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

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ICI, immune checkpoint inhibitors; OS, overall survival; PD-1, programmed cell death protein 1; TIL, tumor infiltrating lymphocytes.

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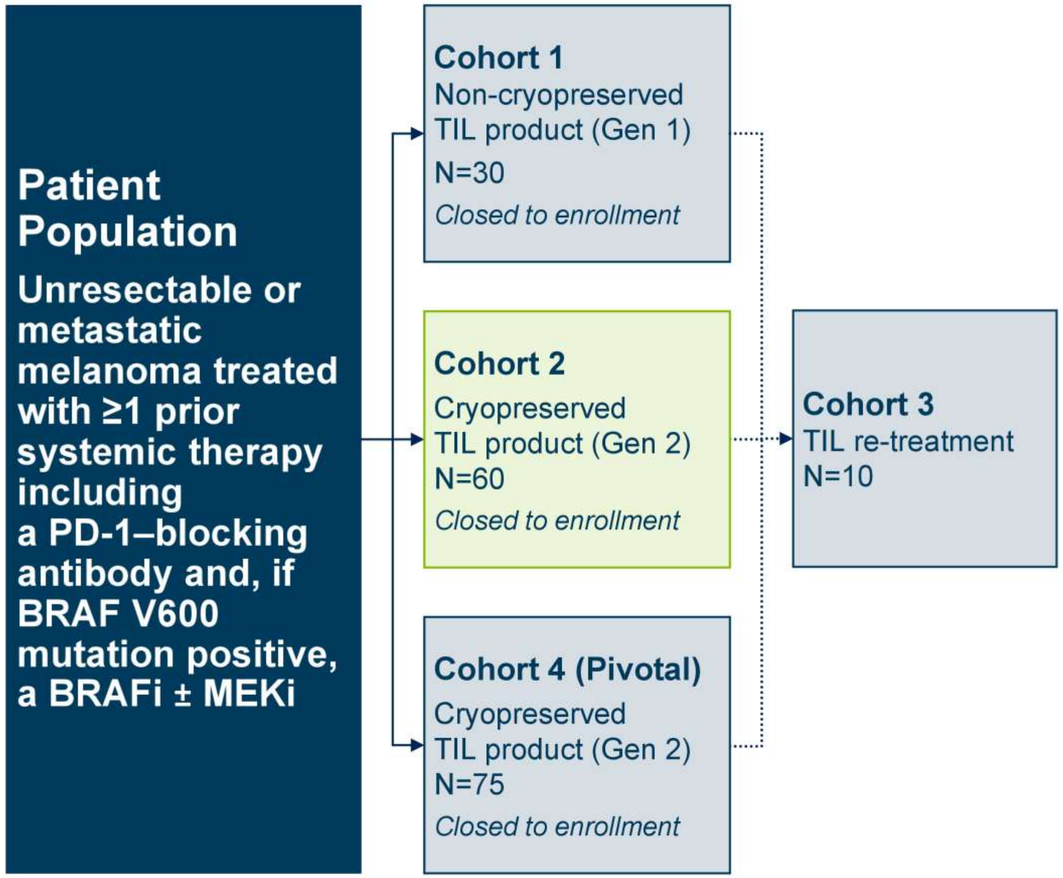
C-144-01 Study Design

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.

