TPS3106

A Phase I Study of Lirilumab (BMS-986015), an Anti-KIR Monoclonal Antibody, Administered with Ipilimumab, an Anti-CTLA-4 Monoclonal Antibody, in Patients with Select Advanced Solid Tumors

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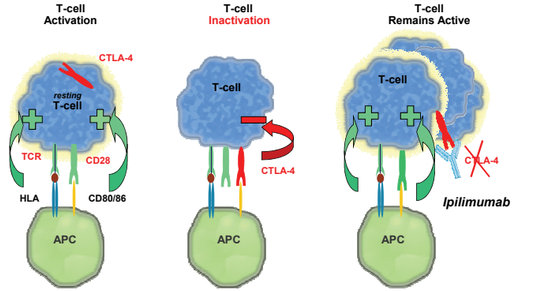
Background

Ipilimumab

- Fully human, IgG_1 monoclonal antibody which blocks CTLA-4[1]
  - Cytotoxic T-lymphocyte antigen-4 (CTLA-4) down-regulates pathways of T-cell activation[2]
- Augments antitumor T-cell responses[1,3]
- Approved for treatment of unresectable or metastatic melanoma
  - First therapy to improve OS in either previously treated or treatment-naive patients with metastatic melanoma[4,5]

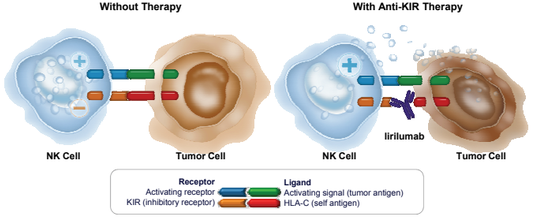
Figure 1. Mechanism of Action for ipilimumab



Killer Cell Immunoglobulin-like Receptors (KIR)

- NK cells play an important role in the ability of the innate immune system to fight viral infections and cancer[6]
- Inhibitory killer cell immunoglobulin-like receptors (KIR) are receptors expressed by natural killer (NK) cells[7]
  - signaling results in suppression of normal NK-cell activation
  - KIR are also expressed on natural killer T (NKT) cells and a small subset of conventional T cells[8]
- 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 is currently being investigated in an ongoing Phase 1 monotherapy trial (EudraCT# 2009-011526-33)

Figure 2. Mechanism of Action for Lirilumab

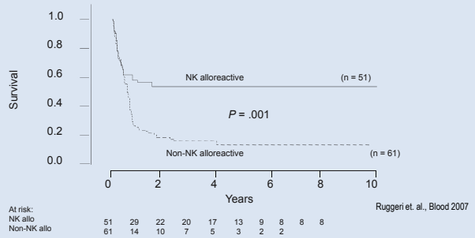


HLA = human leukocyte antigen; NK = natural killer cell

- 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 apoptosis of the tumor cell

Preclinical Data and Lirilumab

- AML patients transplanted with KIR-mismatched donor NK cells (KIR on donor NK cells do not interact with host HLA) have lower relapse rates compared to their counterparts (3% versus 47%; P<0.01)[9]



- Preclinical studies with murine-specific anti-KIR and anti-CTLA-4 antibodies in a acute leukemia model showed improved survival in mice given both antibodies together compared to either agent alone[10]

Study Rationale

- We hypothesized that coordinate modulation of innate and adaptive immunity with anti-KIR and anti-CTLA4 antibodies could recapitulate the biology seen in KIR mismatch post-allogeneic transplant patients. Combined administration of lirilumab and ipilimumab could, therefore, achieve more favorable clinical activity than either agent alone in patients with select advanced tumors advanced tumors.
- Here, we describe a Phase 1, multicenter, open label study of lirilumab given in combination with ipilimumab in patients with select advanced (metastatic or unresectable) solid tumors. (CA223-002; clinicaltrials.gov identifier: NCT01750580)

Study Objectives

Primary objective

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

Secondary objectives

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

Study Design

- This open-label, Phase 1 study will enroll approximately 120 patients with any of the following advanced solid tumors;
  - Non small cell lung cancer
  - Melanoma
  - Castrate resistant prostate cancer
- The study will be conducted in 2 parts:
  - Dose escalation (up to 60 patients)
  - Cohort expansion (approximately 60 patients)
- Dose escalation
  - A 3+3+3 design will be used to assess the safety of lirilumab in combination with ipilimumab
  - Dosages during dose escalation are shown in Table 2

Table 2. Dosages during dose escalation[a]

Dose Level Number	Total Patients	Lirilumab, mg/kg	Ipilimumab, mg/kg
1	3–9	0.1	3
2	3–9	0.3	3
3	3–9	1	3
4	3–9	3	3
5	3-9	3	10
Total	15–45		

[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.

