Efficacy and Safety of Lifileucel Tumor-Infiltrating Lymphocyte (TIL) Cell Therapy in Patients With Advanced Melanoma Enrolled in Consecutive Cohorts of the C-144-01 Study

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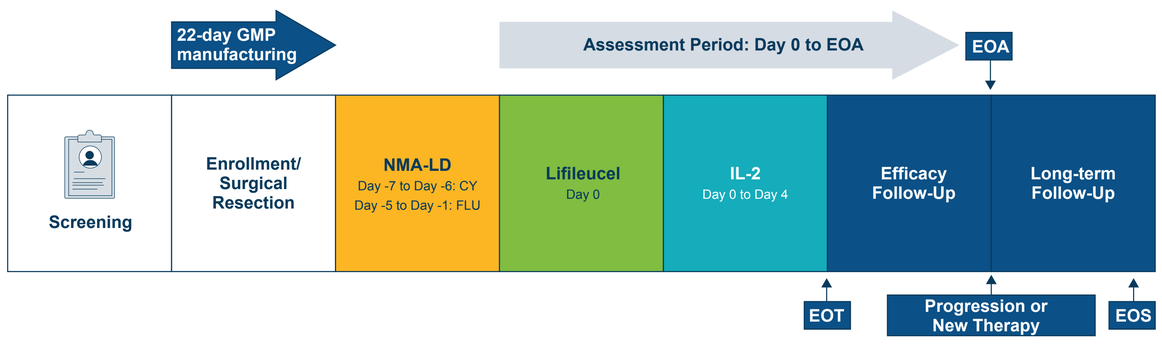
Background

- Treatment options are limited for patients with advanced (unresectable or metastatic) melanoma whose disease progresses on or after ICI and targeted therapy[1-5]
- Lifileucel, an investigational adoptive cell therapy using cryopreserved autologous TIL, demonstrated encouraging activity in Cohort 2 of the C-144-01 study (NCT02360579), a multicenter, phase 2 study in advanced melanoma
  - Investigator-assessed ORR, 36.4%; median follow-up, 33.1 months[6]
- High-dose aldesleukin (IL-2) is approved as monotherapy in metastatic melanoma, and its activity is mediated through endogenous T-cell activation; however, IL-2 monotherapy shows limited efficacy and considerable toxicity[7,8]
- An abbreviated course of high-dose IL-2 (600,000 IU/kg, ≤6 doses) is used as part of the lifileucel regimen to promote T-cell activity[9]
  - Prior studies found no association between IL-2 dose and TIL cell therapy efficacy[10,11]
- Here, we report lifileucel treatment outcomes in the largest cell therapy trial of patients with advanced melanoma that progressed after ICI and targeted therapy, if appropriate (study design in **Supplement Figure 1***) and explore the potential association between number of IL-2 doses and outcomes

*Supplement is available by scanning the QR code at the top of the poster.

Methods

Figure 1. Treatment Regimen and IL-2 Dosing



IL-2 Dosing Per Protocol

- 600,000 IU/kg IV starting 3–24 hours after lifileucel infusion and every ~8–12 hours for up to 6 doses
  - Allowed for up to 4 days after lifileucel infusion for IL-2 toxicity management
  - Number of doses based on tolerance
  - If toxicities could be easily reversed within 24 hours by supportive measures, then additional doses of IL-2 (up to maximum of 6 doses) were given[12-14]
  - Held or stopped at the discretion of the investigator; skipping IL-2 doses was permitted in the event of Grade 3 or 4 toxicity[12-14]

Analyses

- Association of number of IL-2 doses with lifileucel ORR, DOR, safety, and TCR repertoire was explored
- TCR repertoire of tumors, TIL infusion product, and pre- and postinfusion patient blood samples were assessed using RNAseq

Results

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Full Analysis Set (N=153)
Median age (range), years	56.0 (20, 79)
Sex, n (%)	
Male	83 (54.2)
Female	70 (45.8)
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)
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	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,[15] n (%)	109 (71.2)
IL-2 doses§	
Median IL-2 doses (range)	6.0 (0, 6)
1–2 doses, n (%)	16 (10.5)
3–4 doses, n (%)	26 (17.0)
5–6 doses, n (%)	109 (71.2)
Median cumulative IL-2 dose (×10^3 IU/kg)	3528.31
Median relative dose intensity, %¶	100

*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.
§2 patients in the Full Analysis Set did not receive IL-2 due to clinical condition.
¶Up to maximum of 6 doses of IL-2 at 600,000 IU/kg.

- Median number of IL-2 doses administered was 6
- The median cumulative IL-2 dose was 79% lower than the maximum cumulative dose of 1 full treatment course (two 5-day cycles separated by a rest period) of IL-2 monotherapy[12]
- Patients were heavily pretreated (**Table 1**; additional details in **Supplement Figure 2***)

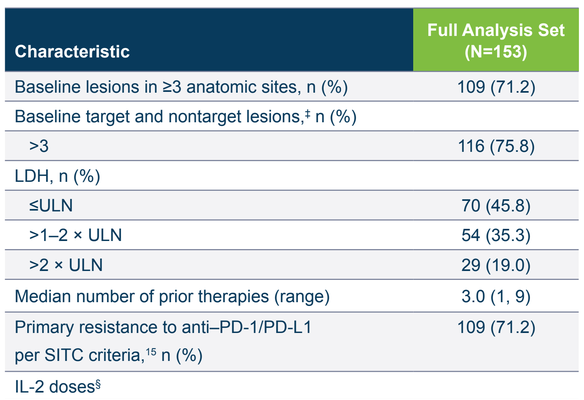
*Supplement is available by scanning the QR code at the top of the poster.

Table 2. ORR and BOR (IRC-Assessed)

Characteristic	Full Analysis Set (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)

*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 anti-cancer therapy).

