Abstract
#3013

Poster Discussion
Session Board
#108

A Phase 1/1b Study of the Anti-PD-1 Monoclonal Antibody BGB-A317 (A317) in Combination with the PARP Inhibitor BGB-290 (290) in Advanced Solid Tumors

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BACKGROUND

- 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 antitumor activity of checkpoint inhibitors
- BGB-A317, a humanized IgG4 variant monoclonal antibody with no 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
- 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 BGB-A317 and BGB-290 in patients with advanced solid tumors likely to harbor DNA damage repair deficiencies and who are susceptible to treatment with a PARP inhibitor or considered to be responsive to PD-1 blockade
- This study is being conducted in 2 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 BGB-A317
  - Part B is dose-expansion phase that will further evaluate the PK, safety, and tolerability of this combination, and assess the preliminary antitumor activity in each of 7 disease-specific arms
- Preliminary results for 43 patients enrolled in Part A are presented here (data cut-off date 31 March 2017)

METHODS

Study Design (Figure 1)

Part A: Dose Escalation (3+3)
Patients with advanced solid tumors

Dose Level	BGB-A317 IV Q3 Week	BGB-290 PO BID	Enrolled N=43
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	7
5	200 mg	60 mg	6

Primary Endpoints
- Safety and tolerability
  - Estimate the MTD
  - Select the R2PD

Secondary Endpoints
- Anti-tumor activity
- PK/immunogenicity

Exploratory Endpoints
- Biomarker correlation

RP2D

Dose Expansion (n=20/cohort)
Ovarian
TNBC
CRPC
Gastric/GEJ
Urothelial
Pancreatic
SCLC

Each cycle of treatment: 21 days
Tumor assessments: Q63 days
Abbreviations: CRPC, castration-resistant prostate cancer; GEJ, gastroesophageal junction; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; SCLC, small cell lung cancer; TNBC, triple negative breast cancer.

Patients

- 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

Patient Disposition, Demographics, and Baseline Disease Characteristics

Table 1: Patient Demographics and Disease Characteristics

		Total (N=43)
Median age, years (min, max)		63 (34, 75)
Sex	**Male/female**	7/36
Race	**White**	38
	Asian/other	4/1
Median cycles of treatment (min, max)		4 (1, 18)
Primary site of tumor	**Ovary/fallopian tube/peritoneum**	29
	Pancreas	3
	Prostate	3
	Breast	2
	Bile duct	1
	Bladder	1
	Cervix	1
	Lung	1
	Peripheral nerve sheath	1
	Uterus	1

- Thirty-three patients (77%) have discontinued treatment due to progressive disease (n=26), AE (n=7), and/or consent withdrawal (n=2)
  - Two patients discontinued BGB-A317 and BGB-290 at different times for different reasons

Safety and Tolerability

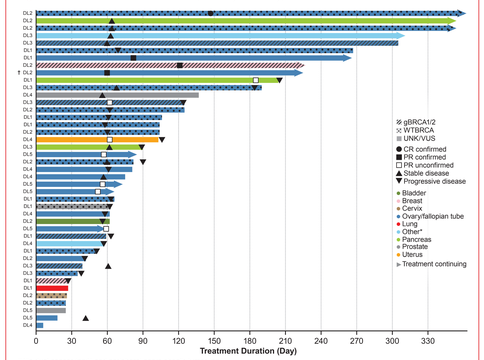
Table 2: Summary of Treatment-Emergent Adverse Events Across Cohorts

	Total (N=43)
Patients reporting ≥1 TEAE	43
Patients reporting ≥1 serious TEAE	17
Patients who experienced ≥1 DLT	3
Related TEAEs	38
Related to BGB-A317	32
Related to BGB-290	37
Related to both	26
Immune-related adverse events	17
TEAEs leading to discontinuation of both study drugs	3
TEAEs leading to discontinuation of BGB-A317	10
TEAEs leading to discontinuation of BGB-290	5

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

Preliminary Assessments of Antitumor Activity

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



*Bile duct cancer (n=1) and peripheral nerve sheath tumor (n=1).
†Patient had a confirmed PR until Feb 2017 and has a CR as of April 2017.
Abbreviations: CR, complete response; DL, dose level; PR, partial response.

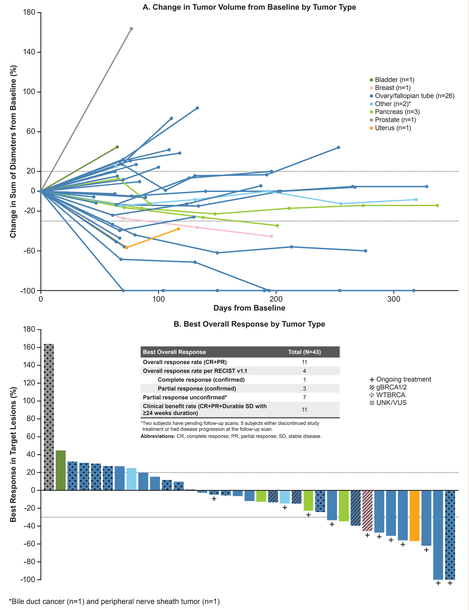
- A total of 35 patients had measurable disease and at least one post baseline radiologic tumor assessment; antitumor activity of BGB-290 plus BGB-A317 combination treatment are presented in **Figures 2 and 3**

