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PARP Inhibitors in the Treatment of Ovarian Cancer- a review of the latest research

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Abstract

Introduction

Ovarian cancer is a leading cause of cancer mortality globally due to late-stage diagnosis and limited treatment options. PARP inhibitors have shown promise as effective treatments for recurrent and various stages of ovarian cancer.

Aim of the Study

This study reviews the efficacy and application of PARP inhibitors in ovarian cancer treatment over the past 15 years, focusing on literature from the PubMed database post-2009 and considering FDA and EMA guidelines.

Review methods

A literature review was conducted using the PubMed database, focusing on studies published after 2009. The review also incorporated recommendations from the FDA and the European Medicines Agency regarding the use of PARP inhibitors in ovarian cancer treatment.

Results

The findings highlight the substantial impact of PARP inhibitors on ovarian cancer treatment, improving PFS and overall outcomes. Olaparib, niraparib, and rucaparib have become integral to ovarian cancer management, offering effective options for patients with BRCA mutations or homologous recombination deficiencies. These inhibitors have been validated in multiple clinical trials, underscoring their robustness and effectiveness. Combination therapies, such as olaparib with bevacizumab, further enhance therapeutic outcomes, showcasing the potential for synergistic effects.

Summary

PARP inhibitors represent a significant advancement in ovarian cancer treatment, offering improved survival outcomes for patients with specific genetic profiles. Their integration into

standard care protocols underscores their importance and efficacy, providing valuable therapeutic options in the fight against ovarian cancer.

Keywords: PARP inhibitors, ovarian cancer, ovarian cancer treatment

Introduction

Ovarian cancer is the fifth most common cause of cancer death in the USA, and approximately 140,000 people die annually around the world. This disease is very insidious, its symptoms appear very subtle, ovarian cancer is usually diagnosed at an advanced stage, which means that treatment options are quite limited.[1] PARP inhibitors are effective against recurrent ovarian cancer and are also effective in various stages of this disease. In the article we present information about this group of drugs that are available in Ovarian Cancer treatment. [2]

Material and method of research

In this work, we used a literature review using the PubMed database, we excluded works from before 2009, this work is a summary of information on PARP inhibitors from the last 15 years, with most of the works we used were published after 2020. The work also takes into account the recommendations of the FDA and the European Medicines Agency regarding: applications of PARP inhibitors.

PARP inhibitors

Surgery with complementary chemotherapy is the current standard of care for the treatment of advanced ovarian cancer. Despite treatment, the prognosis for patients is poor due to rapid relapse and frequent development of resistance to therapy. Therefore, therapies

targeting DNA repair mechanisms, particularly PARP proteins, are becoming more important. [3]

The PARP family of proteins consists of 17 enzymes, of which PARP-1, PARP-2 and PARP-3 are mainly involved in the repair of DNA damage. [4]

The discovery in 1980 by Sydney Shall's research group of the increased cytotoxic effects of methylating agents after inhibition of the PARP-1 enzyme contributed to the development of PARP inhibitors. [5]

The development of PARP inhibitor therapy is based on a new concept in oncology called "synthetic lethality". According to this, two genetic defects are lethal if they occur in the same cell. There are many mechanisms of repairing damaged DNA. Two of these are of particular interest to scientists because they offer the possibility of new therapies for ovarian cancer patients. These include PARP family protein-dependent mechanisms related to the recognition and excision of base pairs in a single strand of DNA and homologous recombination (HR) repair mechanisms mediated by BRCA1 and BRCA2 proteins play a key role in repairing double-stranded DNA breaks. [6] This knowledge has been applied to the treatment of PARP inhibitors, which block the activity of the PARP protein by acting through competition with NAD + in the PARP catalytic domain. This consequently leads to blockage and collapse of the replication fork, resulting in a double-strand break (DSB). Cells in which the HR mechanism works properly can repair DSB. In turn, the accumulation of DSBs that have a cytotoxic effect leads to cell death. This occurs when HR-mediated double-stranded DNA repair mechanisms are impaired (as is the case with BRCA1/ BRCA2 mutations or other HR deficiencies). [4,6,7]

