A PHASE 1 STUDY OF THE ANTI-PD-1 MONOCLONAL ANTIBODY TISLELIZUMAB (BGB-A317) IN COMBINATION WITH THE PARP INHIBITOR PAMIPARIB (BGB-290) IN ADVANCED SOLID TUMORS

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INTRODUCTION

- Several reports describe a direct link between DNA damage and the upregulation of ligands that activate natural killer (NK) and T-cell mediated immune responses
- Upregulation of tumor associated antigens with PARP inhibitors may improve the anti-tumor activity of checkpoint inhibitors
- Tislelizumab (BGB-A317), a humanized IgG4 variant monoclonal antibody engineered to have minimal Fc gamma receptor binding, targets the programmed cell death-1 (PD-1) receptor and is being developed for the treatment of solid and hematologic malignancies
- Pamiparib (BGB-290) is a potent and selective PARP 1/2 inhibitor that has been engineered to facilitate unique properties such as brain penetration and PARP–DNA complex trapping for improved cytotoxicity via cell-cycle arrest and apoptosis
- This ongoing phase 1/1b study (NCT02660034) will evaluate the combined use of tislelizumab and pamiparib in patients with advanced solid tumors likely to harbor DNA damage repair deficiencies susceptible to treatment with a PARP inhibitor or considered to be responsive to a PD-1 blockade
- The rationale for combining tislelizumab and pamiparib is that upregulation of tumor-associated antigens with PARP inhibitor treatment may improve the antitumor activity of checkpoint inhibitors
- The malignancies studied are those likely to harbor DNA damage repair deficiencies or tumors potentially responsive to a PD-1 blockade
- This study is being conducted in two parts:
  - Part A is a dose-escalation/dose-finding phase to establish the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D), evaluate the pharmacokinetics (PK) of the drug combination, and assess the immunogenicity of tislelizumab
  - Part B is dose-expansion phase which will further evaluate the PK, safety and tolerability of this combination, and assess the preliminary antitumor activity in each of seven disease-specific arms (ovarian/fallopian tube/peritoneal, triple-negative breast, castration-resistant prostate, gastric/gastroesophageal junction, urothelial, pancreatic, and lung cancers)
- Preliminary results for 49 patients enrolled in Part A are presented here (data cut-off date 31 July 2017)

METHODS

Study Design

Figure 1: Study Design

Part A: Dose Escalation (3+3) Patients with advanced solid tumors			
Dose Level	Tislelizumab IV Q3W	Pamiparib PO BID	Enrolled N=49
1	2 mg/kg	20 mg	12
2	2 mg/kg	40 mg	12
3	2 mg/kg	60 mg	6
4	200 mg	40 mg	13
5	200 mg	60 mg	6

Primary Endpoints
- Safety and tolerability
  - Estimate the MTD
  - Select the RP2D

Secondary Endpoints
- Anti-tumor activity
- PK/immunogenicity

Exploratory Endpoints
- Biomarker correlation

RP2D

Dose Expansion (n=20/cohort)
- Ovarian/fallopian tube/peritoneal
- Triple-negative breast
- Castration-resistant prostate
- Gastric/gastroesophageal junction
- Urothelial
- Pancreatic
- Lung

Each cycle of treatment: 21 days.
Tumor assessments: Q63 days.
Abbreviations: BID, twice daily; IV, intravenous; MTD, maximum tolerated dose; PO, perioral; Q3W, every three weeks; RP2D, recommended phase 2 dose.

