2024 ASCO Annual Meeting
May 31–June 4, 2024 | Chicago, IL, USA

Efficacy and safety of lifileucel, an autologous tumor-infiltrating lymphocyte cell therapy, and pembrolizumab in patients with immune checkpoint inhibitor-naive unresectable or metastatic melanoma: updated results from IOV-COM-202 Cohort 1A

Sajeve Thomas,[1] Helen Gogas,[2] Young Ki Hong,[3] Gino K. In,[4] Bernard Doger de Speville Uribe,[5] Andrew J.S. Furness,[6] Almudena Garcia Castano,[7] Simon Häfliger,[8] Kai He,[9] Theresa Medina,[10] Donald Lawrence,[11] Sylvia Lee,[12] Juan Martin-Liberal,[13] Friedrich Graf Finckenstein,[14] Brian Gastman,[14] Jeffrey Chou,[14] Rana Fiaz,[14] Melissa Catlett,[14] Guang Chen,[14] Patrick Terheyden[15]

[1]Orlando Health Cancer Institute, Orlando, FL, USA; [2]Laiko General Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [3]Cooper University Hospital, Camden, NJ, USA; [4]University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [5]START Madrid Fundación Jiménez Díaz, Madrid, Spain; [6]The Royal Marsden NHS Foundation Trust, London, UK; [7]Hospital Universitario Marqués de Valdecilla, Santander, Spain; [8]Inselspital, Bern University Hospital, Bern, Switzerland; [9]James Cancer Center, The Ohio State University, Columbus, OH, USA; [10]University of Colorado Cancer Center – Anschutz Medical Campus, Aurora, CO, USA; [11]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [12]Fred Hutchinson Cancer Center, Seattle, WA, USA; [13]ICO L'Hospitalet – Hospital Duran i Reynals, Barcelona, Spain; [14]Iovance Biotherapeutics, Inc., San Carlos, CA, USA; [15]University of Lübeck, Lübeck, Germany

Takeaways

- In this phase 2 trial, ICI-naive patients with advanced melanoma treated with lifileucel + pembrolizumab had deep and durable responses
  - Two thirds of patients had a confirmed response by RECIST v1.1
  - Almost a third of patients had confirmed complete response
  - All evaluable patients had regression of target lesions
  - The vast majority of responses were ongoing
- The safety profile for one-time treatment with lifileucel combined with pembrolizumab monotherapy is differentiated from the safety profiles of ICI combination regimens
- These results support TILVANCE-301, a registrational, randomized trial assessing lifileucel + pembrolizumab in frontline advanced melanoma

ICI, immune checkpoint inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors.

Advanced Melanoma: Unmet Need for Front-line Treatments That Provide Long-Term Benefit

- At least half of patients who receive front-line combination ICI therapy do not achieve long-term benefit, representing a population in need of new strategies[1]
- Lifileucel was approved as a second-line treatment for advanced melanoma based on results from the C-144-01 trial[2,3]
  - ORR for the heavily pretreated patients was 31.4%[2]
  - Longest duration of IRC-assessed response was ongoing at 55.8 months
  - Responses continued to deepen in many patients even beyond 2.5 years
- Lifileucel has the potential to improve outcomes over current ICI mono- or combination therapy in the frontline/ ICI-naive setting
  - In a retrospective analysis of 192 ICI-naive patients with metastatic melanoma cohort treated with TIL cell monotherapy at the National Cancer Institute, the ORR was 56%, with a CR rate of 25%[4]
- IOV-COM-202 is a multicohort, multicenter study of lifileucel + pembrolizumab in patients with solid tumors, including patients with melanoma naïve to ICI therapy

