

The Efficacy and Safety of Niraparib for Advanced Ovarian Cancer: A Single-center Observational Study From China

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Research

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Abstract

Background

Niraparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, is approved for first/second-line maintenance treatment of ovarian cancer patients with complete or partial response to platinum-based chemotherapy, and multi-line monotherapy in BRCAmt patients or platinum-sensitive recurrence patients with homologous recombination deficiency (HRD) positive. We present real-world experience from China.

Methods

Patients with niraparib in Jiangsu Cancer Hospital between June 2019 to July 2020 were recruited. The initial dose was given according to individualization. Response and adverse events (AEs) were analyzed by Response Evaluation Criteria in Solid Tumors v1.1. and National Cancer Institute Common Terminology Criteria for Adverse Events v5.0, respectively. HRD testing (AmoyDx[®]) was detected in most patients. Treatment was given until unequivocal progression or intolerable toxicity.

Results

Twenty-two patients all received niraparib at an bolus of 200mg/d. 50% of patients with high-grade serous ovarian cancer are HRD-positive. Six patients underwent first-line maintenance therapy. Sixteen patients received exploratory therapy. Ultimately image evaluation revealed that two patients achieved partial response (PR) and one patient achieved stable disease (SD), yielding objective response rate (ORR) of 33.3% (95%CI=0.060-0.759) and DCR of 50% (95%CI=0.140-0.861) in the exploratory multi-line monotherapy group. Commonly AEs were nausea, thrombocytopenia, and anemia. Grade 3-4 thrombocytopenia were managed by dose reduction and interruption. Leg swelling was observed as a new adverse event.

Conclusion

It is feasible for patients received a bolus of 200mg/d in Chinese population with promising efficacy and well tolerated. This is first real world data about niraparib in ovarian cancer patients with HRD status from China.

Background

Ovarian cancer is the most lethal gynecological malignancy, 70% of the patients are diagnosed with advanced stage. Although most ovarian cancer patients are sensitive to standard first-line treatment including cytoreductive surgery and platinum-based chemotherapy, about 80% patients relapse within 1 to 2 years after initial treatment and gradually progress to platinum-resistance ovarian cancer, accompanied by significantly shortened survival[1,2]. How to prolong the platinum free interval (PFI) becomes one of the breakthrough points in ovarian cancer treatment. Recently, poly ADP-ribose Polymerase (PARP) inhibitors have changed the treatment paradigm for ovarian cancer that can

significantly improve the platinum free interval, and finally prolong the overall survival of patients with BRCA mutation [3-6].

PARP is a specific DNA fracture receptor, which is activated after DNA damage, recognizes and binds to the DNA fracture site, and mediates DNA single-strand damage repair in tumor cells[7]. PARP inhibitor can lead to DNA double strand damage inducing by amount of DNA single-strand damage. In homologous recombination deficiency (HRD) tumor cells, such as BRCA mutation or other germline mutations in homologous recombination repair (HRR) pathway genes (e.g., RAD51 and ATM), can not repair DNA single-strand damage, forming the synthetic lethal effect[8]. Therefore, BRCAmt or HRD positive tumor cells are more sensitive to PARP inhibitors in terms of molecular mechanisms.

Niraparib (Zejula[®]), is a highly selective inhibitor of PARP1/2, nuclear proteins that detect DNA damage and promote its repair[9]. In 2017, it was firstly approved for second-line maintenance treatment of ovarian cancer patients who were in complete or partial response to platinum-based chemotherapy by Food and Drug Administration (FDA) according to the study of NOVA[3,10]. Another study observed the significant efficacy of niraparib in patients with newly diagnosed advanced ovarian cancer after response to first-line platinum-based chemotherapy[5]. Both of the NOVA and PRIMA studies found that patients with HRD positive can get more profit from niraparib. Recently the first fully powered, multi-center, phase III clinical study in Chinese population (NORA) showed that median PFS was significantly longer for niraparib as second-line maintenance treatment versus placebo among patients with germline BRCA mutations (not reached vs. 5.5 months; HR was 0.22) and those without germline BRCA mutations (11.1 vs. 3.9 months; HR was 0.40) in 2020 ESMO meeting[11]. QUADRA study demonstrated that niraparib among women with heavily pretreated ovarian cancer, especially in patients with HRD-positive platinum-sensitive disease, which included not only patients with BRCA mutation but also population with BRCA wild-type [12].

