A Phase 2 study of pamiparib in the treatment of patients with locally advanced or metastatic HER2-negative breast cancer with germline *BRCA* mutation

Tao Sun,[1] Yanxia Shi,[2] Jiuwei Cui,[3] Yongmei Yin,[4] Quchang Ouyang,[5] Qiang Liu,[6] Qingyuan Zhang,[7] Yiding Chen,[8] Zhimin Shao,[9] Shouman Wang,[10] Xiaojia Wang,[11] Zhongsheng Tong,[12] Yahua Zhong,[13] Min Yan,[14] Xi Yan,[15] Chuan Wang,[16] Haiyuan Yang,[17] Miao Li,[17] Xiao Xiang,[17] Binghe Xu[18]

[1]Department of Breast Medicine, Cancer Hospital of China Medical University, Cancer Hospital of Dalian University of Technology, Liaoning Cancer Hospital and Institute, Shenyang, Liaoning, China; [2]Sun Yat-sen University Cancer Center, Guangzhou, China; [3]The First Hospital of Jilin University, Changchun, China; [4]Jiangsu Province Hospital, Nanjing, China; [5]Hunan Cancer Hospital, Changsha, China; [6]Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; [7]Harbin Medical University Cancer Hospital, Harbin, China; [8]The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [9]Fudan University Shanghai Cancer Center, Shanghai, China; [10]Xiangya Hospital, Central South University, Changsha, Hunan, China; [11]Zhejiang Cancer Hospital, Hangzhou, China; [12]Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [13]Zhongnan Hospital of Wuhan University, Wuhan, China; [14]Department of Breast Disease, Henan Breast Cancer Center, The affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China; [15]West China Hospital of Sichuan University, Chengdu, China; [16]Fujian Medical University Union Hospital, Fuzhou, China; [17]BeiGene Ltd., Beijing, China; [18]Cancer Institute and Hospital, Chinese Academy of Medical Sciences, Beijing, China

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Introduction

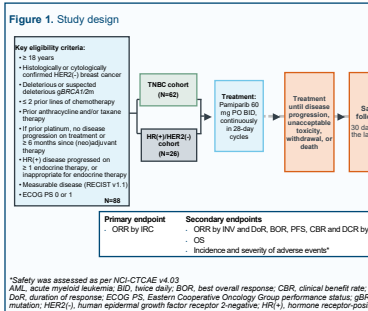
- In 2020, female breast cancer was the leading cause of cancer incidence and mortality in women worldwide, with up to 37.5% of patients harboring a germline *BRCA1/2* mutation (g*BRCA1/2*m)[1–7]
- Clinical guidelines recommend PARP inhibitors (PARPi) for patients with metastatic human epidermal growth factor receptor 2-negative (HER2[-]) breast cancer with g*BRCA*m, who were pre-treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting[8,9]
- In China, platinum-containing chemotherapy is the preferred first-line chemotherapy for triple-negative breast cancer (TNBC). However, there are currently no approved targeted therapies for TNBC with g*BRCA*m in China, highlighting an unmet need for more efficacious treatment options in this patient population[10]
- Pamiparib, an investigational small molecule inhibitor of PARP1/2, is designed to exploit cancer cells with g*BRCA*m, interfering with DNA repair pathways and causing tumor cell synthetic lethality. Pamiparib has demonstrated antitumor activity and has been generally well tolerated in patients with advanced solid tumors in early-phase clinical studies[11–14]
- Here, we report the Phase 2 open-label, single-arm, multi-center study conducted in 25 sites across China (NCT03575065) investigating pamiparib in patients with locally advanced or metastatic TNBC or hormone receptor-positive (HR[+])/HER2(-) breast cancer harboring g*BRCA1/2*m, who had progressed despite standard therapy, or for whom no standard therapy exists

Methods

Study design and patient population

- Study design and endpoints are summarized in **Figure 1**. Tumor responses were assessed separately by independent review committee (IRC) and the investigator (INV) as per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1

Figure 1. Study design



*Safety was assessed as per NCI-CTCAE v4.03
AML, acute myeloid leukemia; BID, twice daily; BOR, best overall response; CBR, clinical benefit rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; gBRCAm, germline BRCA mutation; HER2(-), human epidermal growth factor receptor 2-negative; HR(+), hormone receptor-positive; INV, investigator assessment; IRC, independent review committee; MDS, myelodysplastic syndrome; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, oral; RECIST, Response Evaluation Criteria In Solid Tumors; TNBC, triple-negative breast cancer*

Results

- 88 patients were enrolled into the study and received ≥ 1 dose of pamiparib (safety population)
- 76 patients (TNBC cohort n=55; HR[+]/HER2[-] cohort n=21) had measurable disease at baseline per RECIST v1.1 (efficacy population)
- Patient demographics and baseline characteristics were representative of the target population (**Table 1**)
- At the data cut-off (October 9, 2020):
  - Median study follow-up was 13.8 months (TNBC cohort, 10.9 months; HR[+]/HER2[-] cohort, 18.5 months)
  - 53 patients (60.2%) remained on study and 10 patients (11.4%) remained on treatment
- In the TNBC cohort, treatment with pamiparib demonstrated a confirmed overall response rate (ORR) by IRC of 38.2% (n=21 [95% CI: 25.4–52.3]) and 36.4% (n=20 [95% CI: 23.8–50.4]) by INV (**Table 2**)