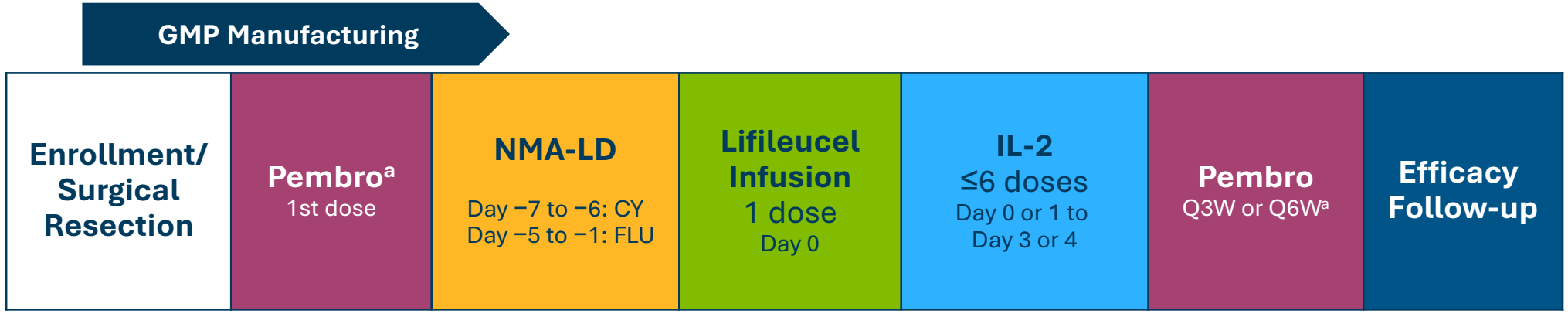
ICI, immune checkpoint inhibitor; ORR, objective response rate; PD-1, programmed cell death protein-1; TIL, tumor-infiltrating lymphocyte.

1. Larkin J, et al. *N Engl J Med*. 2019;381:1535–46. 2. Chesney J, et al. *J Immunother Cancer*. 2022;10:e005755. 3. Amtagvi™: Prescribing Information, 2024. 4. Seitter SJ, et al. *Clin Cancer Res*. 2021;27:5289–98.

IOV-COM-202: Phase 2, Multicohort, Multicenter Study of Lifileucel + Pembrolizumab in Patients With Solid Tumors

- Cohort 1A of IOV-COM-202 (NCT03645928) assesses the efficacy and safety of lifileucel + pembrolizumab in patients with ICI-naive unresectable or metastatic melanoma
  - Patients may have received BRAF/MEK inhibitor treatment if they are *BRAF* mutation positive
  - Eligible patients must have ≥1 resectable lesion (≥1.5-cm diameter) and ≥1 measurable lesion for response assessment per RECIST v1.1
- Trial designed as a proof-of-concept study to support a registrational study in the frontline treatment setting

Treatment Schema



[a]First administration of single-dose pembrolizumab IV 200 mg or 400 mg, followed by pembrolizumab IV 200 mg Q3W or 400 mg Q6W for 24 months or until disease progression or unacceptable toxicity.
CY, cyclophosphamide; EOA, end of assessment; FLU, fludarabine; GMP, Good Manufacturing Practice; ICI, immune checkpoint inhibitor; IL-2, interleukin-2; NMA-LD, nonmyeloablative lymphodepletion; pembro, pembrolizumab; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Baseline Patient and Disease Characteristics

Characteristics	N=23
Median age, y (min, max)	51.0 (18–68)
Male sex, n (%)	15 (65.2)
White	23 (100)
Melanoma type, n (%)	
Cutaneous	16 (69.6)
Acral	1 (4.3)
Mucosal	2 (8.7)
Unknown primary	4 (17.4)
Metastatic staging at study entry, n (%)	
M0	2 (8.7)
M1a	6 (26.1)
M1b–M1d	14 (60.9)
Unknown	1 (4.3)
Baseline ECOG status	
0	17 (73.9)
1	6 (26.1)

Characteristics	N=23
PD-L1 TPS, n (%)	
<1	4 (17.4)
≥1	13 (56.5)
Missing	6 (26.1)
Median target lesion SOD, mm (min, max)	50.0 (14–355)
>3 baseline target and nontarget lesions, n (%)	15 (65.2)
Liver metastasis, n (%)	7 (30.4)
Brain metastasis, n (%)	0
LDH, n (%)	
<ULN	15 (65.2)
1–2 × ULN	7 (30.4)
>2 × ULN	1 (4.3)
BRAF V600 mutated, n (%)	8 (34.8)
Prior BRAF/MEK inhibitor treatment	3 (13.0)
Median number of prior therapies (min, max)[a]	0 (0–2)

Data cutoff: April 17, 2024

[a]3 patients received prior chemotherapy, 2 patients received prior adjuvant immune checkpoint inhibitor >12 months prior to enrollment not counted as line of prior therapy per protocol.
ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-L1, programmed death-ligand 1; SOD, sum of diameters; TPS, tumor proportion score; ULN, upper limit of normal.

