Editorial Commentary

PARP inhibitors, use early in the first-line maintenance therapy setting but with caution

Elena Giudice[1,2], Yong Man Kim[3], Jung-Min Lee[1]

[1]Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA; [2]Institute of Obstetrics and Gynecology, Università Cattolica del Sacro Cuore, Rome, Italy; [3]Department of Obstetrics and Gynecology, Gynecologic Cancer Center, Asan Cancer Institute, Asan Medical Center, University of Ulsan, Seoul, South Korea

Correspondence to: Jung-Min Lee, MD. Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA. Email: leej6@mail.nih.gov.

Comment on: Monk BJ, Parkinson C, Lim MC, *et al.* A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). J Clin Oncol 2022;40:3952-64.

Keywords: Poly-(ADP-ribose) polymerase (PARP) inhibitors (PARPis); mechanism of drug resistance; optimal sequencing for cancer treatment; biomarker-guided cancer treatment.

Submitted Jan 01, 2023. Accepted for publication Jan 10, 2023. Published online Jan 19, 2023.
doi: 10.21037/atm-2022-81
View this article at: https://dx.doi.org/10.21037/atm-2022-81

In recent years, the advent of poly-(ADP-ribose) polymerase (PARP) inhibitors (PARPis) has profoundly changed the treatment landscape of ovarian cancer (OC) (1-5). Mechanistically, PARPis act by blocking the catalytic activity of PARP enzymes as well as by trapping PARP enzymes on their DNA substrates, resulting in toxic PARP-DNA complexes, which in turn trigger the collapse of replication forks (6). It is well documented that such emergent DNA double-stranded breaks (DSBs) are mainly resolved by a homologous recombination DSB repair machinery (7). As such, approximately half of high-grade serous OC attains greater benefit from PARPis because of its homologous recombination-deficient (HRd) phenotypes (8). Notably, earlier clinical trials also demonstrated clinical benefit with PARPis in homologous recombination-proficient (HRp) OC (2-3,5) and rucaparib became one of the three U.S. Food and Drug Administration (FDA)-approved PARPis, for the 2nd or greater line maintenance therapy setting for both HRd and HRp OC based on the findings from ARIEL 3 study (5).

In this ATHENA-MONO trial (9), Monk *et al.* tested the efficacy of rucaparib maintenance therapy in the first line setting for a broad population. ATHENA/GOG-3020/ENGOT-ov45 is a multicentric, randomized, double-blind, placebo-controlled phase III trial, consisting of two independent cohorts, which evaluate rucaparib alone (ATHENA-MONO) or in combination with anti-PD1, nivolumab (ATHENA-COMBO) in the upfront maintenance setting. While ATHENA-COMBO is currently ongoing, results from ATHENA-MONO met its primary endpoints. Specifically, at median follow-up of approximately 26 months, rucaparib monotherapy significantly improved the median PFS (mPFS) compared with placebo in HRd tumors [28.7 *vs.* 11.3 months; hazard ratio (HR) 0.47; 95% confidence interval (CI), 0.31–0.72], as well as in the intent-to-treat (ITT) population (20.2 *vs.* 9.2 months; HR 0.52; 95% CI, 0.40–0.68). Moreover, in preplanned exploratory analysis, HRp population also derived the benefit from rucaparib monotherapy with 12.1 months of mPFS compared to 9.1 months with placebo (HR 0.65; 95% CI, 0.45–0.95) (9).

One of the strengths of ATHENA-MONO is a broad population enrolled, providing more data in non-HRd OC, while other trials investigated the role of PARPis in more specific populations. SOLO-1 was the first trial to demonstrate the clinical benefit of olaparib as a first line maintenance therapy in BRCA mutant OC (1). PRIMA study investigated niraparib in a high-risk OC population e.g., stage IV, or stage III with residual disease, but not limited to BRCA mutation or HRd groups (2). ATHENA-

MONO extends the patient population to both high and low risks of relapse [i.e., patients diagnosed with the International Federation of Gynecology and Obstetrics (FIGO) stage III, and patients undergoing primary debulking surgery with no residual disease] to examine potential benefit from rucaparib maintenance in all advanced OC patients, beyond DNA repair dysfunction or risk of relapse status (8).

