Lifileucel TIL Cell Therapy in Patients With Advanced Melanoma After Progression on Immune Checkpoint Inhibitors (ICI) and Targeted Therapy: Tumor Tissue Procurement Data From the C-144-01 Study

Michael E. Egger, MD, MPH1 Martin McCarter, MD2 Kelly Olino, MD, FACS3 Nikhil Khushalani, MD4 Jason A Chesney, MD, PhD1 Theresa Medina, MD2 Harriet Kluger, MD3 Friedrich Graf Finckenstein, MD5 Parameswaran Hari, MD5 Madan Jagasia, MBBS, MD5 Xiao Wu, PhD5 Wen Shi, MD, PhD5 Amod Sarnaik, MD4

1University of Louisville, Louisville, KY, USA
2University of Colorado Cancer Center – Anschutz Medical Campus, Aurora, CO, USA
3Yale University School of Medicine, Smilow Cancer Center, New Haven Hospital, New Haven, CT, USA
4H. Lee Moffitt Cancer Center, Tampa, FL, USA
5Iovance Biotherapeutics, Inc., San Carlos, CA, USA
DISCLOSURES

Michael E. Egger, MD, MPH reports consultant or advisory role with Iovance Biotherapeutics and receiving research funding from SkylineDx
Treatment options for advanced ( unresectable or metastatic) melanoma are limited after non-response or progression on or after ICI and targeted therapy\textsuperscript{1-5}

One promising treatment option is autologous TIL cell therapy, in which surgeons play a critical role by collecting tumor tissue for TIL cell therapy manufacturing.

Lifileucel, an investigational adoptive cell therapy using cryopreserved autologous TIL, has demonstrated encouraging activity in patients with advanced melanoma who progressed after ICI and targeted therapy (if indicated) in a multicenter phase 2 study (C-144-01, NCT02360579)\textsuperscript{9}

We now report outcomes of lifileucel in a large cohort of patients, with a focus on surgical aspects of the treatment.


ICI, immune checkpoint inhibitor; TIL, tumor-infiltrating lymphocytes.
Role of the Surgeon in the Lifileucel TIL Cell Therapy Process

- Surgeons are key contributors in the patient care journey
- Pre-operative
  - Multidisciplinary discussion
  - Lesion selection
  - Operative approach
- Intraoperative
  - Resection, prosection, maintaining COI/COC
- Postoperative
  - Recovery prior to NMA-LD
  - Coordination of care

**PREOPERATIVE**
- Multidisciplinary evaluation and patient selection
- Surgical resection of tumor tissue at local medical center
- Prosection (trimming and fragmentation)
- Post-operative follow-up with surgeon
- Coordination of care with medical oncologist and cell therapy team

**INTRAOPERATIVE**
- Tumor tissue in transport media
- Shipping/logistics (Transport tumor tissue to manufacturing facility)
- TIL cell therapy manufacturing
- Tumor arrives at manufacturing facility
- TIL cell therapy infusion bag(s) transported back in cryoshipper from manufacturing facility to local medical center
- Final TIL cell therapy product transferred to infusion bag(s) and cryopreserved
- Recovery/Discharge

**POSTOPERATIVE**
- Short course of high-dose IL-2
- One-time TIL cell therapy infusion
- Patient returns to local medical center for TIL cell therapy
- Coordination of care with medical oncologist and cell therapy team

COC, Chain of Custody; COI, Chain of Identity; IL-2, interleukin-2; NMA-LD, non-myeloablative lymphodepletion; TIL, tumor-infiltrating lymphocytes.
C-144-01 Study Design

Patient Population
Unresectable or metastatic melanoma treated with ≥1 prior systemic therapy including a PD-1-blocking antibody and, if BRAF V600 mutation positive, a BRAF inhibitor ± MEK inhibitor

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

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

*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.

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

Eligibility and treatment were identical for consecutively enrolled Cohorts 2 and 4
Patient Disposition and Treatment

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 reasons; 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
- Of the 33 (17.5%) patients who did not receive lifileucel, 25 had patient-related reasons, whereas lifileucel was not available for infusion for 8 patients

*Reasons for death included PD (n=4) and AE (acute kidney injury [n=1]).
†AEs included gastrointestinal bleeding, septic shock, and pleural effusion.
‡Other reasons include study discontinuation (n=2), investigator decision (n=1), and chronic systemic steroid (n=1).
AE, adverse event; PD, progressive disease; TIL, tumor-infiltrating lymphocyte.
## Baseline Patient and Disease Characteristics

