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

- Lifileucel, an investigational adoptive cell therapy using cryopreserved autologous TIL, demonstrated encouraging activity in Cohort 2 of the C-144-01 study.

- Patients were heavily pretreated (median 6 prior systemic therapies).

- The median number of IL-2 doses administered was 6.

- Responses were observed across subgroups, including in ICI primary-resistant disease.

- The number of administered IL-2 doses did not show association with clinical outcomes.

- Safety profile, ORR, and DOR were comparable across the range of IL-2 doses.

- Responses were observed across subgroups, including in ICI primary-resistant disease.

- The authors would like to thank the patients and their families, as well as the practitioners, VJOncology, Agence Unik, Bristol Myers Squibb, and Immatics; and support consultants from iOnctura, Apple Tree, Merck, Bristol Myers Squibb, Eisai, Debio-2020, and Blueprint.

- Efficacy and non-hematologic adverse events were similar across IL-2 dose groups and consistent with those of the overall population (Table 4).

- Translational analyses by number of IL-2 doses.

- Responses were similar between 6 IL-2 dose groups within each sample type (Supplemental Figure 2).

- CDR3 clonotypes identified in both tumor and TIL infusion product expanded and persisted to a similar degree, regardless of number of IL-2 doses.

- IL-2 discontinuation was guided by clinical tolerance, thus limiting safety comparisons across dose groups.

- Median number of IL-2 doses administered was 6.

- The median cumulative IL-2 dose was 70% lower than the maximum cumulative dose of 1 full treatment course (two 3-day cycles separated by a rest period) of IL-2 monotherapy.

- Patients were heavily pretreated (Table 1; additional details in Supplement Figure 2).

- IL-2 (n=153) regimen was an immunotherapy in metastatic melanoma, and its activity is mediated through endogenous T-cell activation; however, IL-2 monotherapy shows limited efficacy and considerable toxicity.

- Grade 3/4 Hematologic Lab Abnormalities, by Number of IL-2 Doses," and did not differ significantly by number of IL-2 doses.
Efficacy and Safety of Lifileucel Tumor-Infiltrating Lymphocyte (TIL) Cell Therapy in Patients With Advanced Melanoma Enrolled in Consecutive Cohorts of the C-144-01 Study

Poster Supplement
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)

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

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

**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 retreatment
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.

Eligibility and treatment were identical for Cohorts 2 and 4
Patient Treatment Patterns

- 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

- Lifileucel was manufactured within specification in 94.7% of patients
- Median time from resection to lifileucel infusion was 33 days
- Median number of TIL cells infused was $21.1 \times 10^9$ (range, $1.2 \times 10^9$ to $99.5 \times 10^9$)
Tumor Burden Reduction and Best Response to Lifileucel

Supplement Figure 3.

- 79.3% (111/140) of patients in the overall population 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.
Univariable and Multivariable Analyses of ORR in the Overall Population

**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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32/84</td>
<td>38.1</td>
<td>(27.7, 49.3)</td>
</tr>
<tr>
<td>≥1</td>
<td>16/69</td>
<td>23.2</td>
<td>(13.9, 34.9)</td>
</tr>
<tr>
<td>BRAF Mutation Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V800E 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>30/112</td>
<td>31.3</td>
<td>(22.8, 40.7)</td>
</tr>
<tr>
<td>PD-L1 Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPS ≥1%</td>
<td>28/76</td>
<td>36.8</td>
<td>(26.1, 46.7)</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>
<tr>
<td>Baseline Target Lesion Sum of Diameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;Median (98 mm)</td>
<td>14/75</td>
<td>18.7</td>
<td>(10.6, 29.3)</td>
</tr>
<tr>
<td>≥Median (98 mm)</td>
<td></td>
<td></td>
<td></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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ULN</td>
<td>27/70</td>
<td>38.6</td>
<td>(27.2, 51.0)</td>
</tr>
<tr>
<td>&gt;ULN</td>
<td>21/83</td>
<td>25.3</td>
<td>(16.4, 36.0)</td>
</tr>
<tr>
<td>&gt;2×ULN</td>
<td>3/29</td>
<td>10.3</td>
<td>(2.2, 27.4)</td>
</tr>
<tr>
<td>Prior Lines of Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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>29.6</td>
<td>(18.0, 43.6)</td>
</tr>
<tr>
<td>Prior Anti–CTLA-4 Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41/125</td>
<td>32.8</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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22/62</td>
<td>26.8</td>
<td>(17.6, 37.8)</td>
</tr>
<tr>
<td>No</td>
<td>20/71</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 Definition†</td>
<td>36/109</td>
<td>33.0</td>
<td>(24.3, 42.7)</td>
</tr>
</tbody>
</table>

