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PHASE 1/2, OPEN-LABEL, MULTIPLE-DOSE, DOSE-ESCALATION AND EXPANSION STUDY TO INVESTIGATE THE SAFETY, PHARMACOKINETICS, FOOD EFFECT, AND ANTITUMOR ACTIVITIES OF BGB-290 IN PATIENTS WITH ADVANCED SOLID TUMORS

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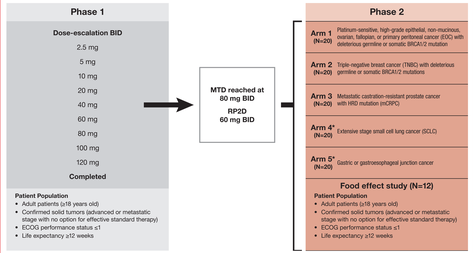
BACKGROUND

- Poly (ADP-ribose) polymerase (PARP) proteins are involved in DNA repair, genome stability, and programmed cell death[1]
- The primary function of PARP proteins is to detect single-strand DNA (SSD) breaks and target the breaks for repair[2]
  - By inhibiting PARP function, tumor cells homologous repair deficiency (HRD) are unable to repair DNA damage leading to inhibition of proliferation and subsequent cell death
- BGB-290 is a potent and selective PARP1/2 inhibitor with strong PARP-trapping and antitumor activity in both in vitro and in vivo preclinical studies
- Given the positive outcomes in preclinical studies, a first-in-human dose-escalation/ dose-expansion phase 1/2 study (NCT02361723) was initiated
  - Data presented here include preliminary clinical profile of BGB-290 across phase 1 and 2 in patients with solid tumors

METHODS

Figure 2: Study Design



*Patients have not yet been enrolled
Abbreviations: BID, twice daily; ECOG, Eastern Cooperative Oncology Group; EOC, epithelial ovarian cancer; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose.

Overall Design and Study Objectives

- This study consists of two phases (**Figure 1**)
  - Phase 1 was a dose-escalation/dose-finding component that followed a 3+3 design to establish the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of BGB-290 administered orally twice daily (BID) in patients with solid tumors
    - MTD was identified as 80 mg BID and RP2D was established as 60 mg
- The first component of phase 2 is currently investigating the safety/tolerability and antitumor activity of oral BGB-290 in patients with selected tumor types
- The second component of phase 2 is currently investigating the effects of food on the pharmacokinetic (PK) profile of a single dose of BGB-290

Study Assessments and Analyses

- Antitumor activity was assessed in all evaluable patients based on RECIST v1.1
- Safety/tolerability were evaluated in all patients who received ≥1 dose of BGB-290
- Safety and tolerability assessments were based on monitoring of treatment-emergent adverse events (TEAEs), as well as on vital signs, electrocardiogram, physical examinations, and clinical laboratory results

RESULTS

- As of 01 June 2017, 68 patients were enrolled (dose-escalation, n=45; dose-expansion, n=23, including 8 in food effect); 47 patients discontinued treatment across the entire study primarily due to progressive disease (n=26)

Patient Disposition, Demographics, and Baseline Disease Characteristics

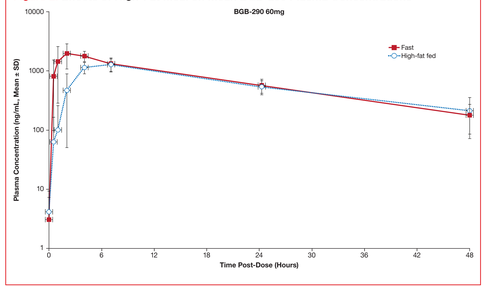
Table 1: Patient Demographics and Disease Characteristics

		Phase 1 (n=45)	Phase 2 (n=23)	Total (N=68)
Median age, years (min, max)		58 (37, 74)	60.0 (37, 81)	59.0 (37, 81)
Sex, n	Male	8	4	12
	Female	37	19	56
Race, n	Caucasian	38	21	59
	Asian	4	1	5
	Other	3	1	4
Baseline ECOG performance status, n (%)	0	16 (35.6)	11 (47.8)	27 (39.7)
	1	28 (62.2)	12 (52.2)	40 (58.8)
	2	1 (2.2)	0	1 (1.5)
Median prior therapies (min, max)		3.0 (1, 9)	3.0 (1, 7)	3.0 (1, 9)
Median time since diagnosis, years (min, max)		3.4 (0.4, 10.4)*	2.6 (0.6, 20.4)**	3.27 (0.4, 20.4)

*Data from one patient missing; **Data from three patients missing.

Effects of Food on the Pharmacokinetic Profile of BGB-290

Figure 2: Effects of High-Fat Meal on Mean BGB-290 Plasma Concentrations

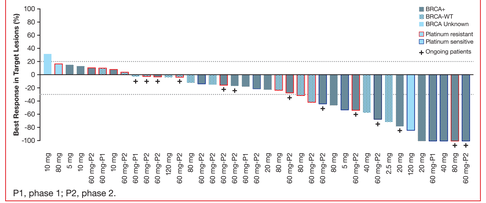


- BGB-290 area under the concentration–time curve (AUC) after a high-fat meal was 85% of the AUC under fasted conditions (**Figure 2**)
- Maximum concentration (C_{max}) of BGB-290 after a high-fat meal was 63% of C_{max} under fasting
- Time of maximum concentration (t_{max}) was prolonged from 2 to 6 hours after administration with a high-fat meal

Antitumor Activity of BGB-290 in Epithelial Ovarian Cancer and Other Solid Tumors

- A total of 39 patients were evaluable per RECIST V1.1
  - 23 patients were BRCA-mutation positive (BRCA+), 13 patients had wild-type BRCA (BRCA-WT), and 3 were of unknown BRCA status

Figure 3: Best Change from Baseline in Target Lesions in Epithelial Ovarian Cancer and Other Associated Tumors



P1, phase 1; P2, phase 2.

