**INTRODUCTION**

- **4-1BB** is a critical costimulatory receptor expressed on the surface of lymphocytes, particularly T cells and natural killer (NK) cells. This receptor is involved in the activation and survival of lymphocytes, promoting a potent antitumor response.
- **PD-L1** (programmed cell death 1 ligand 1) is a negative regulator of the immune response, which is often upregulated in cancer cells. It binds to the PD-1 receptor, thus inhibiting the function of T cells and NK cells.
- **INBRX-105** is a recently developed antibody-drug conjugate (ADC) that consists of 2 single-domain antibodies (sdAbs) that agonize 4-1BB and 2 that antagonize PD-L1. The goal is to enhance the antitumor response by activating 4-1BB and deactivating PD-L1.

**Figure 1. Structure of INBRX-105**

**Figure 2. INBRX-105 Mechanism of Action**

**METHODS**

- The study was a single-agent and combination phase 1-2 trial of INBRX-105 administered as a single-agent or in combination with pembrolizumab.
- **Eligibility criteria** included patients with previously untreated or relapsed/refractory solid tumors.
- **Inclusion** criteria:
  - Locally advanced or metastatic, non-resectable solid tumors, including those with microsatellite instability or mismatch repair defects.
  - PD-L1-positive tumors.
- **Exclusion** criteria:
  - Patients with autoimmune diseases, autoimmune disorders, or a history of autoimmune disease.

**Figure 3. Study Design**

<table>
<thead>
<tr>
<th>Part 1</th>
<th>Part 2</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single agent</td>
<td>Single agent</td>
<td>Single agent</td>
</tr>
<tr>
<td>INBRX-105 single-agent dose escalation</td>
<td>INBRX-105 single-agent dose</td>
<td>INBRX-105 and pembrolizumab dose escalation</td>
</tr>
<tr>
<td>240 mg</td>
<td>400 mg</td>
<td>200 mg q3w</td>
</tr>
</tbody>
</table>

**Table 1. Key Inclusion/Exclusion Criteria**

<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
<th>Key Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced or metastatic, non-resectable solid tumors</td>
<td>Hematologic malignancies</td>
</tr>
<tr>
<td>Locally advanced or metastatic, non-resectable solid tumors</td>
<td>Primary CNS malignancy (e.g., glioblastoma)</td>
</tr>
<tr>
<td>History of PD-L1 or PD-L1 expression</td>
<td>History of significant CNS metastases</td>
</tr>
<tr>
<td>PD-L1-positive tumors</td>
<td>History of significant autoimmune disease</td>
</tr>
</tbody>
</table>

**Table 2. Endpoints**

- **Primary endpoint**:
  - Antitumor activity:
    - Disappearance of measurable disease (CR) or stable disease (SD) for 24 weeks after initiation of therapy.
- **Secondary endpoints**:
  - Safety and tolerability:
    - Frequency and severity of adverse events (AEs) and dose-limiting toxicities (DLTs)
  - Pharmacokinetics:
    - Serum concentrations of INBRX-105 and pembrolizumab
  - Biomarkers:
    - Tumor mutation burden (TMB)
    - Tumor proportion score (TPS)

**PLANNED ENROLLMENT**

- **Northwest Oncology**
- **Nebraska Cancer Center**
- **START Midwest**
- **St. Elizabeth’s Medical Center**
- **University of Nebraska Medical Center**
- **Mayo Clinic**
- **University of Minnesota Medical Center, Fairview**
- **Northwestern University Feinberg School of Medicine**
- **University of Washington**
- **City of Hope**
- **Yale Cancer Center**
- **Boston Medical Center**
- **Northeastern Oncology Associates-Alliance Cancer Center**
- **Virginia Cancer Specialists**
- **Northwell Health**
- **Carolinas Medical Center**
- **MD Anderson Cancer Center**
- **City of Hope**
- **University of Cincinnati**
- **UCF Cancer Center**
- **Cleveland Clinic**
- **Ludwig Institute, University of Melbourne**
- **Johns Hopkins Oncology Center**

**DISCLOSURES**

- **Authors’ conflicts of interest**:
  - All authors declare no conflicts of interest.
  - The study was supported by Inhibrx, Inc.

**REFERENCES**