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

For more information, please contact Sajeve Thomas: sajeve.thomas@orlandohealth.com

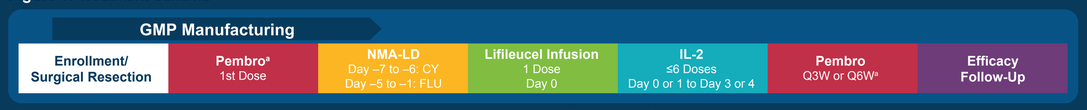
Introduction

- Approximately half of patients who receive frontline 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 patients with ICI-naive metastatic melanoma 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 naive to ICI therapy

Methods

- Cohort 1A of IOV-COM-202 (NCT03645928) assesses the efficacy and safety of lifileucel + pembrolizumab in patients with ICI-naive unresectable or metastatic melanoma (**Figure 1**)
  - 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

Figure 1. 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.

Results

- As of April 17, 2024, 23 patients with a median (range) age of 51.0 (18–68) years received treatment (**Table 1**)

Table 1. 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)
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)

[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.

- Safety was consistent with the underlying disease and known safety profiles of pembrolizumab, NMA-LD, lifileucel, and IL-2 (**Table 2**)

Table 2. 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

[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.

- Hematologic lab abnormalities are shown in **Table 3**

Table 3. Grade 3/4 Hematologic Lab Abnormalities[a]

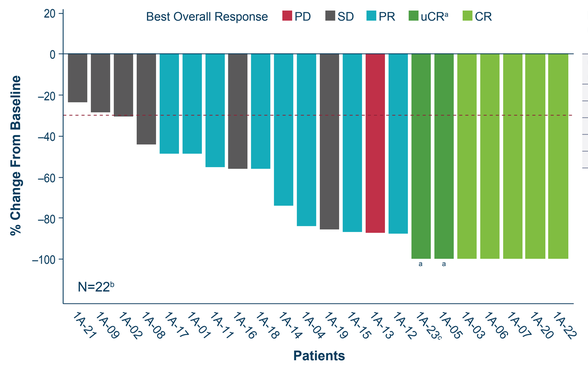
	N=23
Preferred Terms, n (%)	**Grade 3/4**
Neutropenia	23 (100)
Lymphopenia	23 (100)
Leukopenia	22 (95.7)
Thrombocytopenia	22 (95.7)
Anemia	10 (43.5)

[a]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.

- 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

- Confirmed ORR was 65.2% (15/23), including a 30.4% (7/23) CR rate (**Figure 2**)

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

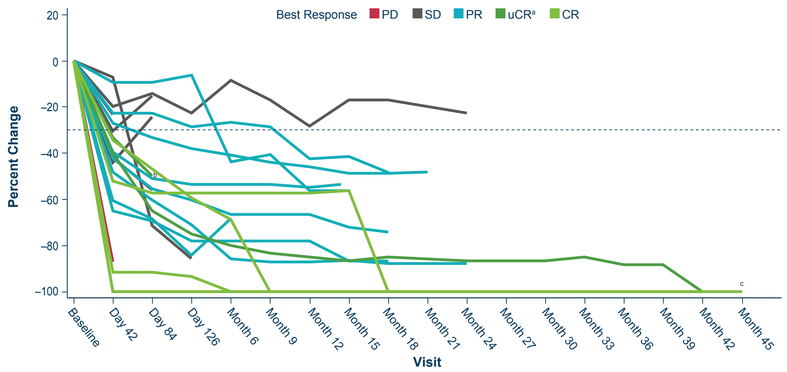


Investigator-Assessed Response (RECIST v1.1)	N=23
ORR, n (%) (95% CI)	15 (65.2) (42.7, 83.6)
CR	7 (30.4)
PR	8 (34.8)
SD	6 (26.1)
PD	1 (4.3)
NE	1 (4.3)

[a]The two uCRs have been confirmed post-data cut. [b]One patient without a postdose tumor response assessment was not included. [c]Target lesion lymph node at baseline decreased by 50% is no longer pathological, and thus is shown here as –100% representing uCR.

