DOSE ESCALATION OF PAMIPARIB IN CHINESE PATIENTS WITH HIGH-GRADE NON-MUCINOUS OVARIAN CANCER OR ADVANCED TRIPLE-NEGATIVE BREAST CANCER

Binghe Xu[1], Yongmei Yin[2], Yan Song[1], Wei Li[2], Xiang Huang[2], Miao Li[3], Xiyan Mu[4], Li Li[3], Song Mu[5], Juan Liang[3], Xiaofang Liang[4], Zhenkai Zhao[3], Yan Qiao[3], Mei Dong[1]

[1]Chinese Academy of Medical Sciences Tumor Hospital, Beijing, China; [2]Jiangsu Province Hospital, Jiangsu, China; [3]BeiGene (Beijing) Co., Ltd., Beijing, China; [4]BeiGene (Shanghai) Co., Ltd., Shanghai, China; [5]BeiGene USA, Inc., San Mateo, CA, USA

Chinese Society of Clinical Oncology
18-22 September 2019 | Xiamen, Fujian, China

BACKGROUND

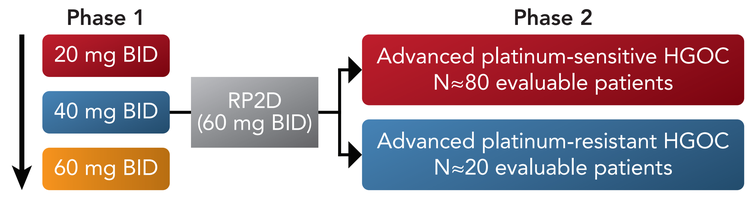
- Poly(ADP-ribose) polymerase (PARP) proteins are involved in DNA repair, genome stability, and programmed cell death[1]
- The primary function of PARP proteins is to detect single-strand breaks (SSBs) in DNA and target the breaks for repair[2]
- Inhibition of PARP proteins allows for accumulation of unrepaired SSBs, which are converted to double-strand breaks (DSBs) during cell division and can lead to apoptosis/cell death[2]
- In normal cells, DSBs are repaired by homologous recombination (HR); however, in the absence of HR components (eg, *BRCA1*, *BRCA2*) repair is compromised[2]
- PARP inhibitors (PARPi) represent a new class of therapeutic agents for the treatment of malignancies associated with *BRCA1/2* mutations
  - Although the exact mechanism of action of PARPi in cell death has not yet been fully elucidated, prevention of DNA repair and PARP trapping have been proposed as the main mechanisms of action[3]
- Pamiparib is an investigational, selective PARP1/2 inhibitor that penetrates the blood-brain barrier, has shown PARP trapping, and has demonstrated antitumor activity in preclinical models
- In a first-in-human (FIH) study (NCT02361723), pamiparib was generally well tolerated and showed preliminary antitumor activity, notably in patients with high-grade non-mucinous ovarian cancer (HGOC)
  - The FIH study established the recommended Phase 2 dose (RP2D) and maximum tolerated dose as 60 mg orally (PO) twice daily (BID) and 80 mg PO BID, respectively
- Data presented here are the results from the dose-escalation phase of an ongoing Phase 1/2 study in Chinese patients with advanced ovarian, fallopian, and primary peritoneal, or advanced triple-negative breast cancer (TNBC) (NCT03333915)

METHODS

Overall Design and Study Objectives

- This study consists of two phases (**Figure 1**):
  - Phase 1 was a dose-escalation phase that followed a 3+3 design to confirm the RP2D of pamiparib in Chinese patients (aged ≥18 years) with locally advanced or metastatic HGOC, including fallopian and primary peritoneal cancer, or TNBC, who had disease progression following at least one line of chemotherapy
    - Patients with germline *BRCA1/2* mutation (*gBRCA*^{mut}) were retrospectively identified by central testing
    - Patients were defined as platinum-refractory if disease progression had occurred during their last platinum treatment; platinum-resistant was defined as disease progression that occurred less than 6 months after the last platinum treatment
  - Phase 2 is a RP2D-expansion phase investigating the safety and tolerability, as well as antitumor activity, of oral pamiparib in adult (aged ≥18 years) patients with advanced platinum-sensitive HGOC (disease progression occurring >6 months after last platinum treatment; *Cohort 1*) or advanced platinum-resistant HGOC (*Cohort 2*)
    - Patients with either known deleterious or suspected deleterious *gBRCA*^{mut} who have received at least two lines of prior therapy will be enrolled

Figure 1: Study Design



Abbreviations: BID, twice daily; HGOC, high-grade non-mucinous ovarian cancer; RP2D, recommended Phase 2 dose.