While exciting, there is recognition that PFS benefit with PARPis may not translate into increased overall survival (OS) in the recurrent setting. Updated survival data of each of the three different PARPis prompted recent revisions to the FDA approvals for PARPis. For instance, no OS benefit was seen in the final analysis of ARIEL3 (10). In the nested primary analysis of ARIEL3, a HR was 0.832 (95% CI, 0.581–1.192) in the BRCA mutant patients, while HR was 1.005 (95% CI, 0.766–1.320) and 0.995 (95% CI, 0.809–1.223) in the HRd and ITT populations, respectively. In subsequent analysis of non-nested exploratory subgroups related to tumor molecular characteristics, no statistically significant differences among treatment arms were found; HRs of 1.280 (95% CI, 0.841–1.948), 1.153 (95% CI, 0.784–1.695), and 0.673 (95% CI, 0.305–1.483) in the BRCA wild-type HRd, BRCA wild-type HRp, and BRCA wild-type homologous recombination unknown subgroups, respectively. Also, in final OS analysis of ARIEL4, a median OS (mOS) favored the standard of care chemotherapy arm over rucaparib monotherapy in relapsed BRCA-mutated OC patients; mOS of 19.4 *vs.* 25.4 months in rucaparib and chemotherapy groups, respectively (HR 1.313; 95% CI, 0.999–1.725) (11). However, it is noteworthy that there was a high crossover rate (69%) in ARIEL4, with a total of 90% of patients having received rucaparib from randomization or after crossover. This may have provided a bias in evaluating the OS data, as they were unadjusted for subsequent PARPis therapy. Despite these challenges of interpreting the results, the FDA withdrew rucaparib indication as monotherapy for the late line treatment of BRCA mutated OC patients and anticipated the future withdrawal from 2nd or greater line maintenance therapy for non-BRCA mutant patients (12). Similarly, niraparib indication was already withdrawn for 2nd or greater line maintenance therapy for non-BRCA mutant patients based on the long-term follow-up data of the NOVA trial, in which OS demonstrated an HR of 1.06 (95% CI, 0.81–1.37) in the non-germline BRCA mutated cohort (12,13). Although it is hard to dissect the exact mechanisms of those contributing to the OS outcomes at this time, it is evident that our approach to the use of PARPis will most likely focus on the earlier maintenance setting based on the updated indications (12).

There are potential explanations to the discrepancies between PFS and OS data. It is possible that OS data may have been influenced by post-progression therapies and cross-over to the investigational treatments, and none of the aforementioned trials were designed to investigate those effects. Secondly, overlapping mechanisms of resistance may have affected those final analyses, thus indicating the importance of tailoring the subsequent treatments. Thus far, several mechanisms of resistance to PARPis have been identified via clinical and preclinical studies. Specifically, mechanisms involved in restoring homologous recombination functionality e.g., BRCA reversion mutations and epigenetic upregulation or RAD51 reversion mutation are well known cross-resistant mechanisms with platinum drugs (14-16). Thus, it is possible that tumors progressed on the PARPis may have had poor response to subsequent platinum-based therapies. Other mechanisms were also studied via various preclinical models e.g., loss of p53-binding protein 1 (53BP1), loss of REV7 gene (17,18), replication fork stabilization and increased drug efflux, all requiring further studies in the clinical settings (16,19-21). Of note, those resistance mechanisms are not mutually exclusive and may cause cross-resistance to other non-platinum agents. Hence, the complexity of PARPis clinical resistance underscores the necessity of tailoring the subsequent treatments in a molecularly selected subgroups after progression on PARPis. As such, molecular analysis of fresh tissue and/or circulating tumor DNA samples will be important to study clinical resistance of PARPis and design the next generation clinical trials for this newly emerging subgroup of patients with unmet medical needs.

In conclusion, given the undisputable benefit of PARPis in the OC treatment landscape, the use of PARPis should not be discouraged, especially in the upfront maintenance therapy setting. It is noteworthy that the 7-year follow-up data from the SOLO-1 trial (22) and the 5-year OS data from the PAOLA-1 study (23) exhibit encouraging OS data (SOLO1: HR for OS of 0.55; 95% CI, 0.40–0.76; PAOLA-1: HR for OS in HRd population of 0.62; 95% CI, 0.45–0.85). As such, long term survival data from ATHENA-MONO are eagerly awaited. At the same time, it is necessary to broaden our understanding on clinically relevant PARPis resistance and conducting hypothesis driven translational studies to identify primary *vs.* acquired resistance to PARPis as well as our best use of PARPis with

caution in the right setting for the right population.