- Adult patients (≥18 years) with histologically or cytologically confirmed advanced malignancy with measurable disease, an Eastern Cooperative Oncology Group performance score of ≤1, a life expectancy ≥12 weeks, and who had failed at least one prior chemotherapy were eligible for enrollment in the study
- Patients who had received prior therapies targeting PD-1 or PARP or vaccine within 4 weeks of study initiation, had active autoimmune disease, or a history of autoimmune disease, were excluded

RESULTS

Table 1: Patient Demographics and Disease Characteristics

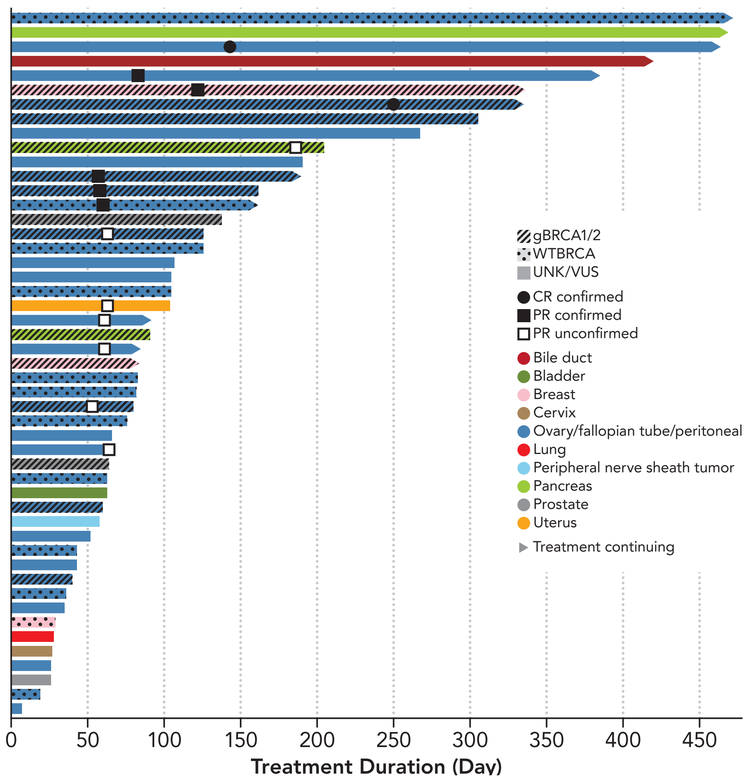
Patient Demographics		Total (N=49)
Median age, years (range)		63 (34–78)
Sex, n (%)	Female	42
	Male	7
Race, n (%)	Caucasian	44
	Asian	5
Primary site of tumor, n	Ovary/fallopian tube/peritoneum	34
	Pancreas	3
	Prostate	3
	Breast	3
	Bile duct	1
	Bladder	1
	Cervix	1
	Lung	1
	Peripheral nerve sheath	1
	Uterus	1
BRCA status – local assessment		25
BRCA WT		11
BRCA 1/2 germline/somatic mutation		13/1

- RP2D was established to be tislelizumab 200 mg IV Q3W + pamiparib 40 mg PO BID
- Dose-limiting toxicities were grade 2 nausea and grade 3 rash (dose-level 4), and grade 2 nausea/vomiting and grade 4 auto-immune (AI) hepatitis (dose-level 5)

Preliminary Assessments of Antitumor Activity

- Eleven patients remain on treatment
- Median duration of response was 168.5 days (range: 64–508)
- Duration of treatment was >200 days in 10 patients

Figure 2: Duration of Treatment and Response by Tumor Type and Germline *BRCA* Mutation Status*



**BRCA* status assessed by local laboratory.
Abbreviations: CR, complete response; g*BRCA*, germline *BRCA*; PR, partial response; UNK, unknown; VUS, variant of uncertain significance; WT*BRCA*, wild-type *BRCA*.

