2021 ASCO® ANNUAL MEETING

Lifileucel (LN-144), a Cryopreserved Autologous Tumor Infiltrating Lymphocyte (TIL) Therapy in Patients with Advanced Melanoma: Evaluation of Impact of Prior Anti–PD-1 Therapy

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Background

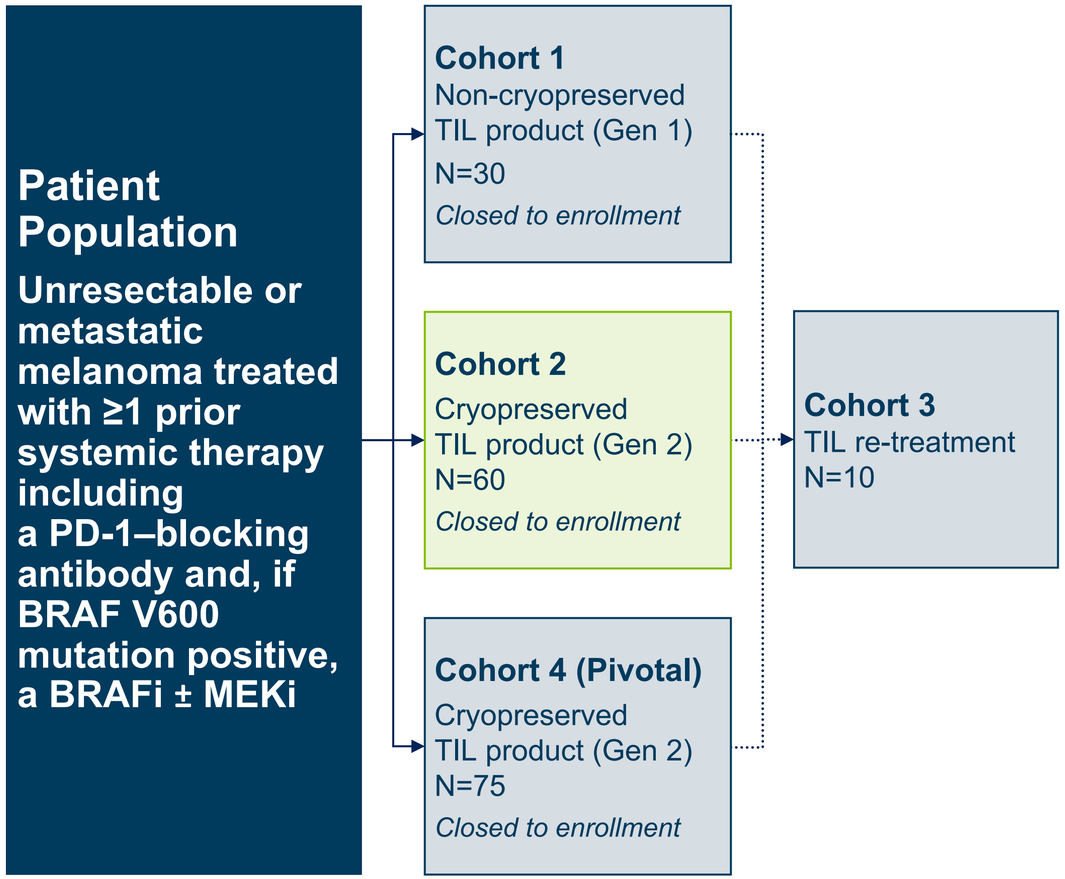
- Currently, no treatment is approved for patients with advanced melanoma whose disease progresses while on or after treatment with ICI and BRAF/MEK inhibitors
- In patients with advanced melanoma who are either primary refractory or develop resistance to ICI, retreatment with ICI or treatment with chemotherapy yields a poor response rate; chemotherapy offers 4-10%[1,2] with median OS of only 7–8 months[3,4]
- Lifileucel is an adoptive cell therapy using autologous TIL that has shown efficacy and durable long-term responses in patients with advanced melanoma who progress on or after anti–PD-1 therapy[5]
- We present 33-month follow-up data from **C-144-01 (NCT02360579)**, a global, Phase 2, open-label, multicohort, multicenter study, and examine the impact of prior anti–PD-1 / anti–PD-L1 use on duration of response of lifileucel

1. Keytruda (pembrolizumab) prescribing information. Whitehouse Station, NJ: Merck & Co., Inc.; 2019.
2. Larkin J, et al. Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial. *J Clin Oncol.* 2018;36:383-90.
3. Goldinger SM, et al. The utility of chemotherapy after immunotherapy failure in metastatic melanoma: A multicenter case series. *J Clin Oncol.* 2018;36:e21588-e.
4. Kirchberger MC, et al. Combined low-dose ipilimumab and pembrolizumab after sequential ipilimumab and pembrolizumab failure in advanced melanoma. *Eur J Cancer.* 2016;65:182-4.
5. Chesney, et al. Lifileucel (LN-144), a cryopreserved autologous tumor infiltrating lymphocyte (TIL) therapy in patients with advanced (unresectable or metastatic) melanoma: sustained duration of response at 28-month follow-up. Presented at AACR 2021.

ICI, immune checkpoint inhibitors; OS, overall survival; 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)



Cohort 2 Endpoints

- Primary: Efficacy per investigator-assessed ORR using RECIST 1.1 response criteria
- Secondary: Safety and additional parameters of efficacy

Key Eligibility Criteria

- Radiographic confirmation of progression
- One 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 the time of consent
- ECOG performance status of 0–1

Methods

- Patients were enrolled from April 2017 to January 2019 at 26 sites across the US and EU
- Concomitant anticancer therapy was not permitted
- Imaging-evaluable disease was required
- All responses required confirmation
- Data cutoff: 22 April 2021

BRAFi, BRAF inhibitor; ECOG, Eastern Cooperative Oncology Group; MEKi, MEK inhibitor; ORR, objective response rate; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria in Solid Tumors; TIL, tumor infiltrating lymphocytes.

