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

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NCT02660034

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PLEASE NOTE, all disclosures are reported as submitted to ASCO, and are available at **immunosym.org.**

Disclosure Information

Relationships with Companies

Mileshkin, Linda R.

Travel, Accommodations, Expenses: BeiGene and Roche

Background

- Tislelizumab (BGB-A317) is a humanized IgG4 monoclonal antibody
  - Minimal Fc gamma receptor binding
  - Targets the PD-1 receptor
  - In development for solid and hematologic malignancies

- Pamiparib (BGB-290) is a potent, selective PARP 1/2 inhibitor
  - Potent PARP–DNA complex trapping
  - Brain penetration in preclinical models

- Rationale for combination
  - Upregulation of tumor-associated antigens with PARP inhibitor treatment may improve the antitumor activity of checkpoint inhibitors
  - Malignancies studied are those likely to harbor DNA damage repair deficiencies or potentially responsive to PD-1 blockade

Abbreviations: PARP, Poly (ADP-ribose) polymerase; PD-1, programmed cell death-1.

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Study Background

- Study aim
  - Evaluate combination tislelizumab and pamiparib treatment in patients with advanced malignancies
- Two part trial
  - Part A: Dose escalation/ dose finding
    - Establish the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D)
    - Evaluate pharmacokinetics (PK) of the combination treatment and immunogenicity of tislelizumab*
  - Part B: Disease-specific expansion
    - Evaluates preliminary antitumor activity
    - Evaluates further PK and safety

*Data will not be presented here

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Study Design

Key Eligibility
- Advanced malignancy
- Measurable disease
- ≥1 prior treatment
- ECOG ≤1
- No prior PARP or anti-PD-1

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

Dose Level	Tislelizumab IV Q3 Week	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

Each cycle of treatment: 21 days; tumor assessments: Q3 cycles.

RP2D

Part B
Dose Expansion
(n=20/cohort)

- Ovarian/fallopian tube/peritoneal
- Triple-negative breast
- Castration-resistant prostate
- Gastric/GEJ
- Urothelial
- Pancreatic
- Lung

Abbreviations: BID, twice daily; GEJ, gastroesophageal junction; IV, intravenous; MTD, maximum tolerated dose; PO, per os; RP2D, recommended phase 2 dose; TNBC, triple-negative breast cancer.

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Dose-Limiting Toxicities and RP2D

Part A: Dose escalation (3+3) Patients with advanced solid tumors			
Dose Level	**Tislelizumab IV Q3 Week**	**Pamiparib PO BID**	**Enrolled N=49**
1	2 mg/kg	20 mg	12
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3	2 mg/kg	60 mg	6
4	200 mg	40 mg	13
5	200 mg	60 mg	6

Each cycle of treatment: 21 days; tumor assessments: Q3 cycles.

RP2D

Tislelizumab200 mg IV Q3W + pamiparib 40 mg po BID (DL4)

Dose-limiting toxicities

DL1–3: none

DL4: Grade 2 nausea (n=1), Grade 3 rash (n=1)

DL5: Grade 2 nausea/vomiting (n=1)
Grade 4 auto-immune hepatitis (n=1)

Abbreviations: BID, twice daily; DL, dose levels IV, intravenous; MTD, maximum tolerated dose; PO, per os; RP2D, recommended phase 2 dose

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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

Baseline Disease Characteristics	Total (N=49)
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

Data cut-off date: July 31, 2017

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Summary of 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.

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Treatment-Related, Non-Immune Adverse Events

	Related to pamiparib		Related to tislelizumab	
	Grade 1–2 (≥5% of pts)	Grade 3–4 (≥2 of pts)	Grade 1–2 (≥5% of pts)	Grade 3–4 (≥2 of pts)
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 (%).

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Immune-Related AEs Reported in ≥2 Patients

Number of patients with ≥1 Grade ≥3 immune-related (IR) AE: 12 (24.5%)

	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.

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Updated Hepatic Adverse Events

- 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 4 ALT/AST elevations were related to pamiparib
  - Three AI hepatitis AEs, 3 hepatitis AEs, and 3 ALT/AST elevations were related to tislelizumab
  - Two ALT/AST elevations were considered related to both drugs
- All patients with treatment-related grade ≥2 transaminitis (n=10) 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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Best Overall Response Rate

RECIST v 1.1 Best Overall Response, n (%)	Total (N=43) 31 March 2017	Total (N=49) 31 July 2017	Total (N=49) 4 January 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 (CR+PR+durable SD with ≥24 weeks)	**11 (26)**	**15 (31)**	**19 (39)**