Table 2: Best Overall Response Rate

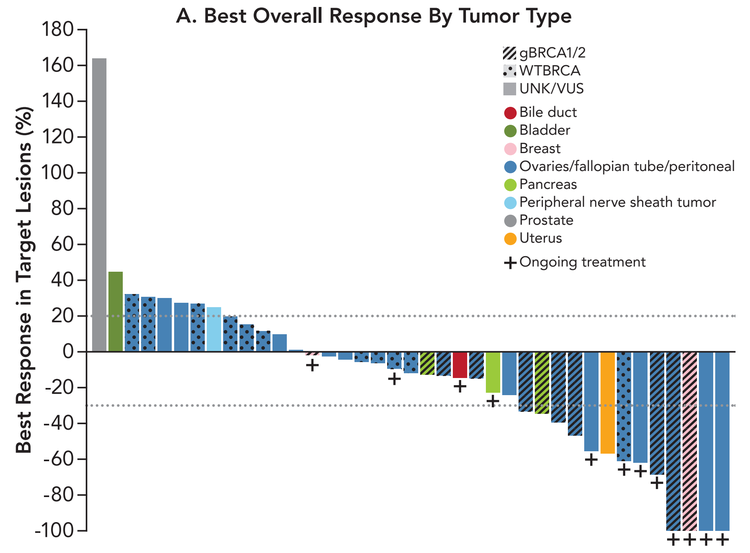
RECIST v 1.1 Best Overall Response, n (%)	Total (N=43) 31/03/2017	Total (N=49) 31/07/2017	Total (N=49) 4/01/2018
Complete response (CR)	1 (2)	2 (4)	2 (4)
Partial response (PR) – confirmed	3 (7)	5 (10)	8 (16)
Partial response (PR) – unconfirmed	7 (16)	7 (14)	4 (8)
Objective response rate (CR+PR)	**4 (9)**	**7 (14)**	**10 (20)**
Clinical benefit rate*	**11 (26)**	**15 (31)**	**19 (39)**
Ovary/Fallopian/Peritoneum			**N=34**
Objective response rate (CR+PR)	**NC**	**NC**	**9[†] (26)**

Data presented as n (%). *CR+PR+durable SD with ≥24 weeks. [†]3 pts with g*BRCA* mutations.
Abbreviation: NC, not calculated.

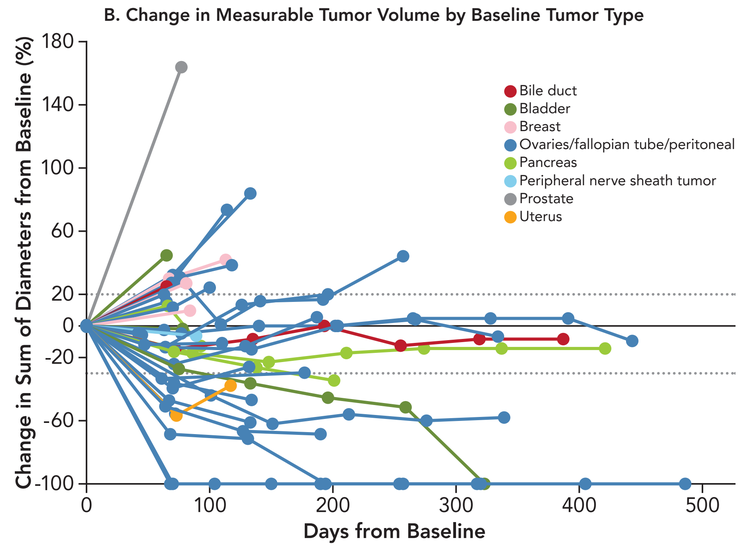
- As of Jan 2018, the overall response rate (ORR) was reported to be 20% with three additional PRs confirmed from the last data cut-off of July 2017
  - All patients who achieved a CR or PR are still on study treatment

Figure 3: Antitumor Activity of Pamiparib/Tislelizumab Combination Treatment

A. Best Overall Response By Tumor Type



B. Change in Measurable Tumor Volume by Baseline Tumor Type



**BRCA* status assessed by local laboratory.

CONCLUSIONS

- The combination of tislelizumab and pamiparib was generally well tolerated in patients with advanced solid tumors
  - Duration of treatment was >200 days for 10 patients
  - RP2D was identified as tislelizumab 200 mg IV Q3W + pamiparib 40 mg PO BID
  - Liver-related AEs were observed in 13 patients; however, all events were manageable and reversible with corticosteroid treatment
    - The biologic mechanism for these liver-related AEs is under investigation and these events are being closely monitored in the study
- As of January 8 2018, evidence of complete or partial response was observed in 10 patients; responses were durable and observed in patients with wild type and mutant g*BRCA*
- Together, these results support the continuation of this trial with continued enrollment into the disease-specific cohorts

