Lifileucel TIL Cell Monotherapy in Patients With Advanced Melanoma After Progression on Immune Checkpoint Inhibitors and Targeted Therapy: Pooled Analysis of Consecutive Cohorts (C-144-01 Study)

Omid Hamid, Amod Sarnaik, Harriet Kluger, Eric Whitman, Sajeve Thomas, Martin Wermke, Mike Cusnir, Evidio Domingo-Musibay, Giao Q. Phan, John M. Kirkwood, Jessica C. Hassel, Melissa Wilson, James Larkin, Jeffrey Weber, Andrew J. S. Furness, Nikhil I. Khushalani, Theresa Medina, Friedrich Graf Finckenstein, Madan Jagasia, Parameswaran Hari, Giri Sulur, Wen Shi, Xiao Wu, Jason Chesney

1The Angeles Clinic and Research Institute, a Cedars Sinai Affiliate, Los Angeles, CA, USA; 2H. Lee Moffitt Cancer Center, Tampa, FL, USA; 3Yale School of Medicine and Smilow Cancer Center, Yale New Haven Hospital, New Haven, CT, USA; 4Atlantic Health System Cancer Care, Morristown, NJ, USA; 5Orlando Health Cancer Institute, Orlando, FL, USA; 6Technical University Dresden – NCT/UCC Early Clinical Trial Unit, Dresden, Germany; 7Mount Sinai Medical Center, Miami Beach, FL, USA; 8University of Minnesota, Masonic Cancer Center, Minneapolis, MN, USA; 9Virginia Commonwealth University, Massey Cancer Center, Richmond, VA, USA; 10UPMC Hillman Cancer Center, Pittsburgh, PA, USA; 11Skin Cancer Center, University Hospital Heidelberg, Heidelberg, Germany; 12The Royal Marsden Hospital NHS Foundation Trust, London, UK; 13Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY, USA; 14The Royal Marsden Hospital NHS Foundation Trust, London, UK; 15University of Colorado Cancer Center-Anschutz Medical Campus, Aurora, CO, USA; 16Iovance Biotherapeutics, Inc., San Carlos, CA, USA; 17UofL Health – Brown Cancer Center, University of Louisville, Louisville, KY, USA
Conflict of Interest Statement

I hereby declare that I do not conduct activities that would involve a conflict of interest with CME-accreditable training, but that in the past 2 years I have received the funding listed below from the following sources:

Arcus, Aduro, Akeso, Amgen, Bioatla, Bristol-Myers Squibb, CytomX, Exelixis, Roche Genentech, GSK, Immunocore, Idera, Incyte, Iovance Biotherapeutics, Merck, Moderna, Merck-Serono, NextCure, Novartis, Pfizer, Rubius, Sanofi-Regeneron, and Seagen
Background

• Treatment options are limited for patients with advanced (unresectable or metastatic) melanoma whose disease progresses on or after ICI and targeted therapy\(^1\)-\(^5\)

• Autologous TIL cell therapy recognizes and targets a multitude of patient-specific neoantigens to mediate tumor cell death

• Prior data from single-center experiences in ICI-naive melanoma patients over 3 decades\(^6\),\(^7\) provide evidence for the potential efficacy of TIL cell therapy

• More recently, a phase 3 study conducted at 2 centers in Europe has shown superior ORR with noncryopreserved TIL cell therapy (49%) versus ipilimumab (21%) (median 1 prior line of therapy; 86% with prior anti–PD-1)\(^8\)

• Lifileucel, an investigational adoptive cell therapy using cryopreserved autologous TIL, has demonstrated encouraging potential efficacy in Cohort 2 of the C-144-01 study (NCT02360579), a multicenter phase 2 study in advanced melanoma
  
  – Investigator-assessed ORR of 36.4%; median follow-up 33.1 months\(^9\)

• We now report outcomes of lifileucel across Cohorts 2 and 4, representing the largest cell therapy study in advanced melanoma in the post-ICI setting

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 1
Noncryopreserved TIL product (Gen 1)

