Supplemental Table 1. Maximum tolerated dose (MTD) level of IL-2 for individual patients

<table>
<thead>
<tr>
<th>ID</th>
<th>Cohort</th>
<th>Individual Dose Level</th>
<th>Reason for Dose Reduction</th>
<th>Timing of Dose Reduction</th>
<th>DLT Status</th>
<th>Response at Wk 8</th>
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<tbody>
<tr>
<td>1</td>
<td>Pedi</td>
<td>0.67 x 10^6</td>
<td>Gr 3 electrolyte abnormalities</td>
<td>Week 29</td>
<td>Yes</td>
<td>PR</td>
</tr>
<tr>
<td>3</td>
<td>Pedi</td>
<td>1 x 10^6</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>PR</td>
</tr>
<tr>
<td>6</td>
<td>Pedi</td>
<td>1 x 10^6</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>PR</td>
</tr>
<tr>
<td>11</td>
<td>Pedi</td>
<td>1 x 10^6</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Mixed</td>
</tr>
<tr>
<td>12</td>
<td>Pedi</td>
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<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>PR</td>
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<tr>
<td>16</td>
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<td>N/A</td>
<td>N/A</td>
<td>PR</td>
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<tr>
<td>17</td>
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<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>PR</td>
</tr>
<tr>
<td>18</td>
<td>Pedi</td>
<td>0.67 x 10^6</td>
<td>Gr 1 flu-like symptoms</td>
<td>Week 20</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>19</td>
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<td>N/A</td>
<td>N/A</td>
<td>SD</td>
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<tr>
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<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>PR</td>
</tr>
<tr>
<td>21</td>
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<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>PR</td>
</tr>
<tr>
<td>2</td>
<td>Adult</td>
<td>0.67 x 10^6</td>
<td>Fever/chills</td>
<td>Week 6</td>
<td>No</td>
<td>PD</td>
</tr>
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<td>4</td>
<td>Adult</td>
<td>2 x 10^6</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>NE</td>
</tr>
<tr>
<td>5</td>
<td>Adult</td>
<td>2 x 10^6</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>PD</td>
</tr>
<tr>
<td>7</td>
<td>Adult</td>
<td>1.35 x 10^6</td>
<td>Fever/chills/nausea</td>
<td>Week 7</td>
<td>No</td>
<td>Mixed</td>
</tr>
<tr>
<td>8</td>
<td>Adult</td>
<td>2 x 10^6</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>PR</td>
</tr>
<tr>
<td>9</td>
<td>Adult</td>
<td>0.67 x 10^6</td>
<td>Increasing LFTs</td>
<td>Week 3</td>
<td>No</td>
<td>PD</td>
</tr>
<tr>
<td>10</td>
<td>Adult</td>
<td>1 x 10^6</td>
<td>Injection site reaction</td>
<td>Week 10</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>13</td>
<td>Adult</td>
<td>2 x 10^6</td>
<td>Gr 3 infection; ≥ 1 mo IL-2 hold</td>
<td>Week 8</td>
<td>Yes</td>
<td>NE</td>
</tr>
<tr>
<td>14</td>
<td>Adult</td>
<td>0.335 x 10^6</td>
<td>Gr 3 transaminitis</td>
<td>Week 1</td>
<td>Yes</td>
<td>SD</td>
</tr>
<tr>
<td>15</td>
<td>Adult</td>
<td>0.67 x 10^6</td>
<td>Gr 2 chills and malaise</td>
<td>Week 4</td>
<td>Yes</td>
<td>NE</td>
</tr>
</tbody>
</table>

N/A, not applicable; Gr, grade; DLT, dose limiting toxicity; Wk, week; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable
## Supplemental Table 2. Patients in extended duration IL-2 therapy