Study Assessments and Analysis

- Safety and tolerability assessments were based on monitoring of treatment-emergent adverse events (AEs), as well as on vital signs, electrocardiograms, physical examinations, and clinical laboratory results
  - Safety and tolerability were evaluated in all patients who received ≥1 dose of pamiparib
- Antitumor activity was assessed in all evaluable patients based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.1
  - Patients were considered response-evaluable if they had measurable disease at baseline per RECIST v1.1 and had ≥1 post-baseline tumor assessment, unless treatment had been discontinued due to clinical progression or death prior to tumor assessment
- CA-125 response rate, per Gynecological Cancer Intergroup (GCIG), was also assessed in patients with HGOC
  - Patients with HGOC had carcinoma antigen 125 (CA-125) tested in a local laboratory at baseline, every 6 weeks in the first year, and then every 12 weeks thereafter; CA-125 responses must have been confirmed and maintained for at least 28 days
  - Patients were evaluated according to CA-125 *only* if they had a baseline sample that was at least twice the upper limit of reference range
- Progression-free survival (PFS) was estimated using the Kaplan-Meier method along with the corresponding 95% confidence interval (CI) constructed with a generalized Brookmeyer and Crowley method

RESULTS

Patient Demographics and Baseline Disease Characteristics

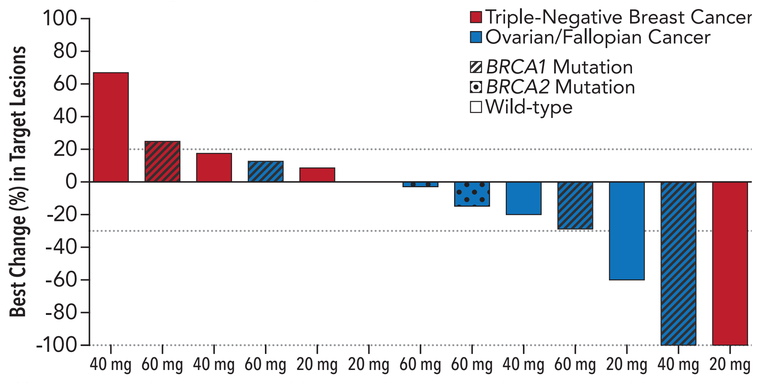
- A total of 15 Chinese female patients (HGOC, n=9; TNBC, n=6) were enrolled in the dose-escalation phase of the study (**Table 1**)
- As of 14 March 2019, 14 patients have discontinued from treatment
  - Patients discontinued due to disease progression (n=6), AEs (n=2), lost to follow-up (n=1), investigator decision (n=1), and other (n=4)
  - Across the 15 patients, median duration of treatment was 2.5 months (range: 0.3, 26.1) and median study follow-up was 3.45 months (range: 1.2, 26.1)
- The majority of patients (60%) were heavily pretreated with at least four prior lines of therapy, and eight HGOC patients were resistant and one refractory to systemic platinum chemotherapy
- A total of seven patients had confirmed *gBRCA*^{mut} status (HGOC, n=5; TNBC, n=2); eight patients were *gBRCA* wild-type (HGOC, n=4; TNBC, n=4)

Table 1: Patient Demographics and Baseline Disease Characteristics

		20 mg BID (n=4)	40 mg BID (n=4)	60 mg BID (n=7)	Total (N=15)
Tumor type, n (%)	Ovarian*	1 (25)	1 (25)	4 (57)	6 (40)
	Fallopian*	1 (25)	1 (25)	1 (14)	3 (20)
	TNBC	2 (50)	2 (50)	2 (29)	6 (40)
Median age, years (range)		52.5 (48-62)	47.0 (32-66)	49.0 (46-70)	49.0 (32-70)
ECOG score, n (%)	0	0	1 (25)	1 (14)	2 (13)
	1	4 (100)	3 (75)	6 (86)	13 (87)
Number of prior lines of therapy, n (%)	1-3	2 (50)	3 (75)	1 (14)	6 (40)
	≥4	2 (50)	1 (25)	6 (86)	9 (60)
gBRCA status, n (%)	*BRCA1* mutation	0	1 (25)	4 (57)	5 (33)
	BRCA2 mutation	0	0	2 (29)	2 (13)
	Wild-type	4 (100)	3 (75)	1 (14)	8 (53)
Years from initial diagnosis, median (range)		3.7 (1.0-7.6)	2.0 (0.4-3.4)	5.2 (1.4-14.1)	3.4 (0.4-14.1)

