TPS3110

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

Rachel E. Sanborn,[1] William H. Sharfman,[2] Neil H. Segal,[3] F. Stephen Hodi,[4] Jedd D. Wolchok,[3] Walter J. Urba,[1] Bernard A. Fox,[1] Suzanne L. Topalian,[2] Drew M. Pardoll,[2] Kelly Covello,[5]* Dan McDonald,[5] Su Young Kim,[5] Ashok Gupta,[5] Jon M. Wigginton,[5] Thomas F. Gajewski[6]

[1]Earle A. Chiles Research Institute and Providence Cancer Center, Portland, OR, USA; [2]Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA; [3]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Bristol-Myers Squibb, Princeton, NJ, USA; [6]The University of Chicago Comprehensive Cancer Center, Chicago, IL, USA; *Former employee of Bristol-Myers Squibb

Email: rachel.sanborn@providence.org

Background

Programmed Death-1

- Programmed death-1 (PD-1) is an immune checkpoint receptor expressed by activated T cells[1,2]
  - Downregulates T-cell activation upon interaction with its ligands: PD-ligand 1 (PD-L1; B7-H1) and PD-ligand 2 (PD-L2; B7-DC)[1]
  - PD-L1/L2 expressed within the tumor environment can engage the PD-1 receptor on activated tumor-infiltrating lymphocytes and impede their effector functions, protecting the tumor from T-cell attack[2]

Nivolumab

- Nivolumab is a fully human IgG4 PD-1 receptor-blocking monoclonal antibody that selectively prevents interaction with PD-L1, thereby inhibiting the downregulation of antitumor T-cell function (Figure 1)[3]
  - Binds with high affinity to PD-1 receptors on T cells, disrupting negative signaling triggered by PD-L1 and restoring T-cell antitumor function[4,5]
  - Antibody-dependent cell-mediated cytotoxicity (ADCC) undetectable in model systems, consistent with IgG4 Fc-domain[6]
  - Pharmacokinetics linear with a dose-proportional increase in C_{max} and $AUC_{(0\text{–}14\ days)}$ in the dose range of 0.1–10 mg/kg[7]
- Nivolumab showed encouraging antitumor activity in patients with advanced solid tumors in a phase 1 study[6,8-10]
  - The adverse event profile for nivolumab was acceptable, manageable, and consistent with the mechanism of action

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 cancer[11]
- Inhibitory killer cell immunoglobulin-like receptors (KIRs) are receptors expressed by NK cells[12]
  - KIR signaling results in suppression of normal NK cell activation
  - KIR are also expressed on natural killer T cells and a small subset of conventional T cells[13]
- Blockade of KIR signaling may thus allow activation of NK cells and some antitumor T cells, improving the antitumor immune response
- 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)
  - Lirilumab currently is being investigated in an ongoing phase 1 monotherapy trial (EudraCT# 2009-011526-33)

Preclinical Data and Lirilumab

- Acute myeloid leukemia patients transplanted with KIR-mismatched (KIR on donor NK cells do not interact with host human leukocyte antigen) donor NK cells have lower relapse rates compared with their counterparts (3% vs 47%; $P < .01$)[14]
- Preclinical studies of mice treated with murine-specific anti-KIR and anti-PD-1 demonstrate 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 than activation of one or the other

Study Rationale

- We hypothesized that coordinate modulation of innate and adaptive immunity with KIR and PD-1–blocking antibodies, respectively, could achieve more favorable biologic and clinical activity than either agent alone
- Study CA223-001 (NCT01714739) was initiated to assess lirilumab in combination with nivolumab in patients with advanced solid tumors
  - This is the first collaborative clinical trial being conducted by the International Immuno-Oncology Network (II-ON), www.bmsimmunooncology.org

Study Objectives

Primary Objective

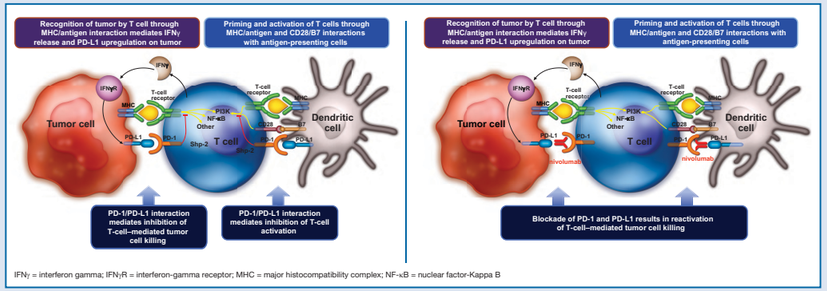
- Assess the safety, tolerability, dose-limiting toxicities, and maximum tolerated dose (MTD) of lirilumab given in combination with nivolumab in patients with advanced (metastatic and/or unresectable) solid tumors

Secondary Objectives

- Assess preliminary antitumor activity
- Characterize pharmacokinetics
- Monitor immunogenicity
- Assess the pharmacodynamic effect in tumor tissue on tumor-infiltrating lymphocyte subsets from melanoma patients treated with the combination