Safety

Nonhematologic TEAEs in ≥30% of Patients[a]

	N=23	
Preferred Terms, n (%)	Any grade	Grade 3/4
Chills	19 (82.6)	3 (13.0)
Pyrexia	18 (78.3)	4 (17.4)
Nausea	18 (78.3)	0
Vomiting	15 (65.2)	0
Fatigue	14 (60.9)	1 (4.3)
Febrile neutropenia	11 (47.8)	10 (43.5)
Headache	11 (47.8)	0
Diarrhea	10 (43.5)	1 (4.3)
Cough	10 (43.5)	0
Dyspnea	9 (39.1)	1 (4.3)
Alopecia	9 (39.1)	0
Decreased appetite	9 (39.1)	0
Hypertension	8 (34.8)	5 (21.7)
Rash maculopapular	8 (34.8)	3 (13.0)
Peripheral edema	8 (34.8)	1 (4.3)
Hypokalemia	8 (34.8)	0
Abdominal pain	7 (30.4)	0

Grade 3/4 Hematologic Lab Abnormalities[b]

	N=23
Preferred Terms, n (%)	Grade 3/4
Neutropenia	23 (100)
Lymphopenia	23 (100)
Leukopenia	22 (95.7)
Thrombocytopenia	22 (95.7)
Anemia	10 (43.5)

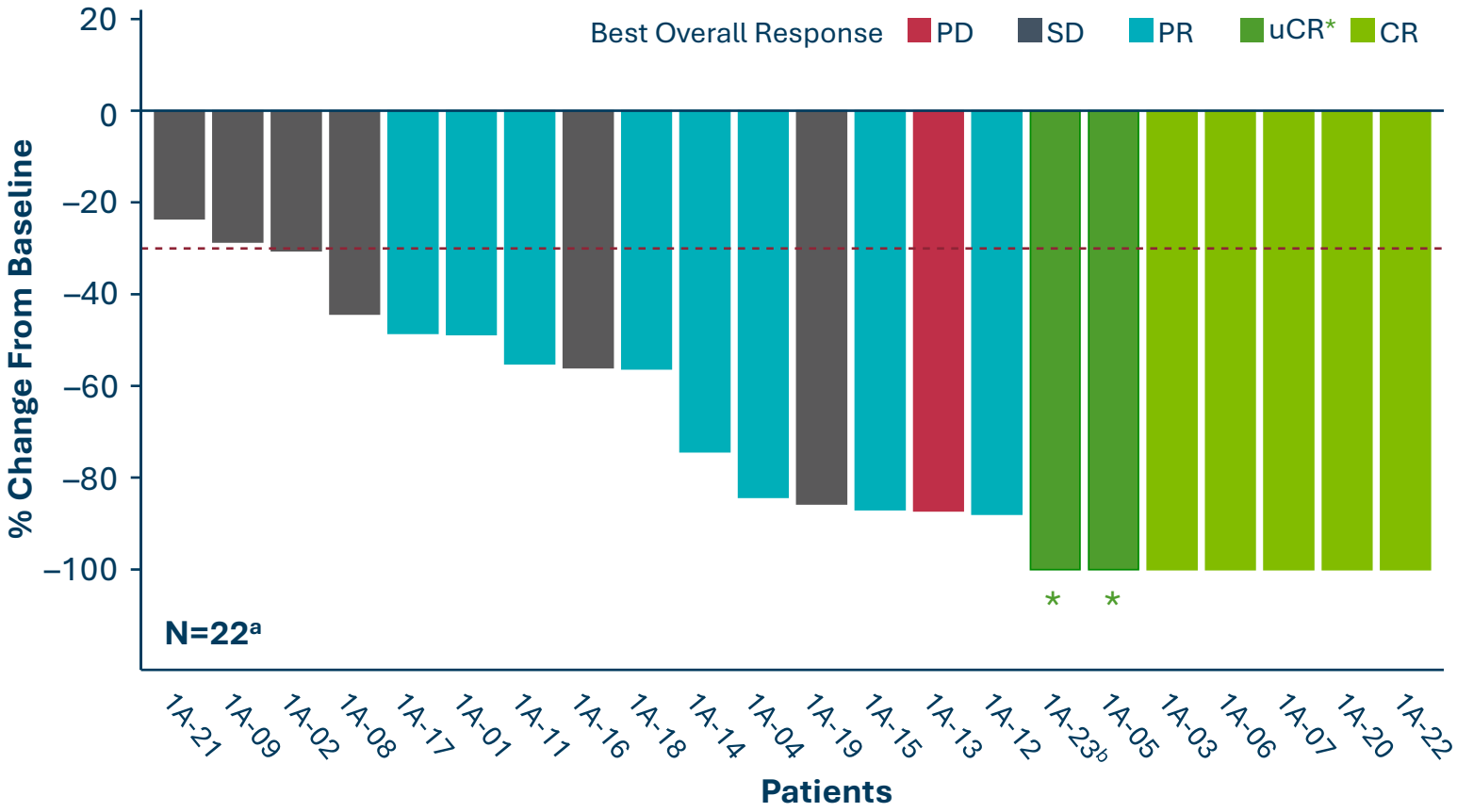
- By Day 30, Grade 3/4 hematologic lab abnormalities resolved to Grade ≤2:
  - Neutropenia: 91.3%
  - Lymphopenia: 78.3%
  - Leukopenia: 95.5%
  - Thrombocytopenia: 95.5%
  - Anemia: 90.0%
- No unexpected AEs
- AEs consistent with the lifileucel regimen occurred and resolved early
- AEs occurring later than 30 days after lifileucel infusion were generally consistent with pembrolizumab monotherapy
- **Safety was consistent with the underlying disease and known safety profiles of pembrolizumab, NMA-LD, lifileucel, and IL-2**