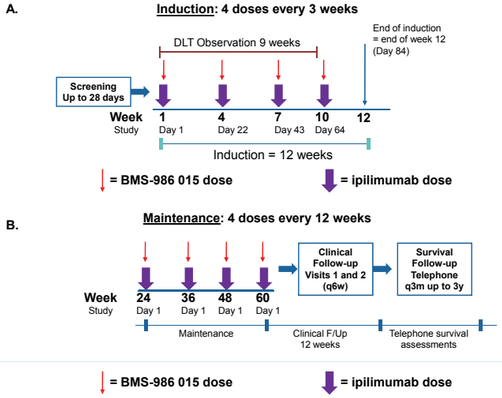
- Cohort expansion
  - Once the safety profile of all doses tested has been characterized and the MTD of combined administration of lirilumab and ipilimumab has been defined, the cohort expansion will be initiated at the MTD, the maximum administered dose (MAD), or an alternate dose
  - Treatment doses in the cohort expansion groups will not exceed the MAD
  - Three expansion cohorts will be enrolled as outlined in Table 3

Table 3. Tumor types eligible for cohort expansion

	Total Patients
Tumor Type	**Total Patients**
NSCLC – squamous histology	10
NSCLC – non-squamous histology	10
Castration Resistant Prostate Cancer	20
Melanoma	20
Total	60

NSCLC = non–small-cell lung cancer

Figure 3. Dosing Schedule



*Each dose of study therapy will be given on Day 1 of each week specified.

Study Assessments

- Adverse events (AEs) will be graded according to the Common Terminology Criteria for Adverse Events, version 4.0
  - AEs will be assessed continuously during the study and for 90 days after the last treatment
- Patients will be assessed for response according to the RECIST 1.1 guidelines, as well as by immune-related RECIST guidelines
  - Disease assessment will be performed at baseline and every 6-12 weeks until confirmed disease progression, at the completion of follow-up, or until patients withdraw from the study

Key Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Men and women, ages >18 years	Known or suspected CNS metastases or CNS as the only site of disease
Histologic confirmation of one of the following advanced (metastatic or unresectable) solid tumors: • non small cell lung cancer • castrate resistant prostate cancer • melanoma	Prior therapy with anti-CTLA4 antibody or anti-KIR antibody
	Prior malignancy • 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
Progressed or intolerant to a minimum of ONE and a maximum of FIVE regiments. Patients with melanoma may be treatment naïve.	Active or history of autoimmune disease
	Uncontrolled or significant cardiovascular disease
All patients must have archival tumor tissue available for correlative biomarker studies.	Prior organ allograft or allogeneic bone marrow transplantation
Presence of at least 1 lesion with measurable disease as defined by RECIST v1.1 criteria	Prior therapy with any immune cell modulating antibody (such as anti-CD137 or anti-OX40). Of note, prior therapy with anti-PD-1 or anti-PD-L1 is permitted
ECOG status of 0 or 1	Any anti-cancer therapy within 4 weeks prior to the first dose of study drug administration
Life expectancy of ≥12 weeks	Positive for hepatitis C or B or HIV
Adequate organ function	

ECOG = Eastern Cooperative Oncology Group; PD-1 = programmed death-1; RECIST = Response Evaluation Criteria In Solid Tumors

Study Sites

Site	Location
Dana Farber Cancer Institute	Boston, Massachusetts
Beth Israel Deaconess Medical Center	Boston, Massachusetts
Massachusetts General Hospital	Boston, Massachusetts
Ohio State University	Columbus, Ohio
Masonic Cancer Center, University of Minnesota	Minneapolis, Minnesota
Sarah Cannon Research Institute	Nashville, Tennessee
Memorial Sloan Kettering Cancer Center	New York, New York
Moffitt Cancer Center	Tampa, Florida

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