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PARP inhibitors and overall survival in ovarian cancer, reevaluation advised in all settings

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Abstract

PARP inhibitors in ovarian cancer have been a breakthrough therapy of the past decade, driven by positive trial results, and supported by an original pharmacological rationale. However, with mature data, detrimental survival results led to the withdrawals, in 2022, of all approved PARP inhibitors in the most advanced settings' indication (as monotherapy in third or subsequent lines) by the US Food and Drug Administration (FDA). Two other indications, as maintenance after relapse, were also restricted. In this work, based on pooled meta-analysis in each setting, we question a unique situation in oncology: a survival benefit is seen in front-line settings, with, at the same time, a survival decrement in later lines. Either this original feature is explained by the unique biological action of PARP inhibitors—through synthetic lethality—in patients with ovarian cancer and homologous repair deficiency. Another explanation may be trial design: decrement in later lines could partly explain why beneficial results were seen in early settings, simply by avoiding late exposure to PARP inhibitors in the experimental arm in those trials. High crossover rates seen in some trials further support this alternate hypothesis. We contend our analysis and recent survival results of PARP inhibitors warrant a whole reassessment of the place of these compounds in the landscape of ovarian cancer treatments.

Keywords Ovarian cancer · PARP inhibitors · Clinical trials · Drug development · Drug regulation

With maturing overall survival (OS), marketing authorizations of PARP inhibitors (poly-ADP-ribose polymerase inhibitors) in ovarian cancer have been scrutinized over the year 2022. Between June and September 2022, olaparib, rucaparib, and niraparib were withdrawn in the most advanced ovarian cancer settings, i.e., monotherapy in third or subsequent lines. PARP inhibitor's regulatory saga continued when the US Food and Drug Administration (FDA) planned to reassess niraparib's approval in the maintenance setting after relapse, during its Oncologic Drugs Advisory Committee (ODAC) to be held in November 2022. This was motivated after survival of patients without germline BRCA mutation enrolled in the NOVA trial tended to be shorter in patients receiving niraparib than in the placebo group. In a last minute update, the sponsor decided to restrict this indication, and the FDA meeting was canceled. Soon after, rucaparib was also given an ultimatum, as the FDA asked the company to limit its use, in the maintenance setting after relapse, to patients with BRCA mutations, or face drug advisory meeting. This occurred after updated data were presented from the ARIEL3 study, showing an OS benefit in BRCA-mutated patients, and not in unselected patients of the study (Coleman et al. 2022).

In this analysis by pooling OS data in different settings of ovarian cancer (Fig. 1), we draw important lessons. First, we support the restriction of niraparib and rucaparib as requested by the FDA. Moreover, we question the role of PARP inhibitors in the setting of maintenance in recurrent ovarian cancer. Additionally, the discrepancy between first-line results and third-line results warrants exploration; here, we propose a mechanism to explain this paradox.

PARP inhibitors when used as monotherapy regimens in third or subsequent lines have a numerical detrimental effect on overall survival as compared to chemotherapy. This is reflected by a hazard ratio of 1.21 (95% [CI] 0.98, 1.50) in our metanalysis, yet not statistically significant (Fig. 1A).