However, there was no real-world data to illustrate the efficacy and safety of niraparib in Chinese population. We conducted this study to assess the real-world clinical impact of niraparib in ovarian cancer patients with HRD status.

Materials And Methods

Study population

Patients with advanced ovarian cancer who received niraparib from June 2019 to July 2020 were included in Jiangsu Cancer Hospital. We collected the basic characteristics of these patients, including age, Eastern Cooperative Oncology Group performance status (ECOG PS) before the start of the treatment, histological type, clinical stage on the basis of Federation International of Gynecology and Obstetrics (FIGO), basal body weight, basal platelet count, previous therapy before and after the treatment of niraparib and the follow-up. The study was approved by the ethics committee of Jiangsu Cancer Hospital.

Dosing Regimen

The initial dose was based on the level of basal body weight or platelet count. Patients with basal body weight ≥ 77 kg and basal platelet count of $\geq 150,000/\mu\text{L}$ will take 300 mg daily. While patients with basal body weight < 77 kg and/or basal platelet count $< 150,000/\mu\text{L}$ will take 200 mg daily. Dose reduction (300 mg to 200 mg or 100 mg; 200 mg to 100 mg) or interruption for drug-related AEs was allowed. Serum CA125 and imaging examinations were performed on each patient at baseline, followed by a monthly examination of CA125 and imaging examinations.

HRD testing

The paraffin sections from the cytoreductive surgery were obtained after patients' informed consent. DNA was extracted from FFPE biopsy/surgical specimens; 50 to 200 ng DNA undergoes library construction and hybrid capture with AmoyDx[®] HRD panel, which selected coding sequences (CDS) regions for 54 HRR pathway genes and 72,000 single nucleotide polymorphisms (SNPs) for HRD calling. The selected libraries were pooled and sequenced on the Illumina Novaseq6000 to $> 500\times$ unique coverage for 54 HRR genes and $> 100\times$ for SNP loci.

Sequence data was processed using a customized analysis pipeline designed to accurately detect multiple classes of genomic alterations: base substitutions, short insertions/deletions with detection sensitivity at variant allele frequency (VAF) $\geq 5\%$. Detected mutations were annotated according to American College of Medical Genetics (ACMG) guideline[13] and classified as pathogenic, likely pathogenic, variants of unknown significance, likely benign and benign. HRD score was calculated by the sum of three types of genomic instable events including loss of heterozygosity (LOH), telomeric allelic imbalance (TAI) and large-scale state transition (LST) defined by ref[14]. HRD-positive was defined by either BRCA1/2 pathogenic or likely pathogenic mutation or HRD score ≥ 42 .

Assessments

Demographic and baseline data were summarized and analyzed. The efficacy was assessed as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) by RECIST 1.1. Objective response rate (ORR) was defined as the proportion of patients achieving CR or PR. Disease control rate (DCR) was defined as the proportion of patients achieving CR, PR or SD for at least 8 weeks. Treatment-related adverse events (AEs) were graded according to CTCAE 5.0.

Statistical analysis

The 95% confidence interval was calculated using the Wilson procedure with a correction for continuity. Data were statistically analyzed using SPSS version 19.0 professional statistical software and all the count data were expressed as a percentage (%).

Results

Patients' characteristics

A total of twenty-two patients treated with niraparib were enrolled, of whom twenty-one patients were ovary cancer and one patient was fallopian tube cancer. The median age was 55.0 years (39-77 years). Patient demographics and baseline characteristics were listed in Table 1. Stage FIGO II, III or IV, affected 2 (9.1%), 11 (50.0%) and 8 (36.4%) of patients, respectively. Most patients (86.4%) were high-grade serous cancer. All participants weighed less than 77 kg, 10 of who had basal platelet count less than 150,000 per cubic millimeter. The results of HRD testing were positive in six patients and negative in eight patients.

Group assignment

Patients who progresses during initial treatment, or completely alleviates after initial treatment (cytoreductive surgery and platinum-based chemotherapy), but recur within 6 months are defined as platinum-resistant ovarian cancer, who relapse more than 6 months are considered as platinum-sensitive ovarian cancer. According to the guidelines, patients are treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD-positive defined by either: 1) a deleterious or suspected deleterious BRCA mutation; or 2) genomic instability and progression more than 6 months after response to the last platinum-based chemotherapy. And on this basis, the patients were divided into first-line maintenance treatment group and exploratory treatment group means who did not applied in the scope of indications, with six and sixteen patients in each group. There were three subgroups including exploratory second-line maintenance, front-line (less than three chemotherapy regimens) and multi-line (three or more prior chemotherapy regimens) treatment group, with one, six and nine patients in each group, respectively.