Patient Journey and TIL Manufacturing

1 **Patient Intake**

2 **Tumor Tissue Procurement**
- Surgical resection of a tumor lesion (~1.5 cm in diameter)
- Shipped to a Central GMP facility

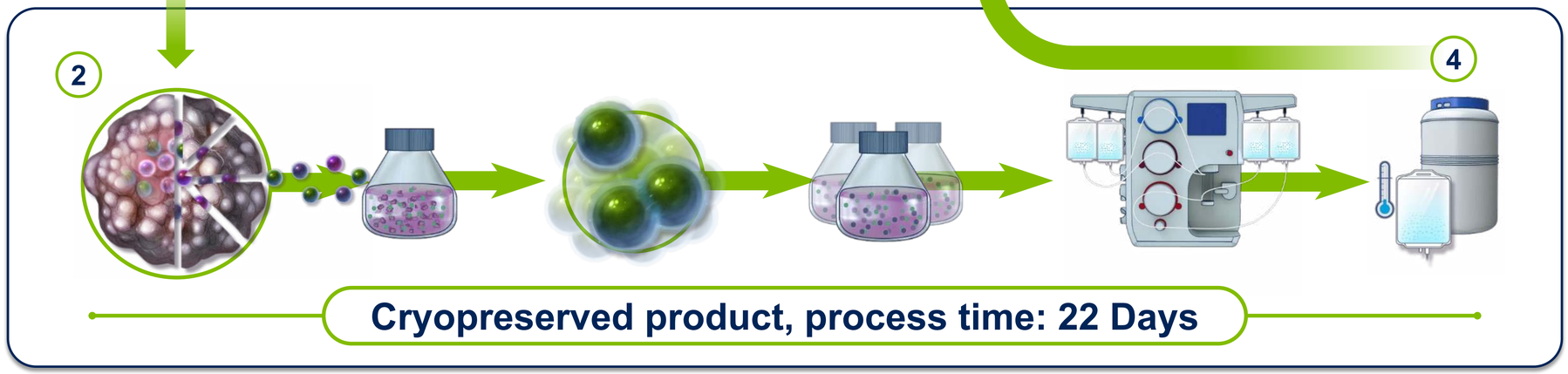
Tumor resection sites include **skin, lymph nodes, liver, lung, peritoneal, musculoskeletal, breast, and other organs**

3 **Non-myeloablative Lymphodepletion**
- Cyclophosphamide followed by fludarabine

4 **Lifileucel Infusion**
- One time treatment
- Lifileucel is a rejuvenated and expanded TIL product

5 **IL-2 Administration**
- Up to 6 doses

6 **Discharge**



GMP, good manufacturing practices; IL-2, interleukin-2; NMA-LD, non-myeloablative lymphodepletion; TIL, tumor infiltrating lymphocytes.

Baseline Patient and Disease Characteristics

Characteristic	N=66
Gender, n (%)	
Female	27 (41)
Male	39 (59)
Age, years	
Median	55
Min, max	20, 79
Prior Therapies, n (%)	
Mean number of prior therapies	3.3
Anti–PD-1 / Anti–PD-L1	66 (100)
Anti–CTLA-4	53 (80)
Anti–PD-1 + Anti–CTLA-4	34 (52)
BRAFi / MEKi	15 (23)
Progressive Disease for ≥1 Prior Therapy, n (%)	
Anti–PD-1 / Anti–PD-L1	65 (99)
Anti–CTLA-4	41 (77)*
ECOG Performance Status, n (%)	
0	37 (56)
1	29 (44)

Characteristic	N=66
BRAF Mutation Status, n (%)	
Mutated V600E or V600K	17 (26)
Wild type	45 (68)
Unknown	3 (5)
Other	1 (2)
Tumor PD-L1 Expression, n (%)	
PD-L1 positive (TPS ≥5%)	23 (35)
PD-L1 negative (TPS <5%)	26 (39)
LDH, n (%)	
≤ULN	39 (59)
>1 to 2 × ULN	19 (29)
>2 × ULN	8 (12)
Target Lesions Sum of Diameter (mm)	
Mean (SD)	106 (71)
Min, max	11, 343
Number of Target and Non-Target Lesions	
>3, n (%)	51 (77)
Mean (SD)	6 (2.7)
Liver and / or brain lesions, n (%)	28 (42)

