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# 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 with 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 diseasespecific 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

Part A: Dose Escalation (3+3) Patients with advanced solid tumors				Primary	Dose Expansion (n=20/cohort)	
Dose Level	Tislelizumab IV Q3W	Pamiparib PO BID	Enrolled N=49	<ul><li>Endpoints</li><li>Safety and tolerability</li><li>Estimate the MTD</li></ul>	Ovarian/fallopian tube/ peritoneal	
1	2 mg/kg	20 mg	12	- Select the R2PD	Triple-negative breast  Castration-resistant	
2	2 mg/kg	40 mg	12	Secondary Endpoints	prostate	
3	2 mg/kg	60 mg	6	<ul><li>Anti-tumor activity</li><li>PK/immunogenicity</li></ul>	gastroesophageal junction	
4	200 mg	40 mg	13	Exploratory Endpoints	Urothelial Pancreatic	
5	200 mg	60 mg	6	Biomarker correlation	Lung	

 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

RP2D, recommended phase 2 dose; Q3W; every three weeks.

 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 Demogra	phics 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 asses	sment	25
BRCA WT		11

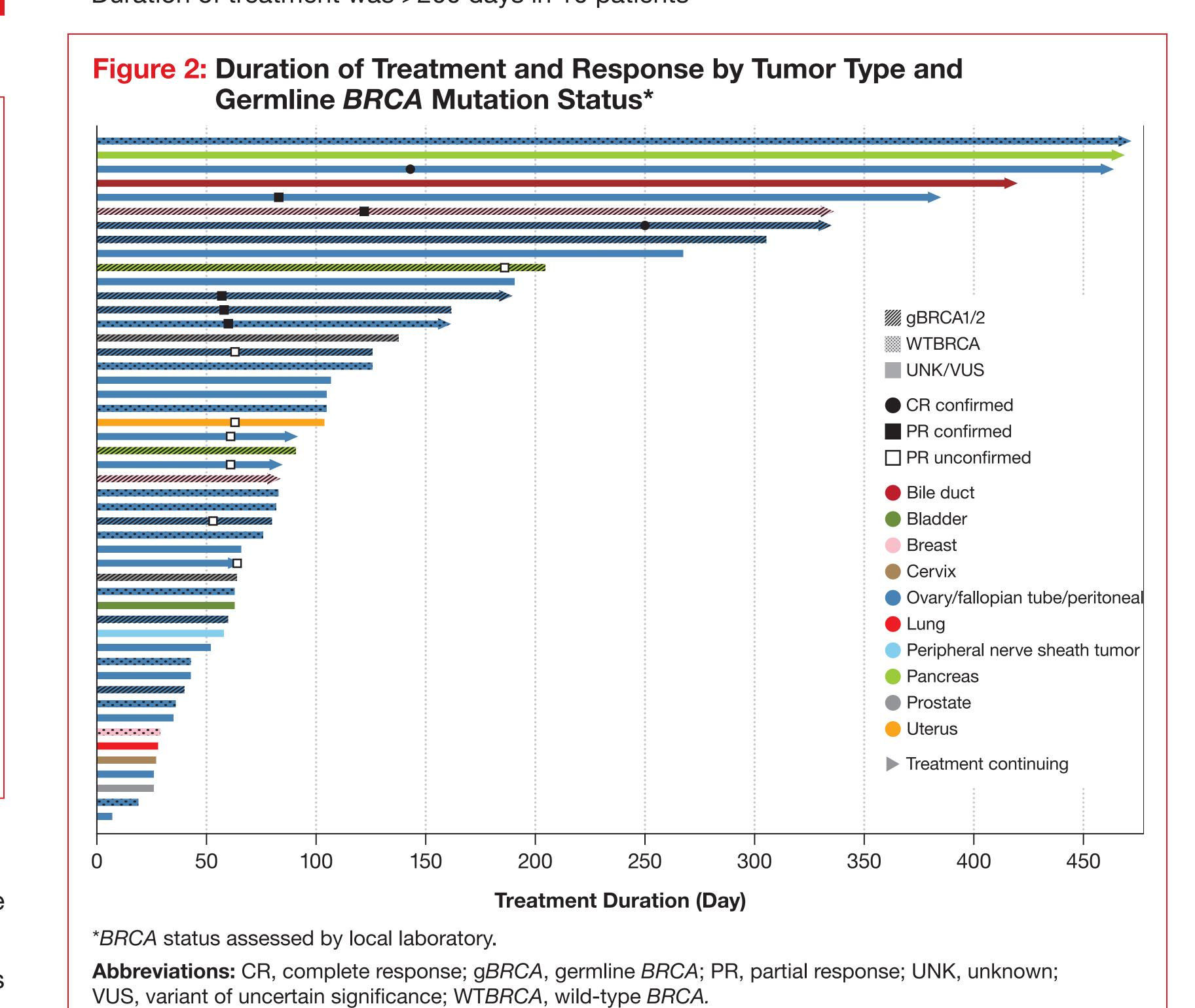
- RP2D was established to be tislelizumab 200 mg IV Q3W + pamiparib 40 mg po BID
- Dose-limiting toxicities were grade 2 nausea and grade 3 rash (dose-level 4), and grade 2 nausea/vomiting and grade 4 auto-immune (AI) hepatitis (dose-level 5)

