ILCA

International Liver Cancer Association

A Phase 1/2 Dose Escalation and Expansion Study to Investigate the Safety Pharmacokinetics and Antitumor Activity of the Anti-PD-1 Monoclonal Antibody BGB-A317 in Subjects With Advanced Solid Tumors

J Desai[1], C-J Yen[2], J Peguero[3], M Hou[4], C Lin[5], J Lee[6], M Brown[7], K Rau[8], C Lu[9], Y Bang[10], J Hou[11] Y Kang[12]

[1]Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [2]Institute of Hematology and Oncology, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan; [3]Oncology Consultants, Houston, TX, USA; [4]Division of Hematology and Oncology, Chang Gung Memorial Hospital, Linkou, Taoyuan County, Taiwan; [5]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; [6]College of Medicine, Seoul National University Bundang Hospital, Seongnam-si, Republic of Korea; [7]Department of Oncology, Royal Adelaide Hospital, Adelaide, Austrailia; [8]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; [9]Division of Hematology and Oncology, Chang Gung Memorial Hospital, Chiayi County, Taiwan; [10]Clinical Trials Center, Seoul National University Hospital, Seoul, Republic of Korea; [12]Department of Oncology, Asan Medical Center, Seoul, Republic of Korea

P-180

15-17 September 2017 - Seoul, South Korea

Increased PD-1/PD-L1 Expression Occurs in Several Solid Tumor Types

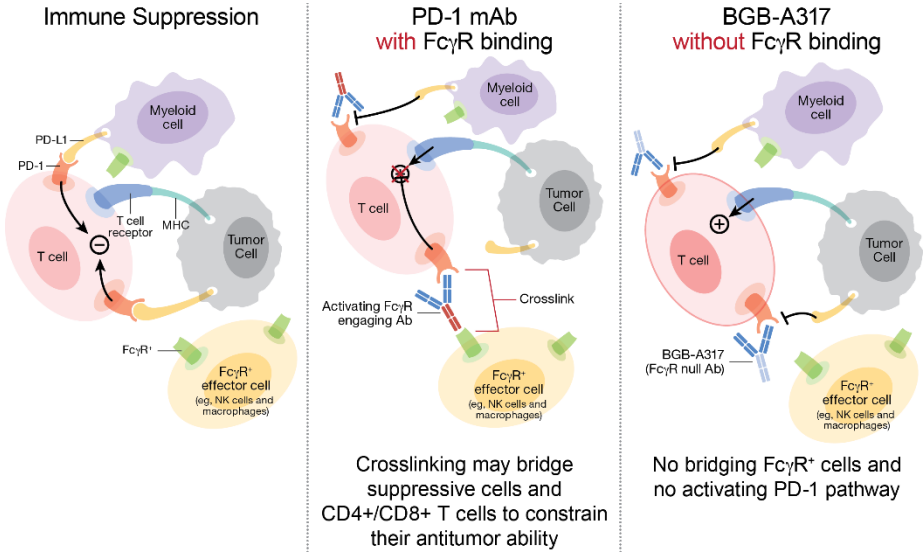
- Programmed cell death-1 (PD-1), the immune checkpoint inhibitory receptor, plays a critical role in immune modulation of tumor progression via regulation of key inhibitory signaling by ligand-bound T-lymphocytes[1]
- Expression of PD-1 is markedly increased in tumor-infiltrating lymphocytes and expression of the PD-1 ligand, PD-L1, is markedly upregulated in tumor cells and tumor-associated immune cells in the presence of cytokines (eg, interferons) in the tumor microenvironment[2]
- Increased expression of PD-1 and PD-L1 is observed in several solid tumor types including melanoma, squamous cell carcinoma, non-small cell lung cancer, head and neck squamous cell carcinoma, triple-negative breast cancer, renal cell carcinoma, hepatocellular carcinoma (HCC), bladder cancer, and ovarian cancer[3-5]