PARP inhibitors approved by the Food and Drug Administration (FDA) for the treatment of ovarian cancer include olaparib, rucaparib and niraparib. [4] PARP inhibitor therapy for ovarian cancer initially included only patients with confirmed BRCA1 or BRCA2 mutations. As further studies are conducted, their usefulness has also been demonstrated in homologous recombination deficiencies (HDR) patients regardless of BRCA1 or BRCA2 mutations. [8]

PARP inhibitors are currently used in first-line and recurrent platinum-sensitive ovarian cancer in patients with known mutations in the BRCA1/BRCA2 or other HDR. [6]

Olaparib

Olaparib is a PARP inhibitor. Used in the maintenance treatment of platinum-sensitive ovarian cancer, it induces synthetic lethality in tumor cells with HDR (including BRCA1/BRCA2 mutations), prolonging survival in first-line treatment and in recurrent disease. [12]

The study that confirmed the efficacy of olaparib in the treatment of recurrent platinum-sensitive advanced ovarian cancer was the randomized Study 19. 265 patients were enrolled in the study. The condition for inclusion was recurrent ovarian cancer after at least 2 courses of platinum-based chemotherapy. Patients were randomly assigned to a group of 136 women who received 400 mg of olaparib twice a day and to a group of 129 women who received a placebo (pills without the active substance). The study showed an improvement in progression-free survival (PFS) in the olaparib group compared to the placebo group (8.4 months vs. 4.8 months). However, it has not been shown to improve overall survival (OS). Subsequent analysis of data from Study 19 showed a significant therapeutic benefit in patients with a BRCA mutation (originally not a necessary condition for inclusion in the study). [13,14]

The efficacy of maintenance treatment in patients with BRCA1/2 mutations advanced platinum-sensitive ovarian cancer was confirmed in the randomised phase 3 SOLO-2 trial. Inclusion criteria were advanced ovarian cancer after at least two lines of platinum-based chemotherapy and a mutation in the BRCA1/2 genes. The trial enrolled 295 patients. A group of 196 patients were randomly assigned to receive olaparib 300 mg twice a day, while 99 patients were assigned to the placebo group (pills without the active substance). The study showed a significant improvement in PFS in patients who received olaparib (19.1 months vs. 5.5 months). [15]

The results of Study 19 and SOLO-2 contributed to the 2017 FDA approval of olaparib for the maintenance treatment of recurrent, platinum-sensitive ovarian cancer. [9]

The phase 3 SOLO-1 trial contributed to the 2018 approval of olaparib as a maintenance treatment for patients with advanced ovarian cancer who have a BRCA1/2 mutation. [10]

The SOLO-1 trial was performed in 391 patients with advanced ovarian cancer. Inclusion criteria were a somatic or germline BRCA1/2 mutation and a complete or partial response to platinum-based chemotherapy. 260 patients were randomly enrolled in the group taking olaparib 300 mg twice daily, while 131 were enrolled in the placebo group (pills without the active substance). After a median follow-up of 41 months, patients taking olaparib had a 70% lower risk of disease progression or death compared to the placebo group. [16]

Patients from the SOLO-1 trial were followed for an additional 5 years. It was conducted to determine the median PFS, which was 56 months in the olaparib group compared to 13.8 months in the placebo group. [17]

Another treatment for ovarian cancer is combination therapy with olaparib and bevacizumab. The efficacy of this therapy was evaluated in the randomized Phase 3 PAOLA-1/ENGOT-ov25 trial. The inclusion criteria for this study was advanced ovarian cancer that showed a partial or complete response to platinum-based chemotherapy. Regardless of BRCA mutation status, patients were eligible. Of the 806 patients randomized, 537 received olaparib pills at a dose of 300 mg twice daily and 269 received placebo (pills without the active substance). In addition, all patients received bevacizumab every three weeks for a total of up to 15 months. The median follow-up period in the trial was 22.9 months. The final results were as follows: PFS for the combination therapy (olaparib and bevacizumab) was 22.1 months compared to 16.6 months for the placebo group. Patients from the above study underwent additional analysis for therapeutic benefit with BRCA or HDR mutations. It was shown that in patients with a BRCA mutation who received olaparib, the median PFS was 37.2 months compared to 21.7 months in the placebo group. In contrast, in patients with HDR, the median PFS was 37.2 months in the olaparib group and 17.7 months in those taking placebo. [18]

The PAOLA-1/ENGOT-ov25 trial contributed to the FDA approval in 2020 of olaparib and bevacizumab as combination maintenance therapy for advanced ovarian cancer in patients with HR mutations. [11]

For this reason, in the case of ovarian cancer patients, it is important to evaluate not only BRCA mutations but also other HDRs, so it seems important to develop new tests for biomarkers in patients.

