A PHASE I STUDY OF INTRAVENOUS RECOMBINANT HUMAN IL-15 (rhIL-15) IN ADULTS WITH METASTATIC MALIGNANT MELANOMA AND METASTATIC RENAL CELL CANCER

Society for the Immunotherapy of Cancer
4 November 2011
Presenter Disclosure Information

Kevin Conlon

The following relationships exist related to this presentation:

No relationships to disclose
Protocol Eligibility

- Metastatic melanoma or renal cell carcinoma
  - Refractory, intolerant or refused standard treatments
  - No prior treatment with IL-2 (October 2010)
- Measurable disease, adequate physiologic and laboratory parameters, ECOG ≤ 1, life expectancy > 3 months
- Negative serology for HIV, hepatitis A, B and C
- Treated CNS metastases allowed
  - (> 3 months radiographic stability)
- No history of autoimmune diseases or systemic corticosteroids
  - prior Ipilimumab immune related adverse events allowed (October 2010)
- Medical or psychiatric illness that would preclude safe participation in the trial
Treatment Plan

Drug administration
- rhIL-15 as 30 min intravenous infusion daily X 12 days
- Dose levels: 0.3*, 1*, 3, 7, 10, 15, 20 and 25 μg/kg/day
  - added after first patient had DLT

Fluid management
- Basal: IVF NS at 100 cc/hr → increased up to 150 (200) cc/hr for anticipated BP nadir in 3 μg/kg pts
- IV 25% albumin and furosemide PRN

Antipyretics
- Initially no empiric premedication
- If Temperature > 38°C start q6 hour acetaminophen → if persistent temperature > 38.5°C
  → acetaminophen 4g/day in combination with timed ibuprofen (400 to 800 mg)

Anti-emetics
- Initially no antiemetic premedication
- If nausea or vomiting → routine premedication for all subsequent cycles

Other treatments
- Blood products PRN
- If rigors: IV meperidine (Demerol)
- If O₂ saturation <92% → intranasal O₂
## Patient Histories

<table>
<thead>
<tr>
<th>Diagnosis/Age</th>
<th>Prior treatment</th>
<th>Number of doses</th>
<th>Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3 μg/kg Patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma/83 F</td>
<td>None</td>
<td>1</td>
<td>DLT grade 3 hypotension</td>
</tr>
<tr>
<td>Ocular melanoma/43 M</td>
<td>None ineligible for HD IL-2</td>
<td>12</td>
<td>Completed Rx</td>
</tr>
<tr>
<td>Melanoma/53 M</td>
<td>HD IL-2, Ipilimumab, TILs with LD IL-2, AZD-6244, XRT</td>
<td>10</td>
<td>Non-DLT hypotension, pleural effusion</td>
</tr>
<tr>
<td>Ocular melanoma/57 F</td>
<td>Anti-CD137, Ipilimumab, CR011 Immunotoxin, XL-184</td>
<td>12</td>
<td>Completed Rx</td>
</tr>
<tr>
<td>Melanoma/34 M</td>
<td>HD IL-2, TILs with HD IL-2, young TILs with HD IL-2, Ipilimumab, XRT</td>
<td>6</td>
<td>DLT grade 3 thrombocytopenia</td>
</tr>
<tr>
<td><strong>1 μg/kg Patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Cell/57 M</td>
<td>IMRT to jaw, XRT to pelvis, TroVax vaccine with sunitinib, pazopanib, everolimus</td>
<td>4</td>
<td>DLT persistent grade 3 AST/ALT abnormalities</td>
</tr>
<tr>
<td>Renal Cell/67 M</td>
<td>Sunitinib, axitinib, sorafenib with LBH589, everolimus</td>
<td>12</td>
<td>Completed Rx</td>
</tr>
<tr>
<td>Melanoma/21 F</td>
<td>Young TILs with HD IL-2, Ipilimumab, IL-12 transduced TILs</td>
<td>12</td>
<td>Completed Rx</td>
</tr>
<tr>
<td>Mucosal melanoma/50 M</td>
<td>None</td>
<td>4</td>
<td>DLT persistent grade 3 AST/ALT abnormalities</td>
</tr>
</tbody>
</table>
# Clinical Toxicities

