Received: 11 March 2023 | Revised: 12 December 2000 | Accepted: 21 March 2023

DOI: 10.1002/cac2.12418

CANCER COMMUNICATIONS Open Access

LETTER TO THE EDITOR

Real-world outcomes of niraparib treatment in patients with ovarian cancer: a multicenter non-interventional study in China

Dear Editor,

Ovarian cancer remains the deadliest among all gynecological cancers. Although most patients at advanced stage respond to initial treatment, the majority experience recurrence [1]. It was estimated that 55,342 new cases and 37,519 deaths from ovarian cancer occurred in China annually [2]. Contemporarily, the treatment landscape has changed rapidly since the role of poly(adenosine diphosphate-ribose) polymerase inhibitors (PARPi) in ovarian cancer treatment was explored. Based on data from the PRIMA/ENGOT-OV26/GOG-3012 [3] and ENGOT-OV16/NOVA trials [4], niraparib has been approved globally as maintenance therapy for newly diagnosed and platinum-sensitive recurrent ovarian cancer. The indication of niraparib for salvage treatment was based on the results of the QUADRA (NCT02354586) trial [5]. Although niraparib has been tested in prospective randomized clinical trials (RCTs), no multicenter study on its real-world application in China had been conducted. Considering the differences in population, accessibility and affordability of drugs, the results of the real-world settings may differ from those of RCTs. Therefore, we conducted this multicenter, non-interventional study at 8 hospitals.

Data were collected from electronic records of a prospective cohort of patients who initiated niraparib treatment between December 2018 and September 2021. The inclusion and exclusion criteria (Supplementary Figure S1) and the methodology are presented in Supplementary Materials and Methods. Of the total 142 patients, 93 received niraparib as first-line maintenance therapy, 31 as maintenance therapy for platinum-sensitive recurrent ovarian cancer, and 18 as salvage treatment. The median age was 57 years (interquartile range [IQR], 51-64 years). The BReast CAncer (*BRCA*) gene status of 124 (87.3%) patients was wild-type or unknown Overall, 140 (98.6%) patients had an International Federation of Gynecology and Obstetrics (FIGO) stage III or IV ovarian cancer at diagnosis. Additional baseline characteristics are presented in Supplementary Tables S1-S2.

The overall median follow-up time was 12.8 months (95% confidence interval [CI], 12.0-14.0 months). For patients receiving first-line maintenance therapy, the median progression-free survival (mPFS) was not reached (95% CI, 11.7 months-not evaluable [NE]) by January 2022, with a probability rate of 84.8% (95% CI, 75.6%-90.7%) at 6 months and 58.6% (95% CI, 46.9%-68.6%) at 12 months; the mPFS for the platinum-sensitive recurrent ovarian cancer subgroup was 8.4 months (95% CI, 3.9 months-NE), with a probability rate of 61.3% (95% CI, 42.0%-75.8%) and 39.2% (95% CI, 21.5%-56.5%) at 6 and 12 months; for patients receiving niraparib as salvage treatment, the mPFS was 5.5 months (95% CI, 3.0-13.0 months), with 6- and 12-month probability rates of 38.9% (95% CI, 17.5%-60.0%) and 32.4% (95% CI, 12.7%-54.0%) (Figure 1A). Multivariate analysis revealed that response to the last chemotherapy was a significant factor for PFS improvement in the first-line maintenance subgroup (complete response [CR] vs. partial response [PR]: HR = 0.356, 95% CI = 0.164-0.771; $P = 0.009$); while the CA-125 level (≤35 UI/mL vs. >35 UI/mL: HR = 0.292, 95% CI = 0.106-0.803; $P = 0.017$) was statistically significant for PFS improvement in the platinum-sensitive recurrent ovarian cancer subgroup (Figure 1B-C, Supplementary Tables S3).

