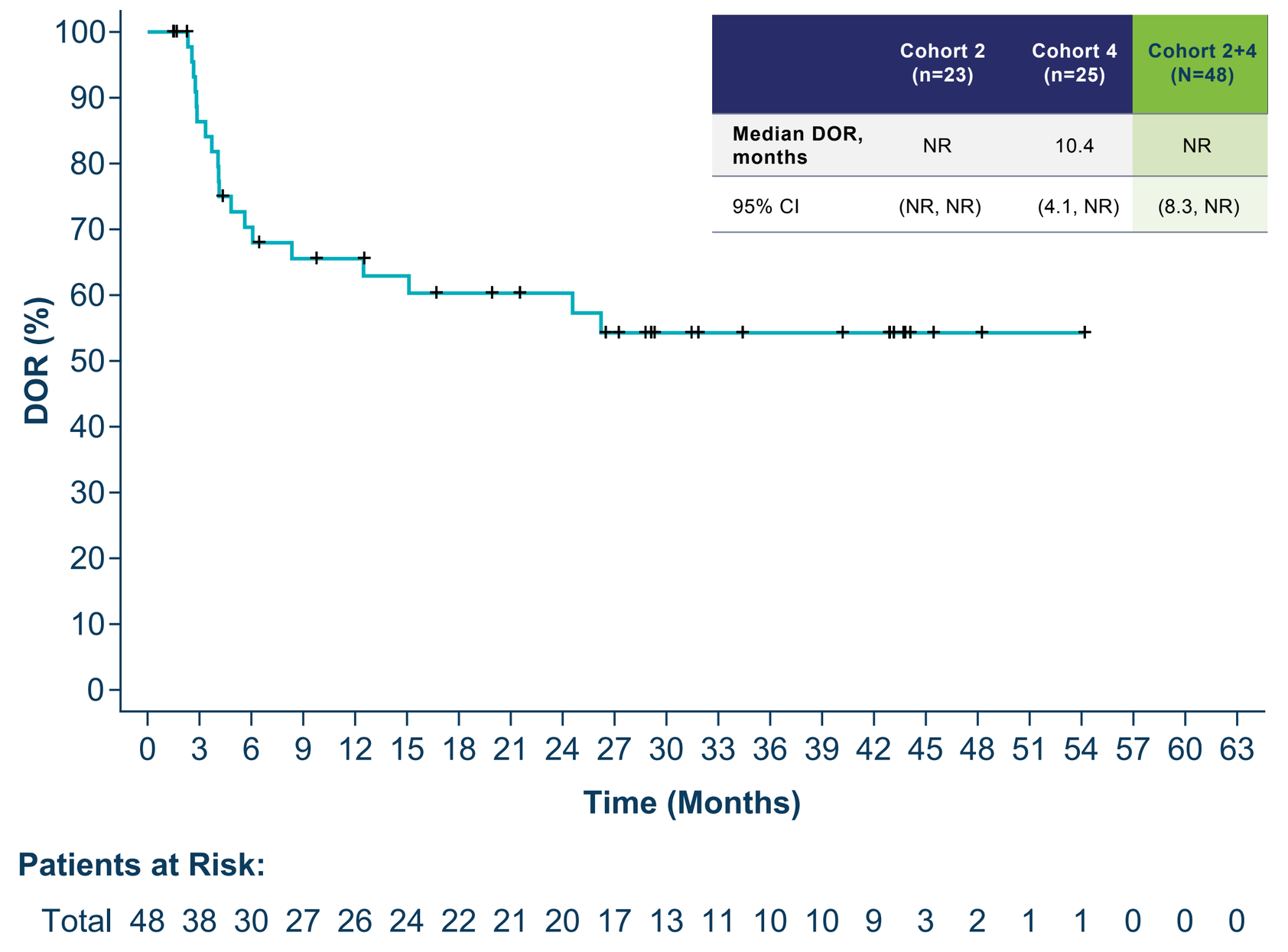
- Response to lifileucel was observed across all subgroups analyzed (**Figure 7**)
- In adjusted (ECOG PS) multivariable analyses, LDH and target lesion SOD were correlated with ORR (P=0.008)
  - Patients with normal LDH and SOD <median had greater odds of response versus patients with either or both risk factors (OR: 2.08 and 4.42, respectively)

Figure 8. Time to Response, DOR, 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 (**Figure 8**)
  - 7 patients (14.6%) initially assessed as PR were later confirmed CR
  - 4 patients (8.3%) converted to CR >1 year post-lifileucel; 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 at data cutoff

