Lifileucel tumor-infiltrating lymphocyte (TIL) cell therapy in patients with advanced mucosal melanoma after progression on immune checkpoint inhibitors (ICI): Results from the phase 2 C-144-01 study

Harriet Kluger,[1] Götz Ulrich Grigoleit,[2] Sajeve Thomas,[3] Jason A Chesney,[4] Evidio Domingo-Musibay,[5] Miguel F Sanmamed,[6] Theresa Medina,[7] Mirjana Ziemer,[8] Eric Whitman,[9] Friedrich Graf Finckenstein,[10] Jeffrey Chou,[10] Xiao Wu,[10] Giri Sulur,[10] Wen Shi,[10] Amod Sarnaik[11]

[1]Yale Cancer Center, New Haven, CT, USA; [2]Helios Klinikum Duisburg, Duisburg, Germany; [3]Orlando Health Cancer Institute, Orlando, FL, USA; [4]Brown Cancer Center, Louisville, KY, USA; [5]Masonic Cancer Center, Minneapolis, MN, USA; [6]Clínica Universitaria de Navarra, Pamplona, Navarra, Spain; [7]University of Colorado Cancer Center, Aurora, CO, USA; [8]Universitätsklinikum Leipzig, Leipzig, Germany; [9]Atlantic Health System, Morristown, NJ, USA; [10]Iovance Biotherapeutics, Inc., San Carlos, CA, USA; [11]H Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

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Advanced Mucosal Melanoma: Difficult to Treat After ICI Therapy

- Advanced mucosal melanoma is rare and difficult to treat[1–3]
  - Responses to first-line anti–PD-1 therapy are only seen in 13–26% of patients[2-5]

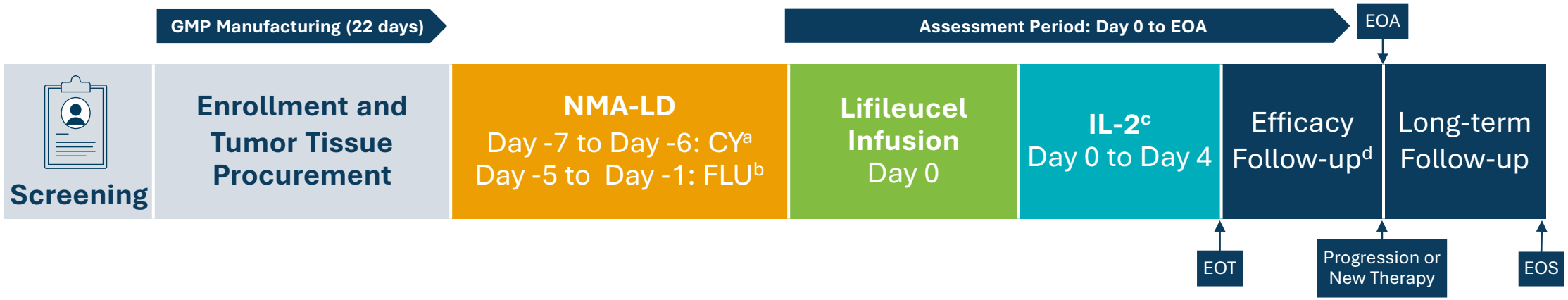
- C-144-01 (NCT02360579) is a phase 2 multicenter study of lifileucel autologous TIL cell therapy in patients with advanced (unresectable or metastatic) melanoma whose disease had progressed on or after anti–PD-1/PD-L1 therapy[6]
  - With a median study follow-up of 27.6 months, lifileucel demonstrated an ORR of 31.4% in heavily pretreated patients (N=153) with advanced melanoma (prior therapies, median [range]: 3.0 [1–9])
  - The median OS was 13.9 months, and 12-months OS rate was 54.0%

1. D'Angelo SP, et al. J Clin Oncol. 2017;35:226–235. 2. Mignard C, et al. J Oncol. 2018;2018:190806. 3. Hamid O, et al. Br J Cancer. 2018;119:670–674. 4. Teterycz P, et al. Cancers (Basel). 2020;12:3131. 5. Nakamura Y, et al. ESMO Open. 2021;6:100325. 6. Chesney J, et al. J Immunother Cancer. 2022;10:e005755.
ICI, immune checkpoint inhibitor; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; TIL, tumor-infiltrating lymphocyte.