Overall, the efficacy results of niraparib in the real-world setting were consistent with those of RCTs. An mPFS of 13.8 months was reported in the PRIMA study [3], while it was not reached after a median follow-up of 12.8 months in the real-world study. For maintenance therapy for platinum-sensitive recurrent ovarian cancer, the mPFS of the NORA trial was 18.3 months, while it was

Abbreviations: AE, Adverse event; CI, confidence interval; CR, complete response; BRCA, BReast CAncer gene; FIGO, International Federation of Gynecology and Obstetrics; HR, Hazard ratio; IQR, Interquartile Range; ISD, Individualized starting-dose; PARPi, poly (adenosine diphosphate-ribose) polymerase inhibitors; PFS, progression-free survival; PR, partial response.

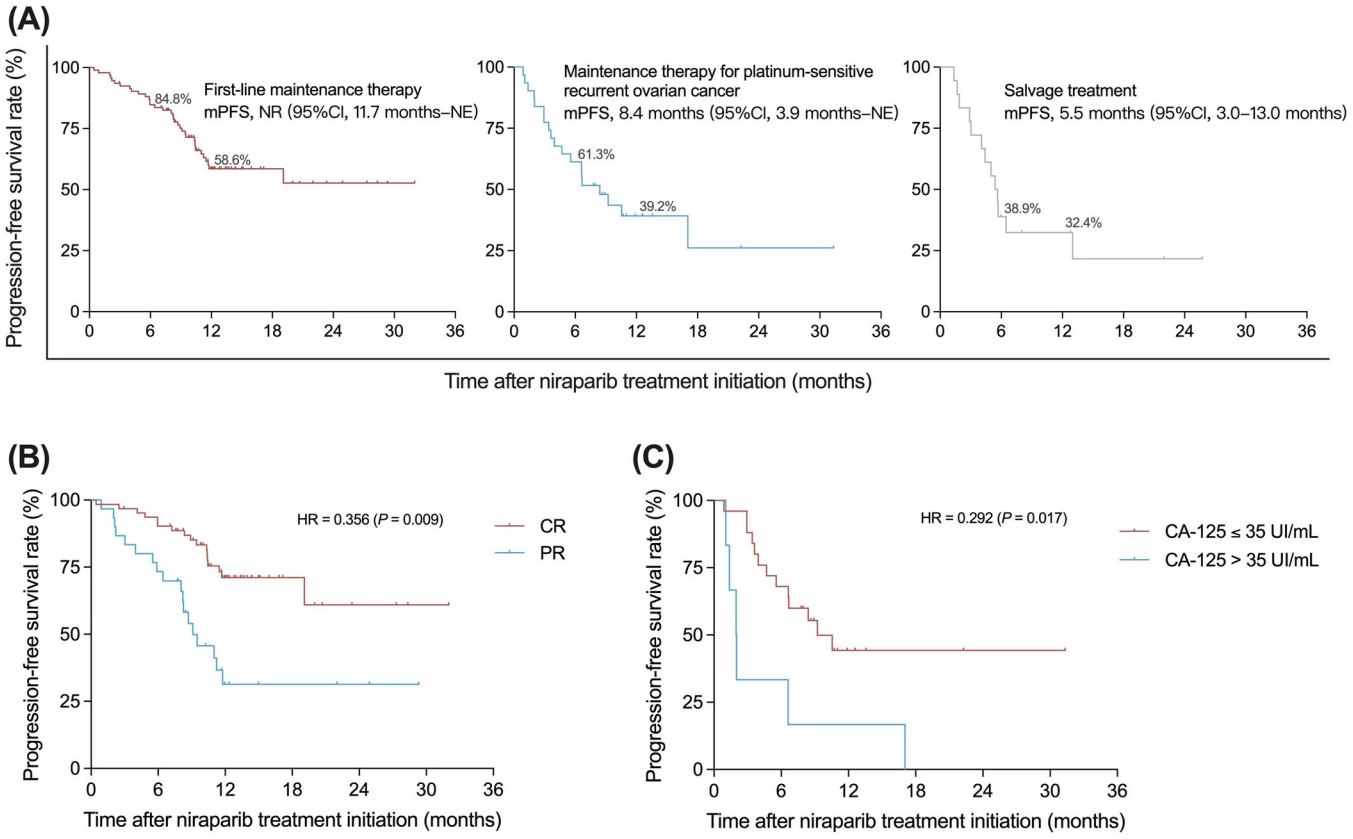

FIGURE 1 Kaplan-Meier PFS curves for patients treated with niraparib for ovarian cancer in the real-world setting. (A) Kaplan-Meier plots showing the PFS for patients receiving niraparib in different treatment phases (first-line maintenance therapy; maintenance therapy for platinum-sensitive recurrent ovarian cancer; salvage treatment). (B) Kaplan-Meier plot showing the PFS among patients receiving niraparib as first-line maintenance therapy with different responses to last chemotherapy (multivariate analysis showing $P = 0.009$). (C) Kaplan-Meier plot showing the PFS among patients with platinum-sensitive recurrent ovarian cancer receiving niraparib as maintenance therapy with different baseline levels of CA-125 (multivariate analysis showing $P = 0.017$).

Abbreviations: mPFS, median progression-free survival; CI, confidence interval; HR, hazard ratio; CA-125, cancer antigen 125; NE, not evaluable; NR, not reached.

8.4 months in the real-world study. The minor discrepancy was associated with several factors. First, patients in real-world setting had poorer baseline characteristics. In the NORA trial [6], 51.4% of patients achieved CR after chemotherapy while it was 16.1% in the real-world setting; all patients in the NORA trial had 2 lines of prior chemotherapy, while 35.5% in the real-world study had ≥3 lines of prior chemotherapy. Further, PFS was calculated from the time of randomization in RCTs, in which the maintenance therapy of niraparib was usually initiated within 8-12 weeks after chemotherapy. There was no such restriction on the time interval in the real-world setting. Thus, the differences in the definition of PFS between real-world studies and RCTs should also be considered.

