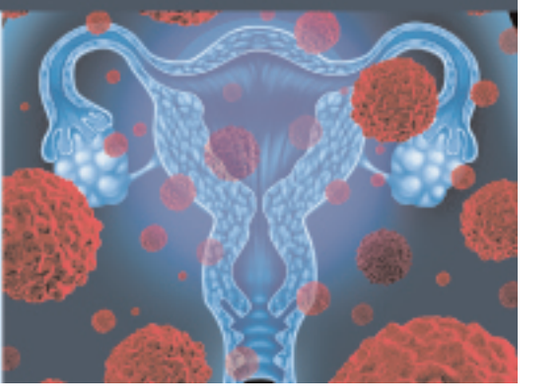
PEER-TO-PEER JOURNAL CLUB

EXPLORING THE EVOLVING ROLE OF PARP INHIBITION AND IMMUNOTHERAPY IN GYNECOLOGIC CANCERS



Moore KN, Secord AA, Geller MA. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): A multicentre, open-label, single-arm, phase II trial. *Lancet Oncol*. 2019;20:636-648.

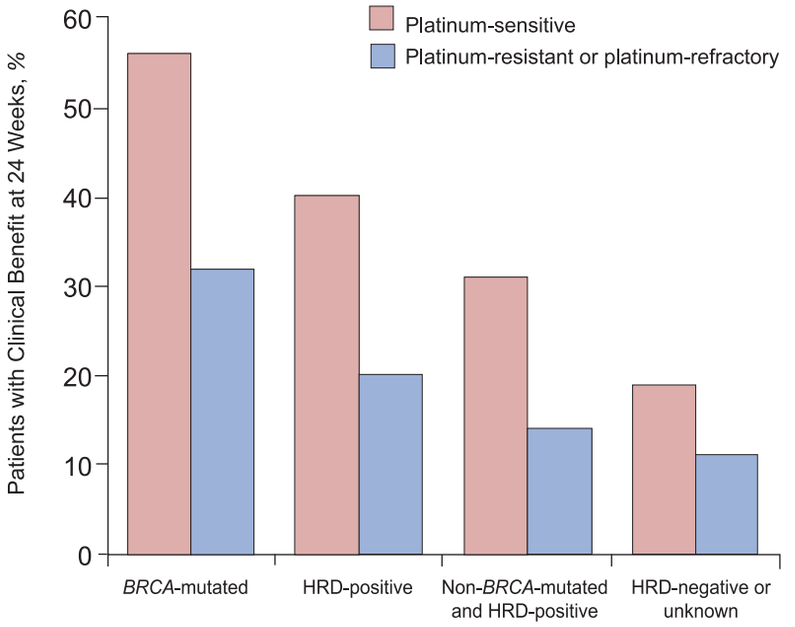
Summary:

A Study of Niraparib in Patients with Ovarian Cancer Who Have Received Three or Four Previous Chemotherapy Regimens (QUADRA) is a multicenter (United States and Canada) open-label, single arm, phase II study of niraparib in adult patients (*N* = 419) with relapsed, high-grade serous (grade 2 or 3) epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more previous chemotherapy regimens. The primary objective was the proportion of patients achieving an investigator-assessed confirmed overall response (OS) in those with homologous recombination deficiency (HRD)-positive tumors (including patients with and without BRCA mutations), who were sensitive to their last platinum-based therapy and had received 3 or 4 previous anticancer therapy regimens (primary efficacy population). The study design is notable both for its size to evaluate a poly-(ADP ribose)-polymerase (PARP) inhibitor in the late-line treatment setting and for the real-world, broad-study patient population, including patients with and without BRCA mutations as well as HRD-positive and -negative patients.

In the primary efficacy population (ie, 47 patients with HRD-positive tumors, who received 3 or 4 previous anticancer therapies, that were sensitive to the most recent platinum-based therapy, and were PARP-inhibitor naïve), 28% (*n* = 13) achieved an OS (95% CI 15.6–42.6, one-sided *p* = .00053). The median duration of progression-free survival in this population was 5.5 months (95% CI 3.5–8.2), and the median duration of response was 9.2 months (5.9–not estimable). Sixty-eight percent of these patients achieved disease control.

Also observed was a "clinical continuum of benefit," in which the proportion of patients achieving an OS was highest in those with BRCA-mutated and HRD-positive tumors, but response was still observed in patients with HRD-negative/unknown tumors who were platinum-resistant or refractory.