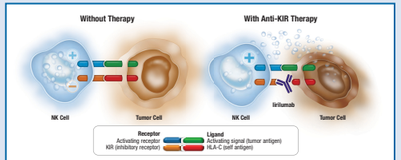
Study Design

- Open-label, phase 1 study
- Approximately 150 patients with various advanced refractory solid tumors
- The study will be conducted in 2 parts
  - Dose escalation (up to 48 patients)
    - Patients with any tumor type (with the exception of primary central nervous system [CNS] tumors) are eligible to enroll
    - A 3 + 3 + 3 design will be used to assess the safety of lirilumab in combination with nivolumab
    - Dosages during dose escalation are shown in Table 1
  - Cohort expansion (~96 patients)
    - Once the safety profile of all doses tested has been characterized and the MTD of combined administration of lirilumab and nivolumab has been defined, the cohort expansion will be initiated at the MTD, the maximum administered dose (MAD), or an alternate dose
    - Enrollment to the 6 expansion cohorts will be restricted to the tumor types listed in Table 2
- Patients will complete up to 4 study periods (Figure 3)
  - Screening (≤28 days)
  - Treatment (≤2 years of study therapy)
  - Clinical follow-up (100 days)
  - Survival follow-up (≤3 years after the first dose of study drug)
- The total time on study for any individual patient will not exceed 3.1 years



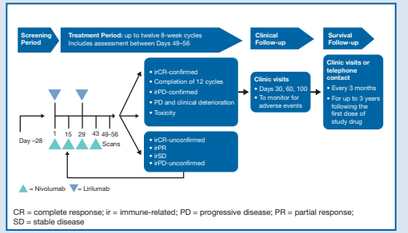
IFNγ = interferon gamma; IFNγR = interferon-gamma receptor; MHC = major histocompatibility complex; NF-κB = nuclear factor-Kappa B

Figure 1. Nivolumab mechanism of action



- NK cell activation is determined by the balance of activating (positive) and inhibitory (negative) receptor stimulation
- Tumor cells are able to evade innate immunity through the interaction of KIR with HLA-C
- By blocking this interaction, lirilumab facilitates the activation of NK cells and subsequent killing of the tumor cell

Figure 2. Lirilumab mechanism of action



CR = complete response; ir = immune-related; PD = progressive disease; PR = partial response; SD = stable disease

Figure 3. CA223-001 study design

Table 1. Dosages during dose escalation[a]

Dose Level Number	Total Number of Patients	Lirilumab, mg/kg (IV every 4 weeks)	Nivolumab, mg/kg (IV every 2 weeks)
1	3–9	0.1	3
2	3–9	0.3	3
3	3–9	1	3
4	3–9	3	3
Total	12–36		

[a]Additional patients may be added to each dose level after completion of the dose-escalation period of the study for a total of up to 12 patients per dose level
IV = intravenously

Table 2. Tumor types eligible for cohort expansion

Tumor Type	Patients/Cohort
NSCLC – squamous histology	16
NSCLC – non-squamous histology	16
RCC with a clear cell component	16
Melanoma	16
Colorectal cancer	16
Serous ovarian carcinoma	16
Total	**96**

NSCLC = non-small cell lung cancer; RCC = renal cell cancer

Study Design (Cont.)

- Adverse events will be graded according to the Common Terminology Criteria for Adverse Events, version 4.03
  - To be assessed continuously during the study and for 100 days after the last treatment
- Response will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines and by immune-related RECIST guidelines
  - Assessment will be performed at baseline and every 8 weeks until confirmed disease progression, completion of follow-up, or patient withdrawal

Inclusion/Exclusion Criteria

Table 3. Key inclusion criteria

Men and women aged ≥18 years
Histologically/cytologically confirmed advanced (metastatic and/or unresectable) solid malignancy • Dose escalation: all solid tumors except for primary CNS tumors • Cohort expansion: 1 of the 6 tumor types
Progressed or intolerant to ≥1 standard treatment regimen • Patients with melanoma may be treatment naïve
For cohort expansion, patients must have ≤5 prior treatment regimens
Patients must consent to allow the acquisition of existing formalin-fixed paraffin-embedded tissue • 10 patients in the melanoma cohort will be required to undergo pretreatment and ontreatment biopsies
Presence of ≥1 lesion with measurable disease as defined by RECIST 1.1 criteria
ECOG performance status of ≤1
Life expectancy of ≥12 weeks
Adequate organ function

ECOG = Eastern Cooperative Oncology Group

Table 4. Key exclusion criteria

Known or suspected uncontrolled CNS metastases or CNS as the only site of disease
Concomitant active malignancy within 2 years Excludes 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
Active or history of autoimmune disease
Uncontrolled or significant cardiovascular disease
Prior therapy with an anti-KIR, anti-PD-1, anti-PD-L1, anti-CD137 or anti-OX40 antibody • Prior ipilimumab is allowed
Participation in any prior clinical study with ipilimumab or nivolumab (including patients in comparator arms) in which overall survival is listed as the primary or coprimary endpoint and that has not completed analysis
Any anticancer therapy within 4 weeks before the first dose of study drug administration
Positive for hepatitis C or B or HIV, or history of chronic hepatitis (other than resolved hepatitis A)

Study Sites

- 7 study sites in the United States are involved in CA223-001 (Table 5)

Table 5. Study sites

Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland
Beth Israel Deaconess Medical Center, Boston, Massachusetts
Dana-Farber Cancer Institute, Boston, Massachusetts
Massachusetts General Hospital, Boston, Massachusetts
University of Chicago Medical Center, Chicago, Illinois
Memorial Sloan-Kettering Cancer Center, New York, New York
Earle A. Chiles Research Institute, Providence Cancer Center, Portland, Oregon

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