Figure 2. ORR, by Number of IL-2 Doses

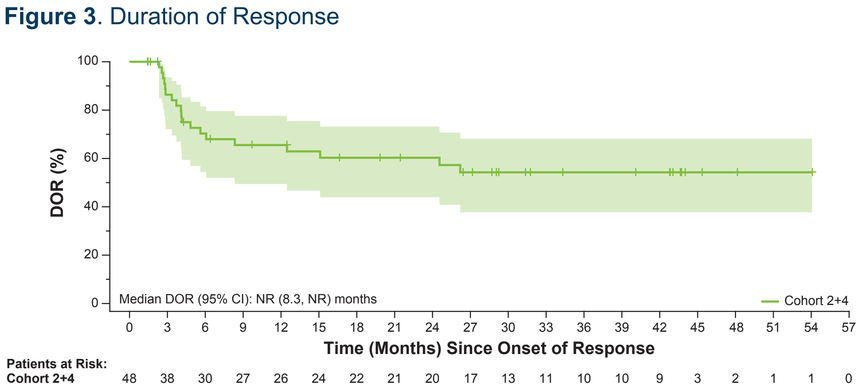


- IRC-assessed ORR was 31.4% (**Table 2**; additional details in **Supplement Figures 3-5‡**) and did not differ significantly by number of IL-2 doses (*p*=0.87; **Figure 2**)
  - ORR was 40% in 5 patients who received prior IL-2 in metastatic setting (all had progressed on or after prior IL-2 therapy)

‡Supplement is available by scanning the QR code at the top of the poster.

Results

Figure 3. Duration of Response



- At a median study follow-up of 36.5 months, median DOR was not reached (**Figure 3**)
- 41.7% of responses were maintained ≥24 months
- There was no significant difference in DOR by number of IL-2 doses (*p*=0.25; **Table 3**)

Table 3. DOR, by Number of IL-2 Doses

	Median DOR,* months (95% CI)	DOR ≥12 months, by number of IL-2 doses, n/N1 (%)
All patients (up to 6 IL-2 doses)	**NR (8.3, NR)**	**26/48 (54.2)**
1–2 IL-2 doses	NR (2.7, NR)	4/6 (66.7)
3–4 IL-2 doses	NR (8.3, NR)	6/8 (75.0)
5–6 IL-2 doses	24.6 (4.1, NR)	16/34 (47.1)

* Based on Kaplan-Meier estimate.

Overall Survival

- The median OS was 13.9 months, and the 12-month OS rate was 54.0% (95% CI: 45.6, 61.6) (**Supplement Figure 6***)
- Response to lifileucel was associated with a 73.4% reduced risk of death compared with nonresponse (HR, 0.266; *p*<0.0001)†
- 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 (**Supplement Figure 7***)

*Supplement is available by scanning the QR code at the top of the poster.
†Using a Cox proportional hazards model with objective response as a time-dependent covariate.

Table 4. Nonhematologic TEAEs in ≥30% of All Patients, by Number of IL-2 Doses*,†,‡

	1–2 IL-2 Doses (n=16)		3–4 IL-2 Doses (n=26)		5–6 IL-2 Doses (n=111)		Safety Analysis Set (N=156)	
Preferred Term, n (%)	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Chills	10 (62.5)	1 (6.3)	18 (69.2)	2 (7.7)	89 (80.2)	5 (4.5)	117 (75.0)	8 (5.1)
Pyrexia	10 (62.5)	2 (12.5)	14 (53.8)	5 (19.2)	57 (51.4)	10 (9.0)	81 (51.9)	17 (10.9)
Hypotension	8 (50.0)	2 (12.5)	9 (34.6)	3 (11.5)	34 (30.6)	12 (10.8)	52 (33.3)	17 (10.9)
Febrile neutropenia	7 (43.8)	7 (43.8)	13 (50.0)	13 (50.0)	45 (40.5)	45 (40.5)	65 (41.7)	65 (41.7)
Fatigue	6 (37.5)	0	7 (26.9)	0	38 (34.2)	6 (5.4)	51 (32.7)	6 (3.8)
Diarrhea	6 (37.5)	1 (6.3)	8 (30.8)	0	34 (30.6)	1 (0.9)	48 (30.8)	2 (1.3)
Hypophosphatemia	5 (31.3)	4 (25.0)	9 (34.6)	5 (19.2)	44 (39.6)	32 (28.8)	58 (37.2)	41 (26.3)

Table 5. Grade 3/4 Hematologic Lab Abnormalities, by Number of IL-2 Doses*,†

Preferred Term, n (%)	1–2 IL-2 Doses (n=16)	3–4 IL-2 Doses (n=26)	5–6 IL-2 Doses (n=111)	Safety Analysis Set (N=156)
Leukopenia	16 (100)	26 (100)	111 (100)	156 (100)
Lymphopenia	16 (100)	26 (100)	111 (100)	156 (100)
Neutropenia	16 (100)	26 (100)	111 (100)	156 (100)
Thrombocytopenia	16 (100)	25 (96.2)	103 (92.8)	147 (94.2)
Anemia	12 (75.0)	22 (84.6)	74 (66.7)	111 (71.2)

*Per CTCAE v4.03; Safety Analysis Set (N=156).
†3 patients in the Safety Analysis Set (defined as patients who received any lifileucel infusion) did not receive IL-2.
‡Grade 5 TEAEs included pneumonia (n=1), acute respiratory failure (n=1), arrhythmia (n=1), and intra-abdominal hemorrhage (n=1). Of these, pneumonia, acute respiratory failure, and intra-abdominal hemorrhage occurred in patients receiving 5–6 IL-2 doses, and arrhythmia occurred in a patient who did not receive IL-2.

- 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
- IL-2 discontinuation was guided by clinical tolerance, thus limiting safety comparisons across dose groups
- Reported Grade 3/4 TEAEs were similar across IL-2 dose groups and consistent with those of the overall population (**Table 4**)
- All patients developed Grade 3/4 lymphopenia (per lab values) after NMA-LD (Day 0–4) (**Table 5**)

Translational Analyses by Number of IL-2 Doses

- Polyclonality was similar between IL-2 dose groups within each sample type (**Supplement Figure 8***)
- uCDR3 clonotypes identified in both tumor and TIL infusion product expanded and persisted to a similar degree, regardless of number of IL-2 doses (**Supplement Figure 9***)

*Supplement is available by scanning the QR code at the top of the poster.