Acknowledgments

Funding: This research was funded by the Intramural Research Program of the National Cancer Institute Center for Cancer Research (NCI CCR), National Institutes of Health (grant No. ZIA BC011525 awarded to JML).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-2022-81/coif). JML received grant (No. ZIA BC011525) from National Cancer Institute Center for Cancer Research (NCI CCR) and National Institutes of Health. The other authors have no conflicts of interests to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med 2018;379:2495-505.
2. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med 2019;381:2391-402.
3. Del Campo JM, Matulonis UA, Malander S, et al. Niraparib Maintenance Therapy in Patients With Recurrent Ovarian Cancer After a Partial Response to the Last Platinum-Based Chemotherapy in the ENGOT-OV16/NOVA Trial. J Clin Oncol 2019;37:2968-73.
4. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1274-84.
5. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390:1949-61.
6. Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. Cancer Res 2012;72:5588-99.
7. Moynahan ME, Jasin M. Mitotic homologous recombination maintains genomic stability and suppresses tumorigenesis. Nat Rev Mol Cell Biol 2010;11:196-207.
8. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science 2017;355:1152-8.
9. Monk BJ, Parkinson C, Lim MC, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). J Clin Oncol 2022;40:3952-64.
10. Coleman RL, Oza AM, Lorusso D, et al. Overall Survival Results From ARIEL3: A Phase 3 Randomized, Double-blind Study of Rucaparib vs Placebo Following Response to Platinum-Based Chemotherapy for Recurrent Ovarian Carcinoma. Presented at: IGCS 2022 Annual Global Meeting; September 29-October 1, 2022.
11. Kristeleit R, Lisyanskaya A, Fedenko A, et al. Rucaparib versus standard-of-care chemotherapy in patients with relapsed ovarian cancer and a deleterious BRCA1 or BRCA2 mutation (ARIEL4): an international, open-label, randomised, phase 3 trial. Lancet Oncol 2022;23:465-78.
12. Available online: https://www.sgo.org/resources/revisions-to-fda-approvals-for-parp-inhibitors/
13. Matulonis UA, Herrstedt J, Oza A, et al. Long-term safety and secondary efficacy endpoints in the ENGOT-OV16/NOVA phase III trial of niraparib in recurrent ovarian cancer. Presented at: Society of Gynecological Oncology 2021 Annual Meeting on Women's Cancer; March 19-25, 2021;abstr 11139.
14. Swisher EM, Kwan TT, Oza AM, et al. Molecular

and clinical determinants of response and resistance to rucaparib for recurrent ovarian cancer treatment in ARIEL2 (Parts 1 and 2). Nat Commun 2021;12:2487.
15. Wang Y, Bernhardy AJ, Cruz C, et al. The BRCA1-Δ11q Alternative Splice Isoform Bypasses Germline Mutations and Promotes Therapeutic Resistance to PARP Inhibition and Cisplatin. Cancer Res 2016;76:2778-90.
16. Le Page C, Amuzu S, Rahimi K, et al. Lessons learned from understanding chemotherapy resistance in epithelial tubo-ovarian carcinoma from BRCA1and BRCA2mutation carriers. Semin Cancer Biol 2021;77:110-26.
17. Hurley RM, Wahner Hendrickson AE, Visscher DW, et al. 53BP1 as a potential predictor of response in PARP inhibitor-treated homologous recombination-deficient ovarian cancer. Gynecol Oncol 2019;153:127-34.
18. Karakashev S, Fukumoto T, Zhao B, et al. EZH2 Inhibition Sensitizes CARM1-High, Homologous Recombination Proficient Ovarian Cancers to PARP Inhibition. Cancer Cell 2020;37:157-167.e6.
19. Gupta N, Huang TT, Horibata S, et al. Cell cycle checkpoints and beyond: Exploiting the ATR/CHK1/WEE1 pathway for the treatment of PARP inhibitor-resistant cancer. Pharmacol Res 2022;178:106162.
20. Huang TT, Burkett SS, Tandon M, et al. Distinct roles of treatment schemes and BRCA2 on the restoration of homologous recombination DNA repair and PARP inhibitor resistance in ovarian cancer. Oncogene 2022;41:5020-31.
21. Ray Chaudhuri A, Callen E, Ding X, et al. Replication fork stability confers chemoresistance in BRCA-deficient cells. Nature 2016;535:382-7.
22. DiSilvestro P, Banerjee S, Colombo N, et al. Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial. J Clin Oncol 2023;41:609-17.
23. Ray-Coquard I, Leary A, Pignata S, et al. Final overall survival results from the phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced ovarian cancer. Ann Oncol 2022;33:S808-69.

Cite this article as: Giudice E, Kim YM, Lee JM. PARP inhibitors, use early in the first-line maintenance therapy setting but with caution. Ann Transl Med 2023;11(6):272. doi: 10.21037/atm-2022-81