Presented By: **James M. G. Larkin, MD, FRCP, PhD**

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

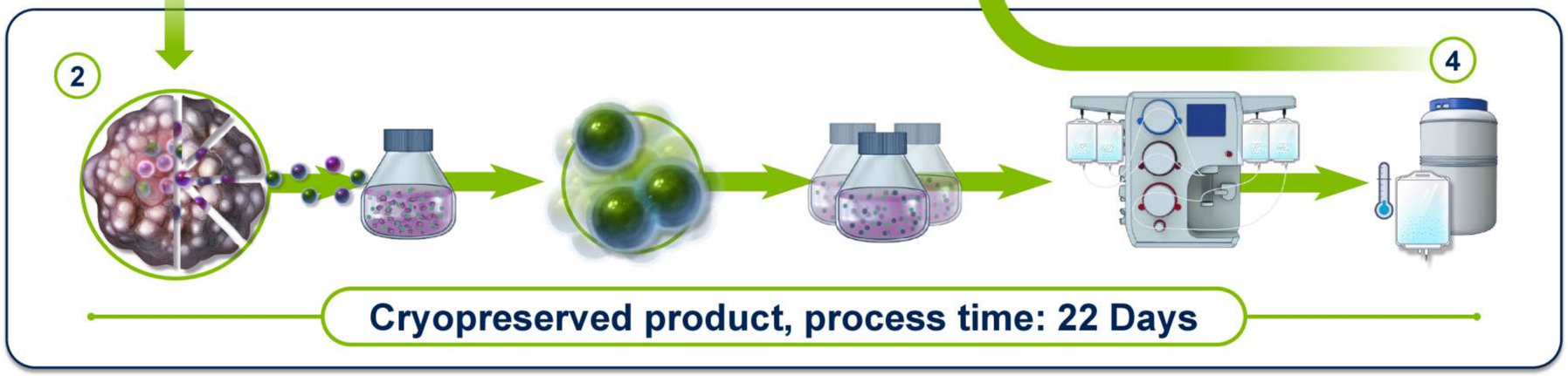
4 **Lifileucel Infusion**

- 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)

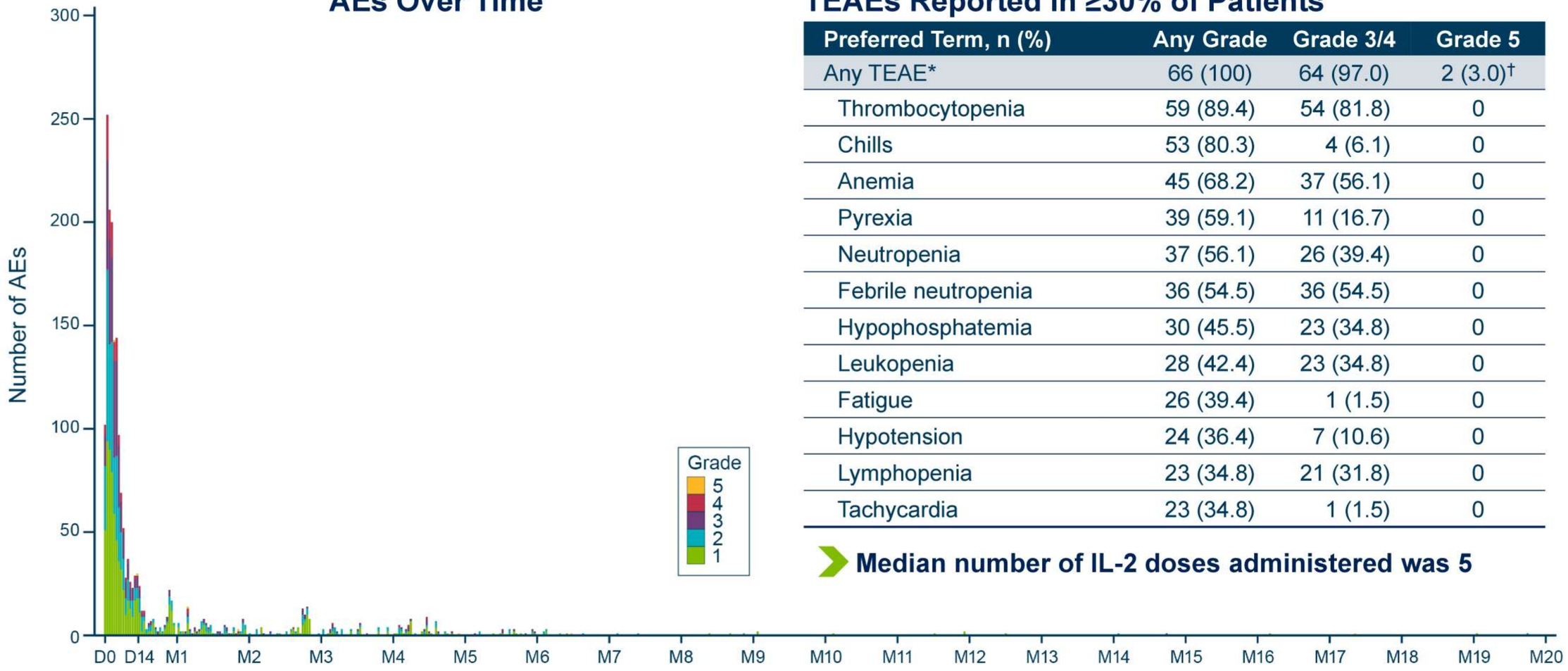
Patients had:

- **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+

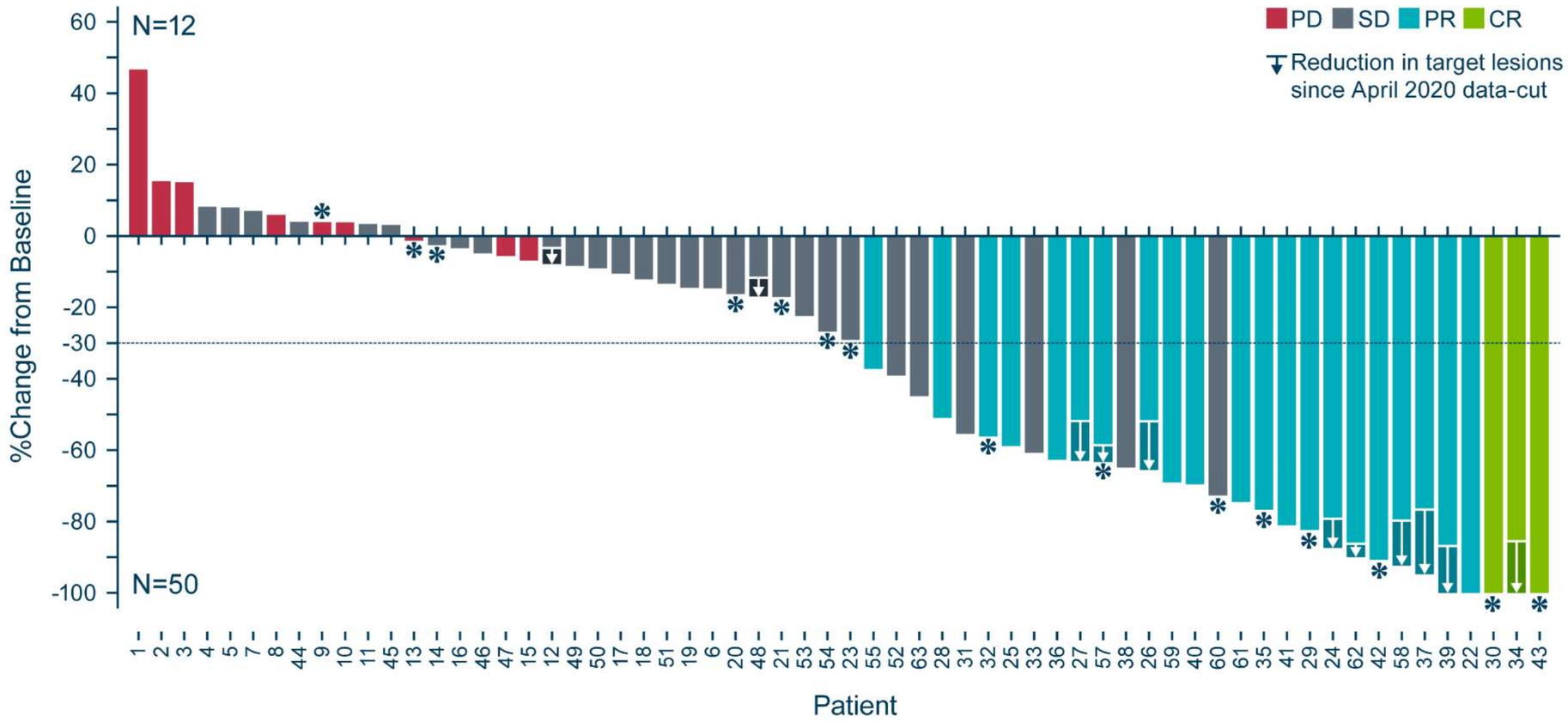
- Mean number of TIL cells infused: 27.3×10^9