246 of the 264 patients experienced one or more adverse events (AEs). AEs with an incidence that was at least 10% higher in the olaparib group than in the placebo group were nausea, fatigue, vomiting and anemia. These adverse reactions did not require treatment discontinuation in either the olaparib or placebo groups. A higher proportion of patients in the olaparib group experienced dose interruptions or dose reductions (27.9% and 22.8%, respectively) as a result of adverse reactions compared to the placebo group (8.6% and 4.7%). AEs leading to permanent discontinuation occurred in three patients receiving olaparib (one each with palpitations and myalgia, erythematous rash, and nausea and small bowel obstruction) and one patient receiving placebo (nausea); The investigator considered all of these AEs to be related to Grade 2 treatment. [13]

Niraparib

Niraparib is a PARP inhibitor that is approved for use as maintenance therapy in adults with advanced ovarian cancer with complete or partial response to platinum-based therapy. [19]. The indications for the use of niraparib are maintenance therapy in adult patients with advanced (FIGO stage III or IV), poorly differentiated ovarian, ovarian, fallopian tube or peritoneal cancer who responded after treatment with first-line chemotherapy based on platinum derivatives. [20] It is an anticancer drug used in the treatment of ovarian cancers, especially those with BRCA1 and BRCA2 gene mutations. Its action is based on the inhibition of PARP1 and PARP2, which are involved in DNA repair processes in cancer cells. [21] The cytotoxic effect of niraparib is observed regardless of disturbances in the expression of tumor suppressor genes - BRCA1 and BRCA2; it has also been shown that the "wild-type" mutation with deficiency in homologous recombination (HR) does not cause disturbances in the action of niraparib. [22]

The effect of niraparib is confirmed by the studies conducted, i.e. ENGOT-OV16/NOVA. In this randomized, double-blind phase III study, patients were stratified according to the presence or absence of a mutation in the germline BRCA gene (gBRCA) and a type of mutation other than the BRCA gene and were assigned to random groups to receive Niraparib at a dose of 300 mg or placebo (pills without the active substance) once a day. The study involved dividing the group into people with a BRCA gene mutation and those without the mutation and comparing OS to the group receiving placebo. Of the 553 patients included in the study, 203 of them belonged to the gBRCA mutation group (138 of them received

niraparib, 65 placebo), another 350 people did not belong to the gBRCA mutation group (234 received niraparib, 116 placebo). The study results were as follows: Patients in the niraparib group had significantly longer median PFS than patients in the placebo group, including 21.0 vs. 5.5 months in the gBRCA mutation group vs. 12.9 months vs. 3.8 months in the gBRCA mutation group without gBRCA mutations [22]. Among patients with platinum-sensitive, recurrent ovarian cancer, the median PFS was significantly longer among patients receiving niraparib than among patients receiving placebo, regardless of the presence or absence of a gBRCA mutation [8].

The PRIMA/ENGOT-OV26/GOG-3012 clinical trial also showed that patients who responded to platinum-based chemotherapy receiving niraparib had a significantly longer PFS, compared to those receiving placebo (pills without the active substance). The results of the mentioned study were as follows: of the 733 randomized patients, 373 (50.9%) had tumors deficient in homologous recombination. The primary endpoint of the study was PFS in patients with homologous recombination (HR)-deficient tumors and in patients in the overall population. Among patients in this category, progression was significantly longer in the niraparib group than in the placebo group (21.9 months vs. 10.4 months). In the overall population (HR-deficient and non-HR-deficient subjects), the corresponding PFS was 13.8 months and 8.2 months. In the 24-month interim analysis, the overall survival rate was 84% in the niraparib group and 77% in the placebo group [23]