### Cohort 2+4 (N=153)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median age (range), y</th>
<th>Sex, n (%)</th>
<th>Screening ECOG performance status, n (%)</th>
<th>Melanoma subtype,* n (%)</th>
<th>BRAF V600-mutated, n (%)</th>
<th>PD-L1 status,† n (%)</th>
<th>Liver and/or brain lesions by IRC, n (%)</th>
<th>Median target lesion SOD (range), mm</th>
<th>Baseline lesions in ≥3 anatomic sites, n (%)</th>
<th>Baseline target and nontarget lesions,‡ n (%)</th>
<th>Median number of prior therapies (range)</th>
<th>Primary resistance to anti-PD-1/PD-L1 per SITC criteria,† n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56.0 (20, 79)</td>
<td>Male 83 (54.2)</td>
<td>0 104 (68.0)</td>
<td>Cutaneous 83 (54.2)</td>
<td>41 (26.8)</td>
<td>TPS ≥1% 76 (49.7)</td>
<td>72 (47.1)</td>
<td>97.8 (13.5, 552.9)</td>
<td>109 (71.2)</td>
<td>≤3 36 (23.5)</td>
<td>&gt;3 116 (75.8)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mucosal 12 (7.8)</td>
<td></td>
<td>TPS &lt;1% 32 (20.9)</td>
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<td></td>
<td>Acral 10 (6.5)</td>
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</table>

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

†145 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.
### Distribution of Anatomic Sites of Resection

<table>
<thead>
<tr>
<th>Anatomic site of resection, n (%)</th>
<th>Cohort 2+4 (N=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral organ</td>
<td>42 (27.5)</td>
</tr>
<tr>
<td>Lymph node/skin/subcutaneous</td>
<td>71 (46.4)</td>
</tr>
<tr>
<td>Other*</td>
<td>40 (26.1)</td>
</tr>
</tbody>
</table>

- 94.9% of pts had a single site of tumor resection
- In the 8 patients (5.1%) with multiple resection sites, all sites were in the same category (eg, 3 skin sites, 2 subcutaneous sites)

*Other sites of resection included muscle, soft tissue, bone, limb/extremity, and others.
### Tumor-Resection AEs* Related to Surgery Occurring in >1 Patient (Any Grade), n (%)

<table>
<thead>
<tr>
<th>Number of patients reporting &gt;1 tumor-resection AE related to surgery</th>
<th>Tumor Harvest Set (N=189)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>22 (11.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Flank pain</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Incision site erythema</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Seroma</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Incision site pain</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Localized edema</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Lymphocele</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Postoperative wound infection</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>2 (1.1)</td>
</tr>
</tbody>
</table>

*Tumor-resection AEs refer to AEs that started after tumor resection and before the start of NMA-LD.


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### Treatment-Emergent Adverse Events

- Most TEAEs were expected and manageable, and the incidence decreased rapidly over the first 2 weeks after lifileucel infusion
- As previously described, TEAEs were consistent with known safety profiles of NMA-LD (cyclophosphamide, fludarabine) and IL-2

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- Tumors were resected from diverse sites with minimal surgical morbidity
- Grade 3/4 tumor-resection AEs related to surgery were seen in 6 (3.2%) patients
- No patient had surgery-related AEs that prevented lifileucel infusion or required blood transfusion
## Objective Response Rate (IRC-assessed)

<table>
<thead>
<tr>
<th></th>
<th>Cohort 2+4 (N=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, n (%)</strong></td>
<td>48 (31.4)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(24.1, 39.4)</td>
</tr>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>9 (5.9)</td>
</tr>
<tr>
<td>PR</td>
<td>39 (25.5)</td>
</tr>
<tr>
<td>SD</td>
<td>71 (46.4)</td>
</tr>
<tr>
<td>Non-CR/Non-PD*</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>PD</td>
<td>27 (17.6)</td>
</tr>
<tr>
<td>Nonevaluable†</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%**
- Median number of TIL cells infused was **21.1 \times 10^9** (range, **1.2 \times 10^9** to **99.5 \times 10^9**)
- Median time from resection to lifileucel infusion was **33 days**
- Response to lifileucel was observed across all subgroups analyzed
  - In multivariate analyses, ORR was correlated with baseline target lesion sum of diameters and LDH\(^1,2\)

CR, complete response; IRC, independent review committee; LDH, lactate dehydrogenase; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TIL, tumor-infiltrating lymphocytes.

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-lifelucel target lesion SOD measurements.

*100% change from baseline is presented for CR assessment that includes lymph node lesions.

