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A PHASE 1 DOSE-ESCALATION STUDY OF PAMIPARIB, A PARP INHIBITOR, IN CHINESE PATIENTS WITH ADVANCED OVARIAN, FALLOPIAN, AND PRIMARY PERITONEAL, OR ADVANCED TRIPLE-NEGATIVE BREAST CANCER

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INTRODUCTION

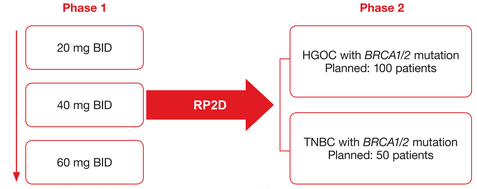
- Poly (ADP-ribose) polymerase (PARP) proteins are involved in DNA repair, genome stability, and programmed cell death[1]
- The primary function of PARP proteins is to detect single-strand breaks (SSBs) in DNA and target the breaks for repair[2]
- Inhibition of PARP proteins allows for accumulation of unrepaired SSBs, which are converted to double-strand breaks (DSBs) during cell division and can lead to apoptosis/cell death[3]
- In normal cells, DSBs are repaired by homologous recombination (HR); however, in the absence of HR components (eg, *BRCA1, BRCA2*) repair is compromised[3]
- PARP inhibitors (PARPi) represent a new class of therapeutic agents for the treatment of malignancies associated with *BRCA1/2* mutations
  - PARPi bind directly to, and inhibit activity of, PARP enzymes[4]
  - 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[5]
- Pamiparib (previously known as BGB-290) is a 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 study (NCT02361723), pamiparib was generally well tolerated and showed preliminary antitumor activity, notably in patients with high-grade non-mucinous ovarian cancer (HGOC)
  - This study has 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 (NCT03333915)

METHODS

Overall Design and Study Objectives

- This study consists of a 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 triple-negative breast cancer (TNBC), who had disease progression following at least one line of chemotherapy
  - Patients with germline *BRCA1/2* mutation (*BRCAm*) were retrospectively identified by central testing

Figure 1: Study Design



Abbreviations: BID, twice daily; *BRCA*, breast cancer susceptibility gene; HGOC, high-grade ovarian cancer; RP2D, recommended Phase 2 dose; TNBC, triple-negative breast cancer.

  - 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 HGOC (Cohort 1) or TNBC (Cohort 2)
    - Cohort 1 will enroll patients with platinum-sensitive/platinum-resistant HGOC with known or suspected deleterious germline *BRCA1/2* mutation as identified by central testing
    - Cohort 2 will enroll patients with TNBC with either known or suspected deleterious germline *BRCA1/2* mutation identified by central testing

Study Assessments and Analysis

- Safety and tolerability were evaluated in all patients who received ≥1 dose of pamiparib
- 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
- Antitumor activity was assessed in all evaluable patients based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.1

RESULTS

Patient Demographics and Baseline Disease Characteristics

- Fifteen female patients (HGOC: n=9; TNBC: n=6) were enrolled in the dose-escalation phase of the study (**Table 1**)
- As of 25 Sep 2017, 10 patients have discontinued
  - Patients discontinued due to disease progression (n=5), adverse events (n=2), lost to follow-up (n=2), and protocol deviation (n=1)
- The majority of patients (60%) were heavily pretreated with at least four prior lines of therapy and all HGOC patients were resistant (progressing within 6 months since last dose, n=8) or refractory (progressed during treatment, n=1) to systemic platinum chemotherapy
- A total of 7 patients had a confirmed *BRCA1/2* mutation (HGOC, n=5; TNBC, n=2); 8 patients were BRCA 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 therapies, n (%)	1–3	2 (50)	3 (75)	1 (14)	6 (40)
	≥4	2 (50)	1 (25)	6 (86)	9 (60)
BRCA status, n (%)	*BRCA1* mutation	0	1 (25)	4 (57)	5 (33)
	BRCA2 mutation	0	0	2 (29)	2 (13)
	BRCA1/2 WT	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: *BRCA*, breast cancer susceptibility gene; ECOG, Eastern Cooperative Oncology Group; HGOC, high-grade ovarian cancer; TNBC, triple-negative breast cancer; WT, wild type.