- 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

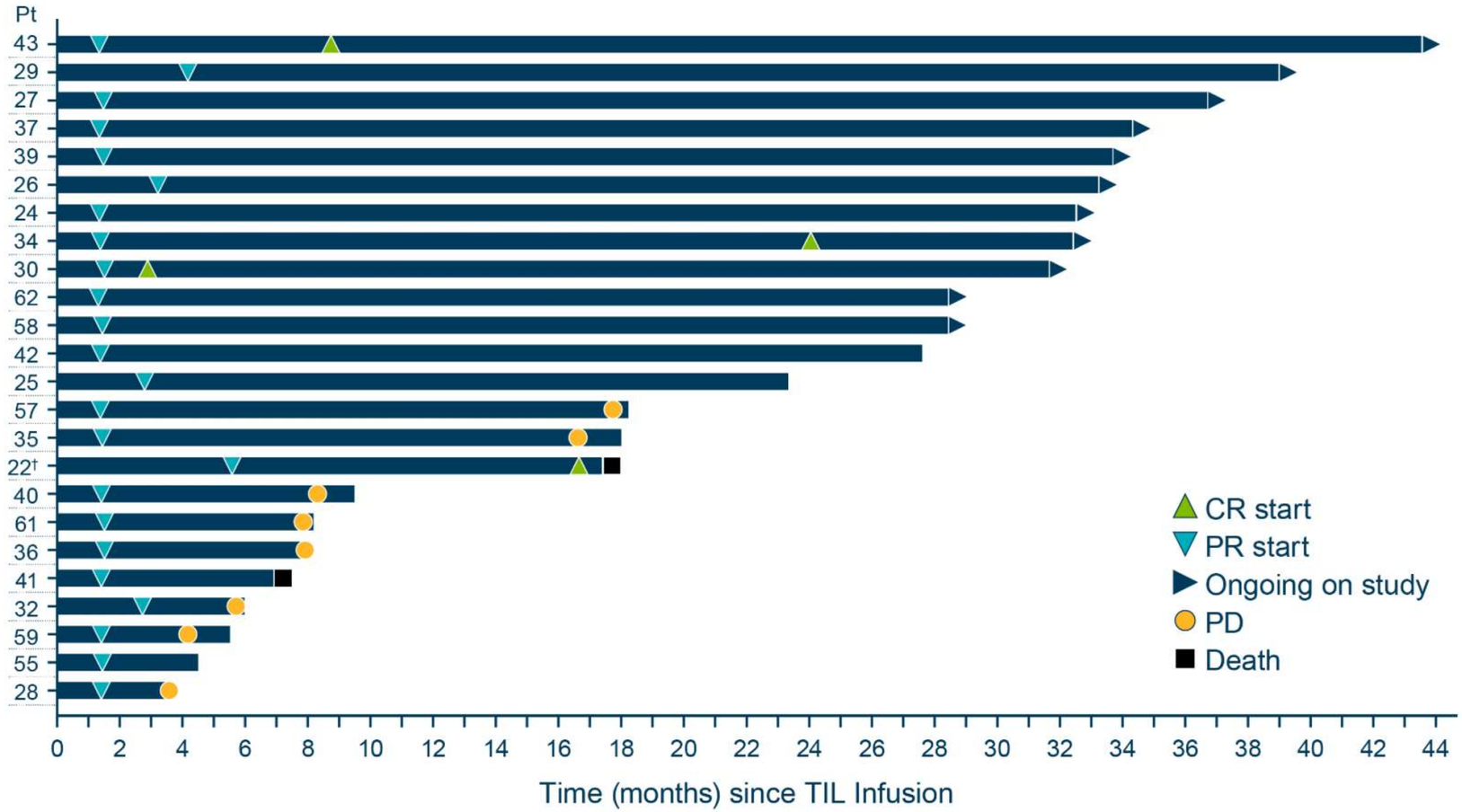
- 81% (50/62) of patients had a reduction in tumor burden
- 11 patients (17.7%) had further SOD reduction since April 2020 datacut



*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.