C-144-01: Lifileucel in Advanced Mucosal Melanoma

- We report data in a subgroup of patients (N=12) with advanced mucosal melanoma treated with lifileucel with a planned follow-up of up to 5 years
- Patients had ≥1 lesion resected for lifileucel manufacturing, then received nonmyeloablative lymphodepletion (NMA-LD; cyclophosphamide 60 mg/kg daily × 2 doses, fludarabine 25 mg/m^2 daily × 5 doses), a single lifileucel infusion, and up to 6 doses of high-dose IL-2 (**Figure 1**)

Figure 1. Treatment Schema



[a]60 mg/kg daily x 2 doses. [b]25 mg/m^2 daily x 5 doses. [c]600,000 IU/kg (≤6 doses). [d]Response was assessed by an independent review committee using RECIST v1.1 criteria.
CY, cyclophosphamide; EOA, end of assessment; EOS, end of study; EOT, end of treatment; FLU, fludarabine; GMP, Good Manufacturing Practice; IL-2, interleukin-2; IU, international units; NMA-LD, nonmyeloablative lymphodepletion; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumors.

Baseline Patient and Disease Characteristics

Most patients with mucosal melanoma had disease that was primary refractory to prior anti–PD-1/PD-L1 therapy

Table 1. Baseline Patient and Disease Characteristics

Characteristics	Mucosal Melanoma (N=12)
Median age, y (min, max)	61.5 (37–79)
Median number of prior therapies, n (min, max)	2 (1–6)
Primary refractory to anti–PD-1/PD-L1,[a] n (%)	**10 (83.3)**
Liver or brain metastasis by IRC, n (%)	5 (41.7)
Tumor tissue procurement site,[b] n (%)	
Lymph node	6 (50.0)
Median target lesion SOD, mm (min, max)	**118.9 (20.7–260.9)**
Median target and nontarget lesions, n (min, max)	**6 (3–13)**
BRAF V600 wild-type, n (%)	12 (100)
LDH>ULN, n (%)	5 (41.7)

- Data cut-off: 15 July 2022
- 12 patients with histologically diagnosed mucosal melanoma received lifileucel
  - The median (range) number of TIL infused was 26.1 × 10^9 cells (3.3–72)
  - The median (range) number of IL-2 doses was 5.5 (3–6)
- Most patients had a high disease burden with a median target lesion SOD of 118.9 mm (**Table 1**)

[a]Primary refractory to anti–PD-1/PD-L1 is defined as best response of progressive disease to prior anti–PD-1/PD-L1; the first anti–PD-1/PD-L1 with documented response was considered if multiple anti–PD-1/PD-L1 therapies were received. [b]6 patients (50%) had other sites for tumor tissue procurement, including lung (n=2), liver (n=1), skin/subcutaneous (n=1), groin (n=1), chest wall (n=1).
IL-2, interleukin 2; IRC, independent review committee; IU, international units; LDH, lactate dehydrogenase; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; SOD, sum of diameters; TIL, tumor-infiltrating lymphocyte; ULN, upper limit of normal.