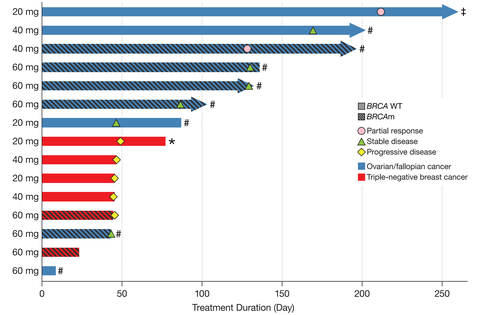
Pharmacokinetics of Pamiparib

- After a single dose, pamiparib was rapidly absorbed (median T_{max}=2 h) with a median $t_{½}$ of approximately 13 h (range: 6–20 h)
- Pamiparib plasma exposure increased in a near dose-proportional manner for both C_{max} and $AUC_{0\text{-}inf}$

Antitumor Activity

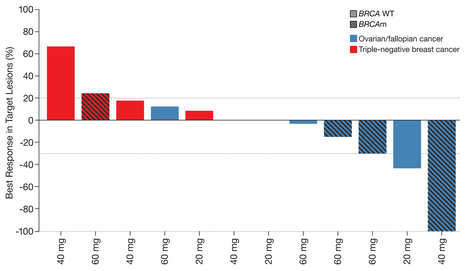
- As of 25 Sep 2017, 13 of the 15 patients were evaluable per RECIST v1.1 and five patients remained on treatment (**Figure 2**)
  - Across all patients, median duration of treatment was 2.5 months (range: 0.26–8.54)
  - Two patients (HGOC, n=1; TNBC, n=1) discontinued treatment prior to first post-baseline scan
- Two of the nine HGOC patients achieved a confirmed partial response (*BRCAm*, n=1) and six HGOC patients achieved stable disease (*BRCAm*, n=4; **Table 2** and **Figures 3–4**)
  - All HGOC patients achieved partial response or stable disease, including one patient who was platinum refractory and seven who were platinum resistant
- All evaluable patients with TNBC (n=5) experienced disease progression
  - Four of these evaluable TNBC patients were BRCA wild type and all experienced disease progression during the previous platinum-based chemotherapy

Figure 2: Duration of Treatment and Response by Tumor Type Using RECIST Criteria and Germline *BRCA* Mutation Status



*Patient remained on study after PD by study approval; †platinum resistant; ‡platinum refractory.
Abbreviation: RECIST, Response Evaluation Criteria In Solid Tumors.

Figure 3: Best Percentage Change From Baseline in Target Lesions by RECIST Criteria



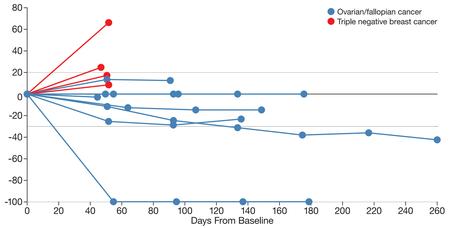
Only patients who had measurable disease at baseline and at least one post-baseline tumor assessment were included.
Among the 13 evaluable patients, one patient had no post-baseline target lesion assessment but had a new lesion.

Table 2: Summary of Best Overall Response in Patients with High-Grade Ovarian Cancer

	20 mg BID (n=2)	40 mg BID (n=2)	60 mg BID (n=4)	Total (n=8)
Complete response (CR)	0	0	0	0
Partial response (PR)	1 (50)	1 (50)	0	2 (25)
Stable disease (SD)	1 (50)	1 (50)	4 (100)	6 (75)
Objective response (CR+PR)	1 (50)	1 (50)	0	2 (25)
Disease control rate (CR+PR+SD) ≥24 weeks	1 (50)	2 (100)	0	3 (38)

Data presented as n (%). Only patients who had at least one post-baseline tumor assessment were included.
Abbreviation: BID, twice daily.

Figure 4: Percentage Change From Baseline in Target Lesions With Respect to Number of Days From Baseline by RECIST Criteria



Only patients who had measurable disease at baseline and at least one post-baseline tumor assessment were included.
Among the 13 evaluable patients, one patient had no post-baseline target lesion assessment but had a new lesion.
Abbreviation: RECIST, Response Evaluation Criteria In Solid Tumors.