- All response-evaluable patients demonstrated regression of target lesions
- Responses were durable and deepening (**Figure 3**)

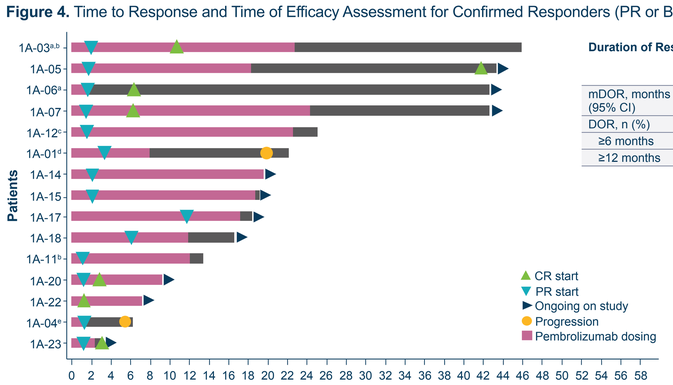
Figure 3. Percent Change From Baseline in Target Lesion SOD



[a]The two uCRs have been confirmed post-data cut. [b]Target lesion lymph node at baseline is no longer pathological and considered uCR. [c]The overlapping lines at –100% represent 5 patients.

- At a median follow-up of 21.7 months, median duration of response was NR (**Figure 4**)
  - 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

Figure 4. Time to Response and Time of Efficacy Assessment for Confirmed Responders (PR or Better)

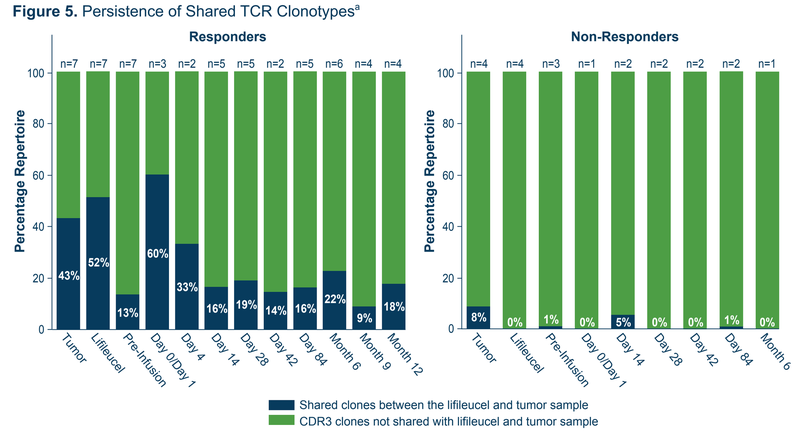


Duration of Response	Responders (N=15/23)
mDOR, months (95% CI)	NR (16.8, NR)
DOR, n (%)	
≥6 months	11 (73.3)
≥12 months	8 (53.3)

[a]CR start based on PET/CT showing no FDG uptake in all lesions and subsequently confirmed per RECIST 1.1. [b]Patient withdrew consent during assessment phase while still in response. [c]Discontinued from study while in response to continue pembrolizumab off-study. [d]Discontinued due to disease progression of new lesion. [e]Discontinued due to disease progression of non-target lesion.

- Responders had higher overlap between tumor and lifileucel TCR clonotypes than nonresponders, and demonstrated persistence of shared clonotypes (**Figure 5**)

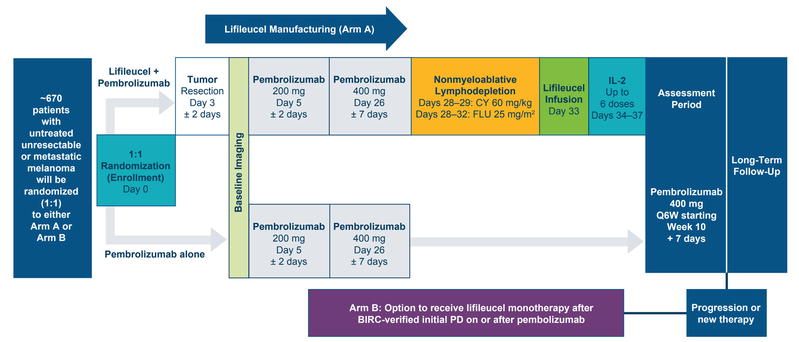
Figure 5. Persistence of Shared TCR Clonotypes[a]



[a]Sample sizes for each bar represent the number of patients with available samples for tumor, lifileucel, and the timepoint indicated in the x-axis, so that overlap could be calculated.

