Identification of a well-tolerated outpatient regimen of intravenous recombinant human interleukin-21 (IL-21) in patients with metastatic melanoma and metastatic renal cell carcinoma

J. A. Thompson  
University of Washington, Seattle, WA

B. D. Curti  
Providence Portland Medical Center, Portland, OR

B. G. Redman  
University of Michigan, Ann Arbor, MI

E. L. Sievers  
ZymoGenetics Inc., Seattle, WA
Interleukin 21

- Novel class I cytokine
- Produced by activated CD4+ T cells
- Signals through dimer of unique IL-21 receptor and common gamma chain
- Recombinant IL-21 has demonstrated anti-tumor efficacy in preclinical models
IL-21 Elicits Pleiotropic Immune Modulation

- Cytotoxic T Lymphocytes (CTL)
  - ↑ number and lifetime of specific tumor killing cells
  - ↑ ability of cells to kill tumor targets

- Natural Killer (NK) Cells
  - enhanced production of mature NK cells
  - enhanced NK cell mediated tumor lysis

- B Lymphocytes
  - ↑ production of mature specific antibodies (IgG)
Open Label, Phase 1 Dose Escalation Study

- **Population**
  - Patients with measurable metastatic melanoma or renal cell carcinoma

- **Objectives**
  - **Primary**
    - Determine maximum tolerated dose of IL-21 (using CTCAE criteria)
  - **Secondary**
    - Pharmacokinetics
    - Immunogenicity
    - Clinical or biological parameters that may correlate with efficacy
    - Anti-tumor effect
Key inclusion criteria

- Metastatic melanoma (non ocular) or metastatic renal cell carcinoma (clear cell)
- ECOG 0 or 1
- “Standard” laboratory parameters
- No more than one prior treatment
- Hemoglobin > 12 g/dL
Part 1a
Study Demographics (n = 15)

- **Gender**
  - Male 13
  - Female 2

- **Age, median (range)** 61 (39 – 76)

- **Malignancy**
  - Melanoma 9
  - Renal Cell 6

- **Mean years since diagnosis** 4

- **Number with prior immunotherapy**
  - IL-2 5
  - Interferon 4
**IL-21 Treatment Schedule**

Dosing cycle = 5 consecutive daily doses of IL-21 delivered by IV push in the outpatient setting
IL-21 Monotherapy Phase 1 Study (U.S.)

<table>
<thead>
<tr>
<th>Dose (µg/kg)</th>
<th>Phase 1a</th>
<th>Phase 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>n = 2</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>n = 1</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>n = 6</td>
<td>n ≤ 30^a</td>
</tr>
<tr>
<td>10</td>
<td>n = 3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>n = 3</td>
<td></td>
</tr>
</tbody>
</table>

^a n = up to 30 subjects (15 of each disease type) including Phase 1a subjects dosed at 30 µg/kg
IL-21 Safety

- All but 2 adverse events were mild to moderate in severity
- Most common adverse events
  - Fatigue, Pyrexia, Arthralgia, Chills, Headache, Myalgia, Rash
- Grade 3 or higher adverse events included
  - Grade 4 acute liver toxicity probably related to IL-21 (occurred in Cycle 4) – 30 µg/kg
  - Grade 3 hemoptysis unrelated to IL-21 – 3 µg/kg
- 0/15 patients treated with \( \leq 2 \) cycles developed specific antibody response
## Most Common Adverse Events through 2 Cycles by Dose (µg/kg)

<table>
<thead>
<tr>
<th></th>
<th>3 (n = 3)</th>
<th>10 (n = 3)</th>
<th>30 (n = 6)</th>
<th>50 (n = 1)</th>
<th>100 (n = 2)</th>
<th>Total (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Chills</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Edema Peripheral</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>
Grade 3 Laboratory Toxicities through 2 Cycles by Dose (µg/kg)

- 7 of 9 patients at doses ≥ 30 µg/kg experienced Grade 3 toxicity
- One patient at 100 µg/kg experienced transient Grade 4 lymphopenia

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>≤ 10 (n = 6)</th>
<th>30 (n = 6)</th>
<th>50 (n = 1)</th>
<th>100 (n = 2)</th>
<th>Total (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Median ALT Over Time for 30 µg/kg

ALT (U/L)a

Cycle 1

Cycle 2

a median with IQR
### IL-21 Pharmacokinetics

The half-life ($t_{1/2}$) of IL-21 was approximately 1.5 hours.

