Lifileucel (LN-144), a Cryopreserved Autologous Tumor Infiltrating Lymphocyte (TIL) Therapy in Patients with Advanced Melanoma: Evaluation of Impact of Prior Anti–PD-1 Therapy

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Background

• Currently, no treatment is approved for patients with advanced melanoma whose disease progresses while on or after treatment with ICI and BRAF/MEK inhibitors.

• In patients with advanced melanoma who are either primary refractory or develop resistance to ICI, retreatment with ICI or treatment with chemotherapy yields a poor response rate; chemotherapy offers 4-10%\(^1,2\) with median OS of only 7–8 months\(^3,4\).

• Lifileucel is an adoptive cell therapy using autologous TIL that has shown efficacy and durable long-term responses in patients with advanced melanoma who progress on or after anti–PD-1 therapy\(^5\).

• We present 33-month follow-up data from C-144-01 (NCT02360579), a global, Phase 2, open-label, multicohort, multicenter study, and examine the impact of prior anti–PD-1 / anti–PD-L1 use on duration of response of lifileucel.

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)

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 BRAFi ± MEKi

Cohort 1
Non-cryopreserved TIL product (Gen 1)
N=30
Closed to enrollment

Cohort 2
Cryopreserved TIL product (Gen 2)
N=60
Closed to enrollment

Cohort 3
TIL re-treatment
N=10

Cohort 4 (Pivotal)
Cryopreserved TIL product (Gen 2)
N=75
Closed to enrollment

Cohort 2 Endpoints
- Primary: Efficacy per investigator-assessed ORR using RECIST 1.1 response criteria
- Secondary: Safety and additional parameters of efficacy

Key Eligibility Criteria
- Radiographic confirmation of progression
- One tumor lesion resectable for TIL generation (~1.5 cm in diameter) and ≥1 target tumor lesion for RECIST 1.1 response assessment
- Age ≥18 years at the time of consent
- ECOG performance status of 0–1

Methods
- Patients were enrolled from April 2017 to January 2019 at 26 sites across the US and EU
- Concomitant anticancer therapy was not permitted
- Imaging-evaluable disease was required
- All responses required confirmation
- Data cutoff: 22 April 2021

BRAFi, BRAF inhibitor; ECOG, Eastern Cooperative Oncology Group; MEKi, MEK inhibitor; ORR, objective response rate; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria in Solid Tumors; TIL, tumor infiltrating lymphocytes.
Patient Journey and TIL Manufacturing

1. Patient Intake
2. Tumor Tissue Procurement
   - Surgical resection of a tumor lesion (~1.5 cm in diameter)
   - Shipped to a Central GMP facility

Tumor resection sites include skin, lymph nodes, liver, lung, peritoneal, musculoskeletal, breast, and other organs.

3. Non-myeloablative Lymphodepletion
   - Cyclophosphamide followed by fludarabine

4. Lifileucel Infusion
   - One time treatment
   - Lifileucel is a rejuvenated and expanded TIL product

5. IL-2 Administration
   - Up to 6 doses

6. Discharge

Cryopreserved product, process time: 22 Days

GMP: good manufacturing practices; IL-2, interleukin-2; NMA-LD, non-myeloablative lymphodepletion; TIL, tumor infiltrating lymphocytes.

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### Baseline Patient and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=66</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27 (41)</td>
</tr>
<tr>
<td>Male</td>
<td>39 (59)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>55</td>
</tr>
<tr>
<td>Min, max</td>
<td>20, 79</td>
</tr>
<tr>
<td><strong>Prior Therapies, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean number of prior therapies</td>
<td>3.3</td>
</tr>
<tr>
<td>Anti–PD-1 / Anti–PD-L1</td>
<td>66 (100)</td>
</tr>
<tr>
<td>Anti–CTLA-4</td>
<td>53 (80)</td>
</tr>
<tr>
<td>Anti–PD-1 + Anti–CTLA-4</td>
<td>34 (52)</td>
</tr>
<tr>
<td>BRAFi / MEKi</td>
<td>15 (23)</td>
</tr>
<tr>
<td><strong>Progressive Disease for ≥1 Prior Therapy, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Anti–PD-1 / Anti–PD-L1</td>
<td>65 (99)</td>
</tr>
<tr>
<td>Anti–CTLA-4</td>
<td>41 (77)*</td>
</tr>
<tr>
<td><strong>ECOG Performance Status, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>37 (56)</td>
</tr>
<tr>
<td>1</td>
<td>29 (44)</td>
</tr>
</tbody>
</table>

Patients had:

- Mean of 3.3 prior therapies, ranging from 1–9
- High tumor burden at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=66</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF Mutation Status, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Mutated V600E or V600K</td>
<td>17 (26)</td>
</tr>
<tr>
<td>Wild type</td>
<td>45 (68)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Tumor PD-L1 Expression, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>PD-L1 positive (TPS ≥5%)</td>
<td>23 (35)</td>
</tr>
<tr>
<td>PD-L1 negative (TPS &lt;5%)</td>
<td>26 (39)</td>
</tr>
<tr>
<td><strong>LDH, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>≤ULN</td>
<td>39 (59)</td>
</tr>
<tr>
<td>&gt;1 to 2 × ULN</td>
<td>19 (29)</td>
</tr>
<tr>
<td>&gt;2 × ULN</td>
<td>8 (12)</td>
</tr>
<tr>
<td><strong>Target Lesions Sum of Diameter (mm)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>106 (71)</td>
</tr>
<tr>
<td>Min, max</td>
<td>11, 343</td>
</tr>
<tr>
<td><strong>Number of Target and Non-Target Lesions</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;3, n (%)</td>
<td>51 (77)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Liver and / or brain lesions, n (%)</td>
<td>28 (42)</td>
</tr>
</tbody>
</table>

*Percent is calculated based on number of patients who received prior anti-CTLA-4.
BRAF, BRAF inhibitor; CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MEK, MEK inhibitor; mm, millimeter; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; SD, standard deviation; TPS, tumor proportion score; ULN, upper limit of normal.
### Safety

#### AEs Over Time

![Graph showing the number of AEs reported over time](image)

#### TEAEs Reported in ≥30% of Patients

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE*</td>
<td>66 (100)</td>
<td>64 (97.0)</td>
<td>2 (3.0)†</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>59 (89.4)</td>
<td>54 (81.8)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>53 (80.3)</td>
<td>4 (6.1)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>45 (68.2)</td>
<td>37 (56.1)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>39 (59.1)</td>
<td>11 (16.7)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>37 (56.1)</td>
<td>26 (39.4)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>36 (54.5)</td>
<td>36 (54.5)</td>
<td>0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>30 (45.5)</td>
<td>23 (34.8)</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>28 (42.4)</td>
<td>23 (34.8)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>26 (39.4)</td>
<td>1 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>24 (36.4)</td>
<td>7 (10.6)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>23 (34.8)</td>
<td>21 (31.8)</td>
<td>0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>23 (34.8)</td>
<td>1 (1.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

*TEAEs refer to all AEs starting on or after the first dose date of TIL for up to 30 days; patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term.

†Of 2 Grade 5 events, 1 was due to intra-abdominal hemorrhage considered possibly related to TIL, and 1 was due to acute respiratory failure assessed per investigator as not related to TIL.

AE, adverse event; D, day; IL-2, interleukin-2; M, month; TEAE, treatment-emergent adverse event; TIL, tumor infiltrating lymphocytes.

**Median number of IL-2 doses administered was 5**

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## Objective Response Rate

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>N=66</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective Response Rate</strong></td>
<td>24 (36.4)</td>
</tr>
<tr>
<td>Complete response</td>
<td>3 (4.5)</td>
</tr>
<tr>
<td>Partial response</td>
<td>21 (31.8)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>29 (43.9)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>9 (13.6)</td>
</tr>
<tr>
<td>Non-evaluable*</td>
<td>4 (6.1)</td>
</tr>
<tr>
<td><strong>Disease control rate</strong></td>
<td>53 (80.3)</td>
</tr>
<tr>
<td><strong>Median Duration of Response</strong></td>
<td>Not Reached</td>
</tr>
<tr>
<td>Min, max (months)</td>
<td>2.2, 38.5+</td>
</tr>
</tbody>
</table>

- Mean number of TIL cells infused: $27.3 \times 10^9$

> After a median study follow-up of 33.1 months, **median DOR was not reached** (range 2.2, 38.5+ months)

*Not evaluable due to not reaching first assessment.

DOR, duration of response; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes.
81% (50/62) of patients had a reduction in tumor burden

11 patients (17.7%) had further SOD reduction since April 2020 data cut.
Time to Response for Evaluable Patients (PR or Better)

- 79% of responders received prior ipilimumab
  - 46% of responders received prior anti–PD-1 / anti–CTLA-4 combination

Responses continued to deepen over time
- 1 PR converted to CR after 24 months post-lifileucel

*BOR is best overall response on prior anti–PD-1 / anti–PD-L1 immunotherapy.
†Patient 22 BOR is PR.

BOR, best overall response; CR, complete response; CTLA-4, cytotoxic T-lymphocyte antigen-4; PD, progressive disease; PD-1, programmed cell death protein-1; PR, partial response; SD, stable disease; TIL, tumor infiltrating lymphocytes; TPS, tumor proportion score; U, unknown.