As with other PARP inhibitors, adverse events occurred less frequently with placebo than with niraparib. Adverse drug reactions (ADRs) were reported in the PRIMA study and may require discontinuation of niraparib. Discontinuation due to AEs occurred in 12.0% (niraparib group) and 2.5% (placebo group) of patients. Adverse reactions related to Grade 3 or 4 hypertension may occur. In the PRIMA study, these events were reported in 6% of patients receiving niraparib and 1% of patients receiving placebo. Monitoring of blood pressure is recommended during treatment with niraparib. During the PRIMA study, the most common grade ≥ 3 adverse events were hematological events. Grade ≥ 3 AEs (defined as MedDRA terms) with an incidence of ≥ 10% in patients treated with niraparib included neutropenia, anemia, platelet counts, and thrombocytopenia. One case of myelodysplastic syndrome (MDS) was reported during treatment with niraparib in the PRIMA study. [24]

Rucaparib

Rucaparib is an inhibitor of PARP polymerase group enzymes, including PARP-1 and PARP-2. In vitro studies have shown that rucaparib-induced toxicity is associated with the inhibition of PARP enzymatic activity and blocking of PARP-DNA complexes, resulting in increased incidence of DNA damage, apoptosis and cell death.[25] It has shown antitumor activity in ovarian cancer [25]. Rucaparib monotherapy has been approved by the FDA for the maintenance treatment of adult patients with recurrent epithelial ovarian cancer who have responded to platinum-based chemotherapy and for the treatment of patients with deleterious BRCA1 or BRCA2 mutations (germline and/or somatic) associated with advanced ovarian cancer that has been treated with ≥2 chemotherapy [26].

The ARIEL3 study demonstrated the exceptional benefit (progression-free survival of ≥2 years) of rucaparib. ARIEL3 is a randomized, placebo-controlled, double-blind study of the oral small molecule PARP of rucaparib, in which rucaparib is used for the maintenance treatment of recurrent ovarian cancer of figo stages III and IV. In this study, patients with recurrent, platinum-sensitive, high-grade ovarian cancer who responded to the last platinum-based regimen were randomized in a 2:1 ratio to receive maintenance therapy with rucaparib (600 mg twice daily) or placebo (placebo group not available). There were 375 patients in the study group and 189 patients in the placebo group. Features such as genomic alterations, BRCA1 promoter methylation, and baseline clinical characteristics were assessed by examining the unique benefits compared to progression in the first study (short-term subgroup) and other efficacy outcomes.[27]

A total of 564 patients were enrolled in the ARIEL 3 study. Based on central (tissue and germline) or local examinations, 218 patients were diagnosed with BRCA-mutated carcinoma (143/375 in the rucaparib group; 75/189 in the placebo group). In the rucaparyb group, 79/375 patients had exceptional benefits and 52/375 had progression-free survival of ≥3 years, including 26/375 with progression-free survival of ≥4 years. Of the placebo group, only 4/189 patients had an exceptional benefit, while 62/189 patients experienced disease progression. [27]

The majority (68/79) of patients treated with rucaparib in the exceptional benefit group achieved a longer PFS in ARIEL3 compared to the penultimate platinum-free period, indicating that patients with exceptional benefits obtained more lasting benefits from

rucaparib maintenance therapy after the last line of platinum-based therapy than from the penultimate treatment. [27]

The molecular characterization of high-grade ovarian cancer also had a strong impact on whether the patient benefited exceptionally from rucaparib maintenance therapy. A higher incidence of exceptional benefit was observed in cancer patients with homologous recombination deficiency; 32.2% of patients with high-grade ovarian cancer who had a change in BRCA experienced exceptional benefits. In the wild-type BRCA population, exceptional benefits were more common in cancer patients with high rates of heterozygosity loss (LOH) (i.e., without evidence of homologous recombination deficiency [HRD]) than in cancer patients with low LOH. Patients in the rucaparib treatment arm with RAD51C or RAD51D alteration showed a very high incidence of exceptional benefit (6/10), in contrast to patients with mutations in other homologous recombination repair genes (1/20), in contrast to patients with mutations in other HRL repair genes. In the placebo arm none of the molecular features summarized above were significantly associated with PFS outcomes. The results of the study suggest that rucaparib may provide exceptional benefits to a diverse group of patients with recurrent high-grade ovarian cancer. [27]