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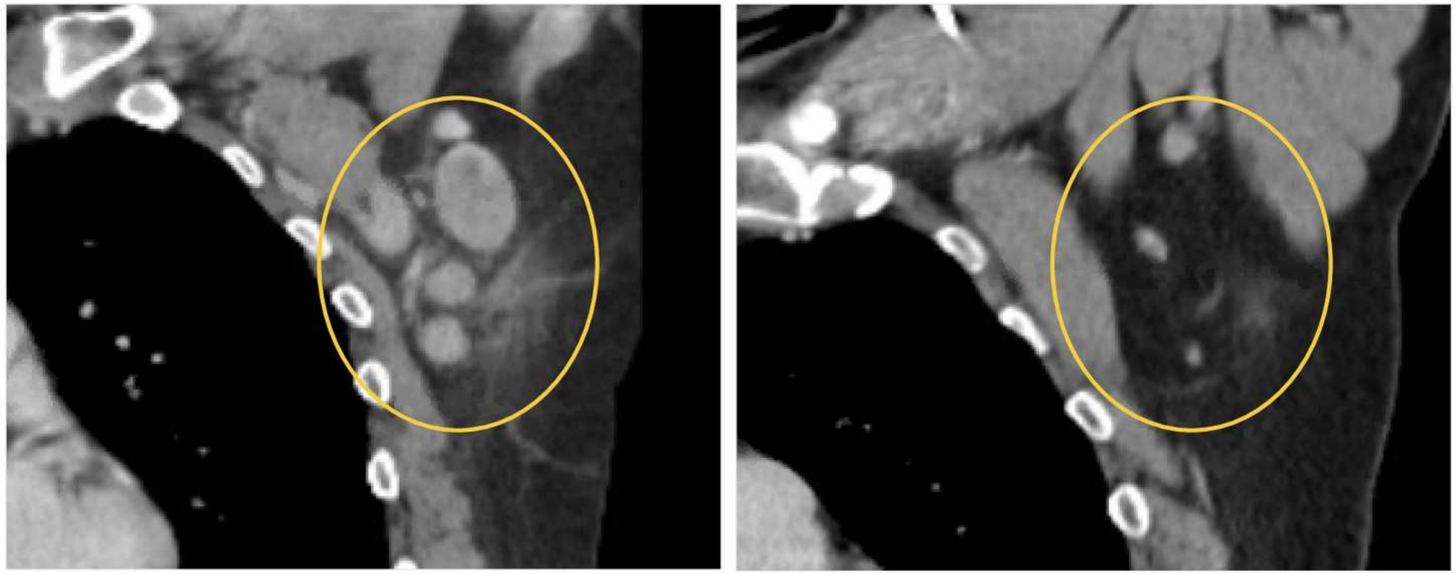
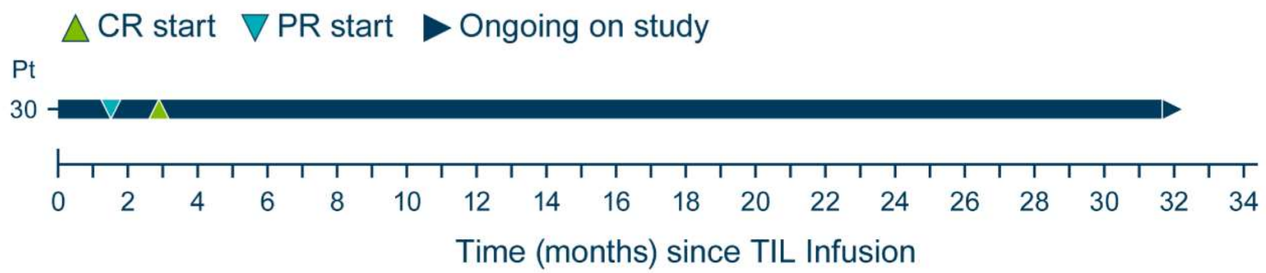
Early and Sustained CR in a Patient with Multiple Failed Prior Therapies

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.