1. Bardhan K, Anagnostou T, Boussiotis VA. The PD1:PD-L1/2 pathway from discovery to clinical implementation. *Front Immunol*. 2016;7:550. **2.** Momtaz P, Postow MA. Immunologic checkpoints in cancer therapy: focus on the programmed death-1 (PD-1) receptor pathway. *Pharmgenomics Pers Med*. 2014;7:357-365. **3.** Calderaro J, Rousseau B, Amaddeo G, et al. Programmed death ligand 1 expression in hepatocellular carcinoma: relationship with clinical and pathological features. *Hepatology.* 2016;64(6):2038-2046. **4.** Hsu PN, Yang TC, Kao JT, et al. Increased PD-1 and decreased CD28 expression in chronic hepatitis B patients with advanced hepatocellular carcinoma. *Liver Int*. 2010;30(9):1379-1386. **5.** Shi F, Shi M, Zeng Z, et al. PD-1 and PD-L1 upregulation promotes CD8(+) T-cell apoptosis and postoperative recurrence in hepatocellular carcinoma patients. *Int J Cancer.* 2011;128(4):887-896.

BGB-A317 is a Humanized IgG4 Monoclonal PD-1 Antibody Engineered to Minimize FcγR Binding

- Recent studies have demonstrated the antitumor activity of anti-PD-1 monoclonal antibodies across a wide range of solid tumor types[1-3]
- BGB-A317 was specifically engineered to minimize FcγR binding on macrophages to abrogate antibody-dependent phagocytosis, a potential mechanism of T-cell clearance[4]
- A Phase 1/2 open-label, dose escalation/ expansion study (NCT02407990) was initiated to investigate the safety, pharmacokinetic (PK) profile, and antitumor activity of BGB-A317 in patients with advanced solid tumors

Figure 1: Mechanism of Action of BGB-A317



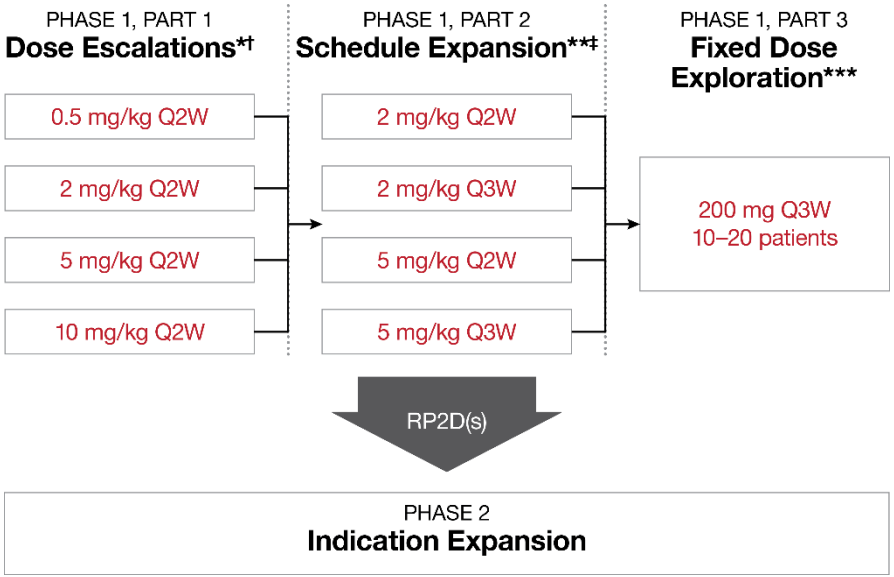
Adapted from Dahan R, et al. *Cancer Cell.* 2015;28:285-295.
Abbreviations: Ab, antibody; mAb, monoclonal antibody; NK, natural killer; PD-1, programmed cell death-1; PD-L1, programmed cell death-1 ligand.

1. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol*. 2010;28(19):3167-3175. **2.** Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454. 3. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med*. 2013;369(2):134-144. **4.** Dai X, Jayapal M, Tay HK, et al. Differential signal transduction, membrane trafficking, and immune effector functions mediated by FcgammaRI versus FcgammaRIIa. *Blood*. 2009;114(2):318-327.

Methods: A first-in-human, Dose-escalation/dose-expansion Study of BGB-A317 in Patients with Advanced Solid Tumors

- This ongoing, first-in-human, dose-escalation/ dose-expansion study of BGB-A317 (NCT02407990) in patients with advanced solid tumors is being conducted in two phases with multiple parts
  - Phase 1, Part 1 was a dose-escalation/dose-finding component that followed a modified 3+3 design to establish the MTD
  - The Phase 1, Part 2 component evaluated the safety, tolerability, and PK profile of two BGB-A317 dosing schedules (Q2W versus Q3W)
  - Phase 1, Part 3 evaluated the safety, tolerability, and PK profile of a fixed dose of BGB-A317

Figure 2: Study Design



*Up to 6 patients per cohort; †Intermediate doses or less frequent schedules may be explored; **In select tumors for RP2D determination and preliminary differentiation; ‡Other doses or schedules may be expanded; ***In select tumors at flat doses that do not exceed the MTD.

