IGCS 2022 ANNUAL GLOBAL MEETING NEW YORK CITY

Impact of Initiation Timing of Niraparib Maintenance Treatment in Newly Diagnosed Advanced Ovarian Cancer

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OBJECTIVE

- To understand the impact of initiation timing of PARP inhibitor maintenance treatment through examining the efficacy and safety of niraparib maintenance treatment initiated after different intervals upon completion of first-line platinum-based chemotherapy (1LCT) in Chinese patients with newly diagnosed advanced ovarian cancer from the PRIME trial

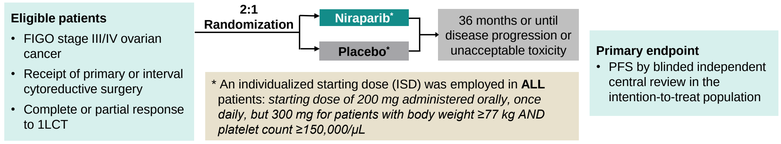
BACKGROUND

- The PARP inhibitor niraparib is approved as maintenance treatment for patients with newly diagnosed advanced ovarian cancer after a response to 1LCT in the United States, Europe, and China, among others.
- The multicenter, double-blind, placebo-controlled, randomized, phase 3 PRIME trial (NCT03709316) evaluated the efficacy and safety of niraparib maintenance treatment in Chinese patients with newly diagnosed advanced ovarian cancer who responded to 1LCT.[1]
- In PRIME, niraparib significantly prolonged progression-free survival (PFS) versus placebo (median: 24.8 vs. 8.3 months; hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.34–0.60; *P*<0.001), regardless of biomarker or postoperative residual disease status.[1]

METHODS

- The design of the PRIME trial is presented in **Figure 1**. Between 29 June 2018 and 11 November 2019, a total of 384 patients were randomized 2:1 to receive niraparib or matched placebo within 12 weeks after completion of 1LCT. The randomization was stratified according to germline *BRCA* mutation status, tumor homologous recombination deficiency status, receipt of neoadjuvant chemotherapy, and response to 1LCT.

Figure 1: PRIME trial design



FIGO, International Federation of Gynecology and Obstetrics.

- This *post hoc* analysis reports PFS assessed by blinded independent central review and HRs of niraparib versus placebo for subgroups by interval (0–<9 weeks or ≥9–12 weeks) between completion of 1LCT and initiation of maintenance treatment. HRs were estimated by stratified Cox proportional hazards models. The data cut-off date for the current analysis was 30 September 2021.

RESULTS

Baseline characteristics

- Of the 384 randomized patients, 172 (44.8%) initiated maintenance treatment (114 niraparib, 58 placebo) after 0–<9 weeks upon completion of 1LCT and 212 (55.2%) did so (141 niraparib, 71 placebo) after ≥9–12 weeks upon completion of 1LCT.
- In each subgroup, the baseline characteristics were overall comparable between the two treatment arms (**Table 1**).