Efficacy and HRD status

In the first-line maintenance treatment group, all six patients are still on medication, two of whom are HRD-positive and four of whom are HRD unknown. In the exploratory treatment group, one patient (HRD-negative) diagnosed with highly differentiated papillary mesothelioma is on the second-line maintenance treatment. Serum CA125 of these patients with maintenance treatment were shown in Figure 1.

According to the different therapeutic strategy in the exploratory first-line therapy, three patients who did not undergo surgery and only receive chemotherapy for their personal willingness achieved SD after treated with niraparib. All three patients are still assessed as SD. Two patients with first platinum-sensitive recurrence ovarian cancer achieved SD, one of which was treated with niraparib monotherapy and the other one was treated with niraparib and anlotinib. One patient who did not receive chemotherapy after the surgery due to poor renal function achieved PD.

The median prior line was 5 (3-8) in the exploratory multi-line therapy group. Ultimately therapeutic evaluation showed that two patients achieved partial response (PR), one patient achieved stable disease (SD) and three patients had progressive disease (PD), yielding the objective response rate (ORR) of 33.3% (95%CI=0.060-0.759) and the disease control rate (DCR) of 50% (95%CI=0.140-0.861) in patients with

exploratory multi-line monotherapy. Also there were three patients treated with exploratory multi-line combined therapy, one patient achieved SD using niraparib combined with topotecan and anlotinib but another patient failed with this combination therapy. The remaining patient achieved PD by niraparib combined with anlotinib (Table 2). The status of HRD and tumor shrinkage in the exploratory front-line and multi-line treatment groups were listed in Figure2.

Safety

The most common AEs were nausea (54.5%), thrombocytopenia (40.9%), anemia (40.9%), fatigue or asthenia(36.4%) and decreased appetite(31.8%). Serious AEs (SAEs) (grade 3-4) were thrombocytopenia (18.2%), anemia (9.1%), neutropenia (9.1%), vomiting (4.5%) and dyspepsia (4.5%). Three patients with thrombocytopenia, neutropenia, or vomiting relieved through dose interruption and followed by dose reduction (200mg to 100mg). One patient given the combination therapy including niraparib, topotecan and anlotinib suffered Grade 4 thrombocytopenia within one week. She stopped taking the medicine and were treated with niraparib (200mg) monotherapy after treatment of elevated platelet count. One patient with dyspepsia could not stand drug-related AE after dose reduction and discontinued the treatment. Serious AEs were not found in two patients with initial dose of 100mg. We observed Leg swelling as a new adverse event in one patient. Summary of AEs were listed in Table 3.

Discussion

PARP inhibitor is a major advance in the treatment of ovarian cancer. Patients with BRCAmt or HRD-positive can get more profit from it. Now there are two kinds of PARP inhibitors including olaparib and niraparib in China. We previously reported the first real word study of olaparib in Chinese population[15].Here we presented the real word experience of niraparib in Chinese ovarian cancer patients.

A retrospective analysis of ENGOT-OV16/NOVA trial suggested that patients with baseline body weight of<77 kg or baseline platelets of<150 000/ml might benefit from a starting dose of 200 mg/day following the NOVA trial [16]. A subsequent study proved that incidence of common clinical trial-reported AEs was lower among patients initiating niraparib 200mg/day in real-world practice versus patients initiating niraparib 300mg/day in ENGOT-OV16/NOVA in Caucasian population[17]. Recently the NORA trail demonstrated that niraparib maintenance therapy administered with an individual starting dose regimen, most subjects received the initial dose of 200mg/day, significantly improved the outcome in patients with recurrent ovarian cancer in 2020 ESMO meeting[11]. All subjects in our real world experience received 200mg/day according to the basal weight that was consistent with the results of prospective studies in Chinese population.

At the 2020 ASCO meeting, an open-label, non-randomized study (LIGHT) showed that patients with platinum-sensitive recurrence, high-grade serous/endometrioid epithelial ovarian cancer and greater than or equal one prior line of platinum chemotherapy could benefit from olaparib monotherapy, especially in patients with HRD-positive[18]. Also in our exploratory front-line therapy group, two patients with first

platinum-sensitive recurrence ovarian cancer achieved SD, one of which was with HRD-positive and the other was with HRD-negative. This finding needs to be confirmed by a prospective study of niraparib as front-line monotherapy.