No new safety signals were observed.



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Discussion Questions:

- Do you think that the benefits of niraparib outweigh the risks in this treatment setting (ie, late-line ovarian cancer)? Specifically, do you think that the benefits of niraparib outweigh the risks in late-line ovarian cancer patients who are not BRCA-positive? Who are HRD-negative? Who are platinum-resistant or platinum-refractory?
- What other information would you like to have to help you decide whether niraparib is appropriate for your late-line ovarian cancer patients?
- The authors discuss and assess disease stabilization. They note, "Historically, the expected OS has been less than 1 year for patients treated in the fourth or later line. Survivorship, including palliation of both treatment-related and disease-related symptoms, is prioritized in this setting, and as such, there is an increasing focus on minimization of toxic effects and spending more time outside the hospital or clinic." Do you think that disease stabilization is a clinically meaningful descriptor of efficacy in this setting?

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, randomized, placebo-controlled, phase III trial. *Lancet Oncol*. 2017;18:1274-1284.

Summary:

The Olaparib Treatment in BRCA Mutated Ovarian Cancer Patients after Complete or Partial Response to Platinum Chemotherapy (SOLO2/ENGOT-Ov21) study was an international (16 countries), double-blind, placebo-controlled, phase III trial that evaluated olaparib tablet formulation in platinum-sensitive, relapsed ovarian cancer patients with BRCA1/2 mutation, who had previously received 2 or more lines of chemotherapy. The investigator-assessed progression-free survival (PFS) (primary endpoint) was 19.1 months (95% CI 16.3–25.7) with olaparib compared with 5.5 months (95% CI, 5.2–5.8) with placebo. Other secondary measures (eg, time to first subsequent therapy, time to second progression or death, time to second subsequent therapy or death) and a prespecified subgroup analysis of PFS in patients who had received bevacizumab therapy before their final platinum regimen, prior to randomization, all showed significant improvement with olaparib treatment compared with placebo.

Serious adverse events (AEs) occurred in 18% of olaparib and 8% of placebo patients. The most common AEs in the olaparib group were anemia, nausea, fatigue, and vomiting; they are considered to be class effects associated with PARP inhibitors. There was no appreciable difference in quality-of-life measures for patients receiving olaparib compared with placebo.

The study is notable because patients were able to maintain a good quality-of-life while experiencing a delay in disease progression, and as a result, a delay in subsequent chemotherapy and its associated side effects. With each disease recurrence and successive treatment in patients with ovarian cancer, the chemotherapy-free interval becomes progressively shorter. As such, the secondary endpoints in SOLO2/ENGOT-Ov21 are also especially clinically meaningful.

Discussion Questions:

- Based on this study, how does the AE profile affect your decision about whether to use olaparib as late-line maintenance therapy in patients with BRCA mutations who are platinum sensitive?
- Based on this study, what information would you like to have to help you decide whether to use olaparib or post-remission bevacizumab in patients who had received prior bevacizumab therapy?

Hinchcliff E, Westin SN, Dal Molin G, et al. Poly-ADP-ribose polymerase inhibitor use in ovarian cancer: Expanding indications and novel combination strategies.
Int J Gynecol Cancer. May 22, 2019. DOI: 10.1136/ijgc-2019-000499.

Summary:

This article reviews the clinical studies that led to the current US Food and Drug Administration (FDA) indications for the 3 available PARP inhibitors (PARPi; olaparib, rucaparib, and niraparib) as well as recently completed and ongoing studies for expanding indications, including frontline maintenance therapy, and novel combinations (with checkpoint inhibitors as initial and maintenance therapy; with antiangiogenic therapy). The article also addresses the understood biological basis for PARP inhibition, the proposed mechanisms for PARPi resistance, and the studies to address this concern (including targeted agents) as PARPis are being used earlier in the standard treatment course.

Discussion Questions:

- Based on what we know to date, what information would you like to have to increase your likelihood of using PARPi in patients who are known to not have BRCA1/2 mutations?
- How concerned are you about PARPi resistance when using a PARPi as front-line treatment? As maintenance treatment?
- The FDA has now approved bevacizumab as a maintenance therapy option for patients with ovarian cancer, but the optimal order of therapy for maintenance is not known. What factors do you consider when choosing maintenance therapy?
- The authors note that the 3 main rationales for PARPi combination therapy are augmenting efficacy, inducing response, and overcoming acquired/adaptive resistance. Of these, which do you think will be the most important rationale?
- Given the wide range of patients who are or have been in enrolled in the PARPi plus checkpoint inhibitor combination studies, where should the focus now be to better define the patient population who will gain the most benefit from this combination strategy?