In an open-label, phase 1/2 Study 10, efficacy, safety and pharmacokinetics were considered, and based on this, the recommended dose of rucaparib administered orally as monotherapy in phase 2 was determined and evaluated. The study included patients with highly malignant, recurrent ovarian cancer with BRCA mutations, following prior 2-4 (part 2A) or 3-4 (part 2B) chemotherapy. Fifty-four patients participated in the study: 42 in group 2A patients had platinum hypersensitivity disease and 12 in group 2B, in this group 4 patients had platinum hypersensitivity disease and 8 patients were platinum resistant. Patients took rukaparib- 600 mg BID by oral route in continuous 21-day cycles until disease progression, treatment was stopped or unacceptable toxicity occurred. When one patient experienced disease progression, but the investigator felt it would still be beneficial for the patient to remain on therapy, treatment could be continued. The results indicate that PARP inhibitors are an effective treatment option for patients with high-grade ovarian cancer with BRCA mutations who have previously received multiple rounds of chemotherapy (≥2). [28]

To date, to our knowledge, only the ARIEL4 and SOLO3 studies have presented data on a direct comparison of a PARP inhibitor with chemotherapy in patients with recurrent advanced ovarian cancer with a BRCA mutation. In both of these studies, the incidence of adverse events leading to discontinuation of treatment was lower with a PARP inhibitor than with chemotherapy. These findings suggest that PARP inhibitors may provide an alternative, better tolerated option for some patients. [28]

In study 10, rucaparib reported both non-haematological (nausea, weakness, vomiting, constipation, increased ALT/AST, abdominal pain, headache, increased blood creatinine, diarrhea) and hematological adverse reactions (TEAE: anemia/decreased hemoglobin followed by thrombocytopenia/low blood platelet count and neutropenia/decreased neutrophil count). Rucaparyb was discontinued due to TEAE in three patients who were considered treatment-related: a patient with anemia, thrombocytopenia and asthenia; patient with nausea and fatigue; and a patient with hyperventilation. [28]

Discussion

Advances in oncological treatment and increasingly better scientific evidence for the effectiveness of PARP have contributed to their increasingly common use in cancer therapy. There are more and more reports in the literature on the safety, effectiveness, and also risk of using PARP inhibitors. The Extensive Guo et all. Meta-analysis on Olaparib included eight RCTs (Randomized Control Trials) describing 1957 patients, of whom 786 were diagnosed with ovarian cancer, 302 with breast cancer, 649 with gastric cancer, and 220 with small cell lung cancer. The above work proved the extension of PFS in ovarian, gastric, and breast cancer [29]. Improved OS was only proven in gastric cancer. Although the effects of treatment are satisfactory, PARP therapy is not free from complications, The Guo study proved a statistically significant occurrence of anemia in patients treated with Olaparib. In the third phase of the SOLO1 study on a Chinese cohort group conducted by WU et al. Anemia was observed in 59.1% of patients. [30]. In the literature, the leading cause of anemia in cases treated with olaparib is considered to be vitamin B12 and folic acid deficiency [31]. In contrast to these reports is the retrospective study conducted by Shirashi et al., where mactocytic or normocytic anemia was observed without folic acid and vitamin B12 deficiency, the authors of the above study draw attention to the cumulative dose of early carboplatin

administration in the studied patients, which is the standard of oncological treatment in ovarian cancer [32]. In the study by Kaye et al., the frequency of adverse events of olaparib was compared in comparison with pegylated doxorubicin, taking into account such adverse events as anemia, nausea, vomiting, fatigue, abdominal pain, diarrhea, gastritis and urinary tract infections. Clearly lower toxicity of olaparib in doses of 200 mg twice daily and 400 mg twice daily than pegylated doxorubicin [33]. The above observations seem to be satisfactory in the context of treatment with Olaparib. However, further studies are required to compare the toxicity of olaparbib with other Chemotherapeutics agents

Also in the case of treatment of patients with advanced ovarian cancer with Niraparib, a significant prolongation of PFS was observed compared to placebo. In the Gonzalez-Martin et al. study, a significant reduction in the risk of disease progression or death was proven in this group of patients regardless of the age of receiving neoadjuvant chemotherapy, total or partial sensitivity to platinum and the status of homologous recombination. Niraparib is also characterized by a wide range of side effects, in the cited study it was determined that the percentage of patients deciding to reduce the dose or discontinue therapy was from 70.9% to 79.5%. The most common side effects were anemia, nausea, thrombocytopenia, constipation, fatigue and headaches [23]. These observations are confirmed by an extensive meta-analysis performed by Pagkali covering 1539 patients. This study showed a significantly significant percentage of side effects of niraparib compared to placebo in terms of nausea, fatigue, anemia, neutropenia, thrombocytopenia, headaches, vomiting and constipation and hypertension [34].