Table 3: TEAE Related to Either BGB-A317 or BGB-290 by Grade in ≥2 Patients

	Grade 1 or 2		Grade 3 or 4	
	Related to BGB-A317	Related to BGB-290	Related to BGB-A317	Related to BGB-290
Fatigue	14	16	1	2
Nausea	7	22	0	2
Anemia	2	6	0	6
Neutropenia	1	3	0	1
Thrombocytopenia	0	3	0	0
Diarrhea	4	9	0	0
Vomiting	1	6	0	1
Pyrexia	2	2	0	0
Autoimmune hepatitis/hepatitis	2	0	5	0
Elevated AST	3	3	1	2
Elevated ALT	2	5	2	2
GGT increased	1	1	1	0
Headache	2	3	0	0
Cough	1	1	0	0
Hyperthyroidism	2	2	0	0
Hypothyroidism	3	1	0	0
Dry mouth	3	2	0	0
Decreased appetite	2	0	0	0
Dermatitis	2	0	0	0
Dry skin	2	1	0	0
Pruritus	2	3	0	0
Rash/macular rash	4	3	0	0

- Three patients (7%) experienced 4 incidences of dose-limiting toxicities: grade 2 nausea (dose level 4), grade 2 nausea and grade 2 vomiting (dose level 5), and grade 4 autoimmune hepatitis (dose level 5)

Figure 3: Antitumor Activity of BGB-290/BGB-A317 Combination Treatment



*Bile duct cancer (n=1) and peripheral nerve sheath tumor (n=1)

Table 4: Immune-Related Treatment-Emergent Adverse Events Occurring in ≥2 Patients

	DL 1 (n=12)	DL 2 (n=12)	DL 3 (n=6)	DL 4 (n=7)	DL 5 (n=6)	Total (N=43)
Elevated ALT	1	0	2	1	1	5
Elevated AST	1	0	2	1	0	4
Autoimmune hepatitis	1	1	0	0	1	3
Hypothyroidism	1	1	1	0	0	3
Diarrhea	0	0	0	0	2	2
GGT increased	0	0	2	0	0	2
Hyperthyroidism	1	0	1	0	0	2

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DL, dose level; GGT, gamma-glutamyltransferase.

CONCLUSIONS

- The combination of BGB-A317 and BGB-290 was generally well tolerated in patients with advanced solid tumors
  - Duration of treatment was >200 days for 10 patients
    - A total of 7 patients remain on treatment
  - MTD was identified as BGB-A317 200 mg IV Q3W + BGB-290 40 mg PO BID
  - Liver-related AEs were observed in 12 patients; all events were reversible with or without corticosteroid treatment
    - The biologic mechanism for these liver-related AEs is under investigation
- Co-administration of BGB-A317 with BGB-290 did not have a significant impact on the pharmacokinetic profile of either compound (data not shown)
- Complete or partial response was observed in 11 patients, 4 of whom had confirmed PR or CR; responses were durable and observed in patients with wild-type and mutant *gBRCA* status
- Together, these results support the continuation of this trial with continued enrollment into the disease-specific cohorts

Table 5: Grade 3/4 Adverse Events (Regardless of Causality) that Occurred in ≥2 Patients

	DL 1 (n=12)	DL 2 (n=12)	DL 3 (n=6)	DL 4 (n=7)	DL 5 (n=6)	Total (N=43)
Anemia	2	1	0	1	2	6
Elevated ALT	0	0	1	2*	0	3
Elevated AST	0	1	0	2*	0	3
Autoimmune hepatitis	1	1	0	0	1	3
Diarrhea	1	0	1	0	0	2
Fatigue	1*	0	0	0	1	2
GGT increased	0	2	1	0	0	3
Nausea	0	0	0	0	2	2
Small intestinal obstruction	1	0	0	1	0	2
Vomiting	0	0	0	1	1	2

*Related to both BGB-A317 and BGB-290 in 1 patient each
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DL, dose level; GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event.

- Eight of the 12 liver-related AEs were grade 3 or higher
  - Five hepatitis, 3 ALT and/or AST elevations
  - Two occurred in dose level 5
- Median time to onset was 55 days (18 – 202 days)
- All received corticosteroids, and all recovered
- Of these 12 patients:
  - Five discontinued both drugs for progressive disease
  - Three discontinued both drugs due to a TEAE
  - Four discontinued BGB-A317 only
    - Two continued on BGB-290
    - Two discontinued due to progressive disease
- Hepatic AEs considered related to study treatment have been reported in 1 of 300 patients treated with BGB-A317 monotherapy and 0 of 65 patients treated with BGB-290 monotherapy in separate ongoing studies (NCT02407990 and NCT02361723, respectively)

REFERENCES

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