PARALLEL 303: Phase 2 randomized study of pamiparib vs placebo as maintenance therapy in patients with inoperable locally advanced or metastatic gastric cancer that responded to platinum-based first-line chemotherapy

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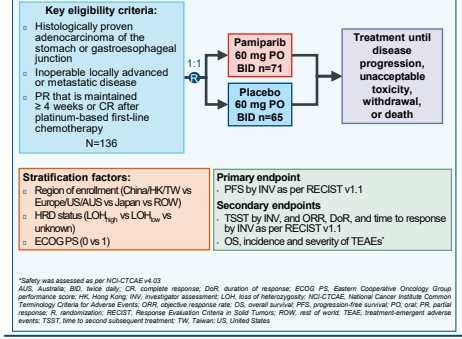
Introduction

- In 2020, gastric cancer accounted for 5.6% of all diagnosed cancers and 7.7% of cancer deaths worldwide[1]
- A subset of gastric cancers exhibit platinum sensitivity and genomic instability that is characteristic of homologous recombination deficiency (HRD). Cells with HRD are sensitive to poly (ADP-ribose) polymerase protein 1 and 2 (PARP1/2) inhibition, as these proteins play a vital role in DNA repair, genome stability, and cell death[2,3,4]
- PARP inhibitor (PARPi) maintenance therapy following platinum-based chemotherapy has been a successful treatment strategy in patients with ovarian cancer. This suggests that PARPi could be effective in other cancers with platinum sensitivity and higher levels of HRD[5–7]
- Pamiparib is an investigational small molecule inhibitor of PARP1/2 that has demonstrated sensitivity to HRD cells, and antitumor activity and tolerability in patients with advanced solid tumors in early-phase clinical studies[8–10]
- Here, we report the results of PARALLEL 303, a Phase 2, double-blind, randomized, multi-center study designed to compare the efficacy, safety, and tolerability of pamiparib vs placebo as a maintenance therapy in patients with inoperable locally advanced or metastatic gastric cancer who responded to first-line platinum-based chemotherapy (NCT03427814)

Methods

- This study changed from a Phase 3 to a Phase 2 study due to slow enrollment and a change in the standard of care for this patient population
- Study design and endpoints are summarized in **Figure 1**
- Tumor assessments using diagnostic-quality computed tomography imaging occurred once every 8 weeks (± 7 days) after day 1

Figure 1. Study design and endpoints



*Safety was assessed as per NCI-CTCAE v4.03
AUS, Australia; BID, twice daily; CR, complete response; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; HK, Hong Kong; INV, investigator assessment; LOH, loss of heterozygosity; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral; PR, partial response; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world; TEAE, treatment-emergent adverse events; TSST, time to second subsequent treatment; TW, Taiwan; US, United States

Conclusions

- In patients with **inoperable locally advanced or metastatic gastric cancer, pamiparib** demonstrated a **numerical difference** in **median PFS vs placebo;** however, this was not statistically significant
  - These results may have been influenced by the fact that the study did not meet the planned target enrolment of patients
- Maintenance therapy with **pamiparib** was **tolerable and manageable** in this patient population, with **few treatment discontinuations due to TEAEs**

Results

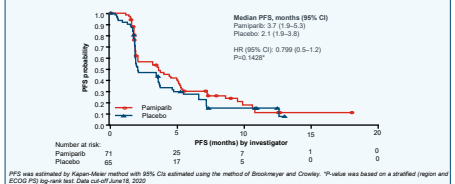
Demographics and baseline characteristics

- Patients were recruited from 128 sites across:
  - China (including Taiwan and Hong Kong): 21 patients (15.4%)
  - Japan: 11 patients (8.1%)
  - Australia/Europe/US: 103 patients (75.7%)
  - ROW: 1 patient (0.7%)
- Demographics and baseline characteristics were generally balanced between groups (**Table 1**)

Efficacy results

- At the data cut-off (June 18, 2020):
  - Median study follow-up was 8.0 months (pamiparib arm, 7.9 months; placebo arm, 8.0 months)
  - 70 patients (51.5%) remained on study and 23 patients (16.9%) remained on treatment
- There was no significant difference in median progression-free survival (PFS) in the pamiparib arm vs the placebo arm (**Figure 2**)
- There was also no significant differences between the pamiparib arm and the placebo arm for the following:
  - Median overall survival (OS) 10.2 months (95% CI: 8.7–16.3) vs 12.0 months (95% CI: 8.2–not estimable [NE])
  - Median time to second subsequent treatment (TSST) 9.8 months (95% CI: 8.1–10.9) versus 9.7 months (95% CI: 7.5–14.0).
  - Overall response rate (ORR) 7.7% (95% CI: 1.6–20.9) vs 6.3% (95% CI: 0.8–20.8)
- Median duration of response (DoR) was 3.6 months (95% CI: 3.5–NE) in the pamiparib treatment arm and NE (95% CI: 5.6–NE) in the placebo arm
- Median time to response was 3.7 months (range: 1.8–7.3) in the pamiparib arm and 1.9 months (1.9–1.9) in the placebo arm