<table>
<thead>
<tr>
<th>ID</th>
<th>Cohort</th>
<th>No. Weeks*</th>
<th>Clinical Response in Extended Therapy</th>
<th>Adverse Events During Extended Therapy</th>
<th>Reason for IL-2 Discontinuation</th>
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<tbody>
<tr>
<td>1</td>
<td>Pedi</td>
<td>113</td>
<td>Wk 61 Mixed: Skin deeper PR, GI tract CR, Lung PD</td>
<td>Gr 3, 4 hypokalemia and hypophosphatemia; Gr 4 sepsis and respiratory failure</td>
<td>Death secondary to respiratory failure from progressive lung GVHD</td>
</tr>
<tr>
<td>3</td>
<td>Pedi</td>
<td>16</td>
<td>Wk 21 PR: Skin SD, GI tract CR, JMF SD, GSS trivial PR</td>
<td>None</td>
<td>Plateaued response, daily injections interfering with QoL</td>
</tr>
<tr>
<td>6</td>
<td>Pedi</td>
<td>44</td>
<td>Wk 52 PD: Skin PD, GI tract PD, JMF PD, Lung PD</td>
<td>None</td>
<td>Progression of cGVHD while weaning other immunosuppression, switched treatment</td>
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<tr>
<td>11</td>
<td>Pedi</td>
<td>115</td>
<td>Wk 41 PR: GI trivial PD, JMF CR, GSS PR</td>
<td>None</td>
<td>Plateaued response, daily injections interfering with QoL</td>
</tr>
<tr>
<td>12</td>
<td>Pedi</td>
<td>89</td>
<td>Wk 48 PR: Lungs SD, GSS PR</td>
<td>None</td>
<td>Progression of lung GVHD following a respiratory infection, switched treatment</td>
</tr>
<tr>
<td>16</td>
<td>Pedi</td>
<td>120+</td>
<td>Wk 45 PR: Skin deeper PR, GSS trivial PR</td>
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<td>N/A, ongoing</td>
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<tr>
<td>17</td>
<td>Pedi</td>
<td>37</td>
<td>Wk 24 PR: Lung SD, Liver PR, GSS trivial PR</td>
<td>None</td>
<td>Relapsed MDS</td>
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<tr>
<td>18</td>
<td>Pedi</td>
<td>86+</td>
<td>Wk 44 PR: Skin PR, Lung PR, GSS PR</td>
<td>Gr 1 flu-like symptoms, Gr 2 hypothyroidism</td>
<td>N/A, ongoing</td>
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<tr>
<td>19</td>
<td>Pedi</td>
<td>78+</td>
<td>Wk 54 PR: Skin SD, JMF SD, Liver CR, GSS trivial PR</td>
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<td>N/A, ongoing</td>
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<tr>
<td>20</td>
<td>Pedi</td>
<td>70+</td>
<td>Wk 27 PR: Skin CR, Lung SD, GSS PR</td>
<td>None</td>
<td>N/A, ongoing</td>
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<tr>
<td>21</td>
<td>Pedi</td>
<td>8</td>
<td>Off study Wk 16 due to systemic infection and liver PD</td>
<td>Gr 3, 4 infections; Gr 4 neutropenia</td>
<td>Death secondary to multiorgan failure from infections and progressive GVHD</td>
</tr>
<tr>
<td>5</td>
<td>Adult</td>
<td>56</td>
<td>Wk 56 SD: Skin SD, JMF SD</td>
<td>None</td>
<td>Plateaued response, considering other available treatments</td>
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<tr>
<td>8</td>
<td>Adult</td>
<td>141</td>
<td>Wk 48 Mixed: JMF CR, Lung PD, Mouth CR</td>
<td>None</td>
<td>Plateaued response, increased systemic steroids</td>
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<tr>
<td>10</td>
<td>Adult</td>
<td>30</td>
<td>Wk 20 PR: Skin SD, Mouth PD, GI SD, JMF SD, Lung CR</td>
<td>None</td>
<td>Plateaued response, considering other available treatments</td>
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<tr>
<td>14</td>
<td>Adult</td>
<td>30</td>
<td>Wk 24 PR: Skin PR, GI SD, JMF SD, Mouth SD, Eye PD</td>
<td>None</td>
<td>Plateaued response</td>
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</table>

*Number of weeks beyond the initial 8-week period. Pedi, pediatric; Wk, week; Gr, grade; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; GSS, global severity score; JMF, joint/muscle/fascia; GI, gastrointestinal; QoL, quality of life; N/A, not applicable; MDS, myelodysplastic syndrome
Supplemental Figure 1. Survival. (A) Overall survival (OS) and (B) progression free survival (PFS) for the adult (red) and pediatric (blue) cohorts. All (black), both cohorts combined.

Supplemental Figure 2. Plasma IL-2 and soluble IL-2 receptor (sIL-2R) levels. (A) Plasma IL-2 concentrations (pg/mL) for adult patients, separated by individual maximum tolerated dose (MTD). Each line represents a different dose level. For dose levels with more than one patient, the mean value is represented at each time point. (B) Plasma sIL-2R concentrations (pg/mL) for the pediatric (blue) and adult (red) cohorts. Median values (dots) and the interquartile range (whisker bars) are shown at each time point. Number of patients evaluated at each time point is indicated at the bottom of the image.