Rucaparib is also a drug characterized by prolonging PFS and OS in patients with Higrade ovarian tumor compared to the control group, its most common side effects include nausea, vomiting, constipation, diarrhea, neutropenia and thrombocytopenia [35]. There are also reports of the possibility of the occurrence of resistance mechanisms to PARP inhibitors induced by Rucaparib, however, this requires confirmation in further studies [36].

Each case of ovarian cancer requires a thorough analysis of the clinical and molecular status, this poses dilemmas for clinicians regarding the effectiveness of individual therapeutic paths, the potential occurrence of adverse effects and patient safety. Reasonable, individualized decisions are most important to enhance therapeutic benefits and minimize potential risks, the progress in oncological treatment and the future of patients require further

large-scale, multi-center studies on representative groups. Such action will certainly contribute to improving the still unsatisfactory treatment results of ovarian cancer patients.

Results

The development of PARP inhibitors enables significant development of ovarian cancer treatment. PARP inhibitors are substances targeting DNA strand repair mechanisms, these drugs inhibit the activity of PARP family proteins, their action is based on the concept of synthetic lethality. In this concept, inhibition of PARP proteins causes the accumulation of cytotoxic DNA strand breaks, with impaired homologous recombination (HR) mechanism, which results in the induction of cancer cell death. Such action is particularly visible in cells with a defect in the BRCA1/2 genes [3-7]

One of the most important and best known PARP inhibitors is Olaparib, this drug has obtained FDA approval for the treatment of recurrent platinum-sensitive ovarian cancer, as well as in maintenance therapy. According to FDA reports, Olaparib also improves progression-free survival (PFS), especially in patients with BRCA mutations [9-11]

The SOLO-1 study highlights that in first-line maintenance treatment of advanced ovarian cancer with BRCA1/2 mutations, the use of olaparib has shown significant improvement in PFS [10,16,17] Additionally, the combination of olaparib with another anticancer drug - bevacizumab, extends PFS, regardless of the presence or absence of BRCA mutations.

Niraparib is another drug from the PARP inhibitor group, this drug, like olaparib, has shown efficacy in maintenance treatment of ovarian cancer, especially in advanced stages of the disease. The PRIMA/ENGOT-OV26/GOG-3012 study demonstrated the efficacy of niraparib, demonstrating improvement in PFS in patients with HR deficiency, extending the time by 10 months [23]. In patients with complete and partial response to platinum-based therapies, niraparib also prolonged PFS, also regardless of BRCA mutation status[19-21].

Rucaparib, the last drug we focused on in our work, has been shown to be effective in the maintenance therapy of recurrent epithelial ovarian cancer, especially in patients with BRCA mutations [26-27]. The ARIEL3 study emphasizes that the use of rucaparib in therapy

prolongs PFS and survival in patients with HR deficiency [27]. Study-10 also emphasizes the efficacy and safety of rucaparib in patients with recurrent ovarian cancer[28].

Treatment with PARP inhibitors is an increasingly important and safe therapeutic option. These substances are an alternative for patients, regardless of the presence of BRCA1/2 mutations. Implementation of PARP inhibitors in therapy is the path to better therapeutic results and prolonged patient survival.

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Conceptualization, KK; methodology, KK; software, AZ; check, AZ, MCP and JN; formal analysis, KK; investigation, JN; data curation, MCP; writing - rough preparation, AZ,MCP, JN; writing - review and editing, AZ; visualization, MCP; supervision, KK; project administration, JN.