The PAOLA1 trial suggested that advanced ovarian cancer patients receiving first-line standard therapy including bevacizumab, the addition of maintenance olaparib provided a significant progression-free survival benefit, which was substantial in patients with HRD-positive tumors, including those without BRCA mutation

[19]. Niraparib plus bevacizumab significantly improved progression-free survival compared with niraparib alone in platinum-sensitive recurrent ovarian cancer[20]. One patient with HRD-negative also achieved SD using niraparib and anlotinib which might be related to the synergistic antitumor effects of PARP inhibitors and antiangiogenic drugs. It is also needed further studies to observe efficacy of the combination treatment in patient with HRD-negative, regardless of as front-line therapy and multi-line therapy.

A multi-center, open-label, single-arm, phase 2 QUADRA trial observed that 10 (27%) of 37 platinum-resistance patients harbored BRCAmt, 12 (10%) of 120 platinum-resistance patients with HRD-positive and 5 (3%) of 169 platinum-resistance patients with HRD-negative in the primary efficacy population achieved an overall response according to RECIST1.1[12]. Regardless of the patients' status of BRCA or HRD, Our results showed that the ORR of 33.3% (95%CI=0.060-0.759) and DCR of 50% (95%CI=0.140-0.861) in platinum-resistance ovarian cancer patients with exploratory multi-line monotherapy. We consider the differences of response to niraparib may be due to the small number of patients enrolled in our study and the criteria for enrollment in our real-world data.

Previous studies confirmed that ovarian cancer patients with HRD-positive were more likely to benefit from niraparib than those with HRD-negative. We did not observe the relationship between efficacy and HRD status, which may be correlated with our small sample size. Approximately 50% of patients with high-grade serous ovarian cancer are HRD positive[21]. Twenty-one participants in our study harbored BRCAwt, 14 of who were tested with HRD panel. Of the 12 patients with high-grade serous ovarian cancer, 6 patients were with HRD- positive and 6 patients were with HRD-negative. The results were correspond to the study on large sample.

The most common AEs were nausea, thrombocytopenia, anemia and fatigue. SAEs were thrombocytopenia, anemia, neutropenia and dyspepsia. The incidence of AEs and SAEs in our observation were similar to other studies. All SAEs occurred within one month after taking the medicine, most of which occurred within one week.

Severe myelosuppression including thrombocytopenia and neutropenia, and vomiting were alleviated by dose reduction and interruption. Only patient with dyspepsia could not stand after dose reduction to 100mg/day and discontinued the treatment. The GOLD study did not meet its primary objective of showing a significant improvement in overall survival with olaparib in combination with a

chemotherapeutic agent and in the overall or ATM-negative population of Asian patients with advanced gastric cancer due to the intolerable AEs[22]. In our study, one patient was given the combination therapy including niraparib, topotecan and anlotinib. She suffered Grade 4 thrombocytopenia within one week. Similar to the GOLD study, we also observed the intolerable AEs in patients using PARP inhibitors combined with chemotherapy.

Conclusion

This is the first real word data about niraparib in ovarian cancer patients with HRD status from China. Our findings demonstrated that Chinese population with niraparib 200mg orally once daily is feasible. Leg swelling was observed as a new adverse event in our study. HRD tests in our small samples confirmed that 50% of patients with high-grade serous ovarian cancer were HRD-positive. However, our data are limited representative due to the lower number of cases. It is needed further clinical trails to verify the exploratory therapy in our study.

Abbreviations

PARP: poly (ADP-ribose) polymerase

HRD: homologous recombination deficiency

HRR: homologous recombination repair

PFI: Platinum-free-interval

RECIST: Response Evaluation Criteria in Solid Tumors;

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of Jiangsu Cancer Hospital, Nanjing Medical University, China. The informed consent requirement was waived. The committee's reference number was Jiangsu Cancer Hospital's Ethical Committee 2020-068.

Consent for publication

Not applicable.

Availability of Data and Materials

We would not share the data and material used in this manuscript, because we need them for further research.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Jing Ni participated in the design of present study and drafted the manuscript. Xianzhong Cheng carried out the cases recruit of present study. Qian Zhao and Hongyuan Gu participated in the cases recruit of present study. Wenwen Guo and Rui Zhou carried out statistical analysis. Zhiqin Dai and Xia Xu participated in the statistical analysis and drafted the manuscript. Xiaoxiang Chen designed of the study, performed the statistical analysis and revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Baseline characteristics in 22 patients. Values are reported as frequency (n [%]) or as mean (range).