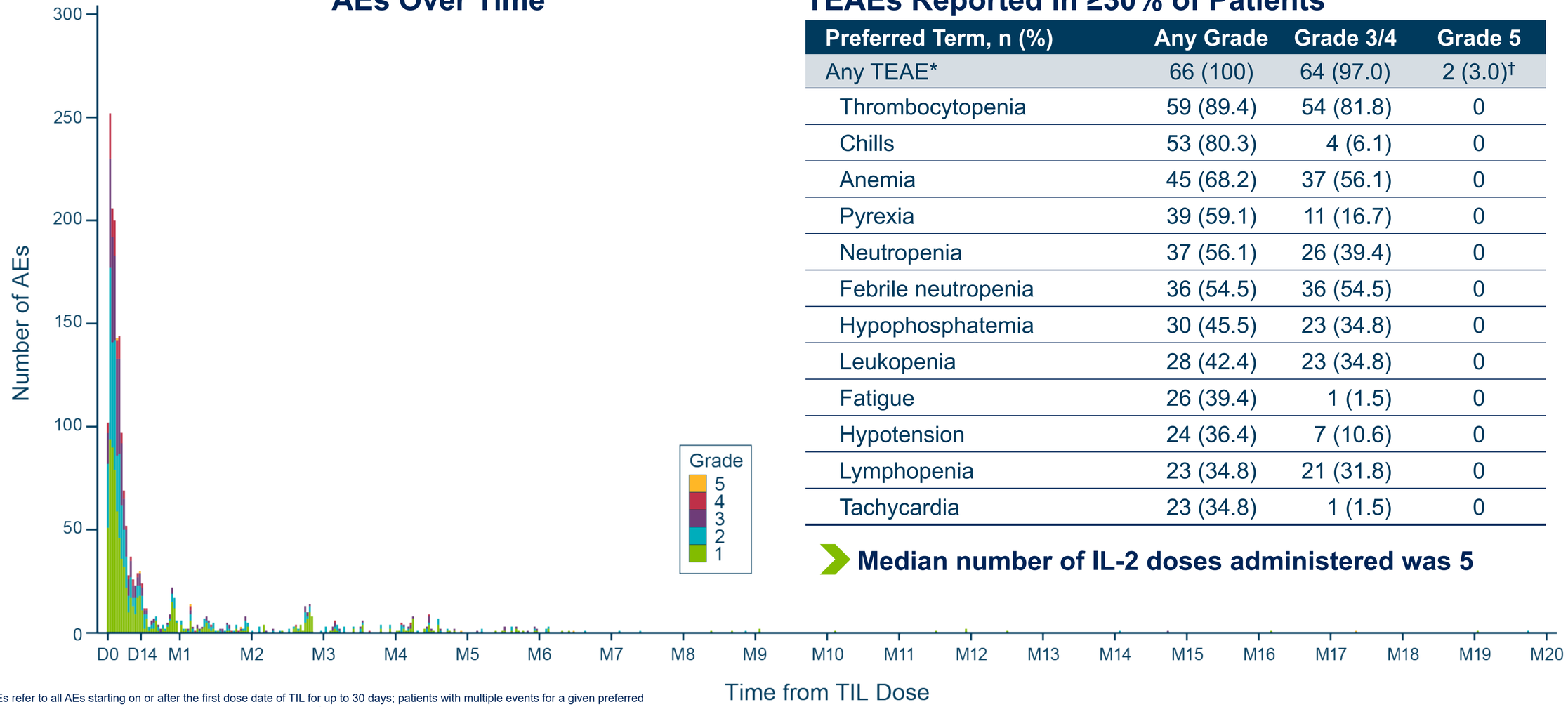
Patients had:

- **Mean of 3.3 prior therapies, ranging from 1–9**
- **High tumor burden at baseline**

*Percent is calculated based on number of patients who received prior anti–CTLA-4.
BRAFi, BRAF inhibitor; CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG, Easter Cooperative Oncology Group; LDH, lactate dehydrogenase; MEKi, MEK inhibitor; mm, millimeter; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; SD, standard deviation; TPS, tumor proportion score; ULN, upper limit of normal.

Safety

AEs Over Time



TEAEs Reported in ≥30% of Patients

Preferred Term, n (%)	Any Grade	Grade 3/4	Grade 5
Any TEAE*	66 (100)	64 (97.0)	2 (3.0)†
Thrombocytopenia	59 (89.4)	54 (81.8)	0
Chills	53 (80.3)	4 (6.1)	0
Anemia	45 (68.2)	37 (56.1)	0
Pyrexia	39 (59.1)	11 (16.7)	0
Neutropenia	37 (56.1)	26 (39.4)	0
Febrile neutropenia	36 (54.5)	36 (54.5)	0
Hypophosphatemia	30 (45.5)	23 (34.8)	0
Leukopenia	28 (42.4)	23 (34.8)	0
Fatigue	26 (39.4)	1 (1.5)	0
Hypotension	24 (36.4)	7 (10.6)	0
Lymphopenia	23 (34.8)	21 (31.8)	0
Tachycardia	23 (34.8)	1 (1.5)	0

Median number of IL-2 doses administered was 5

*TEAEs refer to all AEs starting on or after the first dose date of TIL for up to 30 days; patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term.
†Of 2 Grade 5 events, 1 was due to intra-abdominal hemorrhage considered possibly related to TIL, and 1 was due to acute respiratory failure assessed per investigator as not related to TIL.
AE, adverse event; D, day; IL-2, interleukin-2; M, month; TEAE, treatment-emergent adverse event; TIL, tumor infiltrating lymphocytes.

Objective Response Rate

Response, n (%)	N=66
Objective Response Rate	**24 (36.4)**
Complete response	3 (4.5)
Partial response	21 (31.8)
Stable disease	29 (43.9)
Progressive disease	9 (13.6)
Non-evaluable*	4 (6.1)
Disease control rate	53 (80.3)
Median Duration of Response	**Not Reached**
Min, max (months)	2.2, 38.5+

