Tumor infiltrating lymphocyte recruitment after peri-lymphatic IRX-2 cytokine immunotherapy in resectable breast cancer and head and neck carcinoma

Joanna Pucilowska  
*Earle A. Chiles Research Institute, Providence Portland Medical Center, Portland, OR, Joanna.Pucilowska@providence.org*

Venkatesh Rajamanickam  
*Earle A. Chiles Research Institute, Providence Portland Medical Center, Portland, OR, Venkatesh.Rajamanickam@providence.org*

Nikki Moxon  
*Earle A. Chiles Research Institute, Providence Portland Medical Center, Portland, OR, Nicole.Moxon@providence.org*

Monil Shah  
*IRX Therapeutics, New York, NY*

Maritza Martel  
*Providence Portland Medical Center, Portland, OR, Maritza.Martel@providence.org*

See next page for additional authors.  
Follow this and additional works at:  [https://digitalcommons.psjhealth.org/sitc2018](https://digitalcommons.psjhealth.org/sitc2018)  
Part of the [Oncology Commons](https://digitalcommons.psjhealth.org/sitc2018)

Recommended Citation  
Pucilowska, Joanna; Rajamanickam, Venkatesh; Moxon, Nikki; Shah, Monil; Martel, Maritza; Conlin, Alison; Egan, James E.; and Page, David B., "Tumor infiltrating lymphocyte recruitment after peri-lymphatic IRX-2 cytokine immunotherapy in resectable breast cancer and head and neck carcinoma" (2018). Society for Immunotherapy of Cancer 2018 Annual Meeting Posters. 1.  
[https://digitalcommons.psjhealth.org/sitc2018/1](https://digitalcommons.psjhealth.org/sitc2018/1)
Tumor infiltrating lymphocyte recruitment after peri-lymphatic IRX-2 cytokine immunotherapy in resectable breast and head and neck carcinoma

Joanna Pucilowska, Venkatesh Rajamanickam, Katherine Sanchez, Valerie Conrad, Nikki Moxon, Staci Mellinger, Maritza Martel, Kelly Perlowitz, James Egan, Monil Shah, David B. Page

Background

- IRX-2 is an injectable cytokine-based immunotherapy containing multiple cytokines derived from ex vivo phytohemagglutinin-stimulated donor lymphocytes;
- Measurable constituents include: IFNγ, IL-2, IL-1b, TNFα, IL-6, IL-8, GM-CSF, and G-CSF;
- In preclinical models, IRX-2 activates T cells and natural killer cells, and facilitates dendritic cell maturation;
- In a phase I trial, neoadjuvant IRX-2 increased tumor-infiltrating lymphocytes (TILs) and shrank tumors in resectable head/neck squamous carcinoma (HNSCC);
- Stromal TILs (sTILs) are associated with improved survival in early stage breast cancer (ESBC).

Hypothesis

To assess the feasibility of preoperative IRX-2, and its effect on TIL recruitment and immune priming within breast and HNN tumors, regional lymphatics, and blood.

Methods

- Patients with early stage (I-III) breast cancer were enrolled preoperatively;
- Patients received low dose of cyclophosphamide (DL 300 mg/m2) to facilitate T-regulatory (Treg) cell depletion, followed by 10 days of subcutaneous peri-areolar subcutaneous IRX-2 into the affected breast (1 mL × 2 at tumor axis and at 90°), similar to sentinel lymph node mapping methodology;
- Subjects also received oral indomethacin, which may reverse immunosuppression by modulating myeloid cells;
- Primary endpoint: feasibility
- Secondary endpoint: blinded assessment of sTILs by the 2015 San Antonio working group criteria
- Exploratory endpoints: comprehensive immune monitoring

No treatment-related grade 3/4 toxicities

Primary Endpoint: Feasibility

Table 1: Demographics and tumor characteristics of participants.

<table>
<thead>
<tr>
<th>IRX-2 Group</th>
<th>n</th>
<th>Sex</th>
<th>Race</th>
<th>Stage</th>
<th>Tumor Size</th>
<th>ER%</th>
<th>PR%</th>
<th>HER2</th>
<th>Grade</th>
<th>Lymph Node Status</th>
<th>Pathologic Complete Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Treatment-related toxicities occurring in >15% of subjects. (Note: transient treatment-unrelated grade III syncope was observed in one subject with prior history of vasovagal syncope)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade I/I, any attribution (%)</th>
<th>Grade I/I, attributed to Cy (%)</th>
<th>Grade I/I, attributed to Indo (%)</th>
<th>Grade I/I, attributed to IRX-2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>11 (81%)</td>
<td>3 (19%)</td>
<td>8 (50%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (65%)</td>
<td>5 (63%)</td>
<td>2 (25%)</td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>8 (50%)</td>
<td>8 (50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (25%)</td>
<td>3 (19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3 (21%)</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (13%)</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Regimen

Figure 2: sTIL increases After IRX-2 Therapy

Figure 3: PD-L1 increases After IRX-2 Therapy (IHC and Nanostring)

Exploratory Endpoints: RNA Analysis

Figure 4: IRX-2 Increases immune checkpoint, leukocyte recruitment, cytotoxic T-cell, and leukocyte genes expression

Figure 5: Effects on peripheral T-cells

Conclusions and Future Directions

- IRX-2 was well tolerated, with no treatment-related grade 3 or 4 toxicities or surgical delays;
- In breast cancer, IRX-2 enhances TIL recruitment and PD-L1 expression (by mRNA and miHC);
- Peripheral immune changes were associated with Cy administration but not IRX-2 injections;
- These preliminary findings will be further explored in a follow-up clinical trial that compares anti-PD-1 +/- IRX-2 as induction therapy preceding neoadjuvant chemotherapy in stage II-III triple negative breast cancer, with a primary endpoint of pathologic complete response rate

References