Characteristic	Number of patients (percent)
Age, yrs	
Median age (range)	55 (39-77)
≤55	12 (54.5)
>55	10 (45.5)
Primary tumor location	
Ovary	21 (95.5)
Fallopian tube	1 (4.5)
International FIGO stage	
I	2 (9.1)
II	11 (50.0)
III	8 (36.4)
Unknown	1 (4.5)
Histological type	
High-grade serous	19 (86.4)
Low-grade serous	1 (4.5)
Other	1 (4.5)
Unknown	1 (4.5)
Family history of cancer	
Yes	9 (40.9)
No	13 (59.1)
ECOG	
0	8 (36.4)
1	13 (59.1)
2	1 (4.5)
Baseline body weight	
≥77 kg	0 (0)
<77 kg	22 (100)
Platelet count	

≥150×10 ⁹ /L	12 (54.5)
<150×10 ⁹ /L	10 (45.5)
HRD status	
HRD-positive	6 (27.3)
tBRCA-mutated	1 (4.5)
BRCA-wild type or BRCA-unknown and HRD-positive	5 (22.7)
HRD-negative	8 (36.4)
HRD unknown	8 (36.4)
Prior lines of chemotherapy	
≤1	12 (54.5)
>1	10 (45.5)
Platinum status	
Platinum-sensitive	5 (22.7)
Platinum-resistant	5 (22.7)
Unknown	12 (54.5)
Categories of therapy	
First-line maintenance therapy	6 (27.3)
Exploratory therapy	16 (72.7)
Exploratory second-line maintenance therapy	1 (4.5)
Exploratory Front-line therapy	6 (27.3)
Exploratory multi-line therapy	9 (40.9)
NACT+IDS	
Yes	7 (31.8)
No	15 (68.2)
Primary debulking surgery	
Yes	12 (54.5)
No	10 (45.5)
Secondary cytoreductive surgery	
Yes	3 (13.6)

No	19 (86.4)
Combination with other agents	
Yes	4 (18.2)
No	18 (81.8)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; ECOG, Eastern Cooperative Oncology Group; HRD, homologous recombination deficiency; NACT, Neoadjuvant chemotherapy; IDS, Interval debulking surgery.

Table 2 Short-term efficacy of 9 evaluable patients with exploratory multi-line therapy.

Short-term efficacy	Monotherapy, n (%)	Combined Treatment, n (%)
Complete response (CR)	0 (0)	0 (0)
Partial response (PR)	2 (33.3)	0 (0)
Stable disease (SD)	1 (16.7)	1 (33.3)
Progression disease (PD)	3 (50.0)	2 (66.7)
Objective response rate (ORR)	2 (33.3)	0 (0)
Disease control rate (DCR)	3 (50.0)	1 (33.3)

The table above showed the short-term efficacy of 9 evaluable patients with exploratory multi-line therapy including 6 patients with niraparib monotherapy and 3 patients with combined treatment. Short-term efficacy was classified by modified Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Table 3 Summary of Adverse Events

Adverse Event	Any Grade	Grade 3 or 4
	Number of patients (percent)	
Nausea	12 (54.5)	0 (0)
Thrombocytopenia	11 (50.0)	4 (18.2)
Anemia	9 (40.9)	2 (9.1)
Fatigue or asthenia	8 (36.4)	0 (0)
Decreased appetite	7 (31.8)	0 (0)
Constipation	6 (27.3)	0 (0)
Neutropenia	5 (22.7)	2 (9.1)
Insomnia	5 (22.7)	0 (0)
Vomiting	3 (13.6)	1 (4.5)
Dyspepsia	3 (13.6)	1 (4.5)
Headache	3 (13.6)	0 (0)
Dizziness	2 (9.1)	0 (0)
Abdominal distention	2 (9.1)	0 (0)
Abdominal pain	1 (4.5)	0 (0)
Dysgeusia	1 (4.5)	0 (0)
Back pain	1 (4.5)	0 (0)
Diarrhea	1 (4.5)	0 (0)
Maculopapular rash	1 (4.5)	0 (0)
Stomatitis	1 (4.5)	0 (0)
Dry mouth	1 (4.5)	0 (0)
Newly observed		
Leg swelling	1 (4.5)	0 (0)
Led to discontinuation of intervention	1 (4.5)	-
Led to dose reduction	4 (18.2)	-
Led to dose interruption	4 (18.2)	-