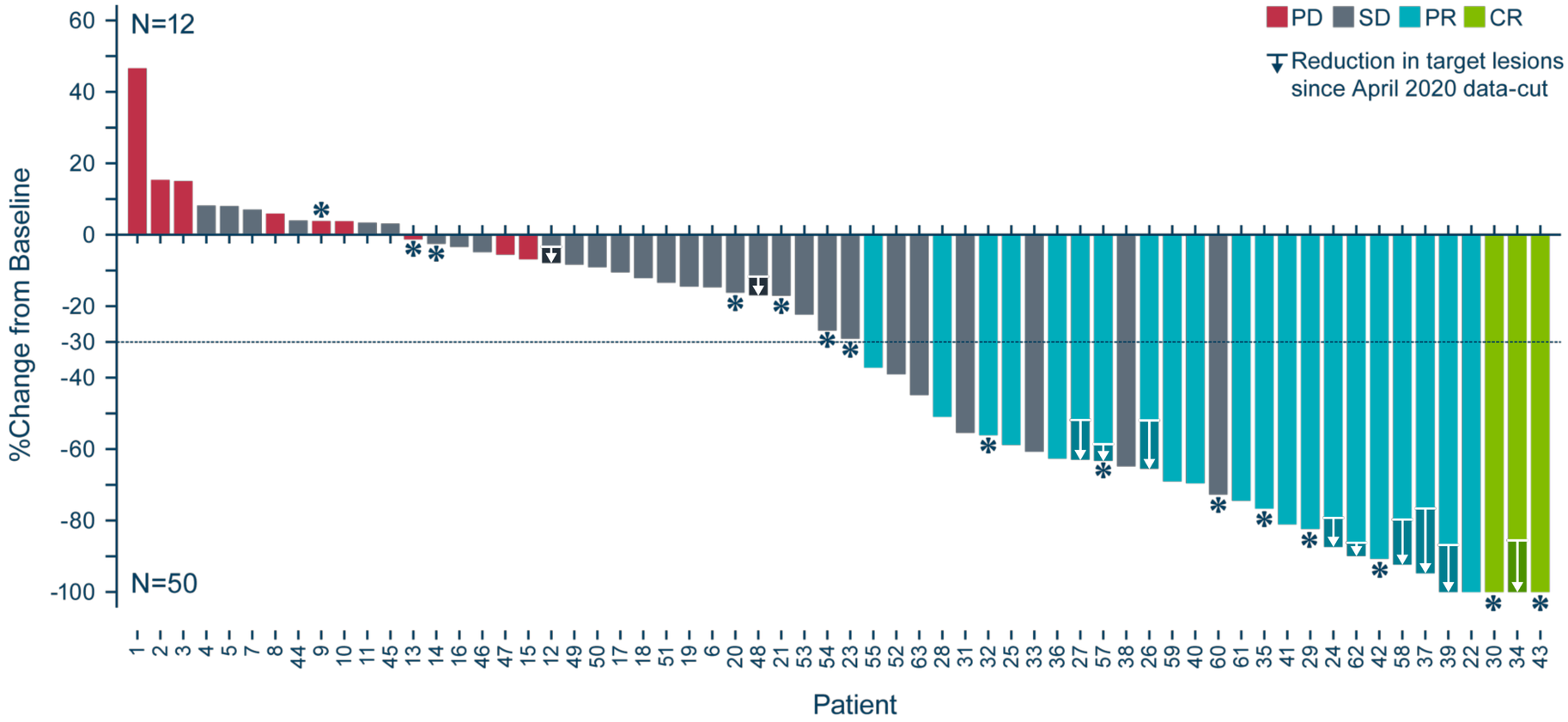
- Mean number of TIL cells infused: 27.3×10^9

- After a median study follow-up of 33.1 months, **median DOR was not reached** (range 2.2, 38.5+ months)

*Not evaluable due to not reaching first assessment.
DOR, duration of response; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes.

Best Overall Response

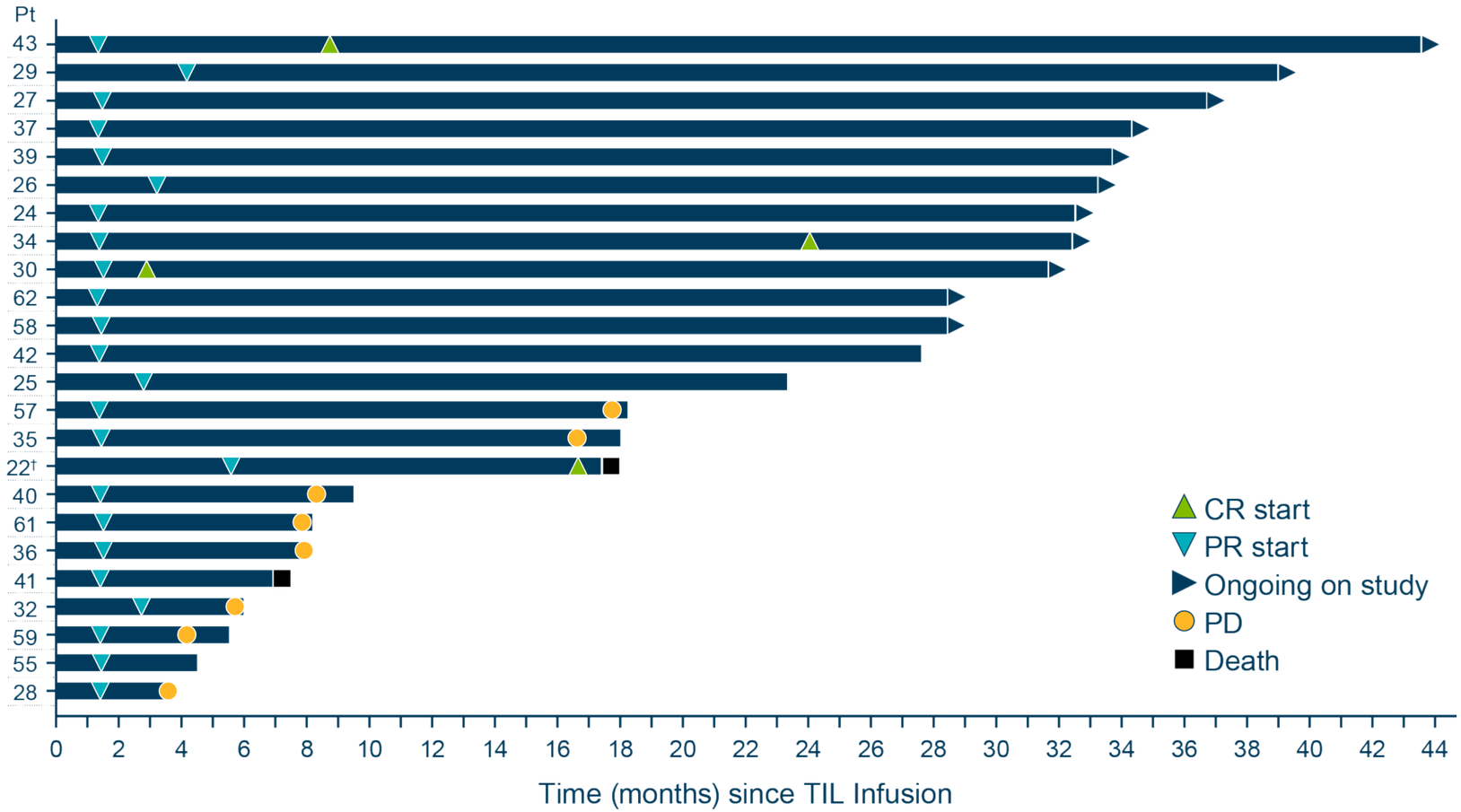
- 81% (50/62) of patients had a reduction in tumor burden
- 11 patients (17.7%) had further SOD reduction since April 2020 datacut



