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 Advanced Solid Tumors

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Background

Programmed-Death-1 (PD-1)

• PD-1 is an immune checkpoint receptor expressed by activated T cells1,2
• Downregulated T-cell activation upon interaction with its ligand(s): PD-L1 (PD-L1, B7-H1) and PD-L2 (PD-L2, B7-DC)
• PD-L1/L2 expressed within the tumor environment can engage the PD-1 receptor on activated tumor-infiltrating lymphocytes, suppressing T-cell-mediated immune response and protecting the tumor from T-cell attack3,4
• PD-1 expression on the surface of tumor cells is associated with poor prognosis in multiple tumor types although some studies have also reported a positive correlation between PD-L1 expression and improved overall survival (OS)5,6

Nivolumab

• Nivolumab is a fully human IgG4 PD-1 immune checkpoint inhibitor antibody that selectively prevents interaction of PD-1 with PD-L1 and PD-L2, thereby blocking the ability of PD-1 to suppress antitumor function (Figure 1)1
• Blocks with high affinity to PD-1 receptors on T cells, disrupting negative signaling triggered by PD-L1/PD-L2 and restoring T-cell antitumor function1,2
• Antibody-dependent cell-mediated cytotoxicity (ADCC) is undetectable in model systems, consistent with IgG4 Fc-domain7
• Pharmacokinetics are linear with a dose-proportional increase in Cmax and AUC0–t in the range of 0.1–1 mg/kg

• Nivolumab showed encouraging antitumor activity and a manageable adverse event profile in patients with advanced non-small cell lung cancer, melanoma, colorectal cancer, prostate cancer, and renal cell carcinoma in a phase 1 study5,6

Killer Cell Immunoglobulin-Like Receptors

• Natural killer (NK) cells play an important role in the ability of the innate immune system to fight viral infections and cancer8,9
• Inhibitory killer immunoglobulin-like receptors (KIRs) are receptors expressed on NK cells
• Inhibitory KIR signaling results in suppression of normal NK cell activation – KIRs are also expressed on NK T cells and a small subset of conventional T cells
• Blockade of inhibitory KIR signaling may thus allow activation of NK cells and some antitumor T cells, improving the antitumor immune response

• Acute myeloid leukemia patients transplanted with KIR-mismatched donor NK cells (KIR on donor NK cells do not interact with host human leukocyte antigen) have lower relapse rates compared with their counterparts (3% vs 47%; P = 0.01)10

Nivolumab and Lirilumab

• Lirilumab is a fully human KIR-blocking antibody that binds specifically, and with high affinity, to a subset of KIRs and potentiates innate immunity (Figure 2)2
• Lirilumab showed only modest side effects (mostly grade 1 or 2) in an ongoing phase 1 monotherapy trial (EudraCT# 2009-011526-33)
• Preclinical studies of mice treated with murine-specific anti-KIR and anti-PD-1 demonstrated increased latency of tumor progression and increased regression of established tumors in mice treated with both antibodies (data on file)
• Tandem activation of innate and adaptive immune responses may be more effective compared with activation of one or the other

Study Rationale

• There is an urgent need for new treatments to improve clinical outcomes and quality of life in patients with advanced solid tumors who currently have poor prognosis and limited treatment options
• We hypothesized that simultaneous KIR and PD-1 blockade would enhance innate and adaptive immunity, resulting in greater clinical activity compared with either agent alone in patients with advanced cancer
• Study CA223-001 (NCT01714738) was initiated to assess lirilumab in combination with nivolumab in patients with advanced solid tumors

Study Objectives

Primary Objective

• Assess the safety, tolerability, dose-limiting toxicities, and maximum tolerated dose (MTD) of lirilumab given in combination with nivolumab in patients with advanced (metastatic and/or unresectable) solid tumors

Secondary Objectives

• Assess preliminary antitumor activity
• Characterize pharmacokinetics
• Monitor immunogenicity
• Assess the pharmacodynamic effect in tumor tissue on tumor-infiltrating lymphocytes in patients undergoing pre-treatment and on-treatment tumor biopsies

Exploratory Objective

• Assess innate and adaptive immune responses in peripheral blood and/or tumor specimens and association with clinical outcome

Inclusion/Exclusion Criteria

Table 2. Key inclusion criteria

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<table>
<thead>
<tr>
<th>Criteria</th>
<th>Value</th>
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<tbody>
<tr>
<td>Men and women aged ≥18 years</td>
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<td>Presence of ≥1 lesion with measurable disease as defined by RECIST 1.1 criteria</td>
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<tr>
<td>Histologically/histopathologically confirmed advanced (metastatic and/or unresectable) solid malignancy</td>
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<td>Dose escalation: all solid tumors except for primary CNS tumors</td>
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<td>Cohort expansion: 1 of 5 select tumor types</td>
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<td>Progressed or intolerant to ≥1 standard treatment regimens</td>
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<td>Patients must consent to allow the acquisition of existing formalin-fixed paraffin-embedded tissue</td>
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<td>ECOG = Eastern Cooperative Oncology Group</td>
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References


Table 3. Key exclusion criteria

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<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>Known or suspected uncontrolled CNS metastases or CNS as the only site of disease</td>
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<td>Concomitant active malignancy within 2 years</td>
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<td>Includes adequately treated basal cell or squamous cell skin cancer, localized prostate cancer, carcinoma in situ of the cervix, or in situ ductal or lobular carcinoma of the breast</td>
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<td>Active or history of autoimmune disease</td>
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<td>Uncontrolled or significant cardiovascular disease</td>
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<tr>
<td>Prior therapy with an anti-KIR, anti-PD-1, anti-PD-L1, anti-CTLA4 or anti-CD40 antibody</td>
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<td>Prior vaccination is allowed</td>
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<tr>
<td>Participation in any prior clinical study with nivolumab or lirilumab (including patients in comparator arms) in which OS is listed as the primary or coprimary endpoint and that has completed analysis</td>
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<tr>
<td>Any antitumor therapy within 4 weeks before the first dose of study drug administration</td>
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<tr>
<td>Positive for hepatitis C or B or HX of liver or chronic hepatitis (other than resolved hepatitis A)</td>
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Table 4. Study sites

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<table>
<thead>
<tr>
<th>Study sites</th>
<th>Location</th>
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<tbody>
<tr>
<td>Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland</td>
<td>Beth Israel Deaconess Medical Center, Boston, Massachusetts</td>
</tr>
<tr>
<td>Dana-Farber Cancer Institute, Boston, Massachusetts</td>
<td>Massachusetts General Hospital, Boston, Massachusetts</td>
</tr>
<tr>
<td>University of Chicago Medical Center, Chicago, Illinois</td>
<td>Memorial Sloan-Kettering Cancer Center, New York, New York</td>
</tr>
<tr>
<td>Earle A. Chiles Research Institute, Providence Cancer Center, Portland, Oregon</td>
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Acknowledgments

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