Note: Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

Figures

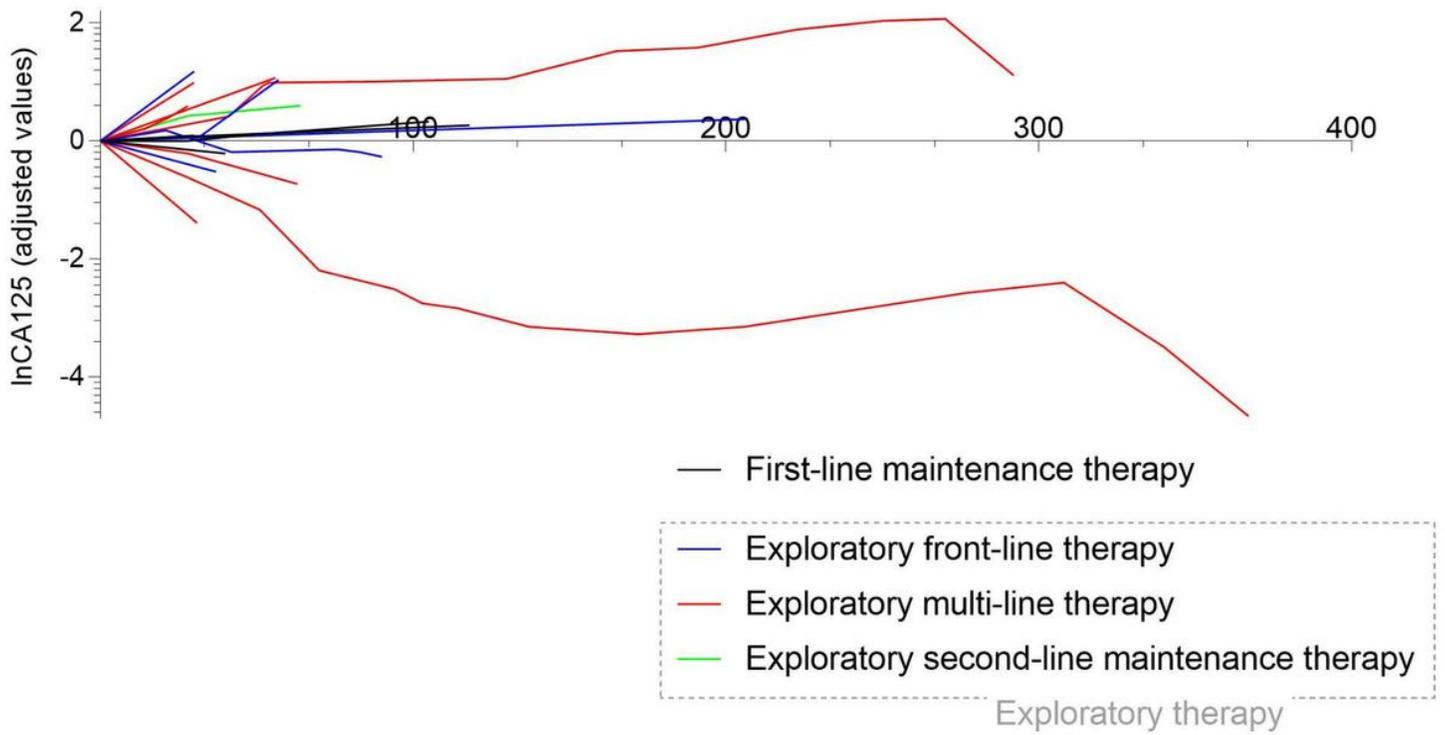


Figure 1

Serum CA125 values in each group. Note: The CA125 level of the first follow-up was used as the reference value, and all data were converted to natural logarithm. CA125 follow-up data were obtained from 6 patients in the first-line maintenance treatment group and 16 patients in the exploratory therapy group.