*Patients with BRAF V600 mutation. 3 patients had no post-TIL disease assessment due to early death, and 1 due to start of new anticancer therapy.
DOR, duration of response; SOD, sum of diameters; TIL, tumor infiltrating lymphocytes.

Time to Response for Evaluable Patients (PR or Better)

- 79% of responders received prior ipilimumab
  - 46% of responders received prior anti–PD-1 / anti–CTLA-4 combination
- Responses continued to deepen over time
  - 1 PR converted to CR after 24 months post-lifileucel

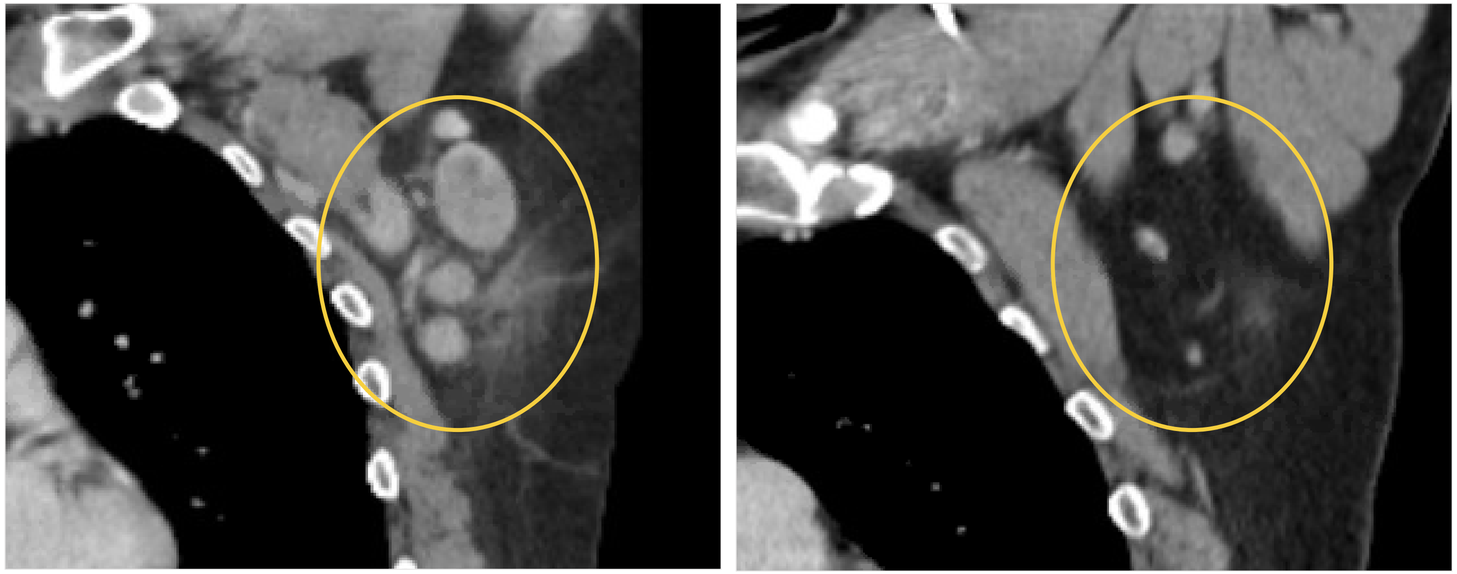


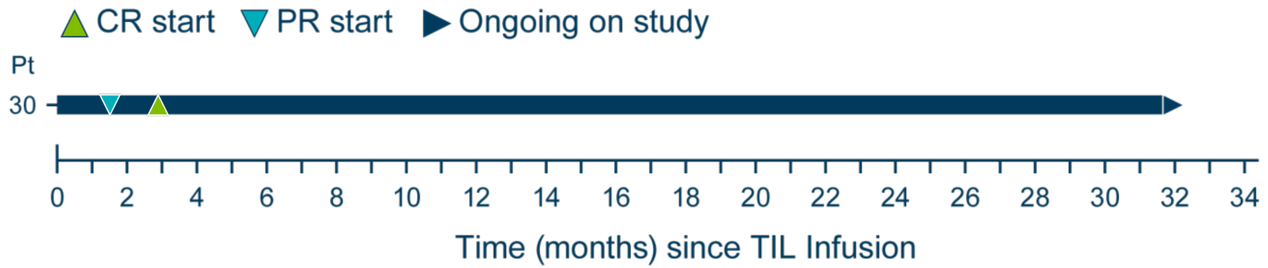
*BOR is best overall response on prior anti–PD-1 / anti–PD-L1 immunotherapy.
†Patient 22 BOR is PR.
BOR, best overall response; CR, complete response; CTLA-4, cytotoxic T-lymphocyte antigen-4; PD, progressive disease; PD-1, programmed cell death protein-1; PR, partial response; SD, stable disease; TIL, tumor infiltrating lymphocytes; TPS, tumor proportion score; U, unknown.