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REFERENCES

1. Penny SM. Ovarian Cancer: An Overview. *Radiol Technol*. 2020;91(6):561-575.
2. Mittica G, Ghisoni E, Giannone G, et al. PARP Inhibitors in Ovarian Cancer. *Recent Pat Anticancer Drug Discov*. 2018;13(4):392-410. doi:10.2174/1574892813666180305165256
3. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. *CA Cancer J Clin*. 2011;61(3):183-203. doi:10.3322/caac.20113.
4. Rose M, Burgess JT, O'Byrne K, Richard DJ, Bolderson E. PARP Inhibitors: Clinical Relevance, Mechanisms of Action and Tumor Resistance. *Front Cell Dev Biol*. 2020;8:564601. Published 2020 Sep 9. doi:10.3389/fcell.2020.564601
5. Drew Y. The development of PARP inhibitors in ovarian cancer: from bench to bedside. *Br J Cancer*. 2015;113 Suppl 1(Suppl 1):S3-S9. doi:10.1038/bjc.2015.394
6. Wu Y, Xu S, Cheng S, Yang J, Wang Y. Clinical application of PARP inhibitors in ovarian cancer: from molecular mechanisms to the current status. *J Ovarian Res*. 2023;16(1):6. Published 2023 Jan 7. doi:10.1186/s13048-023-01094-5
7. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med*. 2009;361(2):123-134. doi:10.1056/NEJMoa0900212
8. Miller RE, Lewis AJ, Powell ME. PARP inhibitors and immunotherapy in ovarian and endometrial cancers. *Br J Radiol*. 2021;94(1128):20210002. doi:10.1259/bjr.20210002
9. U.S. Food and Drug Administration. FDA approves olaparib tablets for maintenance treatment in ovarian cancer. FDA. Published December 19, 2014. Accessed January 9, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-tablets-maintenance-treatment-ovarian-cancer

10. U.S. Food and Drug Administration. FDA approved olaparib (LYNPARZA, AstraZeneca Pharmaceuticals LP) for maintenance treatment in adult patients. FDA. Accessed April 10, 2024. Accessed January 9, 2025. https://www.fda.gov/drugs/fda-approved-olaparib-lynparza-astrazeneca-pharmaceuticals-lp-maintenance-treatment-adult-patients
11. U.S. Food and Drug Administration. FDA approves olaparib plus bevacizumab as maintenance treatment for ovarian, fallopian tube, or primary peritoneal cancer. FDA. Accessed April 10, 2024. Accessed January 9, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-plus-bevacizumab-maintenance-treatment-ovarian-fallopian-tube-or-primary
12. Smith AJB, Apple A, Hugo A, Haggerty A, Ko EM. Prior authorization for FDA-approved PARP inhibitors in ovarian cancer. *Gynecol Oncol Rep*. 2024;52:101335. Published 2024 Feb 13. doi:10.1016/j.gore.2024.101335
13. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366(15):1382-1392. doi:10.1056/NEJMoa1105535
14. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial [published correction appears in Lancet Oncol. 2015 Apr;16(4):e158. doi: 10.1016/S1470-2045(15)70153-1]. *Lancet Oncol*. 2014;15(8):852-861. doi:10.1016/S1470-2045(14)70228-1
15. 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 [published correction appears in Lancet Oncol. 2017 Sep;18(9):e510. doi: 10.1016/S1470-2045(17)30639-3]. *Lancet Oncol*. 2017;18(9):1274-1284. doi:10.1016/S1470-2045(17)30469-2
16. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2018;379(26):2495-2505. doi:10.1056/NEJMoa1810858
17. Banerjee S, Moore KN, Colombo N, et al. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004):

5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial [published correction appears in Lancet Oncol. 2021 Dec;22(12):e539. doi: 10.1016/S1470-2045(21)00672-0]. *Lancet Oncol*. 2021;22(12):1721-1731. doi:10.1016/S1470-2045(21)00531-3

18. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *N Engl J Med*. 2019;381(25):2416-2428. doi:10.1056/NEJMoa1911361
19. Lee A. Niraparib: A Review in First-Line Maintenance Therapy in Advanced Ovarian Cancer [published correction appears in Target Oncol. 2022 Jan;17(1):89. doi: 10.1007/s11523-021-00854-x]. *Target Oncol*. 2021;16(6):839-845. doi:10.1007/s11523-021-00841-2
20. European Medicines Agency. Zejula: EPAR - Product Information. EMA. Accessed January 9, 2025. https://www.ema.europa.eu/en/documents/product-information/zejula-epar-product-information_en.pdf
21. Longoria TC, Tewari KS. Pharmacokinetic drug evaluation of niraparib for the treatment of ovarian cancer. *Expert Opin Drug Metab Toxicol*. 2018;14(5):543-550. doi:10.1080/17425255.2018.1461838
22. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med*. 2016;375(22):2154-2164. doi:10.1056/NEJMoa1611310
23. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, McCormick C, Lorusso D, Hoskins P, Freyer G, Baumann K, Jardon K, Redondo A, Moore RG, Vulsteke C, O'Cearbhaill RE, Lund B, Backes F, Barretina-Ginesta P, Haggerty AF, Rubio-Pérez MJ, Shahin MS, Mangili G, Bradley WH, Bruchim I, Sun K, Malinowska IA, Li Y, Gupta D, Monk BJ; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019 Dec 19;381(25):2391-2402. doi: 10.1056/NEJMoa1910962. Epub 2019 Sep 28. PMID: 31562799.
24. Lee A. Niraparib: A Review in First-Line Maintenance Therapy in Advanced Ovarian Cancer [published correction appears in Target Oncol. 2022 Jan;17(1):89. doi: 10.1007/s11523-021-00854-x]. *Target Oncol*. 2021;16(6):839-845. doi:10.1007/s11523-021-00841-2