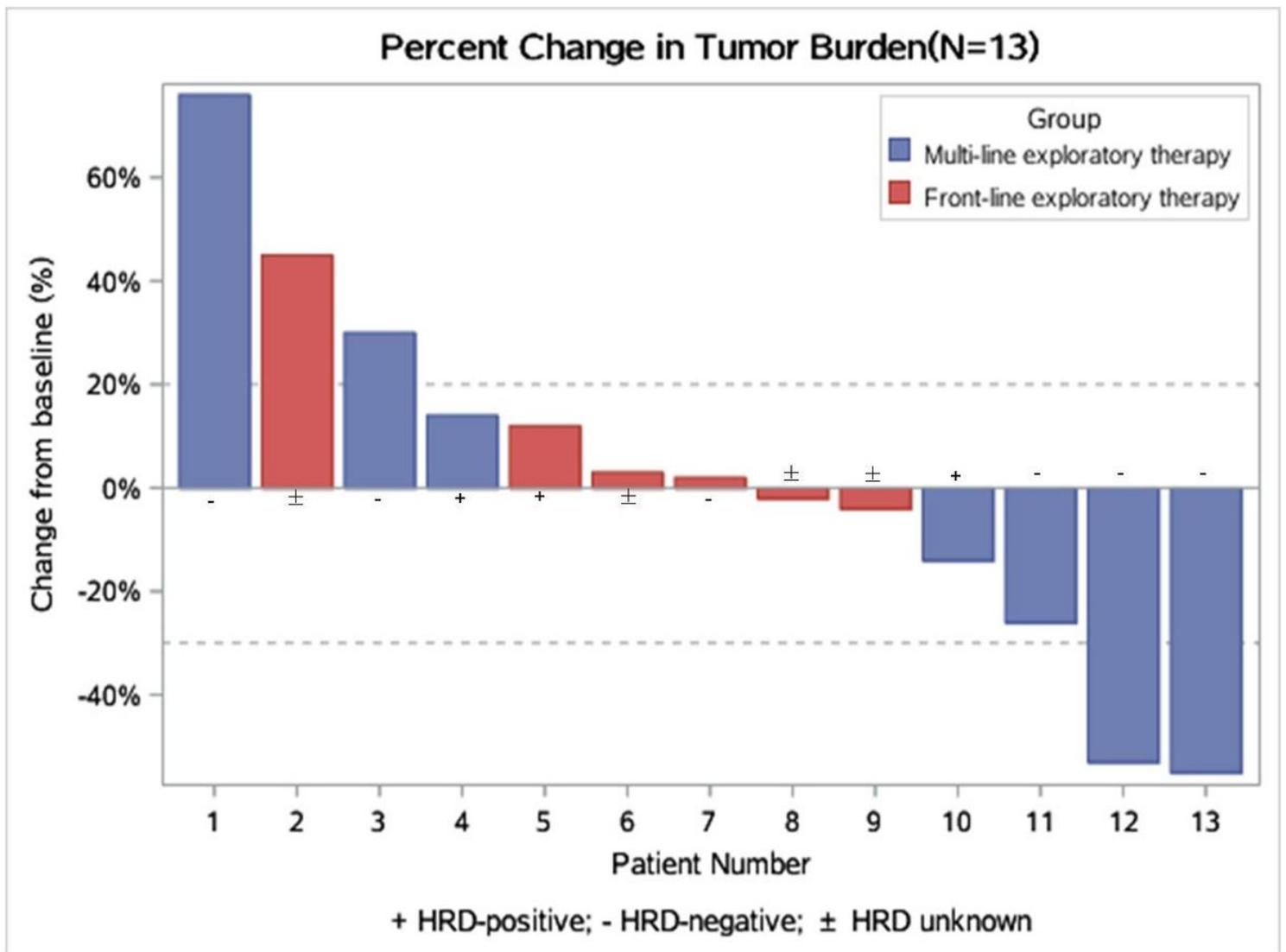


Figure 2

Waterfall plot of 13 evaluable patients with exploratory therapy. Note: Tumor burden change per investigator review. Maximum reduction from baseline (or smallest increase from baseline for patients with no reductions) in the sum of the longest diameters of target lesions. The change from baseline in tumor measurement as assessed by investigator review is shown for 13 evaluable patients (per protocol set). Front-line exploratory subgroup and multi-line exploratory subgroup were shown with different color in the figure. Among them, there were 3 HRD-positive patients, 6 HRD-negative patients and 4 HRD-unknown patients. Ten of them were treated by niraparib monotherapy while 3 of them(patient 1,7,11) were treated by combined strategies. The dotted line represents the threshold for partial response (>30% reduction from baseline sum of longest diameters) and progressive disease (>20% increase from baseline sum of longest diameters). Target lesions were defined according to RECIST 1.1.