Early and Sustained CR in a Patient with Multiple Failed Prior Therapies

Patient Narrative

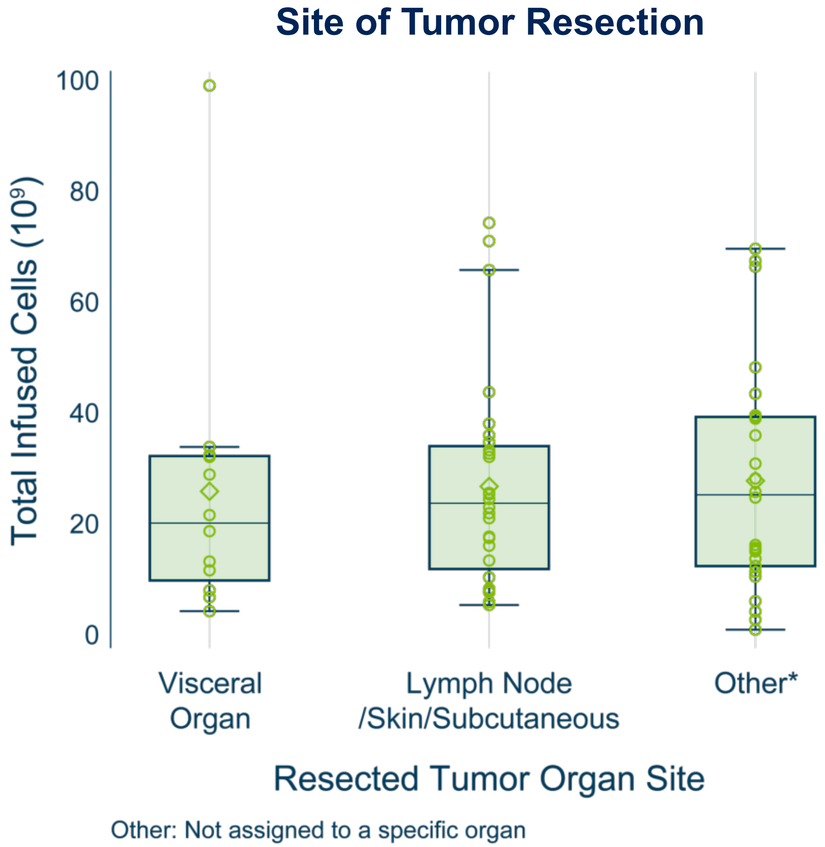
- 44-year-old male
- Initial diagnosis in 2016
- Superficial spreading melanoma
- Prior systemic therapies:
  - Ipilimumab + nivolumab
  - Dabrafenib + trametinib
  - TLR9 agonist + pembrolizumab
  - TVEC + pembrolizumab
- BOR to all prior therapies (including anti–PD-1) was PD
  - Cumulative duration on prior anti–PD-1 was 3.1 months
- Achieved PR at Day 42 and converted to CR on Day 84
  - CR is ongoing