Figure 9. Duration of Response



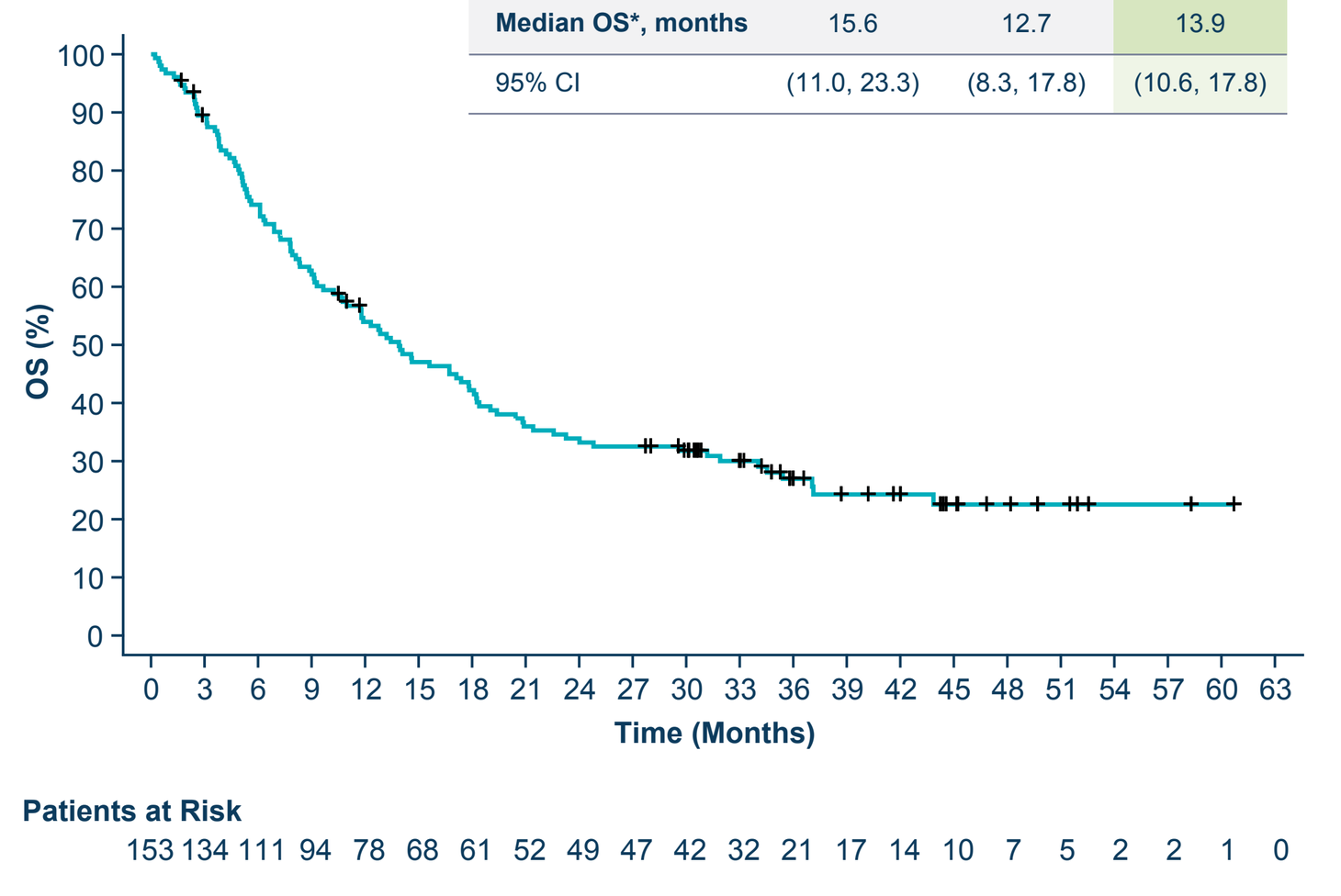
	Cohort 2 (n=23)	Cohort 4 (n=25)	Cohort 2+4 (N=48)
Median DOR, months	NR	10.4	NR
95% CI	(NR, NR)	(4.1, NR)	(8.3, NR)

Patients at Risk:
Total 48 38 30 27 26 24 22 21 20 17 13 11 10 10 9 3 2 1 1 0 0 0

- At a median study follow up of 36.5 months, median DOR was not reached (**Table 2**; **Figure 9**)
- 41.7% of responses were maintained ≥24 months

Figure 10. 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)