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Early and Sustained CR in a Patient with Multiple Failed Prior Therapies

Patient Narrative

• 44-year-old male
• Initial diagnosis in 2016
• Superficial spreading melanoma
• Prior systemic therapies:
  − Ipilimumab + nivolumab
  − Dabrafenib + trametinib
  − TLR9 agonist + pembrolizumab
  − TVEC + pembrolizumab
• BOR to all prior therapies (including anti–PD-1) was PD
  − Cumulative duration on prior anti–PD-1 was 3.1 months
• Achieved PR at Day 42 and converted to CR on Day 84
  − CR is ongoing
Site of Tumor Resection and Infused Cell Dose

Appropriate amount of TIL was manufactured regardless of tumor resection site

Target lesion SOD reductions were seen across the range of total TIL cell doses and CD4⁺ / CD8⁺ TIL ratios

Site of Tumor Resection

- Total Infused Cells (10⁶)

Visceral Organ
Lymph Node /Skin/Subcutaneous
Other:

Resected Tumor Organ Site

Ratio CD4⁺ / CD8⁺ TIL

Best Percent Change from Baseline in SOD

R²=0.0248
R²=0.0074

SOD, sum of diameters; TIL, tumor infiltrating lymphocytes.
Univariable Analyses: ORR of Lifileucel

<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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>19/52</td>
<td>36.5</td>
<td>(23.6, 51.0)</td>
</tr>
<tr>
<td>≥65</td>
<td>5/14</td>
<td>35.7</td>
<td>(12.8, 64.9)</td>
</tr>
<tr>
<td>Prior CTLA-4 Use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7/17</td>
<td>41.2</td>
<td>(18.4, 67.1)</td>
</tr>
<tr>
<td>No</td>
<td>17/49</td>
<td>34.7</td>
<td>(21.7, 49.6)</td>
</tr>
<tr>
<td>BRAF Mutation Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutated (V600E or K)</td>
<td>16/37</td>
<td>43.2</td>
<td>(27.1, 60.5)</td>
</tr>
<tr>
<td>Non-Mutated</td>
<td>8/29</td>
<td>27.6</td>
<td>(12.7, 47.2)</td>
</tr>
<tr>
<td>Baseline ECOG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15/39</td>
<td>38.5</td>
<td>(23.4, 55.4)</td>
</tr>
<tr>
<td>≥1</td>
<td>9/27</td>
<td>33.3</td>
<td>(16.5, 54.0)</td>
</tr>
<tr>
<td>Baseline LDH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ULN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;ULN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Brain/Liver Lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9/28</td>
<td>32.1</td>
<td>(15.9, 52.4)</td>
</tr>
<tr>
<td>No</td>
<td>15/38</td>
<td>39.5</td>
<td>(24.0, 56.6)</td>
</tr>
<tr>
<td>Cumulative Duration on Anti–CTLA-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Median (2.10 mo)</td>
<td>13/29</td>
<td>44.8</td>
<td>(26.4, 64.3)</td>
</tr>
<tr>
<td>&gt;Median (2.10 mo)</td>
<td>6/24</td>
<td>25.0</td>
<td>(9.8, 46.7)</td>
</tr>
<tr>
<td>Cumulative Duration on Anti–PD-1/PD-L1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Median (5.06 mo)</td>
<td>14/33</td>
<td>42.4</td>
<td>(25.5, 60.8)</td>
</tr>
<tr>
<td>&gt;Median (5.06 mo)</td>
<td>10/33</td>
<td>30.3</td>
<td>(15.6, 48.7)</td>
</tr>
<tr>
<td>Time from Stop of Anti–PD-1/PD-L1 to TIL infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Median (4.76 mo)</td>
<td>12/33</td>
<td>36.4</td>
<td>(20.4, 54.9)</td>
</tr>
<tr>
<td>&gt;Median (4.76 mo)</td>
<td>12/33</td>
<td>36.4</td>
<td>(20.4, 54.9)</td>
</tr>
<tr>
<td>Baseline Target Lesion SOD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 mm</td>
<td>14/26</td>
<td>53.8</td>
<td>(33.4, 73.4)</td>
</tr>
<tr>
<td>≥70 mm</td>
<td>10/40</td>
<td>25.0</td>
<td>(12.7, 41.2)</td>
</tr>
</tbody>
</table>

*95% CI is calculated using the Clopper-Pearson Exact test.

CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; mo, months; ORR, objective response rate; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes; ULN, upper limit of normal.