All patients who achieved a CR or PR are still on study treatment

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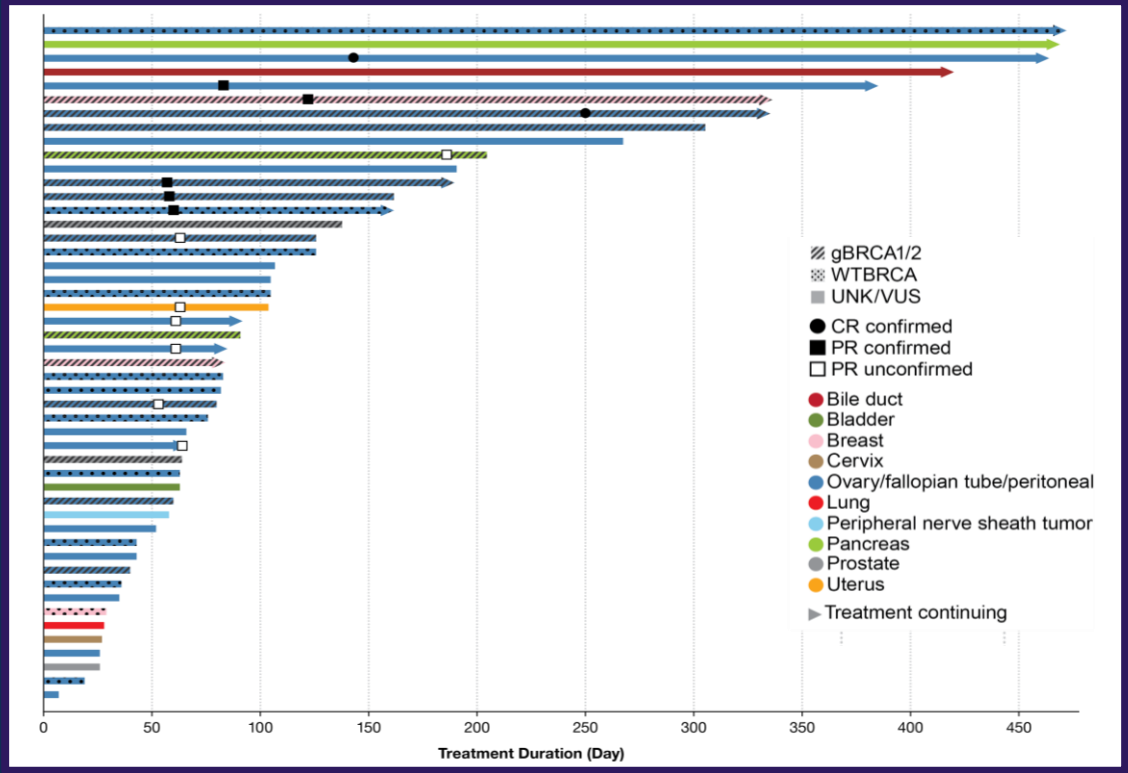
Duration of Treatment and Response

BRCA status assessed by local laboratory

As of data cut-off date, 11 patients remain on treatment

Median duration of response was 168.5 days (range: 64–508)

Duration of treatment was >200 days in 10 patients



Data cut-off date: July 31, 2017

Abbreviations: CR, complete response; DL, dose level; g*BRCA*, germline *BRCA;* PR, partial response; UNK, unknown; VUS, variant of uncertain significance; WTBRCA, wild-type *BRCA*

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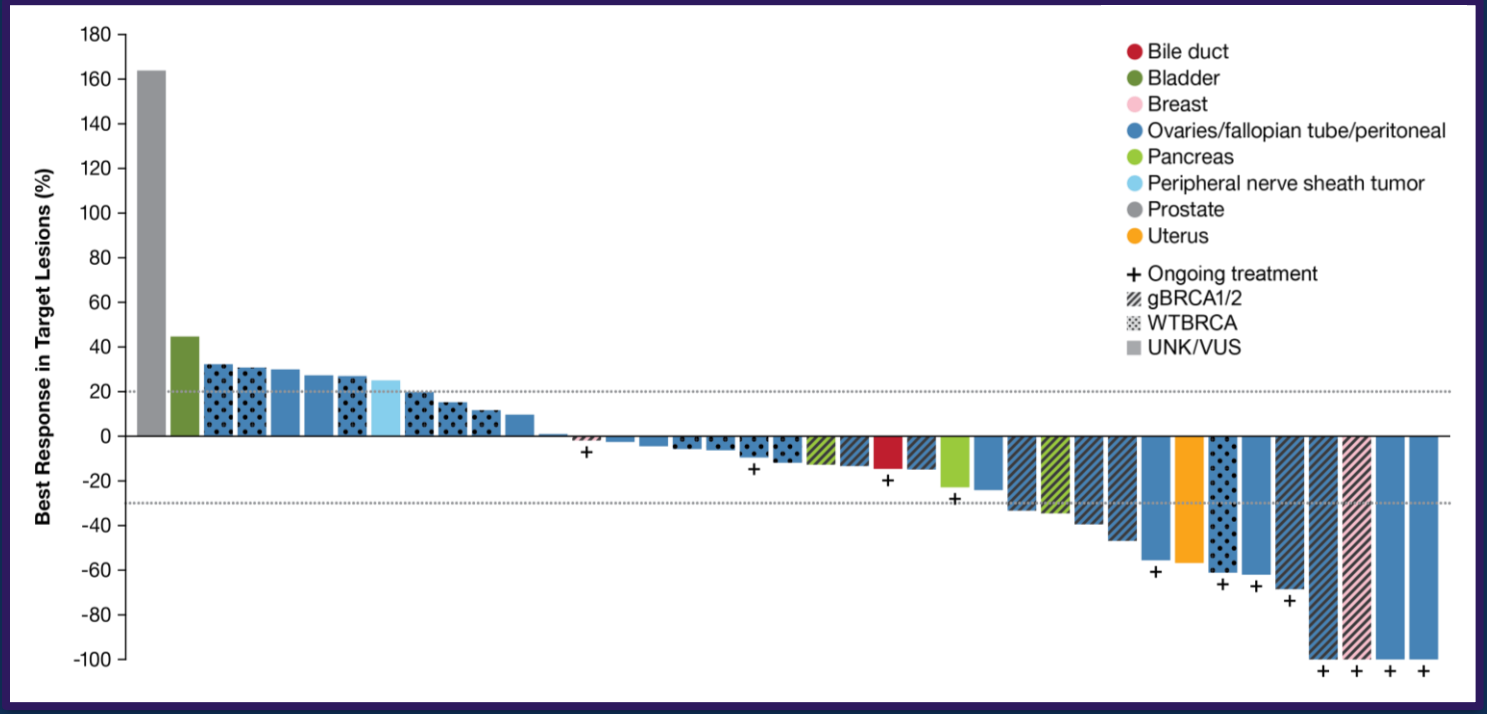
Presented by: Dr Linda Mileshkin