Safety and Tolerability

- Pamiparib was generally well tolerated (**Table 3**) with asthenia and nausea being the most commonly reported treatment-emergent AEs (**Table 4**)
  - Asthenia and nausea were also the most commonly reported AEs considered at least possibly related to pamiparib by the investigators
  - Severity of all AEs, considered at least possibly related to treatment, were Grade ≤3
- No dose-limiting toxicities were reported across the dose range (20–60 mg); RP2D confirmed as 60 mg PO BID
- Overall three patients experienced a serious AE (grade 2 abdominal infection, n=1; grade 3 pleural effusion, n=1; grade 3 ileus, n=1), none of which were considered related to treatment
  - Two of the serious AEs led to treatment withdrawal (abdominal infection, n=1; pleural effusion, n=1)

Table 3: Overview of Adverse Events by Dose Cohort

	20 mg BID (n=4)	40 mg BID (n=4)	60 mg BID (n=7)	Total (n=15)
Patients reporting ≥1 AE	4 (100)	4 (100)	7 (100)	15 (100)
Patients reporting ≥1 TRAE	4 (100)	4 (100)	7 (100)	15 (100)
Patients reporting ≥1 AE Grade 3	2 (50)	2 (50)	5 (71)	9 (60)
Patients reporting ≥1 Grade 3 TRAE	0	1 (25)	4 (57)	5 (33)
Patients reporting ≥1 AE Grade 4–5	0	0	0	0
Patients reporting ≥1 serious AE	0	1 (25)	2 (29)	3 (20)
Patients who experienced ≥1 DLT	0	0	0	0
AEs leading to discontinuation	0	1 (25)	1 (14)	2 (13)

Data presented as n (%).
Abbreviations: AE, adverse event; BID, twice daily; DLT, dose-limiting toxicity; TRAE, treatment-related adverse event as assessed by investigators.

CONCLUSIONS

- Pamiparib at 20, 40, and 60 mg PO BID was generally tolerated well in Chinese patients with advanced HGOC or TNBC
  - Asthenia and nausea were the most commonly reported treatment-related AEs
- Pamiparib, orally administered at 60 mg BID, was confirmed as the RP2D in Chinese patients
- After a single dose, pamiparib was rapidly absorbed and showed near dose-proportional increases in exposure
- Pamiparib continues to demonstrate antitumor activity, notably in patients with epithelial ovarian cancer
  - Confirmed and durable clinical responses were observed in patients with HGOC
  - Antitumor response was observed even among patients with BRCA wild type and reported in patients with HGOC who were resistant or refractory to platinum chemotherapy
- As of 25 Sep 2017, a total of five patients remain on treatment and enrollment is ongoing in the expansion phase

Table 4: Treatment-Emergent Adverse Events (Regardless of Causality) Occurring in ≥25% of All Patients

	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 appetite	3 (75)	0	3 (75)	0	3 (43)	0	9 (60)	0
Decreased white blood cell count	2 (50)	0	2 (50)	0	5 (71)	2 (29)	9 (60)	2 (13)
Anemia	1 (25)	1 (25)	2 (50)	1 (25)	6 (86)	4 (57)	9 (60)	6 (40)
Decreased neutrophil count	1 (25)	0	2 (50)	0	4 (57)	2 (29)	7 (47)	2 (13)
Tachycardia	0	0	2 (50)	0	4 (57)	0	6 (40)	0
Electrocardiogram QT prolonged*	2 (50)	0	1 (25)	0	2 (29)	0	5 (33)	0
Vomiting	1 (25)	0	2 (50)	0	2 (29)	1 (14)	5 (33)	1 (7)
Bilirubin conjugated increased	1 (25)	0	1 (25)	0	2 (29)	0	4 (27)	0
Hypocalcemia	2 (50)	0	1 (25)	0	1 (14)	0	4 (27)	0
Hyponatremia	3 (75)	0	0	0	1 (14)	0	4 (27)	0

*In all five patients, QTcF was 450–480 ms (grade 1, n=4; grade 2, n=1) without clinical sequelae.
Data presented as n (%).
Abbreviations: BID, twice daily.

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