<table>
<thead>
<tr>
<th>Patient</th>
<th>GI Type</th>
<th>Antiemetics</th>
<th>Fever Temp</th>
<th>Antipyretics</th>
<th>Max Weight</th>
<th>IV Albumin</th>
<th>Episodes</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma/ 83 F</td>
<td>N, D</td>
<td>Z PRN</td>
<td>37.8</td>
<td>-</td>
<td>-1 kg</td>
<td>-</td>
<td>C X 1</td>
<td></td>
</tr>
<tr>
<td>Ocular melanoma/ 43 M</td>
<td>N,V</td>
<td>Z Sch</td>
<td>40.7</td>
<td>Tyl, IB Sch</td>
<td>+ 4 kgs</td>
<td>6X</td>
<td>R X 10</td>
<td>D X 10</td>
</tr>
<tr>
<td>Melanoma / 53 M</td>
<td>N,V</td>
<td>Z Sch</td>
<td>38.8</td>
<td>Tyl, IB Sch</td>
<td>+7 kgs</td>
<td>7 X</td>
<td>C X 4, R X 5</td>
<td>D X 5</td>
</tr>
<tr>
<td>Ocular melanoma/ 57 F</td>
<td>-</td>
<td>-</td>
<td>38.6</td>
<td>IB PRN</td>
<td>+6 kgs</td>
<td>4 X</td>
<td>C X 3, R X 7</td>
<td>D X 7</td>
</tr>
<tr>
<td>Melanoma/34 M</td>
<td>-</td>
<td>-</td>
<td>38.2</td>
<td>Tyl Sch</td>
<td>+5 kgs</td>
<td>2 X</td>
<td>C X 3, R X 1</td>
<td>D X 1</td>
</tr>
<tr>
<td>Renal Cell/57 M</td>
<td>-</td>
<td>-</td>
<td>39.6</td>
<td>Tyl Sch</td>
<td>+1 kg</td>
<td>-</td>
<td>R X 4</td>
<td>D X 4</td>
</tr>
<tr>
<td>Renal Cell/67 M</td>
<td>-</td>
<td>-</td>
<td>39.3</td>
<td>Tyl, IB Sch</td>
<td>+4 kgs</td>
<td>3 X</td>
<td>C X 3, R X 7</td>
<td>D X 5</td>
</tr>
<tr>
<td>Melanoma/21 F</td>
<td>N, V*</td>
<td>Z, Com Sch</td>
<td>39.4</td>
<td>Tyl, IB Sch</td>
<td>+ 6 kgs</td>
<td>4 X</td>
<td>C X 12</td>
<td>-</td>
</tr>
<tr>
<td>Mucosal melanoma/50 M</td>
<td>-</td>
<td>-</td>
<td>39.3</td>
<td>Tyl → IB Sch</td>
<td>+ 2 kgs</td>
<td>2 X</td>
<td>C X 4</td>
<td>-</td>
</tr>
</tbody>
</table>

*present a baseline and after Rx patient had multiple liver metastases*
Typical Blood Pressure and Temperature Courses

3 μg/kg Patient

Temperature spike consistently 2 ½ to 4 hours after dosing

1 μg/kg Patient

Temperature spike generally 4 hours after dosing
Daily Mean arterial Blood Pressures

Normalized to time of IL-15 infusion

3 μg/kg Patients

1 μg/kg Patients
Hematologic Effects

No discernible difference between 3 μg/kg and 1 μg/kg patients
↓ Platelets and ANC with recovery late in course or after treatment was stopped
Initial ↓ in WBC and ALC with recovery with lymphocyte expansion day 4-7
Lymphocytosis 2-4 X ↑ due to 2-3 X ↑ CD8 cells and 4-14 X ↑ NK cells → day 21+
Biochemistry abnormalities

Virtually no changes in serum creatinine → one patient CCr ≈ 60 ml/min maximum SCr ↑ 0.18 mg/dl
LFT Abnormalities: Details