25. European Commission. Community Register of Medicinal Products: Annex. EC. Accessed January 9, 2025. https://ec.europa.eu/health/documents/community-register/2018/20180524140802/anx_140802_pl.pdf
26. Shapiro GI, Kristeleit RS, Burris HA, et al. Pharmacokinetic Study of Rucaparib in Patients With Advanced Solid Tumors. *Clin Pharmacol Drug Dev*. 2019;8(1):107-118. doi:10.1002/cpdd.575
27. O'Malley DM, Oza AM, Lorusso D, et al. Clinical and molecular characteristics of ARIEL3 patients who derived exceptional benefit from rucaparib maintenance treatment for high-grade ovarian carcinoma. *Gynecol Oncol*. 2022;167(3):404-413. doi:10.1016/j.ygyno.2022.08.021.
28. Kristeleit RS, Drew Y, Oza AM, et al. Efficacy and safety of rucaparib treatment in patients with BRCA-mutated, relapsed ovarian cancer: final results from Study 10. *Br J Cancer*. 2023;128(2):255-265. doi:10.1038/s41416-022-02022-y
29. Guo XX, Wu HL, Shi HY, Su L, Zhang X. The efficacy and safety of olaparib in the treatment of cancers: a meta-analysis of randomized controlled trials. *Cancer Manag Res*. 2018;10:2553-2562. Published 2018 Aug 10. doi:10.2147/CMAR.S169558
30. Wu L, Zhu J, Yin R, et al. Olaparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer and a BRCA1 and/or BRCA2 mutation: SOLO1 China cohort. *Gynecol Oncol*. 2021;160(1):175-181. doi:10.1016/j.ygyno.2020.10.005
31. Shammo JM, Usha L, Richardson KJ, et al. Olaparib-Induced Severe Folate Deficiency in a Patient With Advanced Ovarian Cancer. *J Oncol Pract*. 2019;15(7):405-407. doi:10.1200/JOP.18.00705
32. Shiraishi C, Hirai T, Kaneda M, et al. Factors for the development of anemia in patients with newly introduced olaparib: A retrospective case-control study. *Medicine (Baltimore)*. 2023;102(30):e34123. doi:10.1097/MD.0000000000034123
33. Kaye SB, Lubinski J, Matulonis U, et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. *J Clin Oncol*. 2012;30(4):372-379. doi:10.1200/JCO.2011.36.9215
34. Pagkali A, Mamais I, Michalinos A, Agouridis AP. Safety Profile of Niraparib as Maintenance Therapy for Ovarian Cancer: A Systematic Review and Meta-Analysis.

Curr Oncol. 2022;29(1):321-336. Published 2022 Jan 12. doi:10.3390/curroncol29010029

35. Adrianto N, Mangkuliguna G, Tandiono EJ, Sibarani CNR. Efficacy and safety of rucaparib in patients with recurrent high-grade ovarian carcinoma: A systematic review and meta-analysis. *Taiwan J Obstet Gynecol*. 2024;63(5):601-609. doi:10.1016/j.tjog.2024.05.020
36. Dockery LE, Gunderson CC, Moore KN. Rucaparib: the past, present, and future of a newly approved PARP inhibitor for ovarian cancer. *Onco Targets Ther*. 2017;10:3029-3037. Published 2017 Jun 19. doi:10.2147/OTT.S114714