MTD, maximum tolerated dose; PK, pharmacokinetic; Q2W, every 2 weeks; Q3W, every 3 weeks; RP2D, recommended phase 2 dose.

Methods: Phase 2 Dose-expansion Component to Assess the Safety/tolerability and Antitumor Activity of BGB-A317

- The Phase 2 dose-expansion component will investigate the safety/tolerability and antitumor activity of BGB-A317 in patients with selected tumor types
- Patients will be enrolled from approximately 30 centers worldwide
- As of May 2017, Phase 1 of the study has been completed with a total of 116 enrolled patients; Phase 2 is ongoing and will enroll approximately 330 patients into 1 of 9 expansion cohorts

Objectives

- The primary objectives of Phase 1 were to assess the safety and tolerability of BGB-A317 in patients with advanced or refractory solid tumors
  - Secondary objectives of Phase 1 included the characterization of the BGB-A317 PK profile as well as determine MTD and RP2D for BGB-A317, assess BGB-A317 preliminary antitumor activity, and host immunogenicity to BGB-A317
- The primary objective of Phase 2 was to assess the antitumor activity of BGB-A317 in select tumor types
  - Secondary objectives of Phase 2 were to further characterize the safety and tolerability, and the PK profile of BGB-317

MTD, maximum tolerated dose; PK, pharmacokinetic; RP2D, recommended phase 2 dose.

Methods: Patient Population

- Adult patients (aged ≥18 years) with a life expectancy of ≥12 weeks who have histologically/cytologically confirmed advanced or metastatic solid tumors for which no effective standard therapy is available
- Eastern Cooperative Oncology Group performance status of ≥1
- Patients must have adequate bone marrow, liver, and renal function:
  - Absolute neutrophil count ≥1500/µL; platelets ≥100,000/µL (or ≥75,000/µL for patients with HCC); hemoglobin level ≥9 g/dL or ≥5.6 mmol/L; and International normalized ratio or prothrombin time ≤1.5 × upper limit of normal (ULN); activated partial thromboplastin time ≤1.5 × ULN
  - Total serum bilirubin ≤1.5 × ULN (or <4 × ULN for patients with Gilbert's syndrome); aspartate aminotransferase and alanine aminotransferase ≤2.5 × ULN (or ≤5 × ULN for patients with liver metastases or HCC)
  - Serum creatinine ≤1.5 × ULN
- Patients were excluded if they had a history of severe hypersensitivity reactions to other monoclonal antibodies; prior PD-1- or PD-L1-targeted therapies; history of or active autoimmune disease; active hepatitis B or hepatitis C infection (except for patients with HCC in Phase 1 or 2); requirement for systemic therapy with corticosteroids or other immunosuppressive agents within 14 days of study drug administration; and receipt of vaccinations against infectious diseases within 4 weeks of study therapy initiation or intended vaccinations within 60 days after the last dose of the study drug

Methods: Indication-expansion Phase

- The indication-expansion component of this study will investigate BGB-A317 in patients with selected tumor types; all patients in all dose-expansion cohorts must have measurable disease per RECIST v1.1 criteria

Treatment Arm	Tumor Type*	Estimated Sample Size
Cohort 1	Non-small cell lung cancer, patients with documented epidermal growth factor receptor mutation or anaplastic lymphoma kinase rearrangement will be excluded	~50
Cohort 2	Ovarian cancer	~20
Cohort 3	Gastric cancer	~50
Cohort 4	Hepatocellular carcinoma (Barcelona Clinic Liver Cancer stage C; stage B not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach, and Child-Pugh A, without encephalopathy of any grade)	~50
Cohort 5	Head and neck squamous cell carcinoma	~20
Cohort 6	Esophageal carcinoma	~50
Cohort 7	Triple-negative breast cancer	~20
Cohort 8	Cholangiocarcinoma	~20
Cohort 9	Renal cell carcinoma, bladder cancer, Merkel-cell carcinoma, sarcoma, gastrointestinal stromal tumor, cutaneous squamous cell carcinoma, any other solid tumors with a high level of microsatellite instability, or DNA mismatch repair (eg, colorectal cancer or pancreatic cancer)	~50