Safety and Tolerability

Table 3: Summary of Treatment-Emergent Adverse Events Across Cohorts

	Total (N=49)
Patients reporting ≥1 TEAE, n	49
Patients reporting serious TEAE, n	21
Patients who experienced DLT, n	4
Related TEAEs, n	44
Related to tislelizumab	39
Related to pamiparib	42
Related to both	31
Immune-related adverse events, n	23
TEAEs leading to discontinuation of both study drugs	3
TEAEs leading to discontinuation of tislelizumab	11
TEAEs leading to discontinuation of pamiparib	6

Abbreviations: DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event.

Table 4: Summary of Non-Immune Treatment-Related Adverse Events

	Related to Pamiparib		Related to Tislelizumab	
	Grade 1–2*	Grade 3–4[†]	Grade 1–2*	Grade 3–4[†]
Nausea	27 (55.1)	2 (4.1)	10 (20.4)	0
Fatigue	19 (38.8)	2 (4.1)	18 (36.7)	1 (2.0)
Diarrhea	10 (20.4)	0	7 (14.3)	0
Vomiting	6 (12.2)	1 (2.0)	1 (2.0)	0
Anemia	6 (12.2)	6 (12.2)	2 (4.1)	0
Dysgeusia	5 (10.2)	0	3 (6.1)	0
Decreased appetite	4 (8.2)	0	2 (4.1)	0
Thrombocytopenia	4 (8.2)	0	0	0
Headache	3 (6.1)	0	2 (4.1)	0
Gastroesophageal reflux disease	3 (6.1)	0	1 (2.0)	0
Pruritus	3 (6.1)	1 (2.0)	1 (2.0)	1 (2.0)
Neutropenia	3 (6.1)	1 (2.0)	1 (2.0)	0
Rash	3 (6.1)	1 (2.0)	3 (6.1)	0
Dry mouth	2 (4.1)	0	3 (6.1)	0

Data presented as n (%). *≥5% of patients. [†]≥2 of patients.

- Twelve patients reported at least 1 grade ≥3 immune-related (IR) treatment-emergent adverse event (IR-TEAE)

Table 5: Immune-Related TEAEs Occurring in ≥2 Patients

	All Grade IR-TEAE	Grade ≥3 IR-TEAE
Increased ALT	6	2
Increased AST	5	1
Hypothyroidism	5	0
Diarrhea	4	0
Auto-immune hepatitis	3	3
Increased GGT	3	1
Hyperthyroidism	3	0
Hepatitis	2	2
Pruritus	2	1

Data presented as number of patients with at least one event; patients may have more than one immune-related AE.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

Hepatic-Related Adverse Event

- Between 31 March and 31 July 2017, one additional patient reported a hepatic AE (n=13) with median time to onset of events reported to be 55 days (range: 18–202 days)
  - Five patients discontinued both drugs for progressive disease
  - Four patients discontinued both drugs for hepatic TEAE
  - Three patients discontinued tislelizumab only
  - One patient continues on both treatments
- Reported as hepatitis/AI hepatitis (n=6); ALT and/or AST elevations (n=7)
- Nine patients reported grade 3/4 hepatic AEs;
  - One hepatitis AE and four ALT/AST elevations were related to pamiparib
  - Three AI hepatitis AEs, three hepatitis AEs, and three ALT/AST elevations were related to tislelizumab
  - Two ALT/AST elevations were considered related to both drugs
- All patients received corticosteroids and recovered
- The protocol was amended to increase real-time hepatic safety monitoring consistent with new ESMO guidance for IR-TEAEs

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