Coleman RL, Oza AM, Lorusso D, et al. Exploratory analysis of the effect of maintenance rucaparib on postprogression outcomes in patients with platinum-sensitive recurrent ovarian carcinoma and updated safety data from the phase III study ARIEL3. Presented at: 2019 ASCO Annual Meeting; June 1, 2019; Chicago, Illinois. Abstract 5522.

Summary:

This study analyzed postprogression outcomes in A Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous, or Endometrioid Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer (ARIEL3) to investigate the durability of clinical benefit from rucaparib maintenance treatment following disease progression. The rationale of this study was that evaluation of overall survival (OS) may require extended follow-up and may be confounded by subsequent treatments. As a result, additional postprogression assessments are needed to help demonstrate the clinical benefit of maintenance therapy. Of note, recent clinical trials of targeted agents in patients with relapsed ovarian cancer (OC) have shown improvements in progression-free survival (PFS) but not OS. This study found that the time from the last dose of chemotherapy prior to randomization to initiation of subsequent chemotherapy, TFST (time from randomization to start of first subsequent therapy), PFS2 (time from randomization to disease progression on the subsequent line of therapy or death), and TSST (time from randomization to start of second subsequent therapy) were significantly longer in the rucaparib group than the placebo group for all 3 molecularly defined cohorts (BRCA-mutant, BRCA-mutant or -wild type/high loss of heterozygosity, intent-to-treat population). The most frequent treatment-emergent adverse events (TEAEs) of any grade were nausea and asthenia/fatigue; and the most frequent grade 3 or higher TEAEs were anemia/hemoglobin decreased and alanine/aspartate aminotransferase increased.

Discussion Questions:

- What role do postprogression endpoints (such as PFS2) play in your treatment decision making for your OC patients and as they progress after front-line therapy?
- Are there other postprogression endpoints that you would like to see studied to help optimize treatment options for OC patients?
- Why do you think some therapies offer improvements in PFS or PFS2 but not OS?

Antill YC, Kok PS, Robledo K, et al. Activity of durvalumab in advanced endometrial cancer according to mismatch repair status: The phase II PHAEDRA trial (ANZGOG1601).
Presented at: 2019 ASCO Annual Meeting; June 1, 2019; Chicago, Illinois. Abstract 5501.

Summary:

This study evaluated the efficacy of durvalumab, an antibody to PD-L1, in 71 patients with advanced endometrial cancer (AEC) with either deficient DNA mismatch repair (dMMR) or proficient DNA mismatch repair (pMMR). dMMR occurs in approximately 15% of patients with AEC and is associated with a high tumor mutation burden. Expression of PD-1 and PD-L1 has been reported in up to 90% of ECs, including those with pMMR, suggesting that checkpoint inhibitor therapy might have an important role to play in treating patients with AEC.

The Phase II Trial of Durvalumab in Advanced Endometrial Cancer (PHAEDRA) results show promising activity and safety in dMMR patients:

- Objective tumor response rate (OTR): 43%
- Rate of stable disease at 16 weeks (DC16w) was 60% (95% CI 44–74).

The activity among pMMR patients was limited (OTR 3%; DC16w 19%).

Discussion Questions:

- Do these study results affect the likelihood of you referring your EC patients for genetic counseling?
- If not, what data would you like to see to further clarify the role of genetic counseling/testing for EC patients?

Konstantinopoulos PA, Liu JF, Luo W, et al. Phase II, two-group, two-stage study of avelumab in patients with microsatellite stable, microsatellite instable, and polymerase epsilon mutated recurrent/persistent endometrial cancer. Presented at: 2019 ASCO Annual Meeting; June 3, 2019; Chicago, Illinois. Abstract 5502.

Summary:

This nonrandomized phase II study of 33 patients with endometrial cancer (EC), in 2 cohorts, evaluated the PD-L1 inhibitor avelumab in: (1) A microsatellite instable (MSI)/polymerase epsilon (POLE) cohort, which included patients with endometrial cancer (EC) with immunohistochemical (IHC) loss of expression of at least 1 of the mismatch repair (MMR) proteins and/or documented mutation in the exonuclease domain of *POLE*; and (2) a microsatellite stable (MSS) cohort, including EC patients who had normal IHC expression of all MMR proteins.