• Three of the five 3 μg/kg patients had grade 2 CTC LFT abnormalities
• Alkaline Phosphatase 2.5, 3 and 4.5 X baseline
• 2 had elevated total bilirubin (2.3 and 1.7 mg/dl maximum) back to baseline by the last treatment day
• 2 of these 3 metastatic ocular melanoma with substantial liver metastases
Pharmacokinetics

Comparison of 3 mcg/kg and 1 mcg/kg

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>3 µg/kg Patients</th>
<th>1 µg/kg Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (pg/ml)</td>
<td>Patient 1  80590</td>
<td>Patient 6  8520</td>
</tr>
<tr>
<td>Anti-IL-15 Antibodies</td>
<td>Patient 2  20211</td>
<td>Patient 7  15520</td>
</tr>
<tr>
<td></td>
<td>Patient 3  11400</td>
<td>Patient 8  9160</td>
</tr>
</tbody>
</table>
Cytokine Production Day 1

**IL-12 p70**

**IFN gamma**

**TNF alpha**

**IL-10**

**IL-8**

**IL-6**
Clinical Activity

<table>
<thead>
<tr>
<th>Patient</th>
<th>Evaluation</th>
<th>Time to progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not evaluable</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>SD (120% day 28 and 42)</td>
<td>3 months +</td>
</tr>
<tr>
<td>3</td>
<td>SD day 28</td>
<td>Day 42</td>
</tr>
<tr>
<td>4</td>
<td>SD</td>
<td>3 months</td>
</tr>
<tr>
<td>5</td>
<td>PD</td>
<td>Day 21</td>
</tr>
<tr>
<td>6</td>
<td>Not evaluable*</td>
<td>6 months +</td>
</tr>
<tr>
<td>7</td>
<td>SD day 28 and 42</td>
<td>3 months</td>
</tr>
<tr>
<td>8</td>
<td>PD</td>
<td>Day 21</td>
</tr>
<tr>
<td>9</td>
<td>TE</td>
<td>TE</td>
</tr>
</tbody>
</table>

Patient 6 Baseline

Day 37

Day 57
Conclusions

Immune activation was observed at either dose 1 or 3 $\mu$ g/kg/day

- 2 to 4 fold increase in absolute lymphocyte counts (ALC)
  - 2-3 fold expansion of CD8+ T-cells and 4-14 fold expansion in NK cell numbers
  - Production of the inflammatory cytokines at early time points

Toxicities were manageable and resolved after treatment was stopped

- Decreases in BP at the 3 $\mu$ g/kg but not 1 $\mu$ g/kg dose level
- Capillary leak was seen, but no significant pulmonary toxicities or end organ dysfunction

PK results

- Half life $\approx$ 1 hour, no anti-IL-15 antibodies
- No significant changes in PK Day 1 vs. 12

Laboratory abnormalities were mild

- Transient decreases in platelets, neutrophils
- Elevation of liver function tests peaking mid cycle (days 5→ 7)
- Clinically Asymptomatic

Clinical Activity

- Biological indications of in vivo activity?
- no responses by RECIST criteria were observed

3 $\mu$ g/kg IVB is above the MTD without dedicated nursing

1 $\mu$ g/kg rhIL-15 given as IVB appears to be a tolerable dose*
Acknowledgements

Metabolism Branch
Thomas A. Waldmann
Tatyana Worthy                        Caroline Goldman          Donn Stewart
Jeanne Decker                        Kathleen Tepas-Wise       Bonnie Bryant
                                      Liyanage Perera

Center for Cancer Research
Bob Wiltrout
Surgery Branch
Steven A. Rosenberg
James Yang

Vaccine Research Center NIAID
Enrico Lugli                         H.Clifford Lane            Michael Sneller
Mario Roederer

Department of Transfusion Medicine Immunogenetics Section
Francesco Marincola
Ena Wang

Immunology Service, Clinical Pathology Department
Thomas Fleisher

Biometric Research Branch DCTD
Joanna Shih                         Steven Creekmore                Jason Yovandich
                                      Medical Oncology Branch
                                      Tito Fojo
                                      Pathology Department
                                      Elaine Jaffe

John Janik Bristol Myers Squibb      John Morris University of Cincinnati