Conclusions

- In a large population of heavily pretreated patients with advanced melanoma that 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 of 31.4%
    - Median DOR not reached at a median follow-up of 36.5 months
    - Responses were observed across subgroups, including in ICI primary-resistant disease
- The number of administered IL-2 doses did not show association with clinical outcomes
  - Safety profile, ORR, and DOR were comparable across the range of IL-2 doses
  - Responses to lifileucel were observed despite IL-2 administration during lymphopenia and in patients who progressed after prior IL-2 monotherapy
  - TCR clonality data suggest similar clonal expansion and persistence of TIL-derived clones across all IL-2 dose groups

One-time lifileucel TIL cell therapy may be a viable option for patients with advanced melanoma after initial progression on ICI. Further, protocol-guided abbreviated high-dose IL-2 dosing, with discontinuation driven by clinical tolerance, is feasible and does not independently contribute to anti-neoplastic activity observed with lifileucel

- A phase 3 trial assessing the efficacy and safety of lifileucel in combination with pembrolizumab compared with pembrolizumab alone in patients with untreated advanced melanoma (TILVANCE-301) is underway

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Abbreviations

BOR, best overall response; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CY, cyclophosphamide; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EOA, end of assessment; EOS, end of study; EOT, end of treatment; FLU, fludarabine; GMP, Good Manufacturing Practice; HR, hazard ratio; ICI, immune checkpoint inhibitor; IL-2, interleukin 2; IRC, independent review committee; LDH, lactate dehydrogenase; N1, number of patients in subgroup; NMA-LD, nonmyeloablative lymphodepletion; NR, not reached ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease; SITC, Society for Immunotherapy of Cancer; SOD, sum of diameters; TCR, T-cell receptor; TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocyte; TPS, tumor proportion score; uCDR3, unique CDR3; ULN, upper limit of normal.

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Disclosures

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P223
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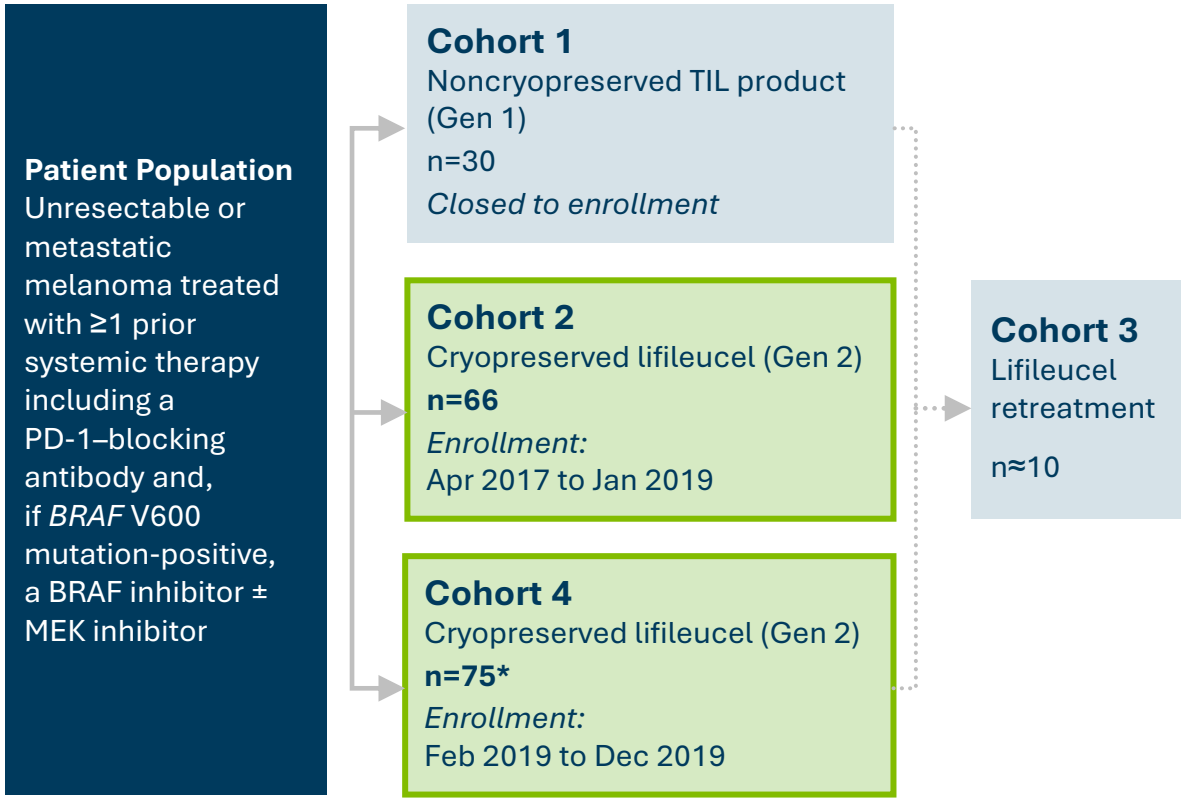
Poster Supplement

Supplement Figure 1.

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)



*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.