ORR was not predicted by any patient or clinical characteristics analyzed, including:

- Baseline LDH (≤ULN vs >ULN)
- Baseline ECOG performance status (0 vs ≥1)
- Baseline brain / liver lesions (yes vs no)
- Cumulative duration on anti–CTLA-4 (≤median vs >median)
- Cumulative duration on anti–PD-1 / anti–PD-L1 (≤median vs >median) in a post–PD-1 patient population

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Univariable Analyses*: DOR of Lifileucel

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Subgroup A vs B</th>
<th>N in Subgroup A</th>
<th>N in Subgroup B</th>
<th>HR (95% CI)</th>
<th>Subgroup A Better</th>
<th>Subgroup B Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
<td>&lt;65 vs ≥65</td>
<td>19</td>
<td>5</td>
<td>0.527 (0.136, 2.046)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior CTLA-4 Use</td>
<td>Yes vs No</td>
<td>19</td>
<td>5</td>
<td>1.320 (0.280, 6.233)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF Mutation Status</td>
<td>Yes vs No</td>
<td>7</td>
<td>17</td>
<td>0.845 (0.218, 3.278)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline ECOG</td>
<td>0 vs ≥1</td>
<td>16</td>
<td>8</td>
<td>1.079 (0.279, 4.179)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline LDH</td>
<td>≤ULN vs &gt;ULN</td>
<td>15</td>
<td>9</td>
<td>0.393 (0.113, 1.364)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Brain/Liver Lesion</td>
<td>Yes vs No</td>
<td>9</td>
<td>15</td>
<td>1.776 (0.513, 6.154)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative Duration on Anti–CTLA-4</td>
<td>≤Median (2.10m) vs &gt;Median</td>
<td>13</td>
<td>6</td>
<td>1.743 (0.350, 8.664)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative Duration on Anti–PD-1/PD-L1</td>
<td>≤Median (5.06m) vs &gt;Median</td>
<td>14</td>
<td>10</td>
<td>0.218 (0.056, 0.854)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Target Lesion SOD</td>
<td>&lt;70mm vs ≥70mm</td>
<td>14</td>
<td>10</td>
<td>2.083 (0.537, 8.079)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Although cumulative duration on prior anti–PD-1 / anti–PD-L1 was not associated with achieving a response to lifileucel (ORR), it was associated with DOR.

*Univariable Cox proportional hazards regression model was used to estimate hazard ratios with 95% confidence intervals between subgroups on DOR.

CTLA-4, cytotoxic T-lymphocyte antigen-4; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; ORR, objective response rate; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; SOD, sum of diameters; TIL, tumor infiltrating lymphocytes; ULN, upper limit of normal.

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Multivariable Model*: Independent Predictors for DOR of Lifileucel

- Variables from the univariable analyses were examined using the best subset approach
- Two parameters were identified:
  - Baseline LDH
  - Cumulative duration of prior anti–PD-1 / anti–PD-L1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comparison</th>
<th>Responders (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Baseline LDH</td>
<td>≤ULN vs &gt;ULN</td>
<td>0.201 (0.040, 0.996)</td>
</tr>
<tr>
<td>Cumulative duration on prior anti–PD-1 / anti–PD-L1</td>
<td>For each 3-month decrease in exposure to prior anti–PD-1 / anti–PD-L1</td>
<td>0.715 (0.518, 0.987)</td>
</tr>
<tr>
<td></td>
<td>For each 6-month decrease in exposure to prior anti–PD-1 / anti–PD-L1</td>
<td>0.511 (0.268, 0.974)</td>
</tr>
</tbody>
</table>

- Cox proportional hazards regression model.
- Assuming the data follow exponential distribution.

For each 6-month decrease in exposure to prior anti–PD-1 / anti–PD-L1, the median DOR to lifileucel will be nearly doubled†
Conclusions

• In heavily pretreated patients with advanced or metastatic melanoma who progressed on or after multiple prior therapies, including anti–PD-1 / anti–PD-L1 and BRAF/MEK inhibitors (if BRAF V600 mutant), lifileucel treatment resulted in:
  – 36.4% ORR
  – **Median DOR not reached at median 33.1 months of study follow-up**

• Responses deepened over time:
  – 11 patients (17.7%) demonstrated further reduction in SOD since April 2020 data cut
  – 1 patient converted from PR to CR at 24 months post lifileucel infusion

• Prior anti–PD-1 therapy:
  – Shorter duration of prior anti–PD-1 therapy maximizes DOR to lifileucel treatment
  – All newly diagnosed patients should be closely monitored for progression on anti–PD-1 therapy
  – **Early intervention with lifileucel at the time of initial progression on anti–PD-1 agents may maximize benefit**
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