Efficacy

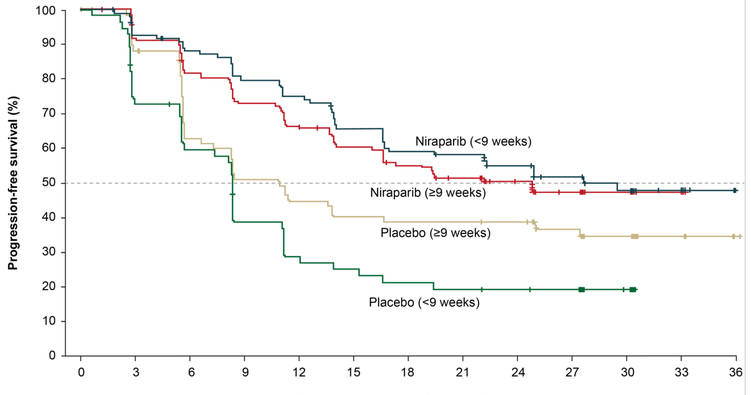
- The median PFS (95% CI) was 29.4 months (16.9–not estimable) with niraparib versus 8.3 months (5.5–11.0) with placebo (HR=0.31; 95% CI, 0.20–0.48) for the 0–<9 weeks subgroup and was 24.7 months (16.5–not estimable) with niraparib versus 10.8 months (6.5–24.9) with placebo (HR=0.60; 95% CI, 0.41–0.89) for the ≥9–12 weeks subgroup (**Figure 2**).
- For niraparib-treated patients, there was no significant difference in PFS between the 0–<9 weeks and ≥9–12 weeks arms (HR=0.88; 95% CI, 0.61–1.28). Further analysis showed that the median PFS was 29.4, 24.8, 24.8, and 24.7 months for patients who initiated niraparib maintenance treatment after 0–<7 (N=52), ≥7–<9 (N=62), ≥9–<11 (N=76), and ≥11–12 (N=65) weeks upon completion of 1LCT, respectively, without significant differences observed between groups (stratified log-rank test, P=0.773).

Table 1: Baseline characteristics

Characteristic	Initiation interval: 0–<9 weeks		Initiation interval: ≥9–12 weeks	
	Niraparib (N=114)	Placebo (N=58)	Niraparib (N=141)	Placebo (N=71)
Median age (range), years	53 (32–77)	54 (40–71)	54 (35–70)	54 (33–77)
ECOG performance status, n (%)				
0	34 (29.8)	24 (41.4)	64 (45.4)	28 (39.4)
1	80 (70.2)	34 (58.6)	77 (54.6)	43 (60.6)
FIGO stage, n (%)				
III	76 (66.7)	41 (70.7)	106 (75.2)	53 (74.6)
IV	38 (33.3)	17 (29.3)	35 (24.8)	18 (25.4)
Neoadjuvant chemotherapy, n (%)				
Yes	54 (47.4)	29 (50.0)	67 (47.5)	30 (42.3)
No	60 (52.6)	29 (50.0)	74 (52.5)	41 (57.7)
Germline *BRCA* mutations, n (%)				
Yes	46 (40.4)	19 (32.8)	39 (27.7)	21 (29.6)
No	68 (59.6)	39 (67.2)	102 (72.3)	50 (70.4)
Cytoreductive surgery outcome, n (%)				
Optimal (R0+R1)	89 (78.1)	46 (79.3)	104 (73.8)	59 (83.1)
Suboptimal (R2) or missing	25 (21.9)	12 (20.7)	37 (26.2)	12 (16.9)
Response to 1LCT, n (%)				
Complete response	92 (80.7)	47 (81.0)	120 (85.1)	56 (78.9)
Partial response	22 (19.3)	11 (19.0)	21 (14.9)	15 (21.1)

ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

Figure 2: PFS by initiation interval



No. at risk													
Niraparib (<9 weeks)	114	101	95	86	81	70	63	61	53	35	23	9	0
Niraparib (≥9 weeks)	141	126	112	100	89	81	73	64	50	37	18	4	0
Placebo (<9 weeks)	58	40	32	20	14	13	11	10	8	7	3	0	0
Placebo (≥9 weeks)	71	61	42	34	30	27	26	26	24	17	14	4	1

	Interval: 0–<9 weeks		Interval: ≥9–12 weeks	
	Niraparib (N=114)	Placebo (N=58)	Niraparib (N=141)	Placebo (N=71)
Events, n (%)	53 (46.5)	43 (74.1)	70 (49.6)	43 (60.6)
Median PFS (95% CI), months	29.4 (16.9–NE)	8.3 (5.5–11.0)	24.7 (16.5–NE)	10.8 (6.5–24.9)
Hazard ratio (95% CI)	0.31 (0.20–0.48)		0.60 (0.41–0.89)	

Safety

- Grade ≥3 hematological adverse events occurred in similar proportions of niraparib-treated patients for the 0–<9 weeks and ≥9–12 weeks subgroups: anemia (19.3% versus 17.0%), platelet count decreased (18.4% versus 10.6%), neutrophil count decreased (15.8% versus 18.4%), and white blood cell count decreased (4.4% versus 8.5%) (**Table 2**).

