cytoTIL™ therapy engineered with mbIL15 demonstrates enhanced \textit{in vivo} persistence in the absence of IL-2, paving the way for durable efficacy and improved safety in patients with solid tumor malignancies.

Mithun Khattar, Rachel Burga, Alex Storer, Kyle Pedro, Colleen Foley, Scott Lajoie, Alonso Villasmil Ocando, Jack Tremblay, Dan Thornton, Stanley Tam, Gwen Wilmes, Gabriel Helmlinger, Jeremy Tchaicha, Dhruv Sethi, Michelle Ols, Gary Vanasse, Jan ter Meulen, and Shyam Subramanian
Un-engineered TILs have shown promising clinical results in solid tumors, but systemic IL2 AE’s limit patient eligibility

<table>
<thead>
<tr>
<th>Benefits of TIL Therapy</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recognize multiple tumor antigens without an engineered binder (polyclonal)</td>
<td>IL2 therapy is highly toxic:</td>
</tr>
<tr>
<td>• Targets intracellular tumor antigens</td>
<td>• TIL therapy in combination with systemic IL2 is associated with a high degree of Grade 3/4 AEs including cardiac &amp; pulmonary.</td>
</tr>
<tr>
<td>• Traffics into solid tumors</td>
<td>• Risk of capillary leak syndrome and multi-organ dysfunction</td>
</tr>
<tr>
<td></td>
<td>— Can be severe and result in death</td>
</tr>
<tr>
<td>→ On track to be 1st cell therapy approved for solid tumors</td>
<td>• Black Box Warning* requires hospitalization and availability of ICU</td>
</tr>
<tr>
<td>• Positive interim Ph2 data</td>
<td>• Limited to patients with normal cardiac and pulmonary functions</td>
</tr>
<tr>
<td>– Lifileucel in Melanoma: 3% CR, 36.4% ORR</td>
<td></td>
</tr>
<tr>
<td>– LN-145 in Cervical Cancer: 11% CR, 44% ORR</td>
<td></td>
</tr>
</tbody>
</table>

AE = Adverse Event | *Proleukin (aldesleukin) package insert
cytoTIL15: A regulated interleukin-15 engineered TIL therapy to drive potent and durable anti-tumor responses

Benefits of TIL-endogenous mbIL15 vs. systemic IL2

- Drive antigen-independent TIL expansion & persistence
- Drive adjacent NK cell expansion & activity
- Drive phenotype towards CD8+ and memory T-cells
- Unlike IL2, suppresses activation-induced cell death, doesn’t affect Tregs or cause capillary leak syndrome-associated toxicity
- IL15 expression of cytoTIL15 controlled by acetazolamide (ACZ), via cytoDRIVE® technology
cytoTIL15 engineering results in an improved TIL product, demonstrating **antitumor potency without need for IL2**

**cytoTIL15 demonstrate enhanced persistence and improved phenotype while maintaining potency**

- **Engineering**
  - Successful transduction & IL15 expression

- **Persistence**
  - Demonstrated superior persistence *in vitro & in vivo without IL2*

- **Phenotype**
  - Exhibit desired phenotype, skewing toward **CD8+ T-cells**

- **Potency**
  - Maintains anti-tumor reactivity with potential for lower cell dose vs. conventional TILs
**cytoTIL15** manufacturing process uses **novel engineered feeders** for REP expansion with **no exogenous cytokines**

- **Tumor Biopsy**
  - **Reduced** source tissue requirement

- **Pre-REP Expansion**
  - **Reduced** duration
  - **High** success rate

- **mbIL15 Engineering**
  - **Efficient** retroviral vector **transduction**

- **REP Expansion**
  - **No IL2** required for TIL expansion
  - **Engineered feeder cell** co-stimulation

- **Infusion to Patient**
  - **Cryopreserved** drug product
  - **Reduced duration** from biopsy

**Automated and closed processing from end to end**

REP = Rapid Expansion Protocol
cytoTIL15 is engineered to express membrane-bound IL15 (mbIL15), regulated by ACZ in a dose-dependent fashion

IL15 expression Post-REP

Regulation of IL15 expression, pSTAT5 & pS6 signaling by ACZ

- Graph on the left shows membrane IL15 expression on TILs at the end of the REP.
- Graphs in the right panel show membrane IL15 expression, pSTAT5 and pS6 levels on cytoTIL15 cultured overnight with different concentrations of ACZ as marked.
cytoTIL15 demonstrate enhanced persistence in vivo

Untransduced TIL + IL2  →  4 Days Proleukin (IL2)
cytoTIL™ + ACZ  →  Daily ACZ until end of study

Curve comparisons performed between treatment groups with AUC summary metrics from Day 7 to endpoint (Day 39/Day42) using Mann-Whitney two-sided tests
cytoTILs have higher CD8 T cell frequencies compared to control TILs, indicating better potency.

*** P<0.0005
**CytoTIL15** maintain TCRVβ diversity through the manufacturing process

Flow cytometry for 24 TCR Vβ families (~70% of total TCR repertoire) in fresh post-REP TIL-006
cyToTIL15 maintain reactivity to HLA-matched tumor cell lines

ns: not significant ($P>0.05$)
cytoTIL15: engineered to make TILs more effective for more patients

- Engineered with mbIL15
- Eliminates toxic IL2 regimen
- Drives improved potency & persistence
- IL15 expression controlled by acetazolamide (ACZ), via cytoDRIVE® technology

mb = membrane-bound