A Phase 1 Dose-escalation and Cohort Expansion Study of Lirilumab (Anti-KIR; BMS-986015) Administered in Combination With Nivolumab (Anti-PD-1; BMS-936558; ONO-4538) in Patients With Advanced Refractory Solid Tumors

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Background

Programmed death-1 (PD-1) is an immune checkpoint receptor (Costello and Weiner 2010). Disruption of this pathway in antitumor immune responses is an emerging area of immunotherapy research. Blockade of PD-1 and PD-L1 signaling results in reactivation of T-cell-mediated tumor cell killing and expansion of tumor-reactive T cells (Figure 1) (Kamide et al. 2010). Costello and Weiner 2010).

Lirilumab is a fully human IgG4 PD-1 receptor-blocking monoclonal antibody that selectively prevents interaction with PD-L1, thereby blocking the downregulation of T-cell activation upon interaction with its ligands: KIR (inhibitory receptor) and the activating receptor HLA-C (self antigen) (Shp-2 = phosphatidylinositol 3-kinase catalytic subunit) (Figure 2) (Kamide et al. 2010). Blockade of PD-1 and PD-L1 results in reactivation of T-cell–mediated tumor cell killing and expansion of tumor-reactive T cells (Figure 1) (Kamide et al. 2010).

Study Sites

Memorial Sloan-Kettering Cancer Center, New York, New York
University of Chicago Medical Center, Chicago, Illinois
University of California San Francisco, San Francisco, California
Massachusetts General Hospital, Boston, Massachusetts
Memorial Sloan-Kettering Cancer Center, New York, New York
Earle A. Chiles Research Institute, Providence Cancer Center, Portland, Oregon

References

1. Nivolumab mechanism of action

Figure 2. Lirilumab mechanism of action

Figure 3. CA223-001 study design

Study Sites

- Patients with melanoma may be treatment naïve
- All patients must be scheduled for a series of conventional T cells
- Patients with adequate organ function
- Any other medical condition that, in the opinion of the investigator, may compromise the patient's ability to complete the study and follow-up; prior ipilimumab is allowed
- ECOG performance status of ≤1
- Blood specimens for pharmacokinetic analysis

Inclusion/Exclusion Criteria

- No new or prior major medical event
- Patients with measurable disease as defined by RECIST 1.1 criteria
- Patients must have failed at least one conventional T cell therapy

Table 1. Dose assignments during dose escalation

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Lirilumab (mg/kg)</th>
<th>Nivolumab (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0.3</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>12</td>
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<tr>
<td>4</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>120</td>
</tr>
</tbody>
</table>

Table 2. Tumor types eligible for cohort expansion

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th># of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>melanoma</td>
<td>96</td>
</tr>
<tr>
<td>non-small cell lung cancer</td>
<td>96</td>
</tr>
<tr>
<td>renal cell cancer</td>
<td>32</td>
</tr>
</tbody>
</table>

Study Design

- Nivolumab is a fully human IgG4 PD-1 receptor-blocking monoclonal antibody that selectively prevents interaction with PD-L1, thereby blocking the downregulation of T-cell activation upon interaction with its ligands: KIR (inhibitory receptor) and the activating receptor HLA-C (self antigen) (Shp-2 = phosphatidylinositol 3-kinase catalytic subunit) (Figure 2) (Kamide et al. 2010).
- Blockade of PD-1 and PD-L1 results in reactivation of T-cell–mediated tumor cell killing and expansion of tumor-reactive T cells (Figure 1) (Kamide et al. 2010).