Table 2: Summary of treatment-emergent adverse events (TEAEs)

Patients, n (%)	Initiation interval: 0–<9 weeks		Initiation interval: ≥9–12 weeks	
	Niraparib (N=114)	Placebo (N=58)	Niraparib (N=141)	Placebo (N=71)
Any TEAEs	114 (66.3)	54 (31.4)	139 (65.6)	67 (31.6)
TEAEs leading to dose interruption	78 (68.4)	10 (17.2)	82 (58.2)	15 (21.1)
TEAEs leading to dose reduction[a]	52 (45.6)	4 (6.9)	51 (36.2)	4 (5.6)
TEAEs leading to treatment discontinuation	6 (5.3)	0	11 (7.8)	7 (9.9)
Grade≥3 TEAEs	65 (57.0)	8 (13.8)	74 (52.5)	15 (21.1)
Anemia	22 (19.3)	2 (3.4)	24 (17.0)	0
Platelet count decreased[b]	21 (18.4)	0	15 (10.6)	1 (1.4)
Neutrophil count decreased[c]	18 (15.8)	1 (1.7)	26 (18.4)	1 (1.4)
White blood cell count decreased[d]	5 (4.4)	1 (1.7)	12 (8.5)	0

[a]Including both direct dose reduction and dose reduction following dose interruption; [b]Including thrombocytopenia; [c]Including neutropenia; [d]Including leukopenia.

CONCLUSIONS

- Whether initiated after 0–<9 weeks or ≥9–12 weeks upon completion of 1LCT, niraparib maintenance treatment conferred clinically significant PFS benefit versus placebo to patients with newly diagnosed advanced ovarian cancer. The initiation timing of niraparib maintenance treatment had no significant impact on its safety profile.
- The two placebo arms appeared to have some differences in terms of PFS curve and treatment discontinuation, which warrants further investigation.
- The long-term monitoring of efficacy and safety profiles of niraparib maintenance treatment is still ongoing for the PRIME trial.

References

1. Li N, et al. Efficacy and Safety of Niraparib as Maintenance Treatment in Patients with Newly Diagnosed Advanced Ovarian Cancer Using an Individualized Starting Dose (PRIME Study): A Randomized, Double-blind, Placebo-controlled, Phase 3 Trial. Presented at: 2022 SGO Annual Meeting on Women's Cancer; March 18-21, 2022. Phoenix, Arizona, United States.

Author contributions

Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: JW, LYW, JQZ, RTY, LYP, BHK, HZ, JHL, XHW, LW, YH, KW, DLZ, HQZ, CYW, WGL, AL, XAZ, WZH, JMH; Drafting of the publication, or revising it critically for important intellectual content: JW, LYW, JQZ, RTY, LYP, BHK, HZ, JHL, XHW, LW, YH, KW, DLZ, HQZ, CYW, WGL, AL, XAZ, WZH, JMH; Final approval of the publication: JW, LYW, JQZ, RTY, LYP, BHK, HZ, JHL, XHW, LW, YH, KW, DLZ, HQZ, CYW, WGL, AL, XAZ, WZH, JMH.

Author disclosure

XAZ, WZH, and JMH are employees of Zai Lab and hold the stock options of Zai Lab; the other authors have nothing to declare.

Acknowledgements

This study was sponsored by Zai Lab and partially supported by the National Major Scientific and Technological Special Project for "Significant New Drugs Development" in 2020, China (Grant No. 2020ZX09101-014). The authors acknowledge Jinlong Guo, PhD, Costello Medical, for medical writing and editorial assistance. All costs associated with development of this poster were funded by Zai Lab.

Abstract No: 876