CT244: A Phase 1a/1b study of STK-012, an α/β IL-2 receptor selective partial agonist as monotherapy and in combination with pembrolizumab in advanced solid tumors (NCT05098132)

Background

- High dose intravenous (IV) interleukin-2 (IL-2) induces complete responses in certain cancers, but its use is limited due to toxicities including severe hypertension and capillary leak syndrome (CLS), and the requirement for inpatient administration.

- Recent approaches to develop IL-2 therapies with an expanded therapeutic index have targeted the dimeric form (ββ) of the IL-2 receptor, which is predominantly expressed on naïve T cells and NK cells, rather than the high affinity trimeric form (αββ), which is highly expressed on antigen activated T cells and constitutively expressed on Tregs.

- STK-012 is a pegylated, α/β IL-2R selective partial agonist engineered to preferentially stimulate antigen-activated T cells and avoid systemic NK and naïve T cell activation.

IL-2R Targeting Approaches

<table>
<thead>
<tr>
<th>IL-2R Bias</th>
<th>mIL-2r CD25+ CD8 T cells/mm³</th>
<th>mIL-2r CD25+ CD8 T cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>High affinity</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate affinity</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Low affinity</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>

Pre-Clinical Rationale

- In syngeneic tumor models, subcutaneously (SQ) injected STK-012 mouse surrogate (αβ/βmIL2-PEG) demonstrated reduced toxicities and improved efficacy relative to mouse IL-2 PEG and non-α IL-2 PEG (Figures 1 & 2).

- In cynomolgus monkeys, acute lung inflammation was induced by aldevlein and non-α-β-2, but not STK-012.

- STK-012 mouse surrogate induced a greater CD8 expansion and higher CD8/Foxp3 ratio relative to mIL-2 PEG and non-α IL-2 PEG in MC38 colon cancer model (Figure 3).

Figure 1: IL-2 induced acute toxicity model

Figure 2: Efficacy in mouse models

Figure 3: Pharmacodynamics in MC38 colon cancer model

Eligibility

- Patients who are relapsed/ refractory to, intolerant for, or refuse standard of care treatment for the below tumor types:
  - Metastatic Melanoma
  - Squamous Cell Carcinoma of the Head and Neck
  - Non-Small Cell Lung Cancer
  - Renal Cell Carcinoma
  - Ovarian Cancer
  - Cervical Cancer
  - MSI-H/BRMS (microsatellite instability-high or mismatch repair deficient) cancers

STK-012-101 (1H STUDY)

- This is a first-in-human, open-label, dose escalation and expansion study in adults with advanced solid tumors.

- The objectives of this study are to evaluate the safety, pharmacokinetics, immunogenicity, preliminary efficacy, and pharmacodynamics of STK-012 as monotherapy and in combination with pembrolizumab.

- Dose escalation will follow a standard 3+3 design for STK-012 monotherapy and in combination with pembrolizumab. STK-012 will be dosed SQ weekly, and pembrolizumab will be dosed IV every 3 weeks.

Study Schema

Study Information

- Enrollment in STK-012 monotherapy dose escalation has been initiated.

- The trial is registered with Clinicaltrials.gov, NCT05098132

References

1. Emmerich, J. et al. STK-012, an alpha/beta selective IL-2 mutein for the activation of antigen-activated T cells in solid tumors. Poster # 1744, Presented at American Association of Clinical Research, 2021