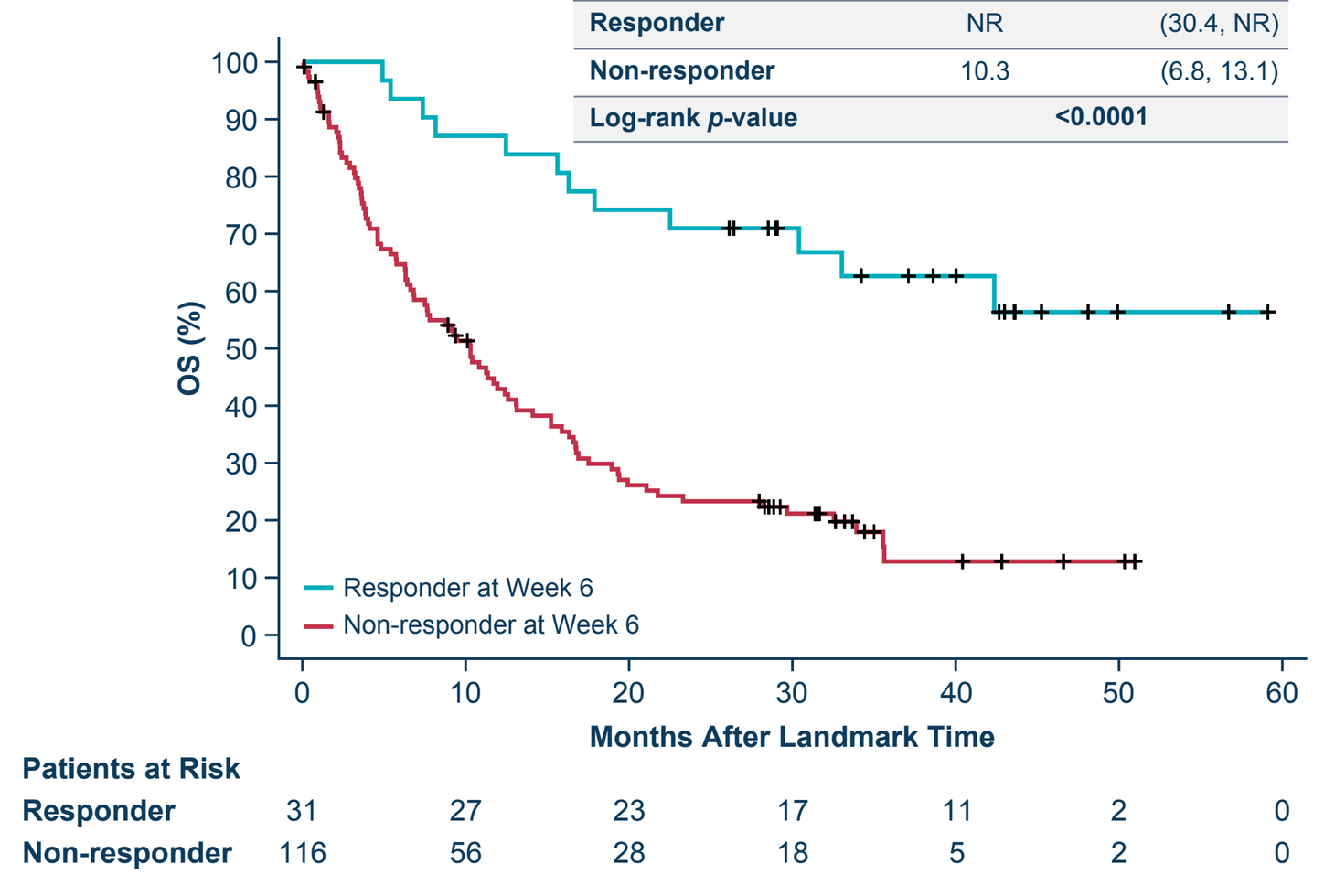


*Based on Kaplan-Meier estimate.

- The median OS was 13.9 months (95% CI: 10.6, 17.8) and the 12-month OS rate was 54.0% (95% CI: 45.6%, 61.6%) (**Figure 10**)

Figure 11. Overall Survival by Response at 6 Weeks After Lifileucel Infusion

	Median OS* (months), by response at 6 weeks[11]	95% CI
Responder	NR	(30.4, NR)
Non-responder	10.3	(6.8, 13.1)
Log-rank p-value	<0.0001	



*Based on Kaplan-Meier estimate.

- In a landmark analysis, in patients who achieved response at first assessment (6 weeks [~1.5 months] post-lifileucel infusion), median OS was not reached (**Figure 11**)

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

References

1. Cybulska-Stopa B et al. Efficacy of ipilimumab after anti-PD-1 therapy in sequential treatment of metastatic melanoma patients - Real world evidence. Adv Med Sci. 2020;65(2):316-23.
2. Olson DJ et al. Pembrolizumab plus ipilimumab following anti-PD-1/L1 failure in melanoma. J Clin Oncol. 2021;39(24):2647-55.
3. VanderWalde A et al. Ipilimumab plus nivolumab versus ipilimumab alone in patients with metastatic or unresectable melanoma that did not respond to anti-PD-1 therapy. Presented at 2022 AACR Annual Meeting.
4. Weber JS et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037).
5. Goldinger SM et al. Chemotherapy after immune checkpoint inhibitor failure in metastatic melanoma: A retrospective multicentre analysis. Eur J Cancer.
6. Rosenberg SA et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res. 2011;17(13):4550-57.
7. Seitter SJ et al. Impact of prior treatment on the efficacy of adoptive transfer of tumor-infiltrating lymphocytes in patients with metastatic melanoma. Clin Cancer Res. 2021;27(19):5289-98.
8. Haanen JBAG et al. Treatment with tumor-infiltrating lymphocytes (TIL) versus ipilimumab for advanced melanoma.
9. Sarnaik AA et al. Lifileucel, a tumor-infiltrating lymphocyte therapy, in metastatic melanoma. J Clin Oncol. 2021;39(24):2656-2666.
10. Kluger HM et al. Defining tumor resistance to PD-1 pathway blockade: Recommendations from the first meeting of the SITC Immunotherapy Resistance Taskforce. J Immunother Cancer.
11. Buyse M, Piedbois P. On the relationship between response to treatment and survival time. Stat Med. 1996;15(24):2797-812.

Abbreviations

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Disclosures