PHASE 2 STUDY OF PAMIPARIB IN CHINESE PATIENTS WITH ADVANCED OVARIAN CANCER

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INTRODUCTION

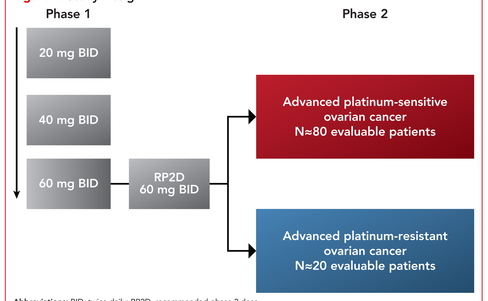
- Poly (ADP-ribose) polymerase (PARP) proteins are involved in the repair of single- and double-strand DNA breaks[1,2]
- Small-molecule PARP inhibitors are a class of therapeutic agents used to treat various malignancies, including tumors harboring *BRCA1/2* mutations[3,4]
  - PARP inhibition impairs DNA repair and traps PARP proteins on damaged DNA, resulting in cytotoxicity that is exacerbated in homologous recombination deficient cells[3]
- Pamiparib is an investigational, potent, selective, oral PARP1/2 inhibitor[5]
  - In preclinical models, pamiparib demonstrated PARP-DNA complex trapping, inhibition of PARylation, brain penetration, and antitumor activity[5]
- Results of the first-in-human study (BGB-290-AU-002) showed that pamiparib was generally well tolerated and had antitumor activity, notably in patients with epithelial ovarian cancer (OC)[6]
  - The recommended phase 2 dose (RP2D) of pamiparib was established as 60 mg orally (PO) twice daily (BID)
- The RP2D was confirmed in Chinese patients with advanced OC or triple-negative breast cancer in the dose-escalation (phase 1) portion of this phase 1/2 study (BGB-290-102)[7]
- Here we present the preliminary results of the RP2D-expansion in Chinese patients with *BRCA1/2* mutation–positive platinum-sensitive OC (PSOC) or platinum-resistant OC (PROC)

METHODS

Study Design

- This phase 1/2 study is an open-label, multicenter study assessing the safety and antitumor activity of pamiparib in adult (≥18 years) Chinese patients with advanced solid tumors whose disease progressed despite standard therapy or for which there is no standard therapy (Figure 1)
- Pamiparib 60 mg was administered PO BID on Day 1 of Cycle 1 (21-day cycle) and continuously in all subsequent cycles until disease progression, toxicity, or patient withdrawal

Figure 1: Study Design



Abbreviations: BID, twice daily; RP2D, recommended phase 2 dose.

Study Population

- Phase 2 enrolled female patients with histologically or cytologically confirmed high-grade, non-mucinous, epithelial OC (including fallopian or primary peritoneal cancer) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1; patients had advanced OC that was either platinum-sensitive (Cohort 1) or platinum-resistant (Cohort 2)
  - Platinum-sensitive was defined as disease progression occurring ≥6 months after last platinum treatment
  - Platinum-resistant was defined as disease progression that occurred <6 months after last platinum treatment
- Both cohorts enrolled patients with either known deleterious or suspected deleterious *gBRCA*^{mut} who received at least two lines of standard chemotherapy and were either currently experiencing relapsed disease or had discontinued the most recent standard treatment due to unacceptable toxicity
- Patients were excluded if they had untreated and/or active brain metastases or received chemotherapy, radiotherapy, biologic therapy, immunotherapy, investigational agent, anticancer Chinese medicine, or anticancer herbal remedies within 14 days of initiating study

Endpoints and Assessments

- The primary endpoint was objective response rate (ORR) based on independent review committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Secondary endpoints included duration of response and progression-free survival (PFS) by IRC and investigator review; disease control rate and clinical benefit rate by IRC and investigator review; ORR by investigator review; overall survival (OS); CA-125 response rate per Gynecologic Cancer Intergroup criteria; and pamiparib safety/tolerability profile
- Tumor imaging and CA-125 testing occurred every 6 weeks after the first dose of pamiparib for the first 18 weeks, every 9 weeks for the remaining period in the first year, and every 12 weeks from the second year onward
- Safety and tolerability assessments were based on monitoring of adverse events (AEs), as well as on vital signs, electrocardiograms, physical examinations, and clinical laboratory results
  - A protocol amendment (PA; protocol v5.0) initiated a more proactive dose modification algorithm and close hematology monitoring; a pre- and post-PA safety analysis was conducted; the post-PA subgroup included patients who signed the first informed consent form under the amended protocol