- A phase 3, randomized study to evaluate lifileucel + pembrolizumab in frontline advanced melanoma is currently enrolling patients in Europe, North America, and Australia (**Figure 6**)

Figure 6. TILVANCE-301 Global Phase 3 and Confirmatory Trial (NCT05727904)



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

Conclusions

- **In this phase 2 trial, a single administration of lifileucel combined with pembrolizumab in patients with ICI-naive advanced melanoma 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**
    - **ORR was 65.2%, with a CR rate of 30.4%**
    - **All evaluable patients demonstrated regression of target lesions**
    - **mDOR was not reached, with a high proportion of ongoing responses**
    - **Rate and depth of responses compare favorably with ICI mono- and combination-regimens for firstline treatment of melanoma**
- **These results serve as rationale for TILVANCE-301, an ongoing registrational, randomized trial assessing lifileucel + pembrolizumab in frontline advanced melanoma**

References

1. Larkin J, et al. *N Engl J Med*. 2019;381:1535–46.
2. Chesney J, et al. *J ImmunoTher Cancer*. 2022;10(12):e005755.
3. AMTAGVI (lifileucel). https://www.amtagvi.com/. Accessed August 2024.
4. Seitter SJ, et al. *Clin Cancer Res*. 2021;27:5289–98.

Abbreviations

AE, adverse event; BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; CY, cyclophosphamide; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EOA, end of assessment; FDG, fluorodeoxyglucose; FLU, fludarabine; GMP, Good Manufacturing Practice; ICI, immune checkpoint inhibitor; IL-2, interleukin-2; LDH, lactate dehydrogenase; mDOR, median duration of response; NE, not evaluated; NMA-LD, nonmyeloablative lymphodepletion; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein-1; pembro, pembrolizumab; PFS, progression-free survival; PFS2, progression-free survival 2; PR, partial response; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOD, sum of diameters; TCR, T cell receptor; TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocyte; TPS, tumor proportion score; uCR, unconfirmed complete response; ULN, upper limit of normal.

Disclosures

Sajeve Thomas: Amgen, Bristol Myers Squibb, Foundation One, Genentech, Ipsen, Merck, Pfizer; **Helen Gogas:** Amgen, Bristol Myers Squibb, Iovance Biotherapeutics, MSD Oncology, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi/Regeneron; **Young Ki Hong:** Castle Biosciences, Iovance Biotherapeutics; **Gino K. In:** Array, Bristol Myers Squibb, Castle Biosciences, Checkmate Pharmaceuticals, Idera, InstilBio, Merck, Novartis, Pfizer, Regeneron, Replimune, Roche/Genentech, Sanofi, Xencor; **Bernard Doger de Speville Uribe:** None to disclose; **Andrew J.S. Furness:** Achilles Therapeutics, Bristol Myers Squibb, Eisai, GSK, Immunocore, Ipsen, Merck, Neogene, Pfizer; **Almudena Garcia Castano:** Bristol Myers Squibb, MSD, Novartis, Pfizer, Pierre Fabre; **Simon Häfliger:** Amgen, Roche, Takeda; **Kai He:** AbbVie, Adaptimmune, Amgen, AstraZeneca, BioNTech SE, Bristol Myers Squibb, Genentech/Roche, GSK, Iovance Biotherapeutics, Lyell Immunopharma, Mirati Therapeutics, Obsidian Therapeutics, OncoC4, Perthera; **Theresa Medina:** BioAtla, Bristol Myers Squibb, Checkmate, Day One Pharmaceutical, Exicure, Iovance Biotherapeutics, Merck, Moderna, Nektar, Pfizer, Regeneron, Replimune, Taiga, Xencor; **Donald Lawrence:** None to disclose; **Sylvia Lee:** Bristol Myers Squibb, Iovance Biotherapeutics, Kite Pharma, Lyell Immunopharma, Seagen; **Juan Martin-Liberal:** Astellas, Bristol Myers Squibb, Highlight Therapeutics, Ipsen, Merck, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Sanofi; **Friedrich Graf Finckenstein:** Employment: Iovance Biotherapeutics. Stock or Stock Options: Iovance Biotherapeutics. Patents, Royalties, Other Intellectual Properties: Bristol Myers Squibb; **Brian Gastman, Jeffrey Chou, Rana Fiaz, Melissa Catlett, and Guang Chen:** Iovance Biotherapeutics; **Patrick Terheyden:** 4SC AG, Almirall, Biofrontera, Bristol Myers Squibb, Kyowa Kirin, Novartis, Pierre Fabre, Merck, Serono, Sanofi, Roche.

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. The authors also thank Behzad Damirchi and Rongsu Qi for their contributions to this work
- This study was sponsored by Iovance Biotherapeutics, Inc. (San Carlos, CA, USA)
- Medical writing and editorial support was provided by Adam Fishbein, PhD, of Peloton Advantage, LLC, an OPEN Health company, and funded by Iovance