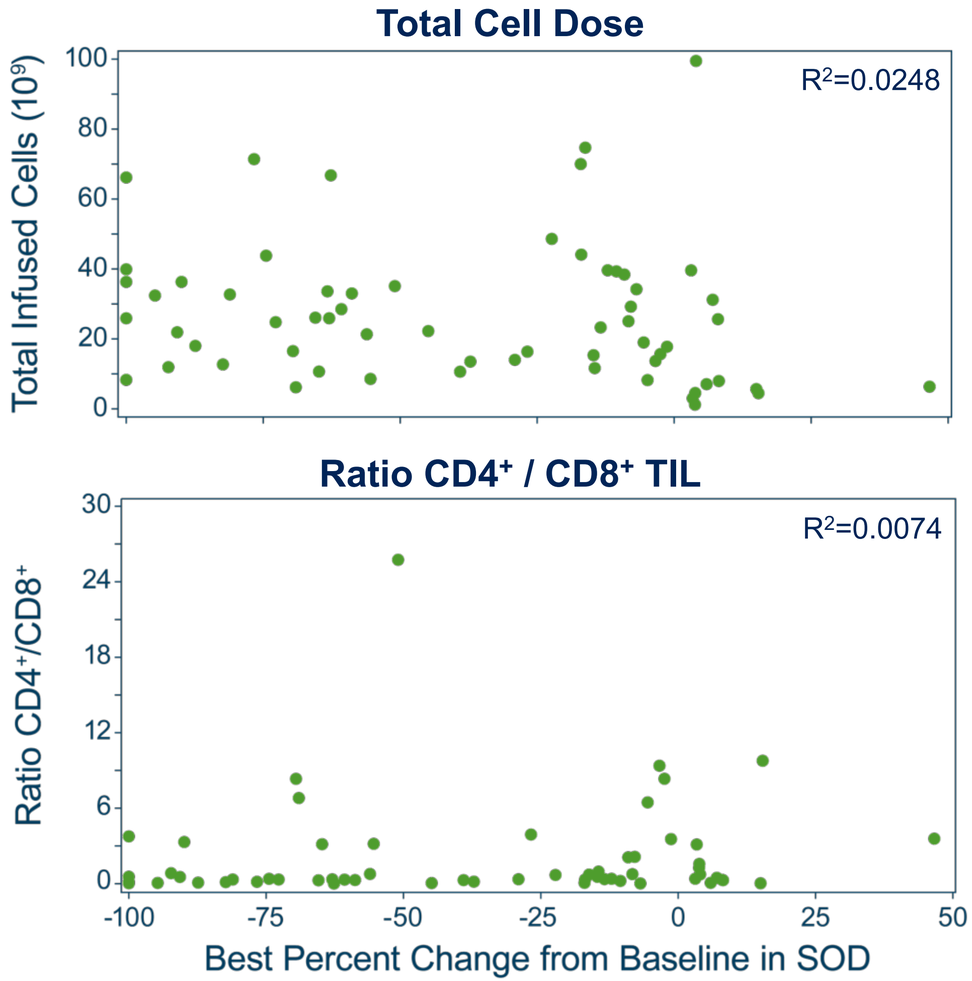




BOR, best overall response; CR, complete response; CTLA-4, cytotoxic T-lymphocyte antigen-4; PD, progressive disease; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; PR, partial response; TIL, tumor-infiltrating lymphocytes; TPS, tumor proportion score; TVEC, talimogene laherparepvec; U, unknown.

Site of Tumor Resection and Infused Cell Dose



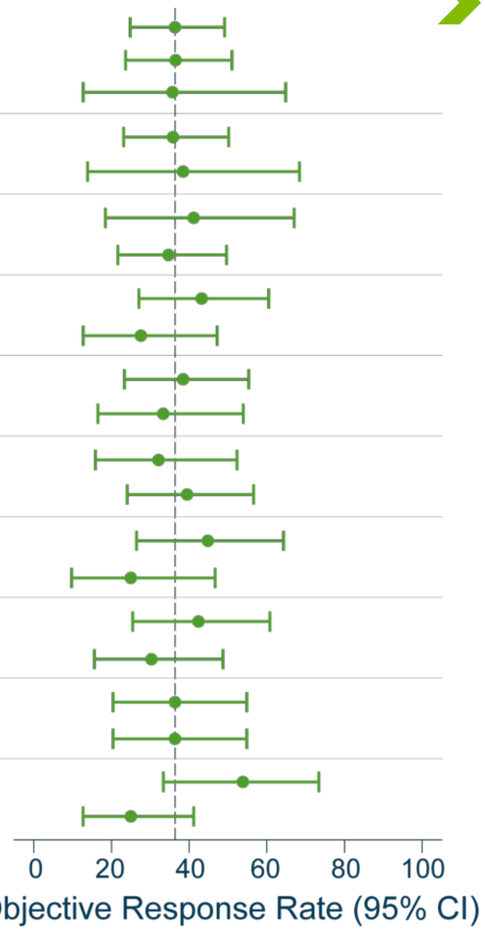


- Appropriate amount of TIL was manufactured regardless of tumor resection site
- Target lesion SOD reductions were seen across the range of total TIL cell doses and CD4+ / CD8+ TIL ratios

SOD, sum of diameters; TIL, tumor infiltrating lymphocytes.

Univariable Analyses: ORR of Lifileucel

Subgroup		n/N	ORR	95% CI*
Overall		24/66	36.4	(24.9, 49.1)
Age Group	<65	19/52	36.5	(23.6, 51.0)
	≥65	5/14	35.7	(12.8, 64.9)
Prior CTLA-4 Use	Yes	19/53	35.8	(23.1, 50.2)
	No	5/13	38.5	(13.9, 68.4)
BRAF Mutation Status	Mutated (V600E or K)	7/17	41.2	(18.4, 67.1)
	Non-Mutated	17/49	34.7	(21.7, 49.6)
Baseline ECOG	0	16/37	43.2	(27.1, 60.5)
	≥1	8/29	27.6	(12.7, 47.2)
Baseline LDH	≤ULN	15/39	38.5	(23.4, 55.4)
	>ULN	9/27	33.3	(16.5, 54.0)
Baseline Brain/Liver Lesion	Yes	9/28	32.1	(15.9, 52.4)
	No	15/38	39.5	(24.0, 56.6)
Cumulative Duration on Anti–CTLA-4	≤Median (2.10 mo)	13/29	44.8	(26.4, 64.3)
	>Median (2.10 mo)	6/24	25.0	(9.8, 46.7)
Cumulative Duration on Anti–PD-1/PD-L1	≤Median (5.06 mo)	14/33	42.4	(25.5, 60.8)
	>Median (5.06 mo)	10/33	30.3	(15.6, 48.7)
Time from Stop of Anti–PD-1 /PD-L1 to TIL infusion	≤Median (4.76 mo)	12/33	36.4	(20.4, 54.9)
	>Median (4.76 mo)	12/33	36.4	(20.4, 54.9)
Baseline Target Lesion SOD	<70 mm	14/26	53.8	(33.4, 73.4)
	≥70 mm	10/40	25.0	(12.7, 41.2)