Statistical Methods

- Antitumor activity per RECIST v1.1 was assessed in all efficacy-evaluable patients
- Safety and tolerability were evaluated in all patients who received ≥1 dose of pamiparib

RESULTS

Patient Demographics and Baseline Disease Characteristics

- As of February 2, 2020, 113 patients who had received multiple lines of therapy (PSOC, n=90; PROC, n=23) with a median age of 54 years were enrolled (Table 1), of which, 74 discontinued from treatment
  - Reasons for treatment discontinuation include progressive disease (n=47), AE (n=14), patient withdrawal (n=10), and investigator's decision (n=3)
- Median study follow-up was 12.2 months (range, 0.2-21.5)

Table 1: Patient Demographics and Baseline Characteristics

		PSOC (N=90)	PROC (N=23)	Total (N=113)
Median age, years (range)		54 (39-79)	54 (34-66)	54 (34-79)
ECOG score, n (%)	<65 years	80 (88.9)	21 (91.3)	101 (89.4)
	0	42 (46.7)	10 (43.5)	52 (46.0)
	1	48 (53.3)	13 (56.5)	61 (54.0)
Number of prior lines of systemic chemotherapy, n (%)	2	52 (57.8)	3 (13.0)	55 (48.7)
	3	19 (21.1)	10 (43.5)	29 (25.7)
	4	8 (8.9)	6 (26.1)	14 (12.4)
	5	4 (4.4)	1 (4.3)	5 (4.4)
	≥6	7 (7.8)	3 (13.0)	10 (8.8)
gBRCA status, n (%)	*BRCA1* mutation	79 (87.8)	19 (82.6)	98 (86.7)
	BRCA2 mutation	11 (12.2)	4 (17.4)	15 (13.3)
Years from initial diagnosis, median (range)		3.9 (1.4-13.6)	3.6 (1.1-7.1)	3.9 (1.1-13.6)
FIGO histology, n (%)	Serous epithelial tumors	85 (94.4)	23 (100.0)	108 (95.6)
	Endometrioid epithelial tumors	4 (4.4)	0	4 (3.5)
	Mixed epithelial tumors	1 (1.1)	0	1 (0.9)
Target lesion diameter per IRC at study entry, n (%)	<50 mm	41 (45.6)	8 (34.8)	49 (43.4)
	≥50 mm	41 (45.6)	11 (47.8)	52 (46.0)
	Missing	8 (8.9)	4 (17.4)	12 (10.6)
CA-125 value at study entry, n (%)	<70 kU/L	16 (17.8)	2 (8.7)	18 (15.9)
	≥70 kU/L	74 (82.2)	21 (91.3)	95 (84.1)

Abbreviations: *BRCA*, breast cancer susceptibility gene; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; IRC, independent review committee; PROC, platinum-resistant ovarian cancer; PSOC, platinum-sensitive ovarian cancer.

Antitumor Activity

- Objective response rate and complete response rate per RECIST v1.1 was similar between IRC and investigator assessment (Table 2)
- CA-125 response rate was 79.7% (95% CI, 68.8-88.2) in PSOC patients and 38.1% (95% CI, 18.1-61.6) in PROC patients

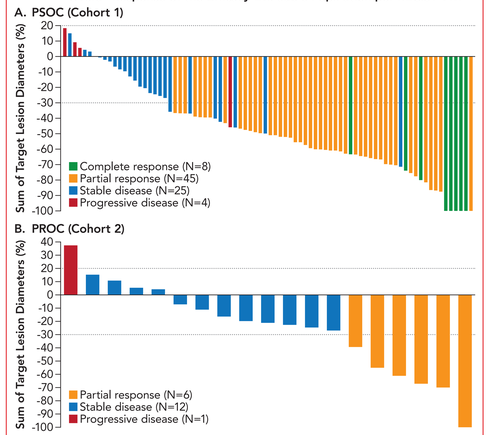
Table 2: Tumor Response by Patient Cohort in the Efficacy-Evaluable Population by IRC and Investigator Assessment Based on RECIST v1.1