# **Preliminary Assessments of Antitumor Activity**

11 patients remain on treatment

BRCA 1/2 germline/somatic mutation

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

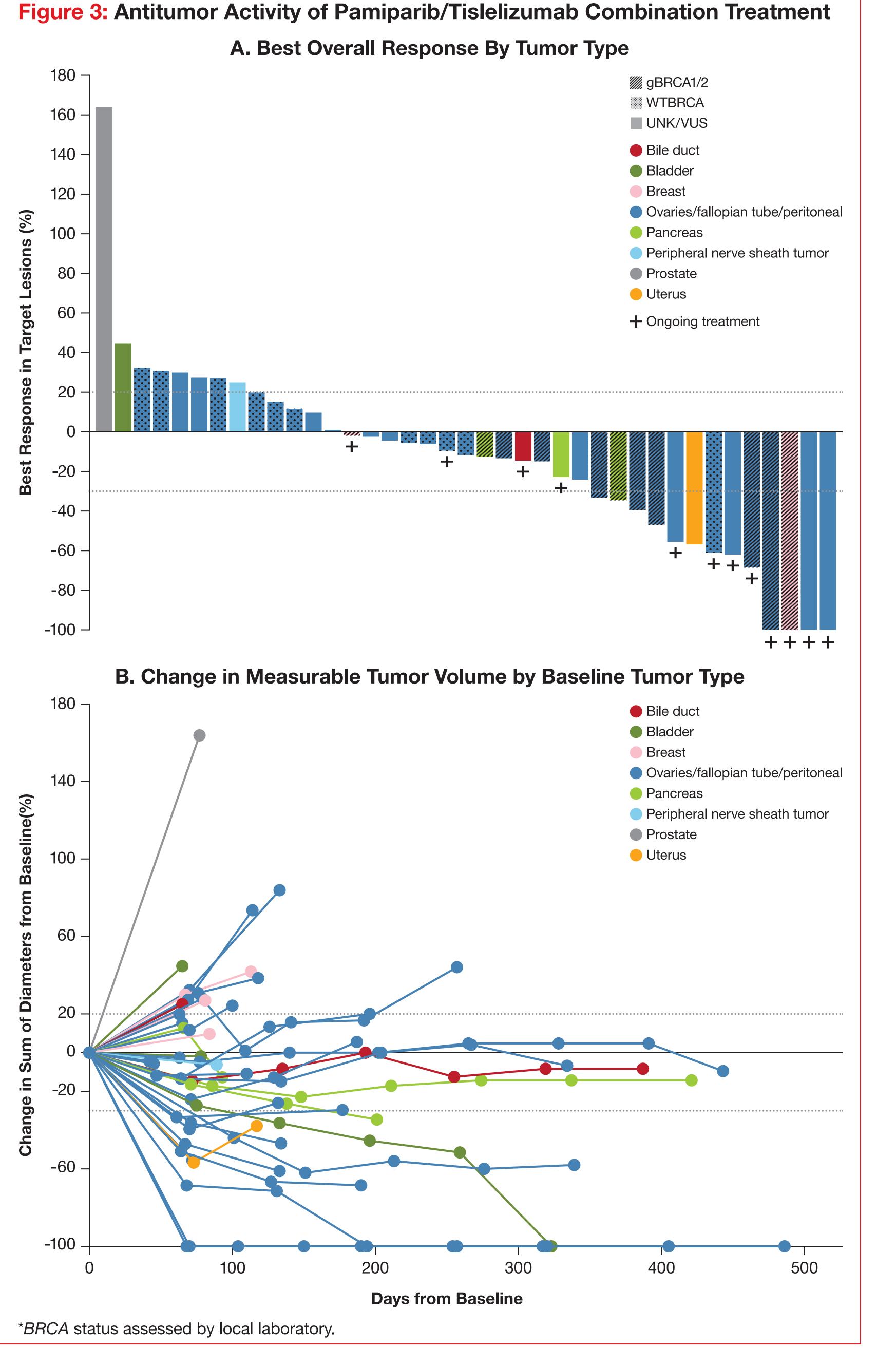


# **Table 2: Best Overall Response Rate**

RECIST v 1.1 Best Overall Response, n (%)	Total (N=49)
Complete response (CR)	2 (4)
Partial response (PR) – confirmed	5 (10)
Partial response (PR) – unconfirmed	7 (14)
Objective response rate (CR+PR)	7 (14)
Clinical benefit rate (CR+PR+durable SD with ≥24 weeks)	15 (31)

#### Data presented as n (%).

- 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



# 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 ≥1 DLT, n	3
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

	Polotod to	naminarih	Related to t	ielolizumah
	Related to Grade 1-2	Grade 3–4	Grade 1–2	Grade 3–4
	(≥5% of pts)	(≥2 of pts)	(≥5% 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 (%).

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

	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

### 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 2018, evidence of complete or partial response was observed in 10 patients; responses were durable and observed in patients with wild type and mutant gBRCA
- Together, these results support the continuation of this trial with continued enrollment into the disease-specific cohorts

# **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/Al 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-TEAEsi

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