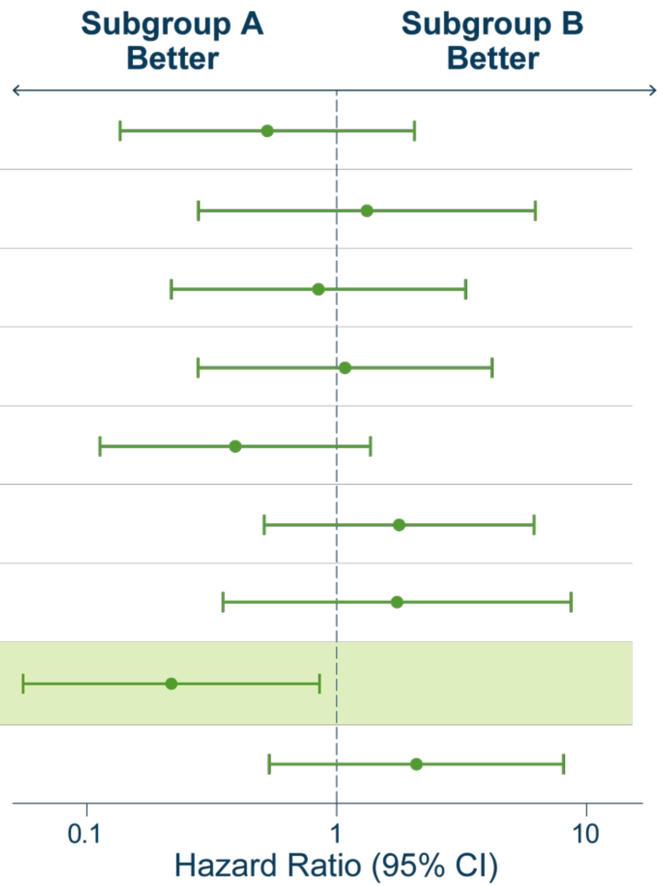


- ORR was not predicted by any patient or clinical characteristics analyzed, including:
  - Baseline LDH (≤ULN vs >ULN)
  - Baseline ECOG performance status (0 vs ≥1)
  - Baseline brain / liver lesions (yes vs no)
  - Cumulative duration on anti–CTLA-4 (≤median vs >median)
  - Cumulative duration on anti–PD-1 / anti–PD-L1 (≤median vs >median) in a post–PD-1 patient population

*95% CI is calculated using the Clopper-Pearson Exact test.
CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; mo, months; ORR, objective response rate; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes; ULN, upper limit of normal.

Univariable Analyses*: DOR of Lifileucel

Parameter	Subgroup A vs B	N in Subgroup A	N in Subgroup B	HR (95% CI)
Age Group	<65 vs ≥65	19	5	0.527 (0.136, 2.046)
Prior CTLA-4 Use	Yes vs No	19	5	1.320 (0.280, 6.233)
BRAF Mutation Status	Yes vs No	7	17	0.845 (0.218, 3.278)
Baseline ECOG	0 vs ≥1	16	8	1.079 (0.279, 4.179)
Baseline LDH	≤ULN vs >ULN	15	9	0.393 (0.113, 1.364)
Baseline Brain/Liver Lesion	Yes vs No	9	15	1.776 (0.513, 6.154)
Cumulative Duration on Anti–CTLA-4	≤Median (2.10m) vs >Median	13	6	1.743 (0.350, 8.664)
Cumulative Duration on Anti–PD-1/PD-L1	**≤Median (5.06m) vs >Median**	**14**	**10**	**0.218 (0.056, 0.854)**
Baseline Target Lesion SOD	<70mm vs ≥70mm	14	10	2.083 (0.537, 8.079)



- Although cumulative duration on prior anti–PD-1 / anti–PD-L1 was not associated with achieving a response to lifileucel (ORR), it was associated with DOR

*Univariable Cox proportional hazards regression model was used to estimate hazard ratios with 95% confidence intervals between subgroups on DOR.
CTLA-4, cytotoxic T-lymphocyte antigen-4; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; ORR, objective response rate; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; SOD, sum of diameters; TIL, tumor infiltrating lymphocytes; ULN, upper limit of normal.

Multivariable Model*: Independent Predictors for DOR of Lifileucel

- Variables from the univariable analyses were examined using the best subset approach
- Two parameters were identified:
  - Baseline LDH
  - Cumulative duration of prior anti–PD-1 / anti–PD-L1

Parameter	Comparison	Responders (N=24)	
		HR (95% CI)	*P*-value
Baseline LDH	≤ULN vs >ULN	0.201 (0.040, 0.996)	0.049
Cumulative duration on prior anti–PD-1 / anti–PD-L1	For each 3-month decrease in exposure to prior anti–PD-1 / anti–PD-L1	0.715 (0.518, 0.987)	0.041
	For each 6-month decrease in exposure to prior anti–PD-1 / anti–PD-L1	0.511 (0.268, 0.974)	

- For each 6-month decrease in exposure to prior anti–PD-1 / anti–PD-L1, the median DOR to lifileucel will be nearly doubled†

*Cox proportional hazards regression model.
†Assuming the data follow exponential distribution.
DOR, duration of response; HR, hazard ratio; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1; ULN, upper limit of normal.

Conclusions

- In heavily pretreated patients with advanced or metastatic melanoma who progressed on or after multiple prior therapies, including anti–PD-1 / anti–PD-L1 and BRAF/MEK inhibitors (if BRAF V600 mutant), lifileucel treatment resulted in:
  - 36.4% ORR
  - **Median DOR not reached at median 33.1 months of study follow-up**
- Responses deepened over time:
  - 11 patients (17.7%) demonstrated further reduction in SOD since April 2020 datacut
  - 1 patient converted from PR to CR at 24 months post lifileucel infusion
- Prior anti–PD-1 therapy:
  - Shorter duration of prior anti–PD-1 therapy maximizes DOR to lifileucel treatment
  - All newly diagnosed patients should be closely monitored for progression on anti–PD-1 therapy
  - **Early intervention with lifileucel at the time of initial progression on anti–PD-1 agents may maximize benefit**

CR, complete response; DOR, duration of response; ORR, objective response rate; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; PR, partial response; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes.

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