[a]TEAEs refer to adverse events that occur from the first dose of pembrolizumab or lifileucel infusion (whichever occurs first) up to 30 days after last dose of pembrolizumab or lifileucel infusion (whichever occurs later) or up to the start of a new anticancer therapy.
[b]Grade 3/4 hematologic laboratory toxicity during the period from the start of NMA-LD to 30 days after the TIL infusion (to any resolution date).
One patient had a grade 5 TEAE of sepsis.
AE, adverse event; IL-2, interleukin-2; NMA-LD, nonmyeloablative lymphodepletion; TEAE, treatment-emergent adverse event.

Efficacy

ORR was 65.2%; CR rate was 30.4%

Best Percentage Change From Baseline in Target Lesion SOD



Investigator-Assessed Response (RECIST v1.1)

	N=23
ORR, n (%) (95% CI)	15 (65.2) (42.7, 83.6)
CR	7 (30.4)
PR	8 (34.8)
SD	6 (26.1)
PD	1 (4.3)
NE	1 (4.3)

All response-evaluable patients demonstrated regression of target lesions

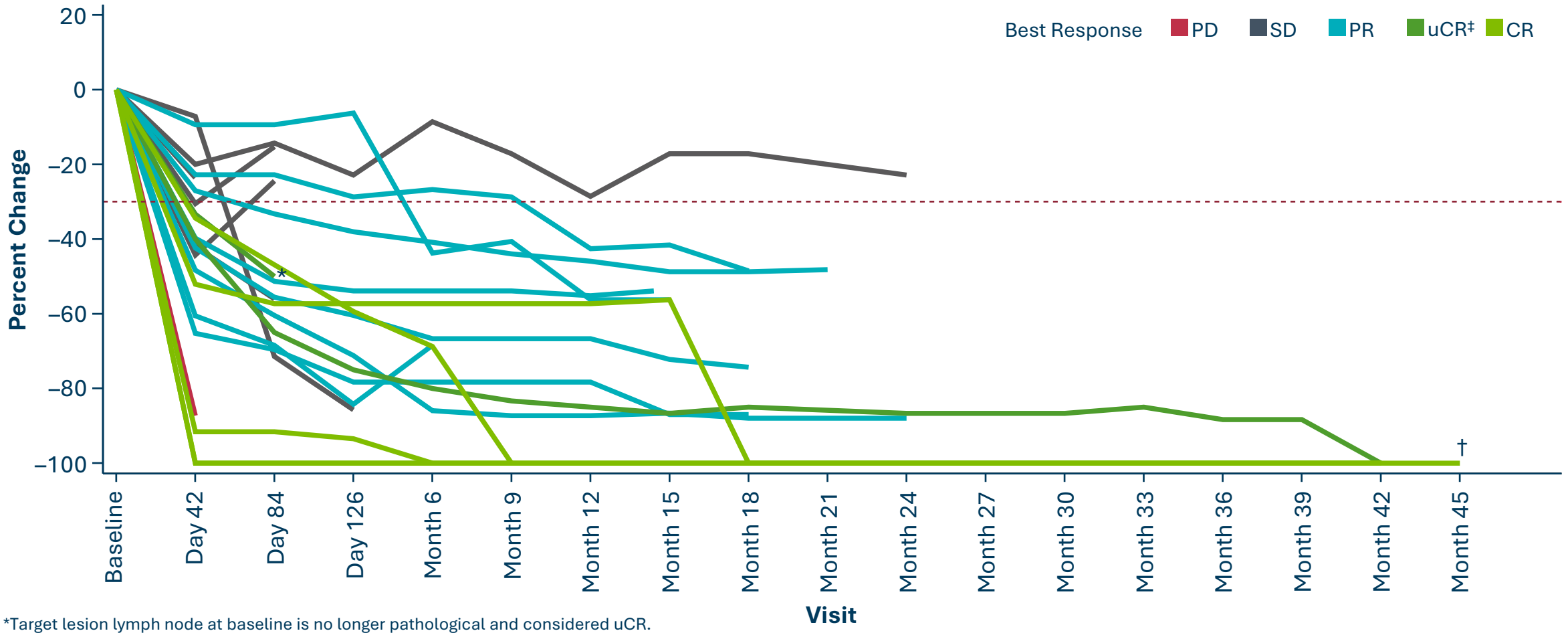
*** The two uCRs have been confirmed post-data cut**

[a]One patient without a postdose tumor response assessment was not included. [b]Target lesion lymph node at baseline decreased by 50% is no longer pathological, and thus is shown here as -100% representing uCR. CI, confidence interval; CR, complete response; NE, not evaluated; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOD, sum of diameters; uCR, unconfirmed complete response.

Efficacy

Lifileucel + pembrolizumab demonstrated durable and deepening responses

Percent Change From Baseline in Target Lesion SOD



*Target lesion lymph node at baseline is no longer pathological and considered uCR.
†The overlapping lines at −100% represent 5 patients.
‡The two uCRs have been confirmed post-data cut.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters; uCR, unconfirmed complete response.

Efficacy

Lifileucel + pembrolizumab demonstrated durable and deepening responses

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

Duration of Response

	Responders (N=15/23)
mDOR, months (95% CI)	Not reached (NR) (16.8, NR)
DOR, n (%)	
≥6 months	11 (73.3)
≥12 months	8 (53.3)