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

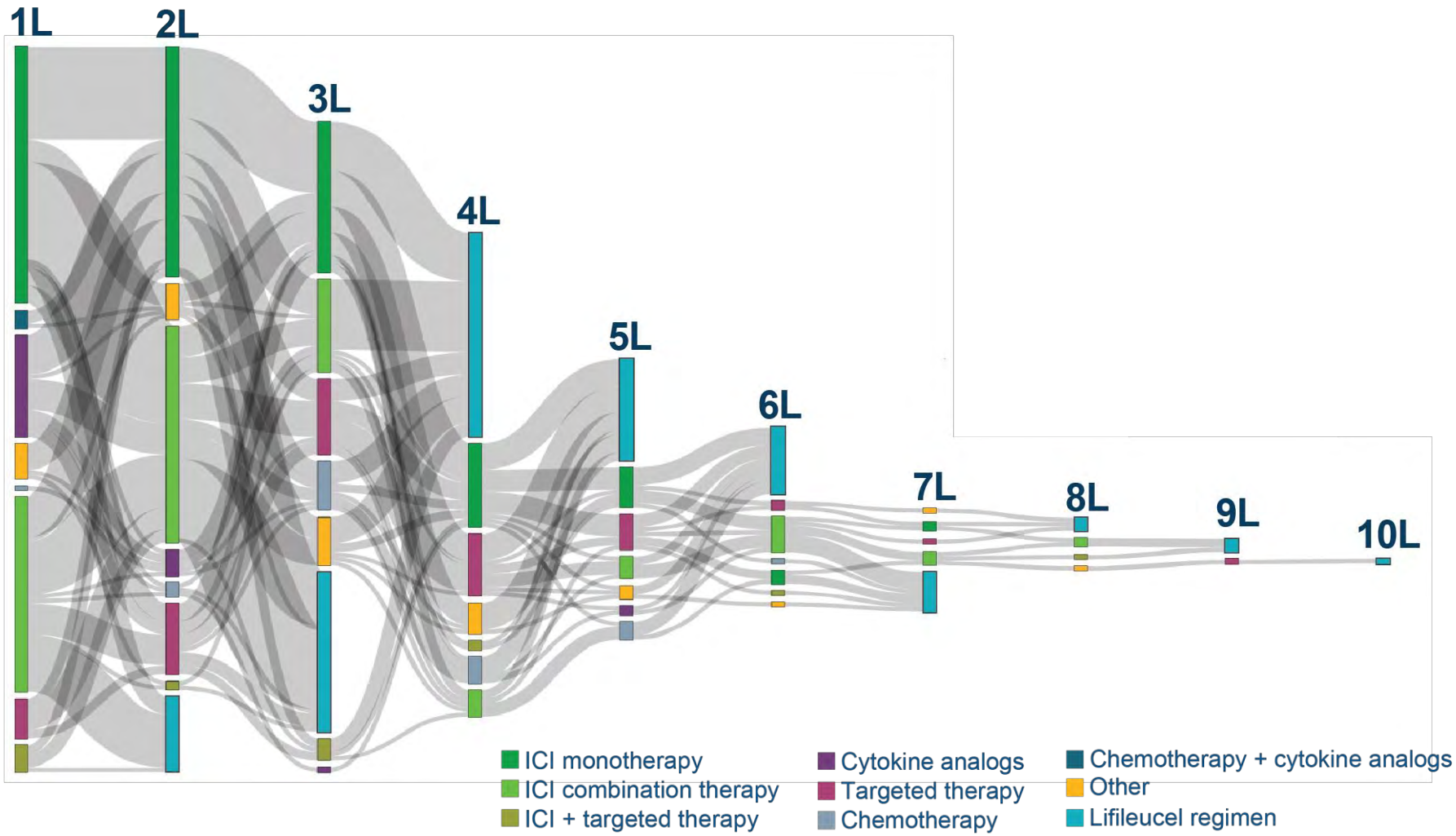
Treatment Regimen

- 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

Supplement Figure 2.

Patient Treatment Patterns

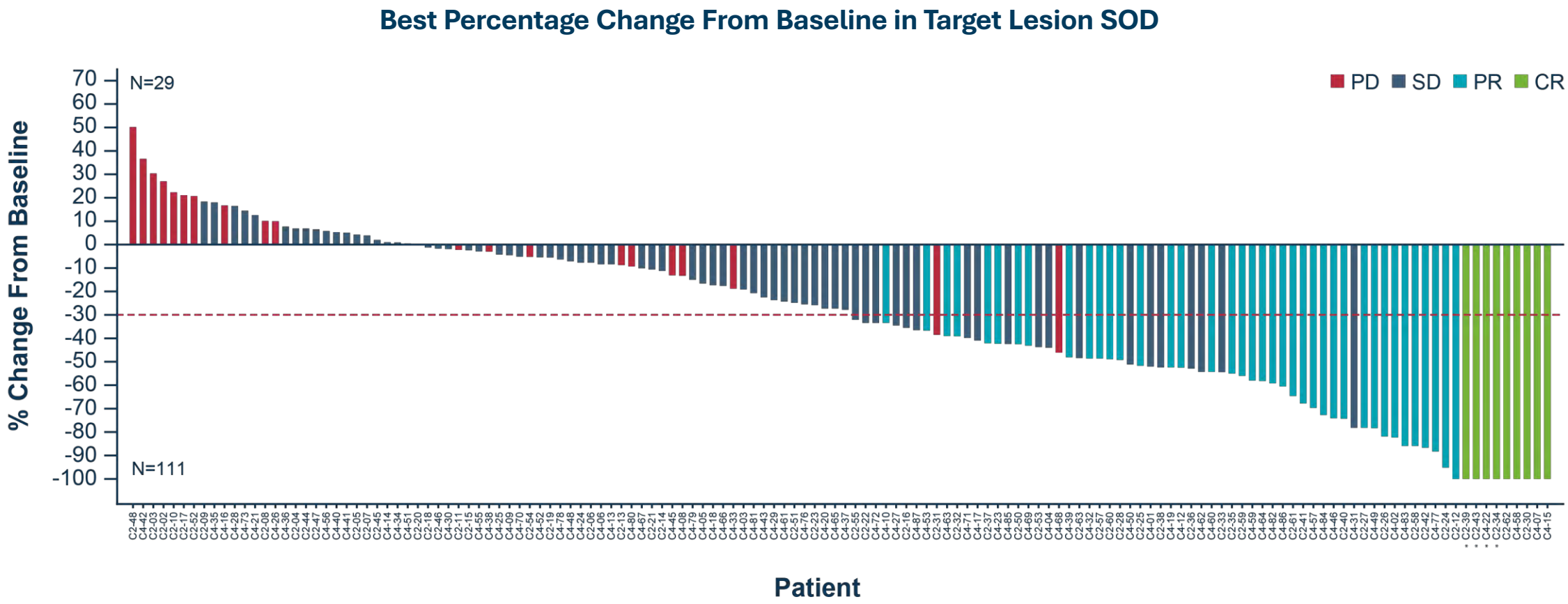


- Patients were heavily pretreated
  - 17 (11.1%) received only 1 line of prior therapy
  - 125 (81.7%) received anti–CTLA-4
  - 82 (53.6%) received anti–PD-1 + anti–CTLA-4 combination
  - Median of 2 lines (range, 1-7) of ICI-containing therapy
  - 113 (73.9%) were retreated with ICI-containing therapy prior to receiving lifileucel
- Lifileucel was manufactured within specification in 94.7% of patients
- Median time from resection to lifileucel infusion was 33 days
- Median number of TIL cells infused was 21.1×10^9 (range, 1.2×10^9 to 99.5×10^9)

The R package networkD3 was used to generate the Sankey plot.