			PSOC (n=82)	PROC (n=19)
IRC Assessment	BOR, n (%)	Complete response	8 (9.8)	0 (0.0)
		Partial response	45 (54.9)	6 (31.6)
		Stable disease	25 (30.5)	12 (63.2)
		Progressive disease	4 (4.9)	1 (5.3)
		Not estimable	0 (0.0)	0 (0.0)
	ORR, % (95% CI)		64.6 (53.3-74.9)	31.6 (12.6-56.6)
	DCR, % (95% CI)		95.1 (88.0-98.7)	94.7 (74.0-99.9)
	CBR ≥24 weeks, % (95% CI)		74.4 (63.6-83.4)	52.6 (28.9-75.6)
	Median time to response, months (min, max)		1.7 (1.3, 6.3)	1.4 (1.2, 1.4)
Investigator Assessment	BOR, n (%)	Complete response	5 (6.1)	0 (0.0)
		Partial response	46 (56.1)	5 (26.3)
		Stable disease	28 (34.1)	10 (52.6)
		Progressive disease	3 (3.7)	3 (15.8)
		Not estimable	0 (0.0)	1 (5.3)
	ORR, % (95% CI)		62.2 (50.8-72.7)	26.3 (9.1-51.2)
	DCR, % (95% CI)		96.3 (89.7-99.2)	78.9 (54.4-93.9)
	CBR ≥24 weeks, % (95% CI)		72.0 (60.9-81.3)	52.6 (28.9-75.6)
	Median time to response, months (min, max)		2.7 (1.2, 8.3)	1.3 (1.2, 4.2)

CBR=CR+PR+SD ≥24 weeks; DCR=CR+PR+SD; ORR=CR+PR.
Abbreviations: BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; DCR, disease control rate; IRC, independent review committee; NE, not estimable; OC, ovarian cancer; ORR, objective response rate; PROC, platinum-resistant ovarian cancer; PSOC, platinum-sensitive ovarian cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

- In both cohorts, most patients had a reduction in target lesions from baseline (Figure 2A and 2B)

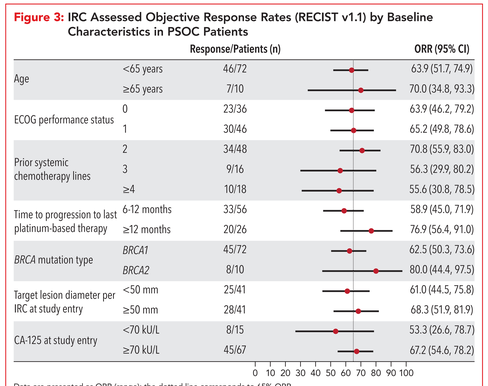
Figure 2: Best Change in Sum of Target Lesion Diameters by Confirmed Best Overall Response of the Efficacy-Evaluable Population per RECIST v1.1



Patients were considered efficacy-evaluable if they had measurable disease at baseline per RECIST v1.1 and had ≥1 postbaseline tumor assessment, unless treatment had been discontinued due to clinical progression or death prior to tumor assessment.
Abbreviations: PROC, platinum-resistant ovarian cancer; PSOC, platinum-sensitive ovarian cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

- Primary endpoint of ORR in PSOC patients was generally consistent across all subgroups analyzed (Figure 3)

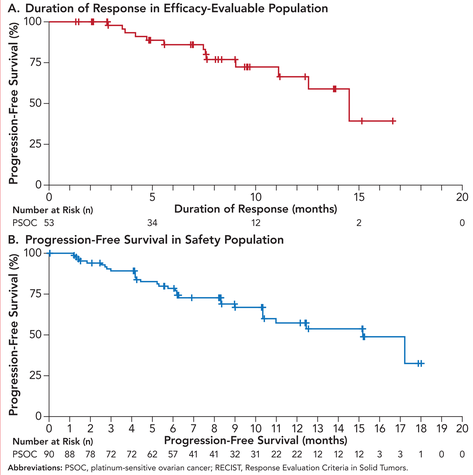
Figure 3: IRC Assessed Objective Response Rates (RECIST v1.1) by Baseline Characteristics in PSOC Patients



Data are presented as ORR (range); the dotted line corresponds to 65% ORR.
Abbreviations: *BRCA*, breast cancer susceptibility gene; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; ORR, objective response rate; PSOC, platinum-sensitive ovarian cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

- In PSOC patients, median duration of response was 14.5 months (95% CI, 11.1-NE) (Figure 4A) and median PFS was 15.2 months (95% CI, 10.35-NE) (Figure 4B)

Figure 4: Duration of Response and Progression-Free Survival in PSOC Patients by IRC Assessment per RECIST v1.1



Abbreviations: PSOC, platinum-sensitive ovarian cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