Clinical Efficacy of Lifileucel in Mucosal Melanoma

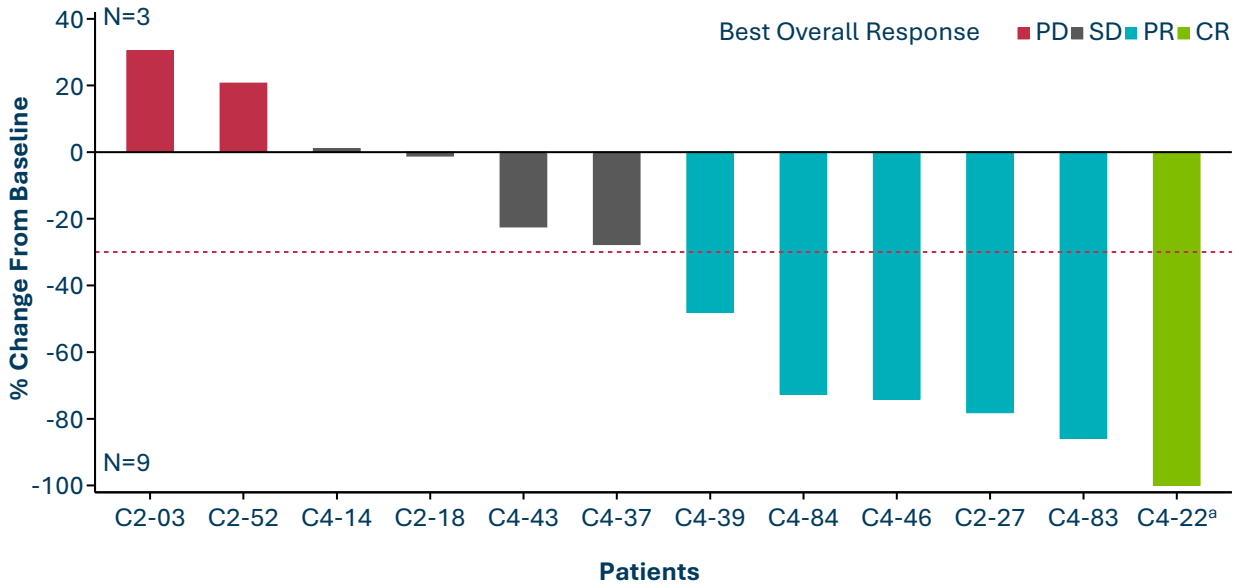
Lifileucel demonstrated clinically meaningful antitumor activity measured by ORR and change in SOD

- The median follow-up was 35.7 months
- The ORR (confirmed responses) was 50.0% (6/12; 95% CI, 21.1–78.9) (**Table 2, Figure 2**)

Table 2. IRC-Assessed Response (RECIST v1.1)

	Mucosal Melanoma (N=12)
Best overall response, n (%)	
CR	1 (8.3)
PR	5 (41.7)
SD	4 (33.3)
PD	2 (16.7)

Figure 2. Best Percentage Change From Baseline in Target Lesion SOD



[a]–100% change from baseline is presented for CR assessment that includes lymph node lesions.
CI, confidence interval; CR, complete response; IRC, independent review committee; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOD, sum of diameters.