- n=30
- Closed to enrollment

Cohort 2
Cryopreserved lifileucel (Gen 2)

- n=66
- Enrollment: Apr 2017 to Jan 2019

Cohort 3
Lifileucel re-treatment

- n=10

Cohort 4
Cryopreserved lifileucel (Gen 2)

- n=75*
- Enrollment: Feb 2019 to Dec 2019

Key Endpoints
- Primary: ORR (IRC-assessed using RECIST v1.1)
- Secondary: DOR, PFS, OS, TEAE incidence and severity

Key Eligibility Criteria
- ≥1 tumor lesion resectable for TIL generation (≥1.5 cm in diameter) and ≥1 target tumor lesion for response assessment
- Age ≥18 years at time of consent
- ECOG performance status 0–1
- No limit on number of prior therapies

Treatment Regimen
- Lifileucel, a cryopreserved TIL cell therapy product, was used in Cohorts 2 and 4 and manufactured using the same 22-day Gen 2 process
- All patients received NMA-LD, a single lifileucel infusion, and up to 6 doses of high-dose IL-2

Data cutoff date: 15 July 2022

Eligibility and treatment were identical for Cohorts 2 and 4

*The planned sample size for Cohort 4 was 75 per statistical plan, but the Full Analysis Set, defined as patients who received lifileucel that met specification, consisted of 87 patients due to rapid enrollment.

Data cutoff dates: 15 July 2022

DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; Gen, generation; IL-2, interleukin 2; IRC, Independent Review Committee; NMA-LD, nonmyeloablative lymphodepletion; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; RECIST, Response evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse events; TIL, tumor-infiltrating lymphocytes.
CONSORT Diagram for Cohorts 2 and 4

189 patients enrolled (Tumor Harvest Set)

156 received lifileucel (Safety Analysis Set)

153 received lifileucel and analyzed for efficacy (Full Analysis Set)

33 (17.5%) did not receive lifileucel
- PD; n=9 (4.8%)
- Lifileucel not available; n=8 (4.2%)
- Death; n=5* (2.6%)
- AE; n=3† (1.6%)
- New anti-cancer treatment; n=2 (1.1%)
- Consent withdrawal; n=1 (0.5%)
- Withdrawal; n=1 (0.5%)
- Other reason; n=4 (2.1%)

- Received lifileucel <1 billion cells; n=1 (0.5%)
- Lifileucel not meeting product specification; n=2 (1.1%)

- Lifileucel was manufactured within specification in 94.7% of patients
- Median time from resection to lifileucel infusion was 33 days

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*Reasons for death included PD (n=4) and AE (acute kidney injury [n=1]).
†AEs included gastrointestinal bleeding, septic shock, and pleural effusion. AE, adverse event; PD, progressive disease.
## Baseline Patient and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort 2 (n=66)</th>
<th>Cohort 4 (n=87)</th>
<th>Cohort 2+4 (N=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>55.0 (20, 79)</td>
<td>58.0 (25, 74)</td>
<td>56.0 (20, 79)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39 (59.1)</td>
<td>44 (50.6)</td>
<td>83 (54.2)</td>
</tr>
<tr>
<td>Female</td>
<td>27 (40.9)</td>
<td>43 (49.4)</td>
<td>70 (45.8)</td>
</tr>
<tr>
<td><strong>Screening ECOG performance status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>42 (63.6)</td>
<td>62 (71.3)</td>
<td>104 (68.0)</td>
</tr>
<tr>
<td>1</td>
<td>24 (36.4)</td>
<td>25 (28.7)</td>
<td>49 (32.0)</td>
</tr>
<tr>
<td><strong>Melanoma subtype, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous</td>
<td>39 (59.1)</td>
<td>44 (50.6)</td>
<td>83 (54.2)</td>
</tr>
<tr>
<td>Mucosal</td>
<td>4 (6.1)</td>
<td>8 (9.2)</td>
<td>12 (7.8)</td>
</tr>
<tr>
<td>Acral</td>
<td>4 (6.1)</td>
<td>6 (6.9)</td>
<td>10 (6.5)</td>
</tr>
<tr>
<td><strong>BRAF V600-mutated, n (%)</strong></td>
<td>17 (25.8)</td>
<td>24 (27.6)</td>
<td>41 (26.8)</td>
</tr>
<tr>
<td><strong>PD-L1 status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPS ≥1%</td>
<td>37 (56.1)</td>
<td>39 (44.8)</td>
<td>76 (49.7)</td>
</tr>
<tr>
<td>TPS &lt;1%</td>
<td>12 (18.2)</td>
<td>20 (23.0)</td>
<td>32 (20.9)</td>
</tr>
<tr>
<td>Liver and/or brain lesions by IRC, n (%)</td>
<td>28 (42.4)</td>
<td>44 (50.6)</td>
<td>72 (47.1)</td>
</tr>
<tr>
<td><strong>Median target lesion SOD (range), mm</strong></td>
<td>95.8 (13.5, 271.3)</td>
<td>99.5 (15.7, 552.9)</td>
<td>97.8 (13.5, 552.9)</td>
</tr>
</tbody>
</table>