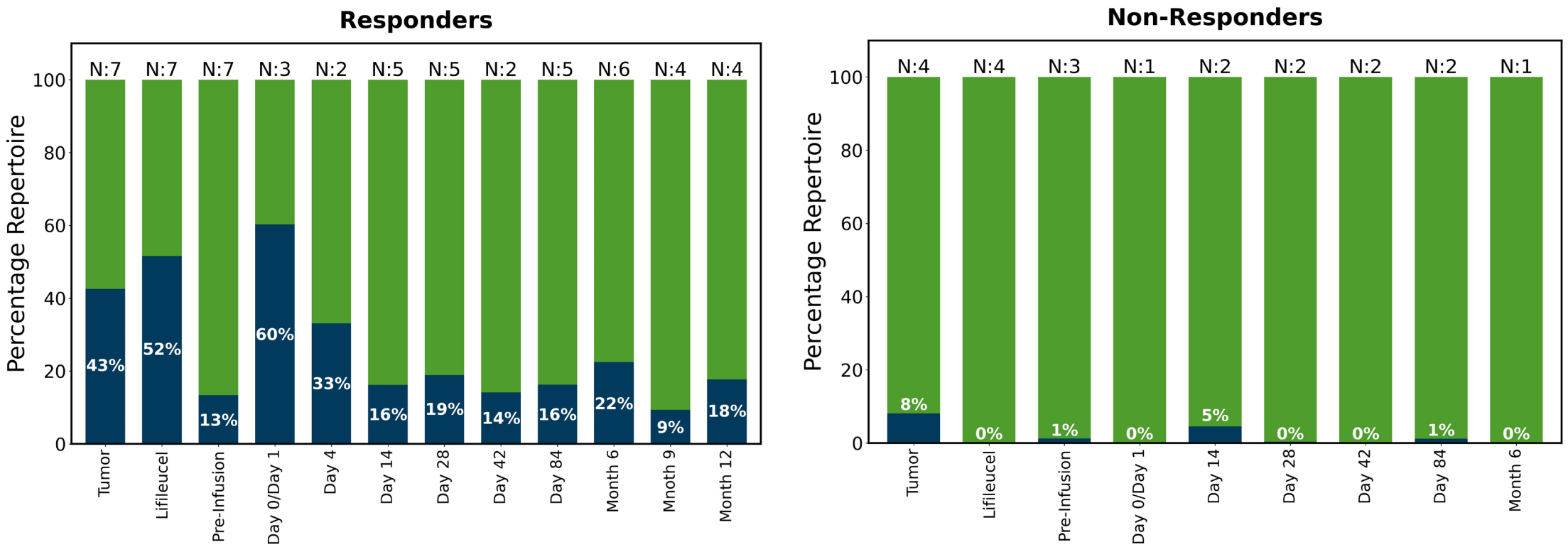
- Median follow-up was 21.7 months
- **mDOR was NR**
- Median time to initial response was 2.6 months
- 10 of 15 responders (66.7%) continue on study with ongoing response and 3 additional patients (20%) discontinued follow-up while in response

*CR start based on PET/CT showing no FDG uptake in all lesions and subsequently confirmed per RECIST 1.1. †Patient withdrew consent during assessment phase while still in response. ‡Discontinued from study while in response to continue pembrolizumab off-study. §Discontinued due to disease progression of new lesion. ¶Discontinued due to disease progression of non-target lesion.
CI, confidence interval; CR, complete response; DOR, duration of response; mDOR, median duration of response; (FDG) fluorodeoxyglucose; NR, not reached; PR, partial response.

TCR Sequencing Analysis

Responders had higher overlap between tumor and lifileucel TCR clonotypes than nonresponders, and demonstrated persistence of shared clonotypes