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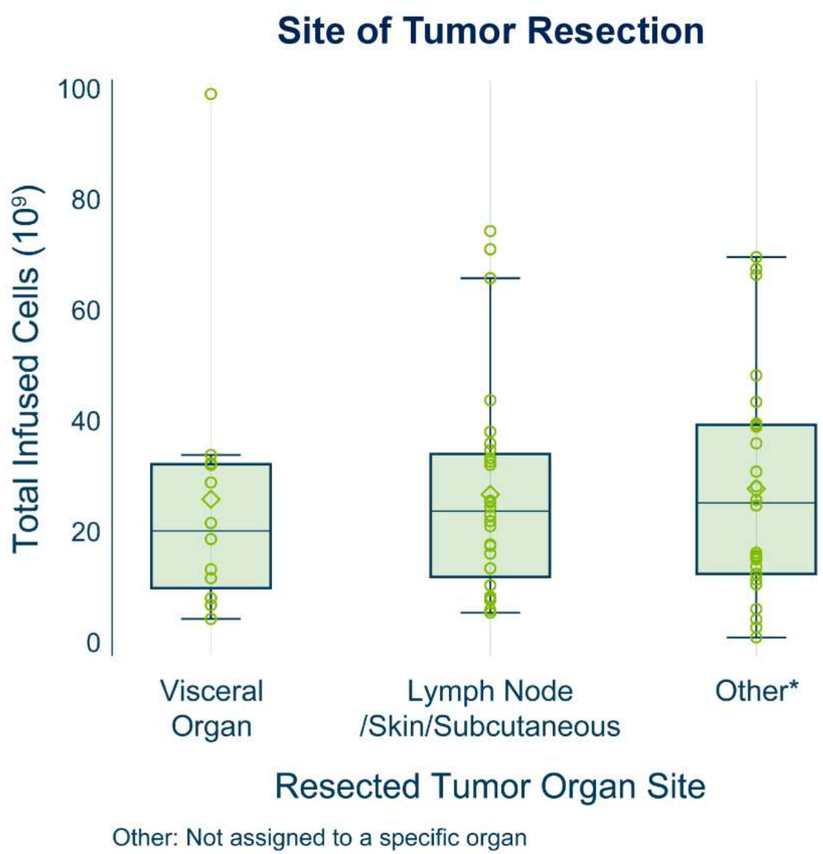
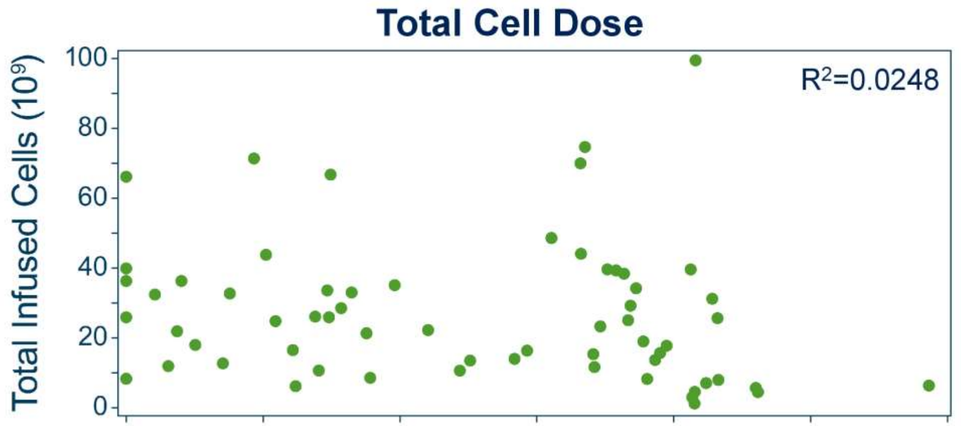
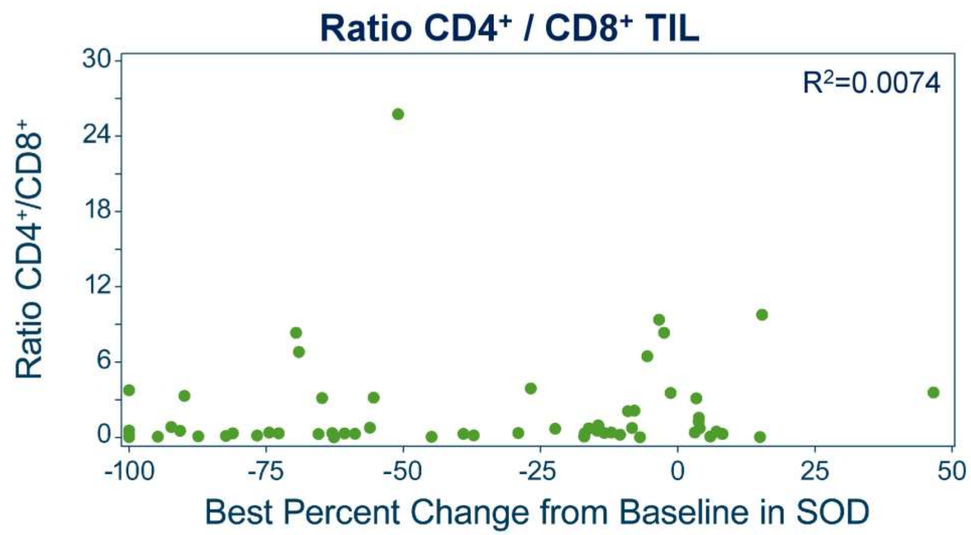
Site of Tumor Resection and Infused Cell Dose