Antitumor Activity of pamiparib/tislelizumab Combination Treatment



BRCA status assessed by local laboratory

Data cut-off date: July 31, 2017

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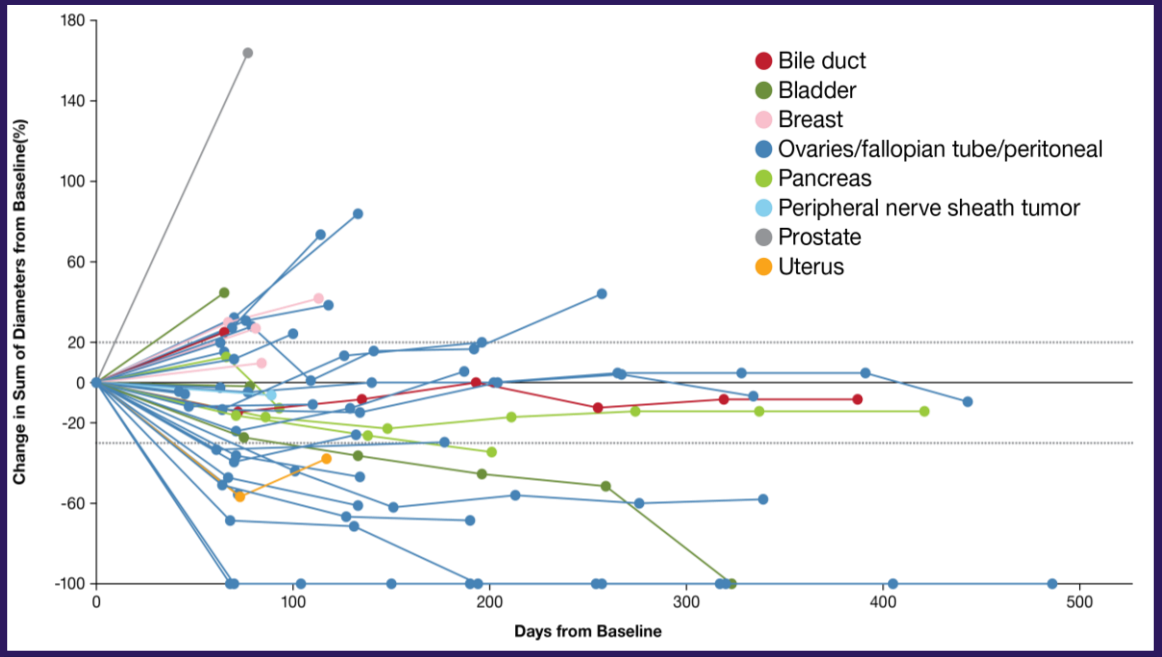
Antitumor Activity of pamiparib/tislelizumab Combination Treatment

Change in Measurable Tumor Volume by Baseline Tumor Type



Data cut-off date: July 31, 2017

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Conclusions

Antitumor activity and safety results support continuation of this trial

- The combination of tislelizumab and pamiparib was generally well tolerated with 10 patients on treatment for >200 days
- RP2D – tislelizumab 200 mg IV Q3W + pamiparib 40 mg PO BID
- Liver-related AEs were observed in 13 patients; events were manageable and reversible with corticosteroid treatment
  - Study is closely monitoring hepatic-related AEs

- As of January 2018, 10 patients had a confirmed CR or PR
  - Responses were durable
  - Observed in patients with wild type and mutant g*BRCA* status
- Enrollment of disease-specific cohorts in Part B is ongoing

Acknowledgments

- Study patients and families
- Investigative center study staff
- BeiGene, Ltd
- SuccinctChoice Medical Communications