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters.
Time to First Response, Duration of Response, and Time on Efficacy Assessment for Confirmed Responders

- Median time from lifileucel infusion to best response was 1.5 months
- Responses deepened over time; 7 patients (14.6%) initially assessed as a PR achieved confirmed CR; 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.
Duration of Response

At a median study follow up of 36.5 months, median DOR was not reached.

- 41.7% of responses were maintained ≥24 months.

**Cohort 2+4 (N=48)**

<table>
<thead>
<tr>
<th>Median DOR*, months</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI</td>
<td>(8.3, NR)</td>
</tr>
<tr>
<td>Min, max (months)</td>
<td>1.4+, 54.1+</td>
</tr>
<tr>
<td>DOR ≥12 months, n (%)</td>
<td>26 (54.2)</td>
</tr>
<tr>
<td>DOR ≥24 months, n (%)</td>
<td>20 (41.7)</td>
</tr>
</tbody>
</table>

*Based on Kaplan-Meier estimate.
CI, confidence interval; DOR, duration of response; NR, not reached.
TIL dose was similar across anatomic sites of resection

- TIL dose was similar across anatomic sites of resection

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

TIL, tumor-infiltrating lymphocyte.
TCR Repertoire Clonality Was Similar Across Anatomic Sites of Resection

The Simpson Clonality Index reflects the mono- or poly-clonality of a sample; values can range from 0 (evenly distributed, polyclonal sample) to 1 (monoclonal sample).

TCR, T cell receptor.

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

†The Simpson Clonality Index reflects the mono- or poly-clonality of a sample; values can range from 0 (evenly distributed, polyclonal sample) to 1 (monoclonal sample).

TCR, T cell receptor.
TCR Clonotypes Present in Tumor and TIL Infusion Product Increased in Relative Abundance Across Resection Sites

The percentage of the TCR repertoire consisting of clonotypes (unique CDR3 sequences) shared between the tumor and TIL infusion product was measured in the patient’s peripheral blood.

The relative abundance of these clones increased at Day 42 compared with pre-infusion regardless of the tumor resection site.

TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.
Target Lesion Sum of Diameters Reductions Were Seen Across Range of Infused Cell Doses and Resection Sites

Disease Control Status per IRC With Anatomic Site of Resection

- CR + PR + SD With Visceral Organ
- CR + PR + SD With Lymph Node/Skin/Subcutaneous
- CR + PR + SD With Other
- PD With Visceral Organ
- PD With Lymph Node/Skin/Subcutaneous
- PD With Other

CR, complete response; IRC, Independent Review Committee; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters.
Clinical Outcomes:

- In a large population of heavily pretreated patients with advanced melanoma who progressed on or after ICI and targeted therapy (where appropriate), lifileucel demonstrated clinically meaningful and durable efficacy, and may address an unmet need.

- Anatomic sites of tumor resection did not correlate with:
  - Infused TIL cell dose
  - Target lesion SOD reductions
  - Relative abundance of tumor/TIL TCR clonotypes

Key Takeaways for the Surgical Community:

- TIL cell therapy is a new paradigm leveraging existing surgical techniques to provide the starting material for TIL cell therapy manufacturing.
- Multidisciplinary care involving the surgeon is integral to optimal patient outcomes.
- Continued education of surgeons and other stakeholders is necessary to allow for broadened patient access.

ICI, immune checkpoint inhibitor; SOD, sum of diameters TCR, T cell receptor; TIL, tumor-infiltrating lymphocytes.
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C-144-01 Investigators

- Ana Arance, MD, PhD
- Tobias Arkenau, MD, PhD
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- Pippa Corrie, MD, PhD
- Brendan Curti, MD
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- Stephane Dalle, MD, PhD
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- Evidio Domingo-Musibay, MD
- Thomas Jeffry Evans, MBBS
- Miguel Fernandez de Sanmamed, MD, PhD
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- Gotz-Ulrich Grigoleit, MD
- Omid Hamid, MD
- Amy Harker-Murray, MD
- Jessica Hassel, MD
- Nikhil I. Khushalani, MD
- Kevin Kim, MD
- John Kirkwood, MD
- Harriet Kluger, MD
- Angela Krackhardt, MD
- James Larkin, MD, PhD
- Sylvia Lee, MD
- Karl Lewis, MD
- Theodore Logan, MD
- Jose Lutzky, MD
- Theresa Medina, MD
- Judit Olah, MD, PhD
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- 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
- Viktoria Gontcharova
- 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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