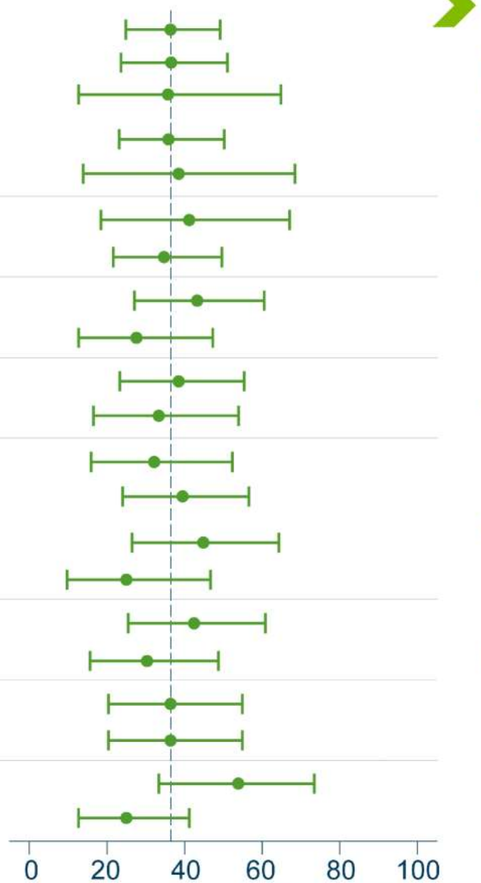


- Appropriate amount of TIL was manufactured regardless of tumor resection site
- Target lesion SOD reductions were seen across the range of total TIL cell doses and CD4+ / CD8+ TIL ratios

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)

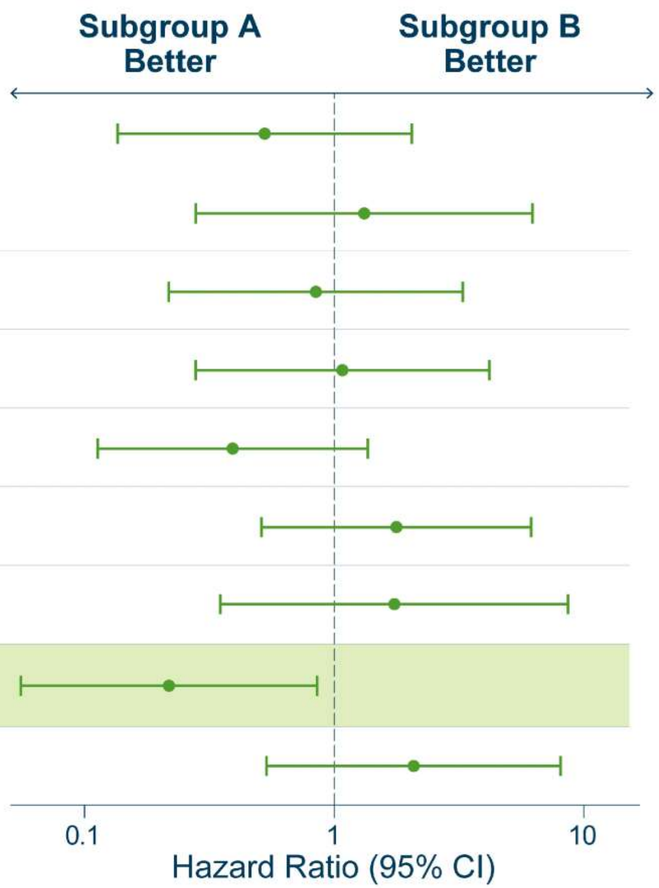


- ORR was not predicted by any patient or clinical characteristics analyzed, including:
  - Baseline LDH (≤ULN vs >ULN)
  - Baseline ECOG performance status (0 vs ≥1)
  - Baseline brain / liver lesions (yes vs no)
  - Cumulative duration on anti–CTLA-4 (≤median vs >median)
  - Cumulative duration on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

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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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18. Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
19. Yale University School of Medicine, Smilow Cancer Center, New Haven Hospital, New Haven, CT, USA
20. Royal Marsden NHS Foundation Trust, London, UK
21. University of Colorado Cancer Center - Anschutz Medical Campus, Aurora, CO, USA
22. University of Szeged - Albert Szent-Györgyi Health Center, Szeged, Hungary
23. Centre Hospitalier Universitaire Vaudois Lausanne, Lausanne, Switzerland
24. Virginia Commonwealth University, Richmond, VA, USA
25. University of Florida Health Cancer Center at Orlando Health, Orlando, FL, USA
26. Atlantic Health System Cancer Care, Morristown, NJ, USA

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