Clinical Efficacy of Lifileucel in Mucosal Melanoma

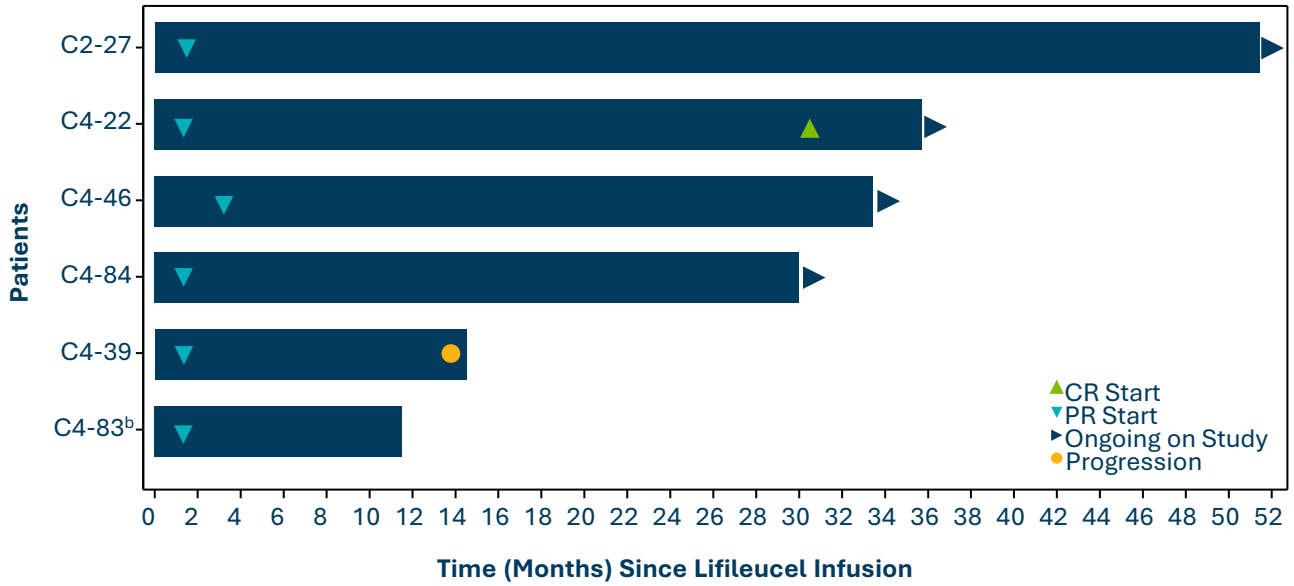
Lifileucel demonstrated clinically meaningful antitumor activity with durable responses

- Median DOR was NR (95% CI: 12.5–NR) (**Table 3**)
- 4 of 6 responders had durable and ongoing responses at the time of the data cut (**Figure 3**)

Table 3. Duration of Response

	Mucosal Melanoma (N=12)
DOR,[a] n (%)	
≥6 months	6/6 (100)
≥12 months	5/6 (83.3)
≥24 months	4/6 (66.7)

Figure 3. Time to Response and Time of Efficacy Assessment for Confirmed Responders (PR or Better)



[a]Includes patients who achieved CR or PR. [b]Patient C4-83 discontinued the efficacy follow-up at time of data cut.
CI, confidence interval; CR, complete response; DOR, duration of response; NR, not reached; PR, partial response; TIL, tumor-infiltrating lymphocyte.

Safety in Mucosal Melanoma

Safety was consistent with known safety profiles of NMA-LD and IL-2

- The most common grade 3/4 nonhematologic TEAEs (≥30% of patients) were febrile neutropenia and hypotension (**Table 4**)
- Grade 3/4 hematologic laboratory abnormalities were consistent with NMA-LD (**Table 5**)

Table 4. Nonhematologic TEAEs in ≥30% of Patients

Preferred Term, n (%)	Mucosal Melanoma (N=12)	
	Any grade	Grade 3/4
Chills	9 (75.0)	0
Febrile neutropenia	7 (58.3)	7 (58.3)
Diarrhea	7 (58.3)	0
Pyrexia	5 (41.7)	0
Pruritus	5 (41.7)	0
Hypotension	5 (41.7)	4 (33.3)
Alopecia	5 (41.7)	0
Hypokalemia	4 (33.3)	0
Hypoxia	4 (33.3)	2 (16.7)

Table 5. Grade 3/4 Hematologic Laboratory Abnormalities

Laboratory Abnormality, n (%)	Mucosal Melanoma (N=12)
Neutropenia	12 (100)
Leukopenia	12 (100)
Lymphopenia	12 (100)
Thrombocytopenia	12 (100)
Anemia	8 (66.7)

IL-2, interleukin-2; NMA-LD, nonmyeloablative lymphodepletion; TEAE, treatment-emergent adverse event.