Supplement Figure 3.

Tumor Burden Reduction and Best Response to Lifileucel



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

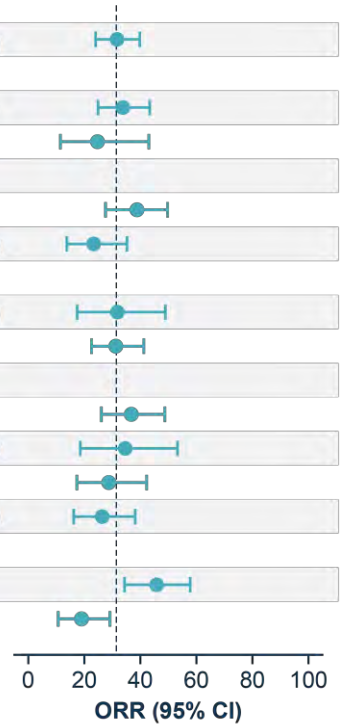
13 patients in the Full Analysis Set are not included (best overall responses included NE [n=6], non-CR/non-PD [n=1], and PD [n=6]) for reasons including having no measurable lesions at baseline or no post-lifileucel target lesion SOD measurements.
*-100% change from baseline is presented for CR assessment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

Supplement Figure 4.

Univariable and Multivariable Analyses of ORR in the Overall Population

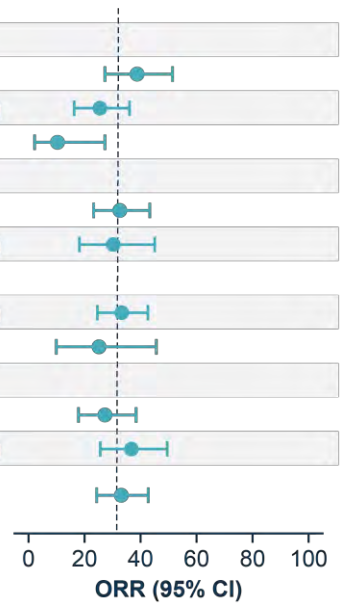
ORR by Patient and Disease Characteristics

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)			
≥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)



- Response to lifileucel was observed across all subgroups analyzed
- 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 than patients with either (OR: 2.08) or both (OR: 4.42) risk factor(s)

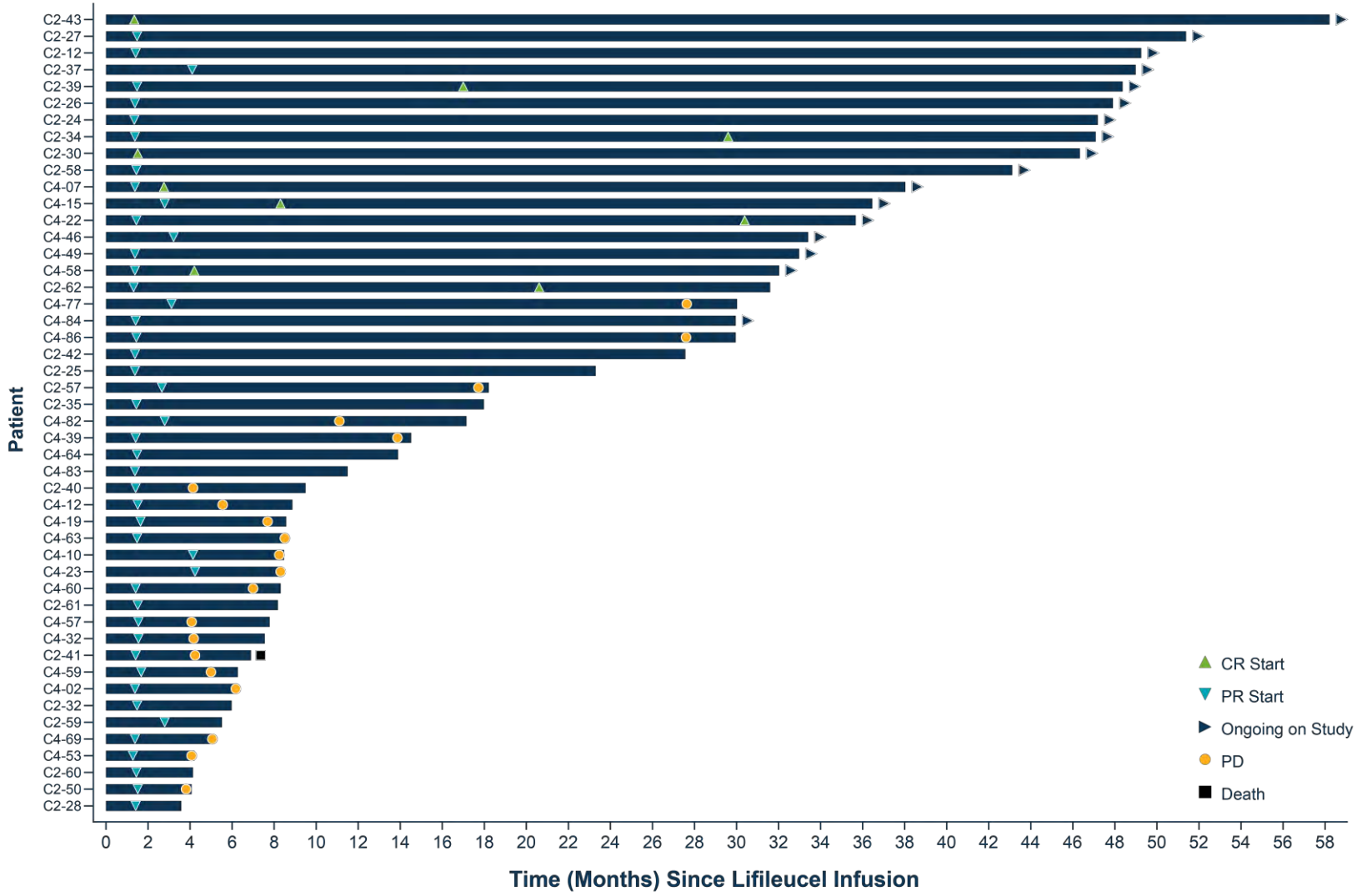
1. Kluger HM et al. *J Immunother Cancer*. 2020;8:e000398.