Conclusions

- Treatment with **pamiparib** demonstrated **meaningful and durable clinical activity** in patients with **locally advanced/metastatic HER2(-) breast cancer** harboring **g*BRCA1/2*m**
  - Observed **ORR** of **38.2%** (TNBC cohort) and **61.9%** (HR[+]/HER2[-] cohort)
- The **safety profile** observed for patients treated with pamiparib in this study was **consistent** with that observed with **pamiparib in other solid tumor types**[14]
- These results demonstrate that **pamiparib** may be a **promising potential treatment option** in patients with **locally advanced/metastatic HER2(-) breast cancer** harboring **g*BRCA1/2*m**

Table 2. Efficacy endpoints by IRC (efficacy population)

	TNBC cohort (N=55)	HR(+)/HER2(-) cohort (N=21)
Primary endpoint, confirmed ORR, n (%) [95%CI]	21 (38.2) [25.4–52.3]	13 (61.9) [38.4–81.9]
BOR, n (%)		
Complete response	3 (5.5)	1 (4.8)
Partial response	18 (32.7)	12 (57.1)
Stable disease	19 (34.5)	6 (28.6)
Progressive disease	15 (27.3)	2 (9.5)
DCR, n (%) [95%CI]	40 (72.7) [59.0–83.9]	19 (90.5) [69.6–98.8]
CBR, n (%) [95%CI]	24 (43.6) [30.3–57.7]	15 (71.4) [47.8–88.7]

Data-cut off October 9, 2020
CI, confidence interval; HER2(-), human epidermal growth factor receptor 2-negative; HR(+), hormone receptor-positive; TNBC, triple-negative breast cancer

Table 1. Demographics and baseline characteristics (safety population)

Characteristics	TNBC cohort (N=62)	HR(+)/HER2(-) cohort (N=26)	Total (N=88)
Median age, years (range)	45.0 (27–65)	47.5 (29–67)	45.5 (27–67)
Female, n (%)	62 (100.0)	26 (100.0)	88 (100.0)
Asian: Chinese, n (%)	62 (100.0)	26 (100.0)	88 (100.0)
ECOG PS, n (%)			
0	31 (50.0)	17 (65.4)	48 (54.5)
1	31 (50.0)	9 (34.6)	40 (45.5)
Number of metastatic sites, n (%)			
1	18 (29.0)	4 (15.4)	22 (25.0)
2	17 (27.4)	9 (34.6)	26 (29.5)
≥ 3	27 (43.5)	13 (50.0)	40 (45.5)
History of brain metastasis, n (%)	6 (9.7)	0 (0.0)	6 (6.8)
Visceral metastasis, n (%)	42 (67.7)	20 (76.9)	62 (70.5)
g*BRCA*m status, n (%)			
BRCA1-mutant	47 (75.8)	9 (34.6)	56 (63.6)
BRCA2-mutant	15 (24.2)	17 (65.4)	32 (36.4)
Prior lines of chemotherapy, n (%)			
0	17 (27.4)	11 (42.3)	28 (31.8)
1	32 (51.6)	10 (38.5)	42 (47.7)
2	13 (21.0)	5 (19.2)	18 (20.5)
Prior platinum, n (%)	31 (50.0)	11 (42.3)	42 (47.7)

Percentages based on N. Data cut-off October 9, 2020
ECOG PS, Eastern Cooperative Oncology Group performance status; gBRCAm, germline BRCA mutation

- Subgroup analyses of ORR by IRC in the TNBC cohort demonstrated that responses were higher in patients with fewer lines of prior chemotherapy (0 prior lines, n=10/15 [66.7%]; 1 prior line, n=10/29 [34.5%]; 2 prior lines, n=1/11 [9.1%]), and in patients without prior platinum therapy (15/30 [50.0%]) compared to those with prior platinum therapy (n=6/25 [24.0%])
- In the HR(+)/HER2(-) cohort, treatment with pamiparib demonstrated a confirmed ORR by IRC of 61.9% (n=13 [95% CI: 38.4–81.9]) and 57.1% (n=12 [95% CI: 34.0–78.2]) by INV (**Table 2**)
- BOR, DCR and BCR are summarized in **Table 2**
- In the TNBC cohort, median duration of response (DoR) was 7.0 months (95% CI: 3.9–NE) by IRC (**Figure 2**) and 5.6 months (95% CI: 4.6–13.0) by INV; median progression-free survival (PFS) was 5.5 months (95% CI: 3.7–7.3) by IRC (**Figure 3**) and 3.8 months (95% CI: 3.7–6.4) by INV; median overall survival (OS) was 17.1 months (95% CI: 13.7–NE) (**Figure 4**)
- In the HR(+)/HER2(-) cohort, median DoR was 7.5 months (95% CI: 5.6–14.8) by IRC (**Figure 2**) and 7.6 months (95% CI: 6.0–13.9) by INV; median PFS was 9.2 months (95% CI: 7.4–11.9) by IRC (**Figure 3**) and 9.7 months (95% CI: 5.6–12.9) by INV; OS was not estimable (95% CI: 18.1–NE) (**Figure 4**)