Tumor Mutational Burden (TMB) and TIL Persistence

TMB was lower in mucosal melanoma than in cutaneous melanoma

- Mucosal melanoma showed lower TMB compared with cutaneous melanoma (**Figure 4**)
  - Mean TMB of mucosal vs cutaneous melanoma: 2.145 mut/Mb vs 10.47 mut/Mb, respectively
- TIL persistence in blood through month 12 was similar in patients with mucosal or cutaneous melanoma (**Figure 5**)

Figure 4. TMB in Patients With Mucosal or Cutaneous Melanoma

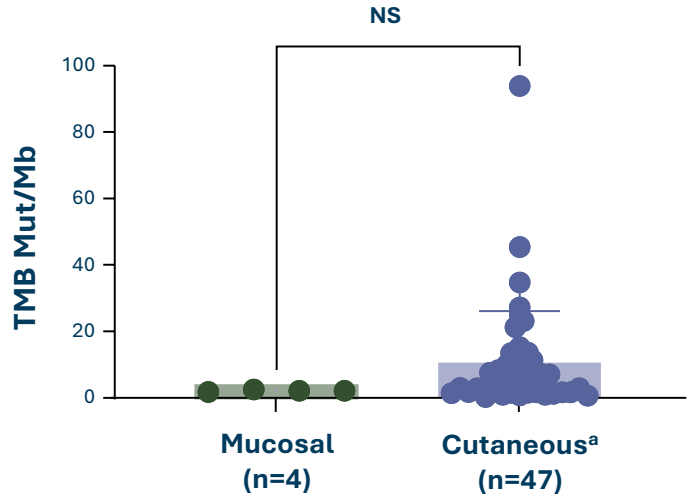
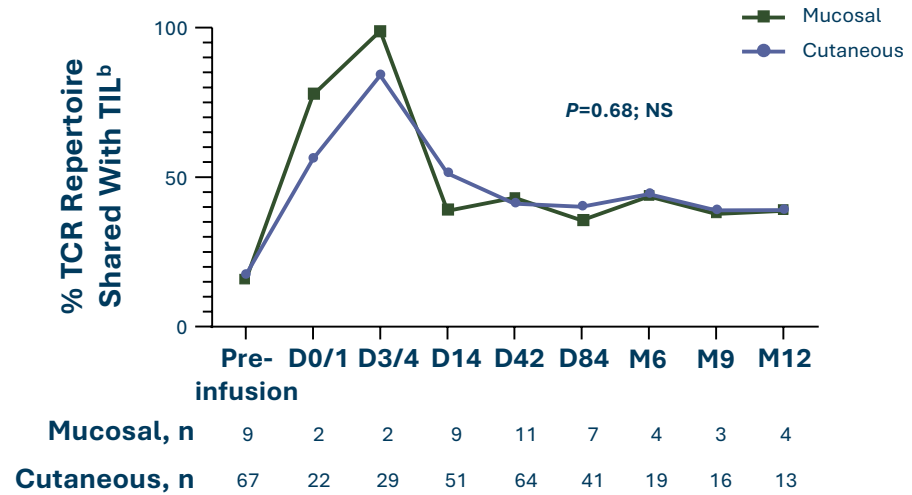


Figure 5. TIL Persistence in Blood Over Time in Patients With Mucosal or Cutaneous Melanoma