Vertical dotted line represents overall ORR (31.4%).

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

Supplement Figure 5.

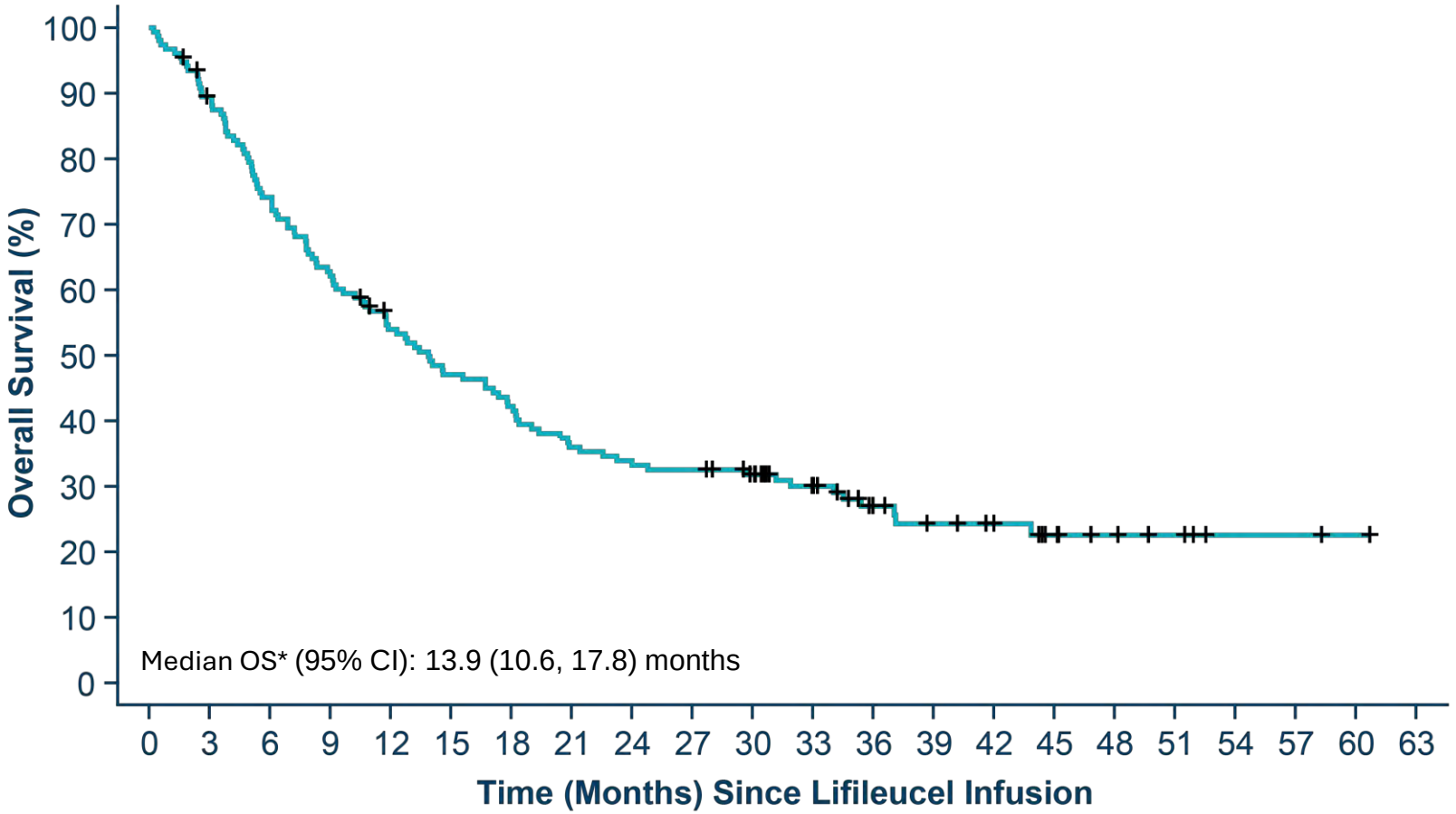
Time to Response, DOR, and Time on Efficacy Assessment for Confirmed Responders (PR or Better)



- Median time from lifileucel infusion to best response was 1.5 months
- Responses deepened over time
  - 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 to CR 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

Supplement Figure 6.