- Response to lifileucel was observed across all subgroups analyzed
- In adjusted (ECOG PS) multivariable analyses, LDH and target lesion 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: 4.2) risk factor(s)

1. Kluger HM et al. *J Immunother Cancer*. 2020;8:e000398. Vertical dotted line represents overall ORR (31.4%). *95% CI is calculated using the Clopper-Pearson Exact test.
Time to Response, DOR, 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 to CR after 2 years.
  - Best response of 10 patients (20.8%) improved from SD to PR.
- 35.4% of responses were ongoing as of the data cutoff.

Supplement Figure 5.
Overall Survival

The median OS was 13.9 months, and 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 nonresponse (HR, 0.266; \( p<0.0001 \))

Supplement Figure 6.

*Based on Kaplan-Meier estimate.
†Using a Cox proportional hazards model with objective response as a time-dependent covariate.
In a landmark analysis in patients who achieved response at first assessment (6 weeks [~1.5 months] post-lifileucel infusion), median OS was not reached.

**Supplement Figure 7.**

**OS, by Response at 6 Weeks After Lifileucel Infusion**

- **Table:**
  - **Responders:** NR (30.4, NR)
  - **Non-responders:** 10.3 (6.8, 13.1)
  - **Log-rank p-value:** <0.0001

- **Graph:**
  - Responder at Week 6
  - Non-responder at Week 6


*Based on Kaplan-Meier estimate.
Polyclonality† was similar between IL-2 dose groups within each sample type.

*Day 42 visit.
†As measured by the Simpson Clonality Index, which reflects the mono- or polyclonality of a sample. Values can range from 0 (evenly distributed, polyclonal sample) to 1 (monoclonal sample).
TCR Clonal Expansion and Persistence in the Overall Population and by IL-2 Dose Groups

- uCDR3 clonotypes identified in both tumor and TIL infusion product expanded and persisted to a similar degree, regardless of number of IL-2 doses
Abbreviations

CR, complete response; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; CY, cyclophosphamide; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; Gen 1, Generation 1; Gen 2, Generation 2; HR, hazard ratio; ICI, immune checkpoint inhibitor; IL-2, interleukin 2; IRC, independent review committee; L, line of therapy; LDH, lactate dehydrogenase; NMA-LD, nonmyeloablative lymphodepletion; OR, Odd’s ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SITC, Society for Immunotherapy of Cancer; SOD, sum of diameters; TCR, T-cell receptor; TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocyte; TPS, tumor proportion score; uCDR3, unique CDR3; ULN, upper limit of normal.
Disclosures

**JL:** Consulting fees from iOnctura, Apple Tree, Merck, Bristol Myers Squibb, Eisai, Debiopharm, and Incyte; payment or honoraria for lectures, presentations, speaker’s bureau, or educational events from Eisai, Novartis, Incyte, Merck, touchIME, touchEXPERTS, Pfizer, Royal College of Physicians, Cambridge Healthcare Research, Royal College of General Practitioners, VJOnco, Agence Unik, Bristol Myers Squibb, and Immatics; and support for attending meetings and/or travel from Pierre Fabre, Roche, GSK, and Immatics.

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**JLu:** Research grants from Bristol Myers Squibb; contracted research with Vyriad, Takeda, Replimune, Foghorn, Bristol Myers Squibb/Dragonfly Therapeutics, Trisalus, Life Sciences, and Agenus; consulting fees for advisory board of Iovance Biotherapeutics, Eisai, and Replimune; payment for CME talk for San Diego 2022 and support for attending CME meeting San Diego 2022 from Cano Health; participation in a Data Safety Monitoring Board for DSMC Agenus; and is on the executive committee of COOG.
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**MWi**: Consulting fees for advisory board of Instil Bio and Pfizer and honoraria from Eisai.

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