Most patients (136/142 [95.8%]) had niraparib at a starting dose of 200 mg once daily, according to the individualized starting dose regimen. Overall, 24 (16.9%) patients reported any grade of hematological treatment-emergent adverse events (TEAEs); 18 (12.7%) patients experienced grade ≥3 TEAEs, including thrombocytopenia in 10 (7.0%), anemia in 9 (6.3%), and neutropenia in 2 (1.4%) patients; 33 (23.2%) patients had dose adjustment, whereas 5 (3.5%) patients discontinued niraparib due to toxicity (Supplementary Tables S4-S5).

These results revealed that niraparib was well tolerated in real-world settings, which may be due to the intense follow-up and flexible management of AEs. Patients completed hematological tests every week during the first month of niraparib use and were prescribed medicines in advance as an early intervention for AEs. Noticeably, our data showed a significant association between the interval from chemotherapy completion to niraparib initiation and occurrence of grade ≥3 AEs (≥21 days vs. <21 days: 10.6% vs. 36.4%, $P = 0.036$), suggesting that initiation of maintenance therapy before complete recovery from myelosuppression might result in unwanted AEs.

This finding may serve as a reference for clinical practice and deserve future investigation.

Analysis of niraparib utilization patterns (Supplementary Tables S6 and S7) showed that 7.0% of patients were treated with other drugs in combination with niraparib, and there was no uniform treatment pattern after progression on niraparib. The percentage of patients receiving niraparib as maintenance therapy (Supplementary Figure S2) had increased from 80.0% in 2019 to 90.2% in 2021. Although approved by US Food and Drug Administration, access to niraparib was initially limited in China because of no therapeutic indications and non-inclusion in China's National Reimbursement Drug List. Niraparib was authorized as a maintenance treatment for platinum-sensitive recurrent ovarian cancer in December 2019 [7] and as first-line maintenance therapy in October 2020 in China [8]. At the beginning of the study period, due to economic reasons, niraparib was often reserved as a last resort when patients were resistant or intolerable to chemotherapy. In January 2022, niraparib was included in China's National Reimbursement Drug List, thereby increasing the affordability and utilization in early-line settings [9]. Additionally, Kaplan-Meir analysis (Figure 1A) showed that the mPFS shortened as the numbers of treatment lines increased. Thus, the early application of PARPi for improving survival and the optimal timing of introduction in the whole-process management remains a matter of interest.