Safety and Tolerability

- Median treatment duration was 8.3 (range, 0.1-19.3) months in PSOC patients and 4.1 (range, 0.1-19.9) months in PROC patients
- Across both PSOC and PROC cohorts, the most frequently reported AEs of any grade were gastrointestinal disorders and hematologic toxicities (Table 3)

CONCLUSIONS

- Statistical and clinical meaningful and durable response were observed in patients with PSOC; clinical meaningful and durable responses were observed in patients with PROC
- Pamiparib 60 mg PO BID demonstrated a generally tolerated and acceptable safety profile
  - The overall safety profile was generally consistent between patients with PSOC and PROC
- Similar to other PARP inhibitors, hematologic toxicities were the most significant safety events observed
  - The hematological toxicities were manageable and could be better managed with a more proactive modification plan and closer hematologic monitoring
  - No myelodysplastic syndrome reported
  - No significant complications (eg grade ≥3 hemorrhage, fever, or infection) potentially related to hematologic toxicity were reported
- In the post-PA subgroup, the percentage of patients who experienced grade ≥3 hematologic AEs was lower, compared with the pre-PA subgroup (Table 3)
- No patient in the post-PA subgroup experienced a hematologic AE that led to treatment discontinuation

Table 3: Treatment-Emergent Adverse Events of Any Grade (≥20% in the Total Population) and of Grade ≥3

	PSOC (n=90)		PROC (n=23)		Total (N=113)		Pre-PA (n=74)		Post-PA (n=39)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Anemia	80 (88.9)	34 (37.8)	21 (91.3)	13 (56.5)	101 (89.4)	47 (41.6)	65 (87.8)	37 (50.0)	36 (92.3)	10 (25.6)
Nausea	61 (67.8)	1 (1.1)	16 (69.6)	0 (0.0)	77 (68.1)	1 (0.9)	48 (64.9)	1 (1.4)	29 (74.4)	0 (0.0)
Decreased neutrophil count	56 (62.2)	28 (31.1)	13 (56.5)	10 (43.5)	69 (61.1)	38 (33.6)	46 (62.2)	29 (39.2)	23 (59.0)	9 (23.1)
Decreased white blood cell count	54 (60.0)	17 (18.9)	14 (60.9)	5 (21.7)	68 (60.2)	22 (19.5)	44 (59.5)	16 (21.6)	24 (61.5)	6 (15.4)
Vomiting	46 (51.1)	4 (4.4)	11 (47.8)	1 (4.3)	57 (50.4)	5 (4.4)	42 (56.8)	5 (6.8)	15 (38.5)	0 (0.0)
Decreased platelet count	25 (27.8)	4 (4.4)	10 (43.5)	1 (4.3)	35 (31.0)	5 (4.4)	22 (29.7)	2 (2.7)	13 (33.3)	3 (7.7)
Decreased appetite	29 (32.2)	0 (0.0)	5 (21.7)	0 (0.0)	34 (30.1)	0 (0.0)	21 (28.4)	0 (0.0)	13 (33.3)	0 (0.0)
Asthenia	26 (28.9)	1 (1.1)	6 (26.1)	0 (0.0)	32 (28.3)	1 (0.9)	20 (27.0)	1 (1.4)	12 (30.8)	0 (0.0)
Diarrhea	19 (21.1)	3 (3.3)	6 (26.1)	0 (0.0)	25 (22.1)	3 (2.7)	19 (25.7)	1 (1.4)	6 (15.4)	2 (5.1)
Increased AST	20 (22.2)	0 (0.0)	4 (17.4)	1 (4.3)	24 (21.2)	1 (0.9)	15 (20.3)	1 (1.4)	9 (23.1)	0 (0.0)
Decreased lymphocyte count	19 (21.1)	6 (6.7)	5 (21.7)	2 (8.7)	24 (21.2)	8 (7.1)	19 (25.7)	7 (9.5)	5 (12.8)	1 (2.6)
Increased ALT	18 (20.0)	1 (1.1)	5 (21.7)	0 (0.0)	23 (20.4)	1 (0.9)	15 (20.3)	1 (1.4)	8 (20.5)	0 (0.0)
Leukopenia	20 (22.2)	9 (10.0)	3 (13.0)	3 (13.0)	23 (20.4)	12 (10.6)	17 (23.0)	11 (14.9)	6 (15.4)	1 (2.6)

Data presented as n (%).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PA, protocol amendment; PROC, platinum-resistant ovarian cancer; PSOC, platinum-sensitive ovarian cancer.

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CONFLICTS OF INTEREST

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