Figure 4: Antitumor Activity of BGB-290 in Patients with Epithelial Ovarian Cancer and Other Associated Tumors

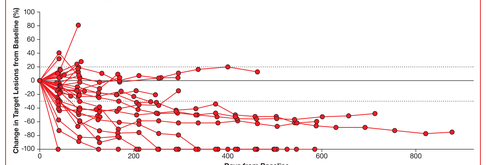


Figure 5: Duration of Treatment in Epithelial Ovarian Cancer and Other Associated Tumors

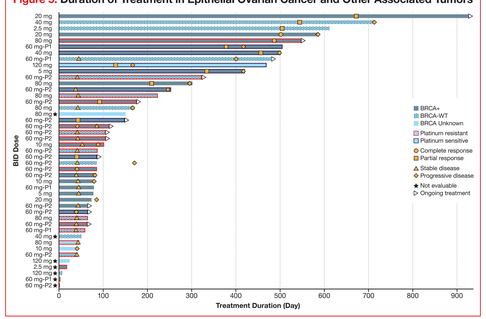
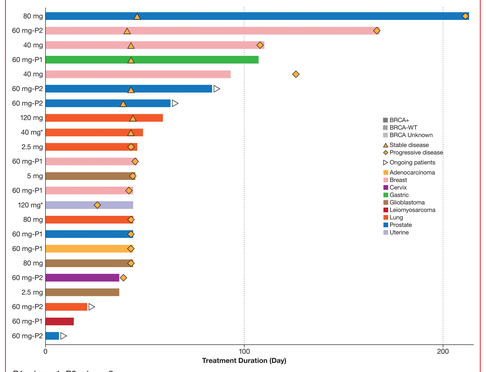


Table 2: Best Overall Response for Epithelial Ovarian Cancer

Best Overall Response, n (%)	Total (N=39)
Overall response rate per RECIST v1.1 (CR+PR)	**13 (33.3)**
Complete response (CR)	3 (7.7)
Partial response (PR)	10 (25.6)
Stable disease (SD)	21 (53.8)
Clinical benefit rate (CR+PR+SD with ≥24 weeks duration)	**18 (46.2)**

- Overall response rates by BRCA status were 43.5% (n=10/23; BRCA+), 15.4% (n=2/13; BRCA-WT), and 33.3% (n=1/3; BRCA unknown)

Figure 6: Duration of Treatment in Other Solid Tumors



P1, phase 1; P2, phase 2.

Safety and Tolerability

Table 3: Summary of Adverse Events Across the Study

	Phase 1 (n=45)	Phase 2 (n=23)	Total (N=68)
Patients reporting ≥1 TEAE	45 (100)	22 (95.7)	67 (98.5)
Patients reporting ≥1 treatment-related TEAE	34 (75.6)	19 (82.6)	53 (77.9)
Patients reporting ≥1 serious TEAE	25 (55.6)	6 (26.1)	31 (45.6)
Patients who experienced ≥1 DLT	4 (8.9)	NA	4 (5.9)
TEAEs leading to discontinuation	4 (8.9)	0	4 (5.9)
TRAEs Occurring in ≥10% of All Patients (N=68)	**Grade 1 or 2**	**Grade ≥3**	**Total**
Nausea	36 (52.9)	2 (2.9)	38 (55.9)
Vomiting	13 (19.1)	1 (1.5)	14 (20.6)
Diarrhoea	12 (17.6)	2 (2.9)	14 (20.6)
Fatigue	25 (36.8)	2 (2.9)	27 (39.7)
Anaemia	10 (14.7)	7 (10.3)	17 (25.0)
Neutropenia/neutrophil count decrease	2 (2.9)	6 (8.8)	8 (11.8)
Decreased appetite	10 (14.7)	0	10 (14.7)

All data are presented as n (%).
Abbreviations: DLT, dose-limiting toxicity; NA, not applicable; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

CONCLUSIONS

- BGB-290 was generally well tolerated with nausea, fatigue, anaemia, vomiting, diarrhoea, anorexia, and neutropenia being the most commonly reported TEAEs
  - As of 01 June 2017, a total of 20 patients remain on treatment
- A high-fat meal reduced BGB-290 AUC and C_{max} by 15% and 37%, respectively, and prolonged t_{max} from 2 to 6 hours
  - Change in plasma exposure of BGB-290 after a high-fat meal is not considered clinically relevant suggesting that food restriction should be removed from future studies if finding is confirmed in an additional 6 patients
- BGB-290 continues to demonstrate promising anti-tumor activity, notably in patients with epithelial ovarian cancer
  - Confirmed complete or partial responses were observed in 13 of the 39 evaluable patients
  - Of the 13 responders, 10 patients were BRCA+, 2 were BRCA-WT, and 1 BRCA unknown
- A dose-escalation study to assess the safety and antitumor activity of BGB-290 given once daily will start in September 2017

- BGB-290 was generally well tolerated with nausea being the most commonly reported TEAE considered related to treatment (**Table 3**)
  - No observed treatment-related TEAE was higher than grade 3 in severity
- Four patients had a TEAE with a fatal outcome, none were assessed as related to treatment, all were associated with disease progression
- Across the study, serious TEAEs considered related to the treatment occurring in more than 1 patients were nausea (n=2) and anaemia (n=2)

REFERENCES

1. Thomas C, Tulin AV. Poly-ADP-ribose polymerase: machinery for nuclear processes. *Mol Aspects Med.* 2013;34(6):1124-1137.
2. Coleman RL, Sill MW, Bell-McGuinn K, et al. A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation - An NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol.* 2015;137(3):386-391.

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