Supplemental Figure 3. Absolute CD4Treg and CD4Tcon numbers during IL-2 therapy. (A) Absolute CD4Treg counts (cells/µL) in the pediatric (blue) and adult (red) cohorts shown at baseline (W0), weeks 1-16, 6 months (6MO), and 1 year (1Y) of daily IL-2 therapy. (B) Absolute CD4Tcon (cells/µL) in the pediatric (blue) and adult (red) cohorts. Median values (dots) and the interquartile range (whisker bars) are shown at each time point. The median CD4Treg:Tcon ratio for the pediatric cohort is indicated by the black line. Number of patients evaluated at each time point is indicated at the bottom of each graph. Gray shading indicates the normal range for absolute CD4Tcon. *p<0.05; pediatric compared with adult, Wilcoxon rank-sum test.

Supplemental Figure 4. Plasma cytokine levels measured by multiplex Luminex® assay. (A) Comparisons of plasma IL-12 and interferon alpha (IFNa) concentrations (pg/mL) at baseline (W0), and weeks 2, 4, and 8 in the pediatric (blue) and adult (red) cohorts. (B) Comparisons of plasma IL-12 and IFNa concentrations (pg/mL) at baseline (W0), and weeks 2, 4, and 8 in the dose escalation (red) vs fixed-dose (gray) regimens. Only the adult patients were included in this analysis. Median values (dots)
and the interquartile range (whisker bars) are shown at each time point. Number of patients evaluated at each time point is indicated at the bottom of each graph. *p<0.05, **p<0.005; pediatric compared with adult, Wilcoxon rank-sum test.

**Supplemental Figure 5. Impact of low-dose IL-2 on CD4Treg memory and naïve subsets.** Relative percentages of effector memory (EM, gray), central memory (CM, orange), and naïve (blue) CD4Treg are shown for the pediatric (left) and adult (right) cohorts. Bar graphs show the median percentage of each population. *p<0.05, **p<0.005; each time point was compared with baseline (W0), 2-sided Wilcoxon signed-rank test. Number of patients evaluated at each time point is indicated at the bottom of each graph.
Supplemental Figure 1. Survival

A

OS

Years from study entry

Probability

0.0 0.2 0.4 0.6 0.8 1.0

Adult

Pediatric

All

B

PFS

Years from study entry

Probability

0.0 0.2 0.4 0.6 0.8 1.0

Adult

Pediatric

All
Supplemental Figure 2. Plasma IL-2 and Plasma sIL-2R Levels

A.

```
<table>
<thead>
<tr>
<th>MTD Level (IU/m²/d)</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
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<td>5</td>
</tr>
<tr>
<td>1.35 x 10^6</td>
<td>1</td>
</tr>
<tr>
<td>0.67 x 10^6</td>
<td>2</td>
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<td>0.335 x 10^6</td>
<td>1</td>
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B.

<table>
<thead>
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<th>Time since IL-2 initiation</th>
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<tbody>
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<td>W6</td>
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<tr>
<td>W8</td>
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</table>

0 2000 4000 6000 8000 10000 12000

Plasma [sIL-2R] pg/mL
Supplemental Figure 3. Absolute cell counts

A. Absolute CD4Treg numbers

B. Absolute CD4Tcon numbers
Supplemental Figure 4: Cytokine Analysis by Luminex

A. Plasma [IL-12] pg/mL vs. Time since IL-2 initiation

- Pediatric
- Adult

B. Plasma [IFNα] pg/mL vs. Time since IL-2 initiation

- Dose-escalated IL-2
- Fixed-dose IL-2

<table>
<thead>
<tr>
<th></th>
<th>Pedi</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>W2</td>
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<td>6</td>
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<td>6</td>
</tr>
<tr>
<td>W8</td>
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<td>6</td>
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<table>
<thead>
<tr>
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<tbody>
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<td>W0</td>
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</tr>
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<td>W4</td>
<td>17</td>
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<tr>
<td>W8</td>
<td>21</td>
</tr>
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</table>

Pedi 10 10 10 10
Adult 7 6 6 6

Dose-escalated IL-2 7 6 6 6
Fixed-dose IL-2 15 14 17 21
**Supplementary Figure 5.** CD4Treg naive and memory subsets