Treatment (1)

- Four dose levels were evaluated in the dose-escalation component (Part 1):
  - **Dose level 1:** 0.5 mg/kg IV BGB-A317 Q2W
  - **Dose level 2:** 2 mg/kg IV BGB-A317 Q2W
  - **Dose level 3:** 5 mg/kg IV BGB-A317 Q2W
  - **Dose level 4:** 10 mg/kg IV BGB-A317 Q2W
- Dose escalation followed a 3+3 design for a maximum of 6 patients per cohort
- Patients received ≤4 28-day treatment cycles
- If none of the first 3 evaluable patients enrolled in a given cohort experience a DLT by the end of Cycle 1, dose escalation may proceed
  - If 1 out of 6 patients experiences a DLT by the end of Cycle 1, escalation will proceed to the next higher dose level
  - No additional patients will be treated at a given dose level if ≥2 patients in a cohort develop a DLT in Cycle 1

DLT, dose limiting toxicity; Q2W, every 2 weeks.

Treatment (2)

- A DLT was defined as a toxicity or AE occurring in the first 28-day cycle that meets one of the following criteria:
  - ***Non-hematologic:***
    - Grade 5 AEs
    - Grade 3 non-hematologic AE*
    - Grade 3 tumor flare (local pain, irritation, rash at sites of known/suspected tumor) of >7-day duration
    - Immune-related AEs Grade ≥3
    - Grade 4 laboratory abnormalities irrespective of duration
    - Grade 2 opthalmologic toxicities
  - ***Hematologic***
    - Grade 3 neutropenic infection, Grade 4 neutropenia lasting >7 days, or febrile neutropenia
    - Grade ≥3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia
    - Grade 4 anemia
- ***Schedule Expansion (Part 2):*** Evaluated IV BGB-A317 2 or 5 mg/kg administered on a Q2W or Q3W schedule
- ***Fixed-Dose Exploration (Part 3):*** Patients received a fixed dose 200 mg dose of BGB-A317 administered IV Q3W
- ***Phase 2:*** In the indication-expansion phase, patients will receive BGB-A317 dosed either at 5mg/kg or 200 mg IV Q3W in 21-day cycles until disease progression, intolerable toxicity, or discontinuation/withdrawal

*with the following exceptions: Laboratory abnormalities, diarrhea, nausea and vomiting, and asymptomatic biochemical abnormalities that improve to grade ≤2 within 3 days with supportive care . AE, adverse event; DLT, dose limiting toxicity; IV, intravenous; Q2W, every 2 weeks; Q3W, every 3 weeks.

Study Assessments and Statistical Analyses

- Safety and tolerability will be assessed by monitoring AEs (NCI-CTCAE v4.03 grade and severity) and by evaluating results from physical examinations, ophthalmologic examinations, electrocardiograms, and laboratory investigations
  - MTD and RP2D were determined based on safety, tolerability, PK parameters, preliminary efficacy and other available data
- Immunogenic response to BGB-A317 will be evaluated based on the presence of anti-drug antibody
- PK parameters include, but are not limited to:
  - Area under the concentration-time curve from 0–14 days ($AUC_{0\text{-}14}$ days), maximum observed plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), lowest observed plasma concentration (C_{trough}), half-life ($t_{½}$), clearance (CL), and volume of distribution (V_d)
- Antitumor effects will be assessed by RECIST v1.1 criteria, and by additional tumor-specific criteria for prostate cancer, ovarian cancer, and glioblastomas, as required
- Trial data will be summarized using descriptive statistics
  - Continuous variables: number of non-missing observations, mean, standard deviation, median, minimum, and maximum
  - Categorical variables: frequencies and percentages
  - Time-to-event variables: number of non-missing observations, median, minimum, and maximum; Kaplan–Meier event rates may also be provided (if applicable) for specific time-to-event variables

Acknowledgements: The authors wish to acknowledge the investigative center study staff and study patients. BeiGene, Ltd., provided financial support for this presentation, including writing and editorial assistance by SuccinctChoice Medical Communications Chicago, IL.

AE, adverse events; MTD, maximum tolerated dose; PK, pharmacokinetic; RP2D, recommended phase 2 dose.