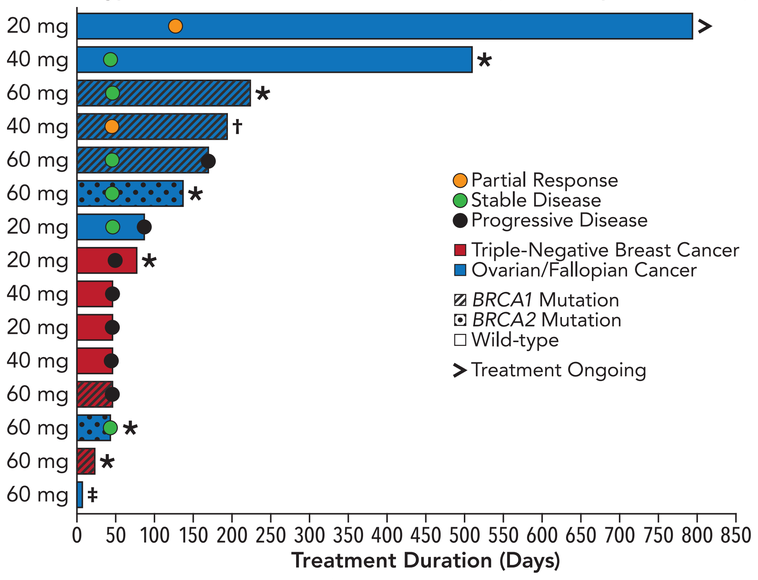
*Included in HGOC population.
Abbreviations: BID, twice daily; *BRCA*, breast cancer susceptibility gene; ECOG, Eastern Cooperative Oncology Group; HGOC, high-grade non-mucinous ovarian cancer; TNBC, triple-negative breast cancer.

Figure 2: Clincal Response Using RECIST Criteria by Tumor Type (Efficacy Evaluable Population, N=13)



Abbreviations: *BRCA*, breast cancer susceptibility gene; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 3: Duration of Treatment and Response Using RECIST Criteria by Tumor Type and Germline *BRCA* Mutation Status (Overall Population, N=15)



*Discontinued due to reasons other than AE or PD; †discontinued due to AE unrelated to treatment; ‡discontinued due to AE that was possible treatment related.
Dots indicate timepoint when best overall response was achieved.
Abbreviations: *BRCA*, breast cancer susceptibility gene; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 2: Best Overall Response by Tumor Type (Efficacy Evaluable Population, N=13)

	HGOC (n=8)	TNBC (n=5)
Complete response (CR), n (%)	0	0
Partial response (PR), n (%)	2 (25)	0
Stable disease (SD), n (%)	6 (75)	0
Progressive disease (PD), n (%)	0	5 (100)
Objective response (CR+PR), % (95% CI)	**25 (3.2, 65.1)**	**0**
Disease control rate (CR+PR+SD)	**100 (63.1, 100)**	**0**
Clinical benefit rate (CR+PR+SD) ≥24 weeks, % (95% CI)	**62.5 (24.5, 91.5)**	**0**

Data presented as n (%). Only patients who had at least one postbaseline tumor assessment were included.
Abbreviations: CI, confidence interval; HGOC, high-grade non-mucinous ovarian cancer; TNBC, triple-negative breast cancer.

Antitumor Activity

- A total of 13 patients were evaluable per RECIST v1.1 criteria
  - Two patients (HGOC, n=1; TNBC, n=1) discontinued treatment prior to first post-baseline scan
- Across the eight RECIST-evaluable HGOC patients, two achieved a confirmed partial response (*gBRCA*^{mut}, n=1) and six achieved stable disease (*gBRCA*^{mut}, n=4) (**Table 2**; **Figures 2-3**)
  - All evaluable HGOC patients achieved partial response or stable disease, including one patient who was platinum refractory and seven who were platinum resistant
- Median treatment duration for the eight HGOC patients was 182 days (range: 43, 795)
- Best overall response was progressive disease (PD) for all five RECIST-evaluable TNBC patients, one of whom was *gBRCA*^{mut} (**Figures 2-3**)
  - All five TNBC patients experienced PD previously during platinum-based chemotherapy
- Eight HGOC patients were CA-125-evaluable; one patient achieved a confirmed complete response and one patient achieved a confirmed partial response
  - Median time to response (per CA-125 criteria) was 1.45 months (range: 1.4, 1.5)

CONCLUSIONS

- Pamiparib at 20, 40, and 60 mg PO BID was generally well tolerated in Chinese patients with advanced HGOC or TNBC
  - Asthenia and nausea were the most commonly reported treatment-related AEs
  - Most reported AEs were of mild or moderate severity
- Pamiparib, orally administered at 60 mg BID, was confirmed as the RP2D in Chinese patients
- Confirmed and durable clinical responses, as assessed by both RECIST and CA-125 criteria, were observed in patients with HGOC
  - Antitumor responses were observed among patients with *BRCA* wild-type as well as in patients with HGOC sensitive or resistant to platinum chemotherapy
- As of 14 March 2019, one HGOC patient from the dose-escalation cohort remained on treatment; enrollment in the expansion phase closed on 2 Aug 2019