Figure 2. Kaplan-Meier plot of PFS as per RECIST v1.1 in the ITT population



*PFS was estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. *P-value was based on a stratified (region and ECOG PS) log-rank test. Data cut-off: June18, 2020*
CI, confidence interval; HR, hazard ratio; ITT, intention to treat; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors

Table 1. Baseline patient demographics and characteristics

	Pamiparib (n=71)	Placebo (n=65)
Median age, years, (range)	64.0 (39–82)	64.0 (27–85)
Age ≥ 65 years, n (%)	32 (45.1)	30 (46.2)
Sex, n (%)		
Female	25 (35.2)	20 (30.8)
Male	46 (64.8)	45 (69.2)
Race, n (%)		
Asian	20 (28.2)	15 (23.1)
Black or African American	0 (0.0)	2 (3.1)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (1.5)
White	38 (53.5)	36 (55.4)
Other	1 (1.4)	3 (4.6)
Not reported/unknown*	12 (16.9)	8 (12.3)
ECOG PS, n (%)		
0	31 (43.7)	30 (46.2)
1	40 (56.3)	35 (53.8)
Number of prior regimens, n (%)†		
1	66 (93.0)	60 (92.3)
2	3 (4.2)	5 (7.7)
≥ 3	2 (2.8)	0 (0.0)
Best overall response for last therapy, n (%)†		
CR	4 (5.6)	6 (9.2)
PR	67 (94.4)	58 (89.2)
Stable disease	0 (0.0)	1 (1.5)
Solid tumor stage, n (%)‡		
Stage IIA/B §	3 (4.2)	1 (1.5)
Stage IIIA–C	4 (5.6)	6 (9.3)
Stage IV	59 (83.1)	51 (78.5)
Unknown	5 (7.0)	7 (10.8)

"Not reported" and "Unknown"' includes patients from France who did not sign the consent of the collection of race. †Percentages are based on the number of patients with any prior systemic therapy. ‡Solid tumor stage at screening. § 3 of the 4 patients enrolled at time of study had metastatic disease. Data cut-off, June 18, 2020

Safety and tolerability

- There was a similar incidence of TEAEs between treatment arms, as summarized in **Table 2**
- The most common all grade TEAEs are summarized in **Table 3**

Table 2. Summary of TEAE incidence in the safety population

	Pamiparib (n=71) N (%)	Placebo (n=65) N (%)
Patients with at least one TEAE	65 (91.5)	61 (93.8)
Treatment-related TEAE	55 (77.5)	34 (52.3)
≥ Grade 3 TEAEs	29 (40.8)	20 (30.8)
Treatment-related TEAEs of ≥ Grade 3	19 (26.8)	6 (9.2)
Serious TEAEs	14 (19.7)	10 (15.4)
Treatment-related serious TEAEs	1 (1.4)	3 (4.6)
TEAE leading to death	2 (2.8)	2 (3.1)
Treatment-related TEAE leading to death	0 (0.0)	1 (1.5)
TEAE leading to treatment discontinuation	8 (11.3)	2 (3.1)

TEAE, treatment-emergent adverse event. Data cut-off, June 18, 2020

Table 3. TEAEs reported in ≥ 10% of patients in the safety population

	Pamiparib (n=71) N (%)	Placebo (n=65) N (%)
Patients with at least one TEAE	**65 (91.5)**	**61 (93.8)**
Anemia	26 (36.6)	8 (12.3)
Nausea	23 (32.4)	11 (16.9)
Decreased appetite	19 (26.8)	8 (12.3)
Asthenia	15 (21.1)	11 (16.9)
Diarrhea	13 (18.3)	7 (10.8)
Abdominal pain	8 (11.3)	12 (18.5)
Abdominal pain upper	12 (16.9)	7 (10.8)
Vomiting	17 (23.9)	1 (1.5)
Constipation	8 (11.3)	7 (10.8)
Aspartate aminotransferase increased	9 (12.7)	5 (7.7)
Alanine aminotransferase increased	8 (11.3)	5 (7.7)
Peripheral sensory neuropathy	4 (5.6)	9 (13.8)
White blood cell count decreased	8 (11.3)	3 (4.6)
Dysphagia	3 (4.2)	8 (12.3)

TEAE, treatment-emergent adverse event. Data cut-off, June 18, 2020

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