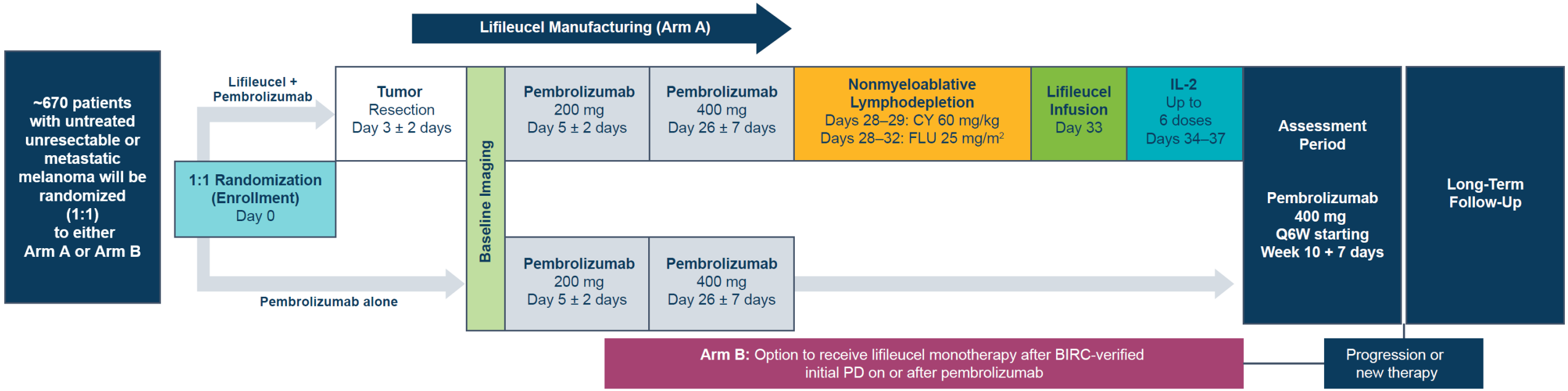
Persistence of Shared TCR Clonotypes



TCR, T cell receptor.

TILVANCE-301[a] Global Phase 3 and Confirmatory Trial

Randomized study to evaluate lifileucel + pembrolizumab in frontline advanced melanoma Enrolling in Europe, North America, and Australia



Study Endpoints

Dual primary efficacy endpoints

- BIRC-assessed ORR per RECIST v1.1
  - Potential for accelerated approval and confirmation of post anti-PD1 approval based on early interim analysis
- BIRC-assessed PFS per RECIST v1.1

Key secondary efficacy endpoint

- OS

Additional secondary endpoints

- BIRC-assessed CR rate, DOR, EFS per RECIST v1.1
- Investigator-assessed ORR, PFS, CR rate, DOR, EFS, PFS2 per RECIST v1.1
- Safety

[a]NCT05727904.

BIRC, blinded independent review committee; CR, complete response; CY, cyclophosphamide; EFS, event-free survival; FLU, fludarabine; IL-2, interleukin-2; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein-1; PFS, progression-free survival; PFS2, progression-free survival 2; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Conclusions

A single administration of lifileucel combined with pembrolizumab demonstrated:

- Manageable and expected safety profile
  - TEAEs consistent with the underlying disease and known, manageable safety profiles of single administration of the lifileucel regimen and continued pembrolizumab
  - Late AEs consistent with anti-PD-1 monotherapy, differentiated from ICI combination therapies
- Efficacy and durability of responses in patients with ICI-naive advanced melanoma
  - ORR was 65.2% and CR rate was 30.4%
  - All evaluable patients demonstrated regression of target lesions
  - mDOR was not reached, with a high proportion of ongoing responses (median follow-up of 21.7 months)
  - Rate and depth of responses compare favorably with ICI mono- and combination-regimens for first-line melanoma patients

These results serve as rationale for TILVANCE-301, an ongoing registrational, randomized trial assessing lifileucel + pembrolizumab in frontline advanced melanoma

CR, complete response; DOR, duration of response; ICI, immune checkpoint inhibitor; mDOR, median duration of response; ORR, objective response rate; PD-1, programmed cell death protein-1; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event.

Acknowledgments

- The authors thank the patients and their families, as well as the investigators and study site team members, who are participating in the study
- This study was sponsored by Iovance Biotherapeutics, Inc. (San Carlos, CA, USA)
- Medical writing and editorial support was provided by Adam Fishbein, PhD, and Sarah Huh, PharmD, of Peloton Advantage, LLC, an OPEN Health company, and funded by Iovance

Lay Summary

- Lifileucel is a T-cell immune therapy made from a patient's own immune cells within a tumor that may recognize and kill cancer cells
- In this study, patients with advanced melanoma that could not be removed surgically or had spread to other parts of the body and had not previously received immune therapy were given lifileucel combined with another immune therapy, pembrolizumab
  - All patients who had follow-up tumor scans had shrinkage of their tumors
  - In two thirds of patients, tumors shrank by at least 30% and responses were long-lasting
  - In almost a third of patients, the cancer became undetectable
- The side effects were manageable and consistent with what would be expected of lifileucel and pembrolizumab
- These results from this study support a larger study, TILVANCE-301, in patients who have not yet been treated for advanced melanoma