Progression-Free Survival

- As of 14 March 2019, median PFS in the nine patients with HGOC was not estimated as only two non-censored events (disease progression) had occurred
  - Reasons for censoring were *no disease progression* (n=5), *new anticancer treatment* (n=1), and *no post-baseline assessment* (n=1)
  - Median follow-up for these nine patients was 5.6 months (95% CI: 0.03, 23.6)
  - The event-free rate at 9 months in patients with HGOC was 68.6% (95% CI: 21.3, 91.2)
- In patients with TNBC, median PFS was estimated as 1.5 months (95% CI: 1.45, 1.61)

Safety and Tolerability

- Pamiparib was generally well tolerated with asthenia and nausea being the most commonly reported AEs considered by the investigators to be at least possibly related to pamiparib (**Table 3**)
  - Decreased hemoglobin (n=3) was the only Grade 3 TRAE reported in more than two patients
  - Other Grade 3 TRAEs were anemia, decrease neutophil count, decrease white blood cell count (n=2, each); decreased platelet count, nausea, prolong QT interval, and vomiting (n=1, each)
  - No ≥ Grade 4 TRAEs were reported
- No dose-limiting toxicities were reported across the dose range (20-60 mg); the RP2D was confirmed as 60 mg PO BID
- Overall, three patients experienced a serious AE (abdominal infection, n=1; pleural effusion, n=1; ileus, n=1), none of which were considered related to treatment
  - Two serious AEs led to treatment withdrawal (abdominal infection, n=1; pleural effusion, n=1)

Table 3: Adverse Events (All Grades) Considered Related to Pamiparib Occurring in ≥20% of the Total Population

	20 mg BID (n=4)		40 mg BID (n=4)		60 mg BID (n=7)		Total (N=15)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Asthenia	3 (75)	0	4 (100)	0	5 (71)	0	12 (80)	0
Nausea	4 (100)	0	3 (75)	0	5 (71)	1 (14)	12 (80)	1 (7)
Decreased white blood cell count	2 (50)	0	3 (75)	0	5 (71)	2 (29)	10 (67)	2 (13)
Decreased appetite	3 (75)	0	3 (75)	0	3 (43)	0	9 (60)	0
Decreased neutrophil count	1 (25)	0	3 (75)	0	4 (57)	2 (29)	8 (53)	2 (13)
Decreased hemoglobin	0	0	1 (25)	0	5 (71)	3 (43)	6 (40)	3 (20)
Bilirubin conjugated increased	1 (25)	0	1 (25)	0	2 (29)	0	4 (27)	0
Electrocardiogram QT prolonged*	1 (25)	1 (25)	1 (25)	0	2 (29)	0	4 (27)	1 (7)
Vomiting	1 (25)	0	1 (25)	0	2 (29)	1 (14)	4 (27)	1 (7)
Decreased platelet count	0	0	0	0	3 (43)	1 (14)	3 (20)	1 (7)
Diarrhea	0	0	1 (25)	0	2 (29)	0	3 (20)	0
Increased GGT	1 (25)	0	1 (25)	0	1 (14)	0	3 (20)	0
Somnolence	1 (25)	0	1 (25)	0	1 (14)	0	3 (20)	0
Tachycardia	0	0	1 (25)	0	2 (29)	0	3 (20)	0

Data presented as n (%).
*In all four patients, QTcF was 450-480 ms without clinical sequelae.
Abbreviations: BID, twice daily; GGT, gamma-glutamyl transferase.

REFERENCES

1. Thomas C, Tulin AV. Poly-ADP-ribose polymerase: machinery for nuclear processes. *Mol Aspects Med.* 2013;34(6):1124-1137.
2. Dziadkowiec K, Gasiorowska E, Nowak-Markwitz, et al. PARP inhibitors: review of mechanisms of action and BRCA1/2 mutation targeting. *Menopause Rev.* 2016;15(4):215-219.
3. Lupo B, Trusolino L. Inhibition of poly(ADP-ribosyl)ation in cancer: old and new paradigms revisited. *Biochim Biophys Acta.* 2014;1846:201-215.

ACKNOWLEDGMENTS

The authors wish to acknowledge the investigative center study staff and study patients, and recognize those from BeiGene, Ltd. who have substantially contributed to the development of this presentation. This study was sponsored by BeiGene, Ltd. Writing and editorial assistance was provided by Regina Switzer, PhD, and Elizabeth Hermans, PhD (OPEN Health Medical Communications, Chicago, IL), and funded by the study sponsor.

Please address any questions or comments regarding this poster to Clinicaltrials@beigene.com