This study was limited by a relatively short follow-up time because of the late approval of niraparib in China. Besides, travel restrictions during the coronavirus pandemic in the past three years limited patients' follow-up. Despite these limitations, this multicenter study evaluated the treatment outcomes of niraparib in a real-world setting in China. The real-world results were generally consistent with those reported in prospective clinical trials. Although niraparib was well tolerated in clinical practice, a significant association between the occurrence of grade ≥3 AEs and an interval of <21 days between chemotherapy completion and niraparib initiation was observed, indicating that a complete recovery from myelosuppression was necessary before niraparib application. With the improvement of drug accessibility and affordability in China, the number of treatment lines of niraparib has gradually moved forward. However, the optimal timing for the introduction of PARPi in the whole-process management of ovarian cancer remains a matter of interest.

DECLARATION

AUTHOR CONTRIBUTIONS

Conceived and designed the study: XHW and JL. Supervised the study: XHW. Investigation and data collection: JHY, HFS, LZ, XHH, XDT, FZ and FL. Patients management and follow-up: HW, HJY, HYW, ZTL, XJC, XZJ, XC, JT and MQZ. Performed the integrity of the data: JL. Verified the data: HW, XZJ and JT. Drafted and revised the manuscript: JL. Final approval of manuscript: All authors.

ACKNOWLEDGMENTS

The authors would like to thank all patients, their families and the medical staff for their valuable contribution to this study. We would also like to acknowledge Anwesha Mandal and Dr. Ramandeep Singh of Indegene Pvt Ltd. for their language support.

CONFLICT OF INTEREST STATEMENT

The authors had no conflicts of interest to disclose.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, and the ethics committee of the main study center Fudan University Shanghai Cancer Center approved the protocol (NO.050432-4-1805C).

CONSENT FOR PUBLICATION

Not Applicable

FUNDING INFORMATION

This study was funded by the National Natural Science Foundation of China (NSFC 81972431).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Menon U, Gentry-Maharaj A, Burnell M, Singh N, Ryan A, Karpinskyj C, et al. Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2021 Jun 5;397(10290):2182–93.
2. 25-Ovary-fact-sheet.pdf [Internet]. [cited 2022 May 10]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/25-Ovary-fact-sheet.pdf
3. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. MA Med Soc. 2019;381:2391–402.
4. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. MA Med Soc. 2016;375:2154–64.
5. Kathleen N Moore, Angeles Alvarez Secord, Melissa A Geller, David Scott Miller, Noelle Cloven, Gini F Fleming, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2019 May;20(5):636–48.
6. Wu XH, Zhu JQ, Yin RT, Yang JX, Liu JH, Wang J, et al. Niraparib maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer using an individualized starting dose (NORA): a randomized, double-blind, placebo-controlled phase III trial. Ann Oncol. 2021;32:512–21.
7. Limited ZL. Zai Lab Announces NMPA Approval of ZEJULA® (Niraparib) in China as Maintenance Therapy for Patients with Recurrent Ovarian Cancer [Internet]. GlobeNewswire News Room. 2019 [cited 2022 May 25]. Available from: https://www.globenewswire.com/news-release/2019/12/27/1964630/0/en/Zai-Lab-Announces-NMPA-Approval-of-ZEJULA-Niraparib-in-China-as-Maintenance-Therapy-for-Patients-with-Recurrent-Ovarian-Cancer.html
8. Limited ZL. Zai Lab Announces NMPA Approval of ZEJULA® (Niraparib) for First-Line Maintenance Treatment of Ovarian Cancer in China [Internet]. GlobeNewswire News Room. 2020 [cited 2022 May 17]. Available from: https://www.globenewswire.com/news-release/2020/09/10/2091603/0/en/Zai-Lab-Announces-NMPA-Approval-of-ZEJULA-Niraparib-for-First-Line-Maintenance-Treatment-of-Ovarian-Cancer-in-China.html
9. Limited ZL. Zai Lab Announces Inclusion of ZEJULA® (Niraparib) in China's National Reimbursement Drug List [Internet]. GlobeNewswire News Room. 2020 [cited 2022 May 17]. Available from: https://www.globenewswire.com/fr/news-release/2020/12/29/2151031/0/en/Zai-Lab-Announces-Inclusion-of-ZEJULA-Niraparib-in-China-s-National-Reimbursement-Drug-List.html

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.