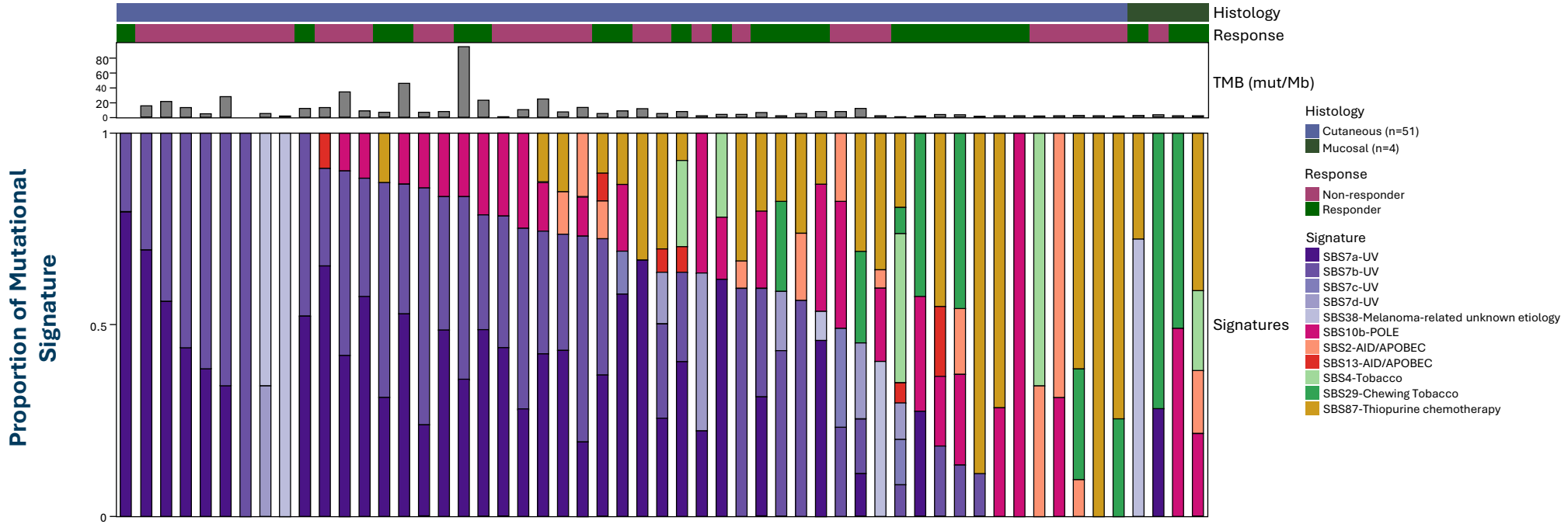


[a]The horizontal bar represents the standard deviation. [b]From TIL infusion product.
D, day; M, month; mut, mutation; NS, not significant; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte, TMB, tumor mutational burden.

Proportion of Mutational Signature

Mutational mechanisms driving mucosal melanoma not attributable to UVR

Figure 6. Mutational Signature Determined From Whole Exome Sequencing of Pretreatment Tumor From Patients With Mucosal or Cutaneous Melanoma



- In contrast to most cutaneous melanoma tumors, mucosal melanoma tumors showed little or no contribution from UVR-related COSMIC mutational signature 7 (**Figure 6**)
- High response rate observed in mucosal melanoma with non-UVR signatures and low TMB

COSMIC, Catalogue of Somatic Mutations in Cancer; mut, mutation; TMB, tumor mutational burden; UVR, ultraviolet radiation.

Conclusions

Lifileucel demonstrated durable clinical benefit in patients with difficult-to-treat mucosal melanoma

- Lifileucel demonstrated clinically meaningful activity and durable responses in patients (N=12) with difficult-to-treat, low-TMB mucosal melanoma with progression after anti–PD1/PD-L1 therapy
  - The ORR was 50% (6/12; 95% CI, 21.1–78.9)
  - At a median follow-up of 35.7 months, median DOR was NR
- Mucosal melanoma tumor mutational signatures showed little or no UVR-related contribution in contrast to most cutaneous melanoma tumors
- Although molecularly distinct from cutaneous melanoma, antitumor responses observed in this subgroup of patients with mucosal melanoma were consistent with responses observed in the overall population of patients with advanced melanoma treated with lifileucel[1]
- TEAEs were consistent with the known safety profiles of NMA-LD and IL-2
- These results demonstrate lifileucel has antitumor activity across tumors with a range of mutational mechanisms and further support the potential benefit of lifileucel as a one-time treatment that is differentiated from other immunotherapies for melanoma

1. Chesney J, et al. J Immunother Cancer. 2022;10:e005755.

DOR, duration of response; IL-2, interleukin-2; NMA-LD, nonmyeloablative lymphodepletion; NR, not reached; ORR, objective response rate; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; TEAE, treatment-emergent adverse event; TMB, tumor mutational burden; UVR, ultraviolet radiation.

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Declaration of Interests

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