*47 patients (31%) had melanoma of other subtype (including unknown primary subtype or insufficient information).

†45 patients in the Cohorts 2+4 had missing PD-L1 status.

‡One patient in Cohort 2 had missing data on number of baseline target and nontarget lesions.


ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; SITC, Society for Immunotherapy of Cancer; SOD, sum of diameters; TPS, tumor proportion score; ULN, upper limit of normal.
Patients were heavily pretreated

- 17 (11.1%) received only 1 line of prior therapy
- 125 (81.7%) received anti–CTLA-4
- 82 (53.6%) received anti–PD-1 + anti–CTLA-4 combination
- Median of 2 lines (range, 1-7) of ICI-containing therapy
- 113 (73.9%) were retreated with ICI-containing therapy prior to receiving lifileucel
Safety

Non-Hematologic TEAEs in ≥30% of Patients*†

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>117 (75.0)</td>
<td>8 (5.1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>81 (51.9)</td>
<td>17 (10.9)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>65 (41.7)</td>
<td>65 (41.7)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>58 (37.2)</td>
<td>41 (26.3)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>52 (33.3)</td>
<td>17 (10.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51 (32.7)</td>
<td>6 (3.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48 (30.8)</td>
<td>2 (1.3)</td>
</tr>
</tbody>
</table>

Grade 3/4 Hematologic Lab Abnormalities*

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>156 (100.0)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>156 (100.0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>156 (100.0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>147 (94.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>111 (71.2)</td>
</tr>
</tbody>
</table>

- Median number of IL-2 doses administered was 6
- All patients experienced ≥1 TEAE (any grade); 94.9% experienced ≥1 Grade 3/4 TEAE
- TEAEs were consistent with known safety profiles of NMA-LD and IL-2 and in line with previous reports
- Incidence of TEAEs decreased rapidly within the first 2 weeks after lifileucel infusion

*Per CTCAE v4.03; Safety Analysis Set (N=156).
†Grade 5 TEAEs included pneumonia (n=1), acute respiratory failure (n=1), arrhythmia (n=1), and intra-abdominal hemorrhage (n=1).

All occurrences of AEs were counted if a patient experienced a new onset of the same AE at different timepoints. If multiple records were reported on the electronic case report form because of toxicity grade decrease of the same AE that had not resolved, then the event was counted once with the highest grade reported.

15 events were reported after Month 12 (Grade 1, n=7; Grade 2, n=6; Grade 3, n=1; Grade 5, n=1).

CTCAE, Common Terminology Criteria for Adverse Events; D, day; IL-2, interleukin 2; M, month; NMA-LD, nonmyeloablative lymphodepletion; TEAE, treatment-emergent adverse event.
Infused TIL Cell Dose By Site of Resection

- Median number of TIL cells infused was $21.1 \times 10^9$ (range, $1.2 \times 10^9$ to $99.5 \times 10^9$)
- The total number of infused cells was consistent across all sites of resection.