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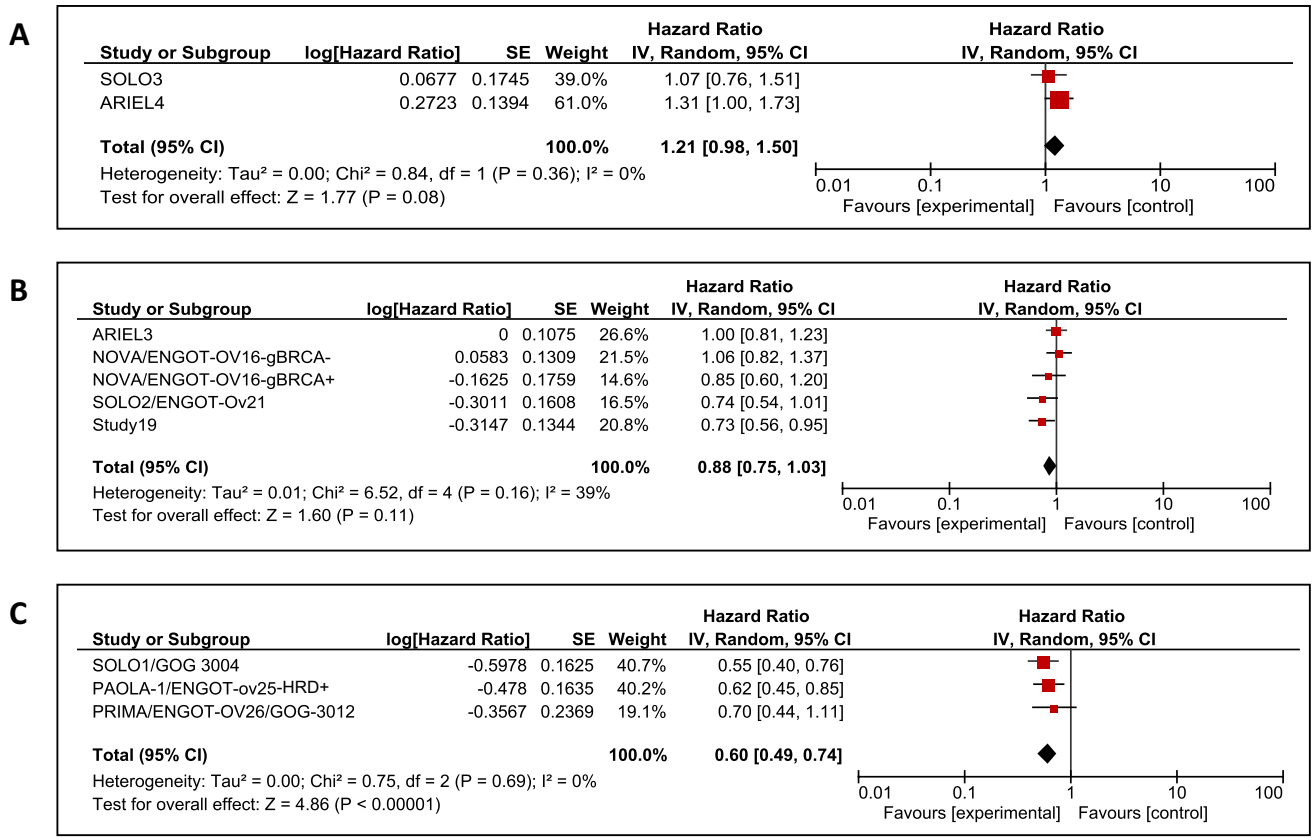

Fig. 1 Meta-analysis of overall survival results in phase 3 trials of PARP inhibitors in ovarian cancer. **A** monotherapy, third or subsequent lines, **B** maintenance after recurrence, and **C** maintenance in the first-line setting

The ARIEL4 trial enrolled patients with ovarian cancer and germline or somatic BRCA1 or BRCA2 mutation after at least 2 previous chemotherapy regimens (Oza et al. 2022). Patients were randomized between rucaparib and chemotherapy. A worse survival (though not statistically significant) was noted in patients receiving rucaparib as compared to chemotherapy (HR = 1.313, 95% [CI] 0.999, 1.725): this finding led to the withdrawal in this indication in June 2022. The SOLO3 trial enrolled patients with germline BRCA mutation in the setting of platinum-sensitive relapse after at least 2 prior platinum-based chemotherapy. Patients were randomized between olaparib and non-platinum chemotherapy. While olaparib was not better than chemotherapy in the overall population (HR = 1.07, 95% [CI] 0.76, 1.49, $p = 0.714$) (Penson et al. 2022), a subgroup analysis of patients enrolled after 3 or more lines of therapy suggested a survival decrement in patients receiving olaparib (HR = 1.33, 95% [CI] 0.84, 2.18), resulting in the withdrawal in this setting occuring in August 2022. Niraparib, approved in 2019 for HRD-positive (Homologous Repair Deficiency) patients as a fourth or subsequent line treatment, experienced the same regulatory fate in September 2022 when the company voluntarily withdrew this indication. According the company, this was "based on a totality of information from PARP inhibitors in the late line treatment setting in ovarian cancer". As a result, PARP inhibitors can no longer be marketed in the US for late-line treatment of ovarian cancer. Importantly, all these trials (and labels) selected patients with either BRCA mutation or HRD positivity (not all comers).

In an intermediary setting: maintenance after recurrence, all 3 PARP inhibitors were approved irrespective of BRCA mutation or HRD status. Olaparib was authorized based on the SOLO-2 and Study19 trials. SOLO-2 restricted enrollment to patients with germline BRCA mutation, while Study 19 included all patients. Interestingly, the survival advantage did not reach statistical significance in the trial enriched with BRCA-mutated patients (SOLO-2, HR = 0.74, 95% [CI] 0.54, 1.00, $p = 0.054$) (Poveda et al. 2020), and was only marginally significant in the non-selected population(Study 19, HR = 0.73, 95% [CI] 0.55, 0.95, $p = 0.02138$, with a predefined threshold for significance = 0.0095) (Friedlander et al. 2018). Rucaparib was approved based on a PFS benefit in ARIEL3, yet recent data shared with the FDA showed survival was not improved in the experimental arm with a median of 36.0 months with rucaparib and 43.2 months

with placebo (HR = 0.995 (95% [CI] 0.809–1.223). The FDA requested the sponsor to limit its indication only to patients with BRCA mutation, where a survival benefit was suggested (HR 0.832; 95% CI 0.581–1.192): the restriction was confirmed by the company in December 2022.