The results showed that MSI versus MSS status appeared to be correlated with avelumab response even in patients with PD-L1-negative tumors. Responses in the MSI/POLE cohort were more frequent in more heavily pretreated patients.

- The MSS cohort was closed at the first stage due to futility, as only 1 patient exhibited an objective response (OR) and progression-free survival (PFS) at 6 months (which was 6.25% [95% CI 0.16%–30.2%]).
- Conversely, the MSI/POLE cohort reached the primary endpoint of 4 ORs after accrual of only 17 patients. Of 15 patients, the ORR was 26.7% (95% CI 7.8%–55.1%) and the PFS6 rate was 40.0% (95% CI 16.3%–66.7%).
- Of note, in the MSI/POLE cohort, 5 of 6 PFS6 responses were observed in patients with 3 or more lines of prior therapy (p = .011) and in patients with tumors who were PD-L1 negative by IHC.

Discussion Questions:

- Do these study results affect the likelihood of you referring your EC patients for genetic counseling?
- If not, what data would you like to see to further clarify the role of genetic counseling/testing for EC patients?

Makker V, Rasco D, Vogelzang NJ, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: An interim analysis of a multicentre, open-label, single-arm, phase II trial. *Lancet Oncol*. 2019;20:711-718.

Summary:

This interim analysis of an open-label, single-arm, phase II study evaluated the combination of lenvatinib (a multikinase inhibitor of VEGFR1, VEGFR2, and VEGFR3, and other receptor tyrosine kinases) and pembrolizumab (an antibody targeting PD-1) in 53 patients with advanced endometrial carcinoma who were unselected for microsatellite instability or PD-L1. The results showed that the combination of lenvatinib plus pembrolizumab had antitumor activity in patients with advanced recurrent endometrial cancer:

- Objective response rate (ORR) was 39.6% (95% CI 26.5–54.0) at week 24.
- The safety profile was similar to those previously reported for lenvatinib and pembrolizumab monotherapies, but there was an increased frequency of hypothyroidism.
- Nine percent of patients discontinued study treatment because of treatment-related adverse events.

Of note, previous studies of pembrolizumab in patients with PD-L1-positive endometrial cancer with microsatellite stable (MSS) disease showed an ORR of only 13%. In this study, the overall responses were recorded in 16 of 45 patients with MSS tumors (the predominant subtype of endometrial cancer). But, only 4 patients had tumors with high microsatellite instability, which precludes a comparison of objective response between groups based on microsatellite stability or instability.

Discussion Questions:

- What other study would you like to see with the combination of a tyrosine kinase inhibitor and an immune checkpoint inhibitor?
- Does the ORR of this combination warrant the safety profile?

Powell MA, Filiaci VL, Hensley ML, et al. A randomized phase III trial of paclitaxel plus carboplatin versus paclitaxel plus ifosfamide in chemotherapy-naive patients with stage I-IV, persistent or recurrent carcinosarcoma of the uterus or ovary: An NRG oncology trial. Presented at: 2019 ASCO Annual Meeting; June 3, 2019; Chicago, Illinois. Abstract 5500.

Summary:

This noninferiority study compared paclitaxel plus carboplatin (PC) to paclitaxel plus ifosfamide (PI) in 637 women with stages I-IV persistent or recurrent uterine, fallopian tube, peritoneum, or ovarian carcinosarcoma, chemotherapy-naïve. The results showed:

- Uterine cohort:
  - Noninferiority of PC compared to PI with regard to overall survival (OS) (primary endpoint): median 37 (PC) versus 29 (PI) months; HR = 0.87; 90% CI = 0.70 to 1.075; p <.01
  - Longer PFS (median 16.3 mos [PC] vs 11.7 [PI] mos; HR = 0.73)

- Ovarian cohort - similar trends were noted:
  - OS: 30 (PC) versus 25 (PI) months
  - PFS: 15 (PC) versus 10 months (PI)
- Both groups had similar decline in quality of life and neurotoxicity scores.
- Neurological adverse events (AEs) were worse with PI; hematologic AEs were worse with PC.

Discussion Questions:

- What other data would you like to see to help you decide whether to treat your patients with PC or PI?
- Why do think that ovarian and endometrial carcinosarcomas were studied together?
- Beyond the AE profile, what other factors will help you decide whether to treat a patient with PC or PI?