*Other sites of resection included muscle, soft tissue, bone, limb/extremity, and others.

Max, maximum; Min, minimum; TIL, tumor infiltrating lymphocytes.
## Objective Response Rate (IRC-assessed)

<table>
<thead>
<tr>
<th></th>
<th>Cohort 2 (n=66)</th>
<th>Cohort 4 (n=87)</th>
<th>Cohort 2+4 (N=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, n (%)</strong></td>
<td>23 (34.8)</td>
<td>25 (28.7)</td>
<td>48 (31.4)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(23.5, 47.6)</td>
<td>(19.5, 39.4)</td>
<td>(24.1, 39.4)</td>
</tr>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>5 (7.6)</td>
<td>4 (4.6)</td>
<td>9 (5.9)</td>
</tr>
<tr>
<td>PR</td>
<td>18 (27.3)</td>
<td>21 (24.1)</td>
<td>39 (25.5)</td>
</tr>
<tr>
<td>SD</td>
<td>24 (36.4)</td>
<td>47 (54.0)</td>
<td>71 (46.4)</td>
</tr>
<tr>
<td>Non-CR/Non-PD*</td>
<td>1 (1.5)</td>
<td>0</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>PD</td>
<td>15 (22.7)</td>
<td>12 (13.8)</td>
<td>27 (17.6)</td>
</tr>
<tr>
<td>Nonevaluable†</td>
<td>3 (4.5)</td>
<td>3 (3.4)</td>
<td>6 (3.9)</td>
</tr>
</tbody>
</table>

*Patient did not have measurable target lesions by IRC and had best overall response of non-CR/non-PD per IRC assessment.

†Six patients were nonevaluable for response (5 due to early death; 1 due to new anticancer therapy).

- IRC-assessed ORR was 31.4%
- The concordance rate between IRC- and investigator-assessed ORR was 91%

CI, confidence interval; CR, complete response; IRC, independent review committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
79.3% (111/140) of patients had a reduction in tumor burden. 13 patients in the Full Analysis Set are not included (best overall responses included NE [n=6], non-CR/non-PD [n=1], and PD [n=6]) for reasons including having no measurable lesions at baseline or no post-lifileucel target lesion SOD measurements. *100% change from baseline is presented for CR assessment that includes lymph node lesions. CR, complete response; NE, nonevaluable; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters.
Univariable and Multivariable Analyses of ORR

**ORR by Patient and Disease Characteristics**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n/N</th>
<th>ORR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>48/153</td>
<td>31.4</td>
<td>(24.1, 39.4)</td>
</tr>
<tr>
<td>Age Group, years &lt;65</td>
<td>39/117</td>
<td>33.3</td>
<td>(24.9, 42.6)</td>
</tr>
<tr>
<td>≥65</td>
<td>9/36</td>
<td>25.0</td>
<td>(12.1, 42.2)</td>
</tr>
<tr>
<td>Baseline ECOG Performance Status 0</td>
<td>32/84</td>
<td>38.1</td>
<td>(27.7, 49.3)</td>
</tr>
<tr>
<td>≥1</td>
<td>16/59</td>
<td>23.2</td>
<td>(13.9, 34.9)</td>
</tr>
<tr>
<td>BRAF Mutation Status V600E or V600K Mutated</td>
<td>13/41</td>
<td>31.7</td>
<td>(18.1, 48.1)</td>
</tr>
<tr>
<td>Non-Mutated</td>
<td>35/112</td>
<td>31.3</td>
<td>(22.8, 40.7)</td>
</tr>
<tr>
<td>PD-L1 Status TPS ≥1%</td>
<td>28/76</td>
<td>36.6</td>
<td>(26.1, 48.7)</td>
</tr>
<tr>
<td>TPS &lt;1%</td>
<td>11/32</td>
<td>34.4</td>
<td>(18.6, 53.2)</td>
</tr>
<tr>
<td>Patients with Baseline Liver Lesions</td>
<td>17/59</td>
<td>28.8</td>
<td>(17.8, 42.1)</td>
</tr>
<tr>
<td>Patients with Baseline Liver and/or Brain Lesions</td>
<td>19/72</td>
<td>26.4</td>
<td>(16.7, 38.1)</td>
</tr>
</tbody>
</table>