Figure 2. DoR by IRC in the (A) TNBC cohort and (B) HR(+)/HER2(-) cohort

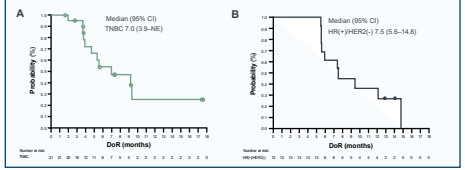


Figure 3. PFS by IRC in the (A) TNBC cohort and (B) HR(+)/HER2(-) cohort

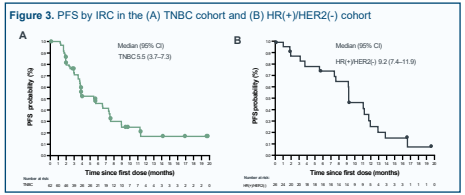
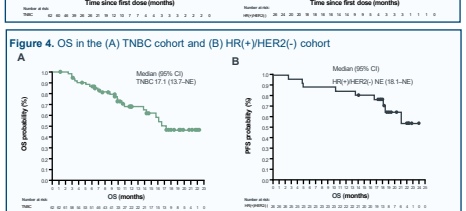


Figure 4. OS in the (A) TNBC cohort and (B) HR(+)/HER2(-) cohort



Median DoR, PFS, and OS were estimated in the safety population by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. Data cut-off October 9,2020
CI, confidence interval; DoR, duration of response; HER2(-), human epidermal growth factor receptor 2-negative; HR(+), hormone receptor positive; IRC, independent review committee; NE, not estimable; OS, overall survival; PFS, progression-free survival

Safety and tolerability

- Median duration of treatment was 3.8 months (range: 0.7–19.4) in the TNBC cohort and 9.6 months (range: 0.9–19.4) in the HR(+)/HER2(-) cohort
- Treatment-emergent adverse events (TEAEs) and treatment-related TEAEs are summarized in **Table 3**
- TEAEs leading to dose interruption and reduction occurred in 71.6% and 64.8% of patients, respectively. This was expected and consistent with protocol defined-dose modification algorithm
- 2 patients experienced TEAEs leading to treatment discontinuation (1 patient in each cohort). All other patients remained on treatment as per proposed dose modification criteria
- No treatment-related TEAEs leading to death were reported
- The most common ≥ Grade 3 treatment-related TEAEs (**Table 3**) in both cohorts were hematologic events including anemia, decreased white blood cell count, and decreased neutrophil count

Table 3. Summary of TEAE and treatment-related TEAE incidence (safety population)

	TNBC cohort (N=62) n (%)	HR(+)/HER2(-) cohort (N=26) n (%)	Total (N=88) n (%)
Patients with at least one TEAE	61 (98.4)	26 (100.0)	87 (98.9)
≥ Grade 3	37 (59.7)	17 (65.4)	54 (61.4)
Serious	12 (19.4)	7 (26.9)	19 (21.6)
Leading to death	1 (1.6)	0 (0.0)	1 (1.1)
Leading to treatment discontinuation	1 (1.6)	1 (3.8)	2 (2.3)
Patients with at least one treatment-related TEAE	61 (98.4)	26 (100.0)	87 (98.9)
≥ Grade 3	36 (58.1)	17 (65.4)	53 (60.2)
Serious	9 (14.5)	6 (23.1)	15 (17.0)
Leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Leading to treatment discontinuation	1 (1.6)	1 (3.8)	2 (2.3)
≥ Grade 3 treatment-related TEAEs occurring in ≥ 5% of patients			
Anemia	22 (35.5)	13 (50.0)	35 (39.8)
White blood cell count decreased	12 (19.4)	7 (26.9)	19 (21.6)
Neutrophil count decreased	18 (29.0)	8 (30.8)	26 (29.5)
Platelet count decreased	5 (8.1)	3 (11.5)	8 (9.1)
Leukopenia	3 (4.8)	2 (7.7)	5 (5.7)
Neutropenia	3 (4.8)	2 (7.7)	5 (5.7)

A patient with multiple AEs under a system organ class and preferred term was counted only once for the preferred term, under the maximum severity category. Percentages were based on N. Data cut-off October 9, 2020
AE, adverse event; HER2(-), human epidermal growth factor receptor 2-negative; HR(+), hormone receptor positive; TEAE, treatment emergent adverse event

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Author contact details: xubinghe@csco.org.cn (Binghe Xu)