Overall Survival



Patients at Risk

153	134	111	94	78	68	61	52	49	47	42	32	21	17	14	10	7	5	2	2	1	0

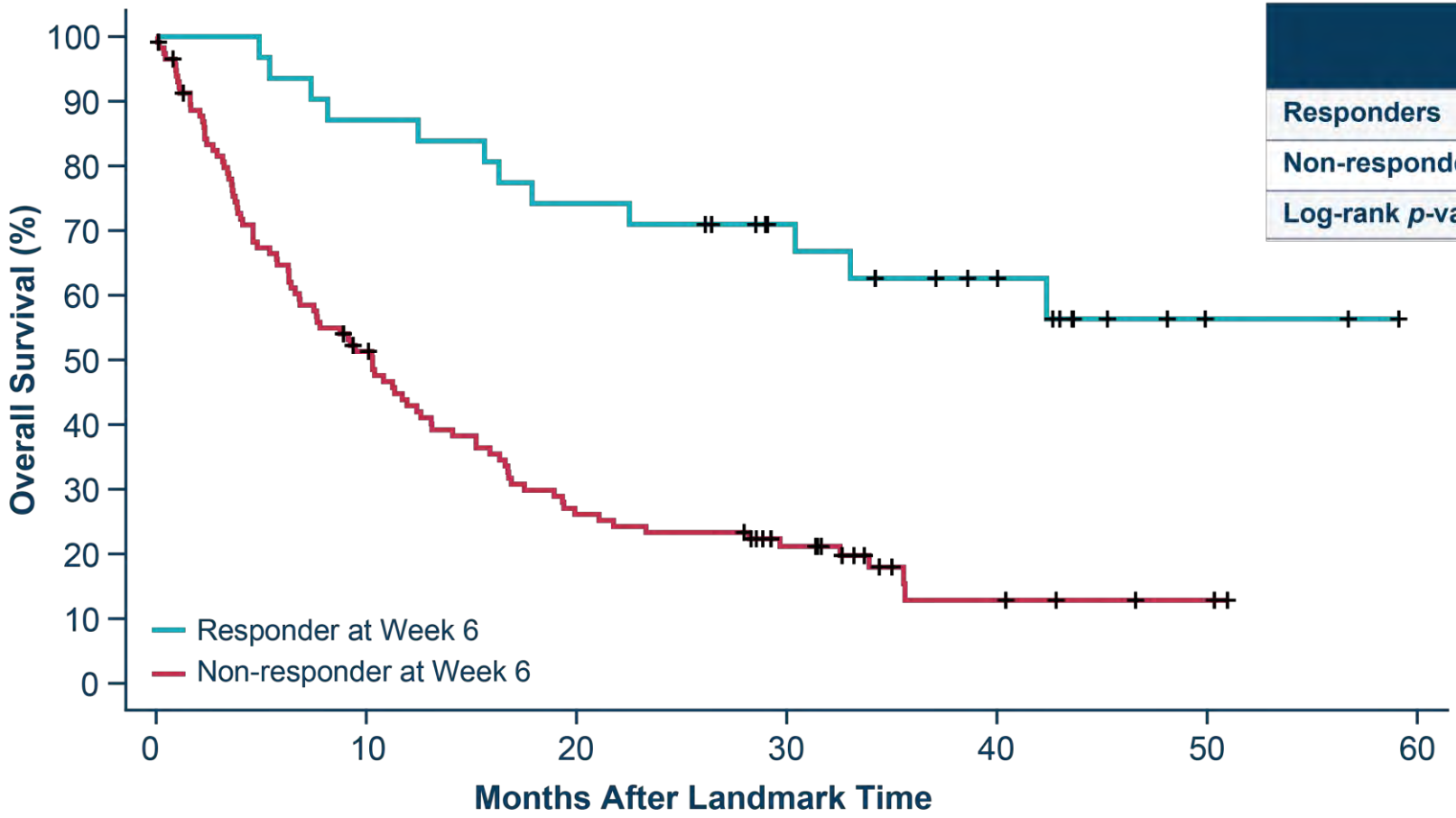
- The median OS was 13.9 months, and the 12-month OS rate was 54.0% (95% CI: 45.6, 61.6)
- Response to lifileucel was associated with a 73.4% reduced risk of death compared with nonresponse (HR, 0.266; $p<0.0001$)†

*Based on Kaplan-Meier estimate.

†Using a Cox proportional hazards model with objective response as a time-dependent covariate.

Supplement Figure 7.

OS, by Response at 6 Weeks After Lifileucel Infusion



	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	

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

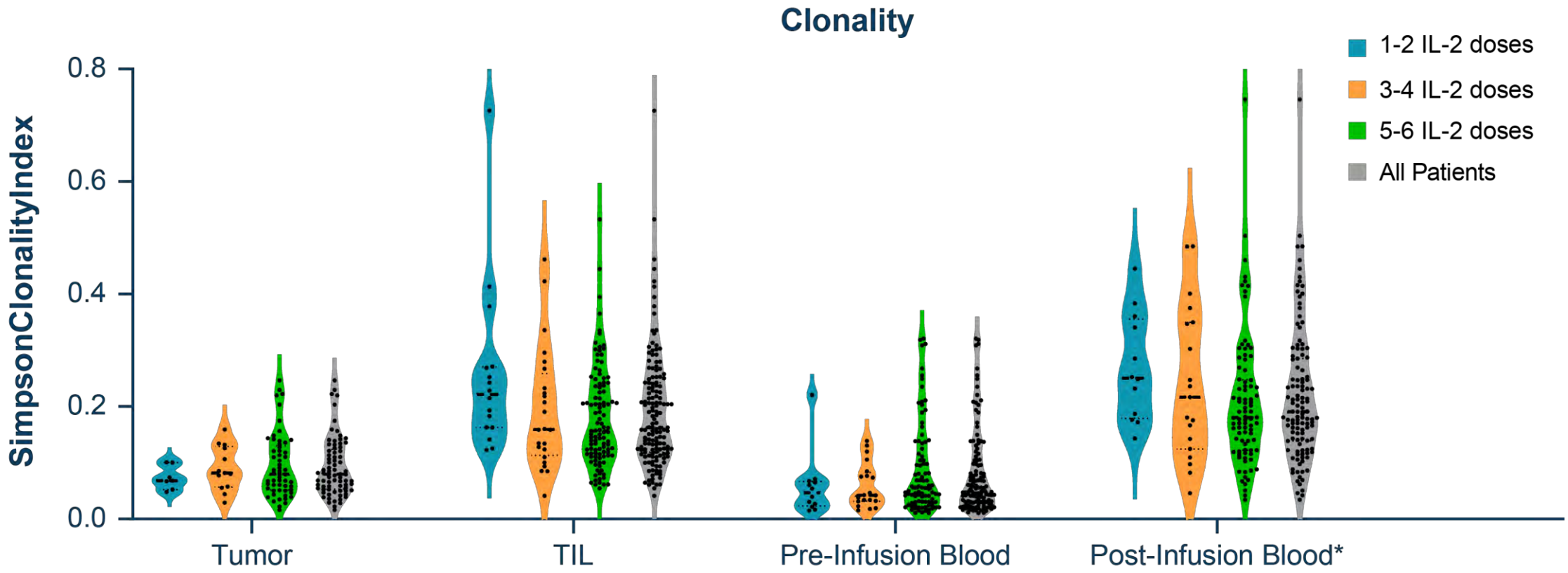
- In a landmark analysis in patients who achieved response at first assessment (6 weeks [~1.5 months] post-lifileucel infusion), median OS was not reached

1. Buyse M, Piedbois P. *Stat Med*. 1996;15:2797-2812.

*Based on Kaplan-Meier estimate.