**ORR by Disease and Prior Therapy Characteristics**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n/N</th>
<th>ORR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LDH SULN</td>
<td>27/70</td>
<td>36.6</td>
<td>(27.2, 51.0)</td>
</tr>
<tr>
<td>&gt;SULN</td>
<td>21/83</td>
<td>26.3</td>
<td>(16.4, 36.0)</td>
</tr>
<tr>
<td>Prior Lines of Therapy 1-3</td>
<td>32/99</td>
<td>32.3</td>
<td>(23.3, 42.5)</td>
</tr>
<tr>
<td>≥4</td>
<td>16/54</td>
<td>29.0</td>
<td>(18.0, 43.6)</td>
</tr>
<tr>
<td>Prior Anti-CTLA-4 Use Yes</td>
<td>41/125</td>
<td>32.6</td>
<td>(24.7, 41.8)</td>
</tr>
<tr>
<td>No</td>
<td>7/28</td>
<td>25.0</td>
<td>(10.7, 44.9)</td>
</tr>
<tr>
<td>Prior Anti-PD-1 + Anti-CTLA-4 Combination Use Yes</td>
<td>22/82</td>
<td>26.8</td>
<td>(17.6, 37.8)</td>
</tr>
<tr>
<td>No</td>
<td>26/11</td>
<td>36.6</td>
<td>(25.5, 48.9)</td>
</tr>
<tr>
<td>Primary Resistance to Prior Anti-PD-1 or PD-L1 by SITC Definition¹</td>
<td>36/109</td>
<td>33.0</td>
<td>(24.3, 42.7)</td>
</tr>
</tbody>
</table>

1. Kluger HM et al. / Immunother Cancer. 2020;8:e000398. 95% CI is calculated using the Clopper-Pearson Exact test. Vertical dotted line represents overall ORR (31.4%).

- Response to lifileucel was observed across all subgroups analyzed
- In adjusted (ECOG PS) multivariable analyses, LDH and target lesion sum of diameters (SOD) were correlated with ORR (P=0.008)
  - Patients with normal LDH and SOD <median had greater odds of response than patients with either (OR: 2.08) or both (OR: 4.42) risk factor(s)

CI, confidence interval; CTLA-4, cytotoxic T lymphocyte-associated protein 4; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; OR, odds ratio; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PS, performance score; SOD, sum of diameters; SITC, Society for Immunotherapy of Cancer; TPS, tumor proportion score; ULN, upper limit of normal.
Time to Response, Duration of Response, and Time on Efficacy Assessment for Confirmed Responders (PR or Better)

• Median time from lifileucel infusion to best response was 1.5 months
• Responses deepened over time
  – 7 patients (14.6%) initially assessed as PR were later confirmed CR
  – 4 patients (8.3%) converted to CR >1 year post-lifileucel infusion; 2 (4.2%) of these 4 patients converted after 2 years
  – Best response of 10 patients (20.8%) improved from SD to PR
• 35.4% of responses were ongoing at the time of data cutoff

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
At a median study follow up of 36.5 months, the median DOR was not reached. 41.7% of responses were maintained ≥24 months.

*Based on Kaplan-Meier estimate. CI, confidence interval; DOR, duration of response; NR, not reached.
Overall Survival

- The median OS was 13.9 months
- The 12-month OS rate was 54.0% (95% CI: 45.6%, 61.6%)
- Response to lifileucel was associated with a 73.4% reduced risk of death compared with non-response (HR 0.266; p<0.0001)

**Overall Survival**

*Based on Kaplan-Meier estimate.
†Using a Cox proportional hazards model with objective response as a time-dependent covariate.
CI, confidence interval; HR, hazard ratio; OS, overall survival.
Overall Survival by Response at 6 Weeks After Lifileucel Infusion

• In a landmark analysis, in patients who achieved response at first assessment (6 weeks [~1.5 mo] post-lifileucel infusion), median OS was not reached.