<table>
<thead>
<tr>
<th>Dose (µg/kg)</th>
<th>N</th>
<th>Cmax (ng/mL)</th>
<th>AUC$_{INF}$ (hr*ng/mL)</th>
<th>$t_{1/2}$ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3</td>
<td>39.7 (70.8)</td>
<td>22.9 (37.3)</td>
<td>1.88 (13.4)</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>33.5 (80.0)</td>
<td>68.2 (14.5)</td>
<td>1.31 (15.5)</td>
</tr>
<tr>
<td>30</td>
<td>6</td>
<td>107 (115)</td>
<td>206 (41.6)</td>
<td>1.69 (11.8)</td>
</tr>
<tr>
<td>50</td>
<td>1</td>
<td>102 (--)</td>
<td>195 (--)</td>
<td>1.40 (--)</td>
</tr>
<tr>
<td>100</td>
<td>2</td>
<td>347 (48.0)</td>
<td>602 (41.3)</td>
<td>1.89 (2.63)</td>
</tr>
</tbody>
</table>
Median Lymphocytes and Median Soluble CD25

- Median Soluble CD25 (ng/mL)
  - Cycle 1
  - 1 5 9 13 1 5 9 13 17 21 25 29
  - 1 5 9 13 1 5 9 13 17 21 25 29

- Median Lymphocytes (x 10⁹/mL)
  - Cycle 1
  - 0.5 1 1.5 2 2.5 3 3.5 4
  - Cycle 2
  - 0.5 1 1.5 2 2.5 3 3.5 4

Dose:
- 100µg/kg
- 50µg/kg
- 30µg/kg
- 10µg/kg
- 3µg/kg
Changes in Target Lesion Diameter after Receiving 2 Cycles of IL-21 Treatment

Percent change from baseline

PD due to new lesion

only four doses per subject

30 10 30 3 3 10 30 100 100 10 30 30 30 50 3

MM = metastatic melanoma
RCC = renal cell carcinoma
Dose units = $\mu$g/kg
## RECIST Responses through 2 Cycles by Dose (µg/kg)

<table>
<thead>
<tr>
<th></th>
<th>3 (n = 3)</th>
<th>10 (n = 3)</th>
<th>30 (n = 6)</th>
<th>50 (n = 1)</th>
<th>100(^a) (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>1 (RCC)</td>
<td>0</td>
<td>0</td>
<td>1 (RCC)</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>2 (MM)</td>
<td>2 (MM)</td>
<td>0</td>
<td>1 (RCC)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (MM)</td>
<td>1 (MM)</td>
<td>1 (RCC)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Each patient at 100 µg/kg received only 4 of 10 planned doses

MM = metastatic melanoma
RCC = renal cell carcinoma
Conclusions

- Outpatient MTD selected for further study in Part b:
  - 2 cycles of 30 µg/kg/day x 5 days with 9-day rest interval
  - Reasonably well-tolerated by 6 patients
- AUC of IL-21 increased in dose-proportional manner
- Dose-related biological effects as measured by sCD25 and lymphocytes
- Objective evidence of anti-tumor activity
Plans

- Completing enrollment of 30 patients treated at 30 µg/kg/day
  - 15 renal cell carcinoma
  - 15 metastatic melanoma

- Goals
  - Further characterize safety of this outpatient regimen
  - Estimate overall response rate for each cancer
  - Plan Phase 2 studies
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Maximum ALT by Patient

ALT (U/L)

Dose (µg/kg)