Supplement Figure 8.

TCR Clonality by Number of IL-2 Doses

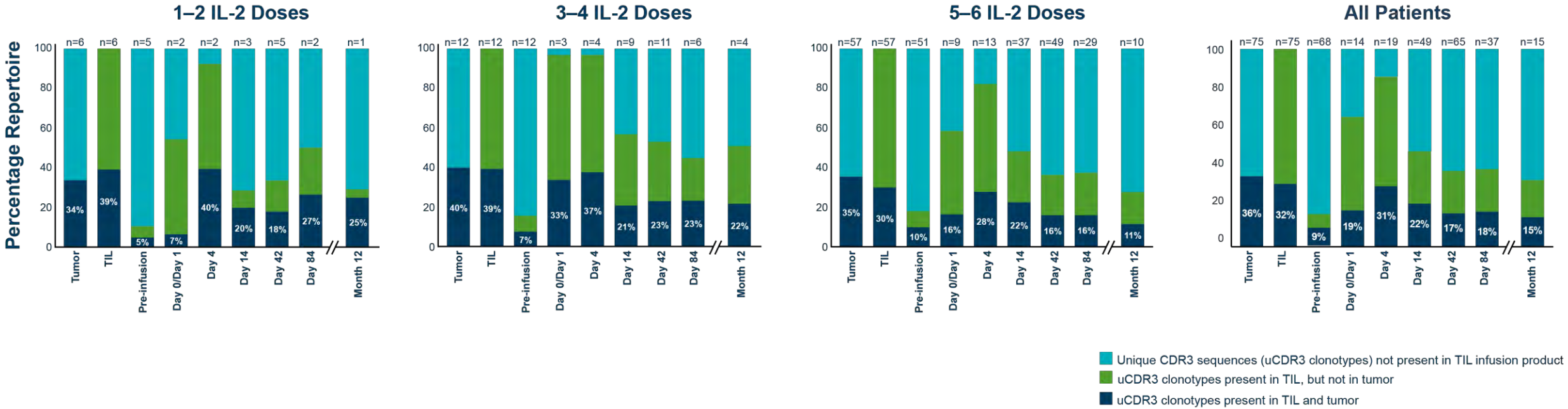


- Polyclonality† was similar between IL-2 dose groups within each sample type

*Day 42 visit.
†As measured by the Simpson Clonality Index, which reflects the mono- or polyclonality of a sample. Values can range from 0 (evenly distributed, polyclonal sample) to 1 (monoclonal sample).

Supplement Figure 9.

TCR Clonal Expansion and Persistence in the Overall Population and by IL-2 Dose Groups



- uCDR3 clonotypes identified in both tumor and TIL infusion product expanded and persisted to a similar degree, regardless of number of IL-2 doses

Abbreviations

CR, complete response; CTLA-4, ; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; CY, cyclophosphamide; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; Gen 1, Generation 1; Gen 2, Generation 2; HR, hazard ratio; ICI, immune checkpoint inhibitor; IL-2, interleukin 2; IRC, independent review committee; L, line of therapy; LDH, lactate dehydrogenase; NMA-LD, nonmyeloablative lymphodepletion; OR, Odd's ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SITC, Society for Immunotherapy of Cancer; SOD, sum of diameters; TCR, T-cell receptor; TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocyte; TPS, tumor proportion score; uCDR3, unique CDR3; ULN, upper limit of normal.

Disclosures

JL: Consulting fees from iOnctura, Apple Tree, Merck, Bristol Myers Squibb, Eisai, Debiopharm, and Incyte; payment or honoraria for lectures, presentations, speaker's bureau, or educational events from Eisai, Novartis, Incyte, Merck, touchIME, touchEXPERTS, Pfizer, Royal College of Physicians, Cambridge Healthcare Research, Royal College of General Practitioners, VJOncology, Agence Unik, Bristol Myers Squibb, and Immatics; and support for attending meetings and/or travel from Pierre Fabre, Roche, GSK, and Immatics.
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JLu: Research grants from Bristol Myers Squibb; contracted research with Vyriad, Takeda, Replimune, Foghorn, Bristol Myers Squibb/Dragonfly Therapeutics, Trisalus, Life Sciences, and Agenus; consulting fees for advisory board of Iovance Biotherapeutics, Eisai, and Replimune; payment for CME talk for San Diego 2022 and support for attending CME meeting San Diego 2022 from Cano Health; participation in a Data Safety Monitoring Board for DSMC Agenus; and is on the executive committee of COOG.

Disclosures (cont'd)

JMK: Consulting role with Amgen, Ankyra Therapeutics, Applied Clinical Intelligence LLC, Axio Research LLC, Becker Pharmaceutical Consulting, Bristol Myers Squibb, Cancer Network, Checkmate Pharmaceuticals, DermTech, Fenix Group International, Harbour BioMed, Immunocore LLC, Iovance Biotherapeutics, IQVIA, Istari Oncology, Merck, Natera, Novartis, Oncocyte, OncoSec, Pfizer, Replimune, Scopus BioPharma, SR One Capital Management LP, Takeda Development Center Americas Inc., and Takeda Pharmaceutical Company Ltd; and research trial support to institution from Amgen Inc., Bristol Myers Squibb, Checkmate Pharmaceuticals, Harbour BioMed, ImmVira, Immunocore, Iovance Biotherapeutics, Novartis, Takeda, and Verastem.
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