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>31</strong></td>
<td><strong>27</strong></td>
<td><strong>116</strong></td>
</tr>
<tr>
<td><strong>23</strong></td>
<td><strong>18</strong></td>
<td><strong>56</strong></td>
</tr>
<tr>
<td><strong>17</strong></td>
<td><strong>18</strong></td>
<td><strong>28</strong></td>
</tr>
<tr>
<td><strong>11</strong></td>
<td><strong>5</strong></td>
<td><strong>11</strong></td>
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<tr>
<td><strong>2</strong></td>
<td><strong>2</strong></td>
<td><strong>2</strong></td>
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<tr>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
<td><strong>0</strong></td>
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|  | **Median OS** (months), by response at 6 weeks
t | 95% CI |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>NR</td>
<td>(30.4, NR)</td>
</tr>
<tr>
<td>Non-responders</td>
<td>10.3</td>
<td>(6.8, 13.1)</td>
</tr>
</tbody>
</table>

*Based on Kaplan-Meier estimate.

CI, confidence interval; NR, not reached; OS, overall survival.

Conclusions

- Lifileucel TIL cell therapy addresses an important unmet need for patients with difficult-to-treat melanoma who lack effective treatment options in the post-ICI setting.

- In a large population of heavily pretreated patients with advanced melanoma who progressed on or after ICI and targeted therapy (where appropriate), lifileucel treatment demonstrated:
  - An expected and manageable safety profile
  - Clinically meaningful and durable efficacy
    - IRC-assessed ORR was 31.4%
    - Median DOR was not reached at a median follow-up of 36.5 months; 41.7% of responders had DOR ≥24 months
    - Responses were observed across subgroups, including in ICI primary-resistant disease

One-time lifileucel TIL cell therapy may be a viable option for patients with advanced melanoma after initial progression on ICI.

DOR, duration of response; ICI, immune checkpoint inhibitor; IRC, independent review committee; ORR, objective response rate; TIL, tumor-infiltrating lymphocytes.
Acknowledgments

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C-144-01 Investigators

- Ana Arance, MD, PhD
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- Alfonso Berrocal Jaime, MD
- Jason Chesney, MD, PhD
- Pippa Corrie, MD, PhD
- Brendan Curti, MD
- Mike Cusnir, MD
- Stephane Dalle, MD, PhD
- Gregory Daniels, MD, PhD
- Evidio Domingo-Musibay, MD
- Thomas Jeffry Evans, MBBS
- Miguel Fernandez de Sanmamed, MD, PhD
- Andrew J. S. Furness, MBBS, PhD
- Gotz-Ulrich Furness, MBBS, PhD
- Amy Harker-Murray, MD
- Jessica Hassel, MD
- Nikhil I. Khushalani, MD
- Kevin Kim, MD
- John Kirkwood, MD
- Harriet Kluger, MD
- Angela Krakhardt, MD
- James Larkin, MD, PhD
- Sylvia Lee, MD
- Karl Lewis, MD
- Theodore Logan, MD
- Jose Lutzky, MD
- Theresa Medina, MD
- Juhit Olah, MD, PhD
- Angela Orcurto, MD
- Marlanna Orloff, MD
- Giao Phan, MD
- Igor Puzanov, MD
- Juan Francisco Rodriguez, MD, PhD
- Belen Rubio Viqueira, MD
- Amod Sarnaik, MD
- Beatrice Schuler-Thurner, MD
- Jan Christoph Simon, MD
- Ioannis Thomas, MD
- Sajeve Thomas, MD
- Jeffrey Weber, MD, PhD
- Martin Wermke, MD
- Eric Whitman, MD
- Johannes Wohlrab, MD

Iovance Contributors

- Friedrich Graf Finckenstein
- Parameswaran Hari
- Madan Jagasia
- Xueying Ji
- Amanda Kelly
- Huiling Li
- Tina Niazi
- Harry Qin
- Devyani Ray
- Wen Shi
- Giri Sulur
- Renee Xiao Wu

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