NOVA (niraparib) was originally intended for discussion in an ODAC meeting, which was canceled after voluntary restriction of the indication. Data presented in 2021 suggested a survival decrement in patients without germline BRCA mutation with a median OS of 31.1 months with niraparib, and 36.5 months in the placebo arm (HR = 1.10, 95% [CI] 0.831, 1.459) (Matulonis et al. 2021). After the FDA asked the company to reduced the initially significant (17%) proportion of missing survival data, the updated results based on 98% of survival data were comparable (HR=1.06, 95% [CI] 0.81–1.37), and amongst women with germline BRCA mutation, there was no significant OS benefit (HR = 0.85, 95% [CI] 0.61, 1.2). The result of our meta-analysis does not find a statistically significant benefit of PARP inhibitors in this setting for unselected patients (Fig. 1B). In NOVA, amongst patients who received placebo, 27% ultimately crossed over. Yet, given the negative survival results in third and subsequent lines, this action would have obscured or diminished the survival decrement. Similar issue may have occur in ARIEL3, where 46% of control arm patients later received a PARP inhibitor, and in SOLO2 where this was 38% of them. In other words, had crossover not occurred PARP inhibitors would appear worse rather than better. Ultimately, the company announced the restriction of niraparib's indication in this setting to patient with deleterious or suspected deleterious germline BRCA mutations, after the FDA request, though this occurred more than 16 months after concerning results were first reported.

Our meta-analysis did not find an indisputable survival benefit for PARP inhibitors in this setting, and it is likely these results were upwardly biased due to some rate of crossover.

Finally, based on individual trial data and confirmed in our meta-analysis (Fig. 1C), PARP inhibitors have what appears to be a clear OS benefit when given as maintenance treatment after the first-line initial therapy. The 7-year OS results from the SOLO-1 trial showed a maintained OS benefit with olaparib in patients with BRCA-mutant ovarian cancer with a median OS still not reached in the olaparib group, as compared with 75.2 months in the placebo arm (HR = 0.55 95% [CI] 0.40–0.76; $p = 0.0004$). The PAOLA-1 trial supported survival benefit, with olaparib in combination with bevacizumab in HRD-positive patients (HR = 0.62, 95% CI 0.45–0.85). Interestingly, niraparib in the PRIMA trial, which was approved regardless the genomic status, did not result in clear beneficial survival outcomes (HR = 0.7, 95% [CI] 0.44–1.11), even though data were not mature.

Yet, recent withdrawals mean that these approvals should be reevaluated. There is no precedent in oncology when a drug increases mortality in latter lines, while decreasing it when given sooner (Parsons et al. 2020). It is possible that the specificities of PARP inhibition and synthetic lethality, in conjunction with BRCA or HRD biology, could explain this unusual pattern. Changes in tumor biology across lines of therapy could also bear original insights.

Another explanation worth considering is patients who receive PARP early derive some benefit simply because they are less likely to receive the same agent later upon relapse. Some of the survival benefit in upfront trials might simply reveal survival decrement if the drug is given later. In PAOLA-1, 50.8% of control arm patients in the HRD-positive subgroup received a PARP inhibitor as part of any subsequent treatment. Comparable rate of crossover was seen in SOLO-1 (44.3%).

PARP inhibition in ovarian cancer has been heralded as a major breakthrough, but recent development forces a reevaluation of the paradigm. Specifically, all these drugs may provide a survival decrement in patients treated with multiple lines of therapy. For patients receiving these drugs in the maintenance setting after relapse, we found no clear evidence of benefit, and worry that harms could have been masked by crossover. Ultimately, all front-line studies, which have showed impressive results, warrant closer examination. One of two things must be true: PARP is an unusual target where early use is beneficial, but latter use is harmful, or elements of trial design explain these discordant results. Understanding which is correct has implications for more than 300 thousand women diagnosed with ovarian cancer worldwide annually.

Author contributions TO: conceptualization, writing, original draft, writing, review, and editing. VP: conceptualization, writing, review, and editing.

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Data availability All data used in this work are publicly available.

Declarations

Conflict of interest Vinay Prasad's disclosures: research funding: Arnold Ventures; royalties: Johns Hopkins Press, Medscape; honoraria: grand rounds/lectures from universities, medical centers, non-profits, and professional societies; consulting: UnitedHealthcare; speaking fees: Evicore; other: Plenary Session podcast has Patreon backers.

Timothée Olivier has no financial nor non-financial conflicts of interest to report.

Ethics approval Because we used publicly available data, and this is not human subjects' research in accordance with 45 CFR §46.102(f), we did not submit this study to an institutional review board or require informed consent procedures.

Consent to participate Not relevant to this work.

Consent to publish Not relevant to this work.

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