VIA MEDICA

REVIEW ARTICLE

Kaja Michalczyk, Anita M. Chudecka-Głaz

Department of Gynecological Surgery and Gynecological Oncology of Adults and Adolescents, Independent Public Clinical Hospital No. 2, Pomeranian Medical University, Szczecin, Poland

Safety of combination therapy with olaparib and bevacizumab in the maintenance treatment of a patients with newly diagnosed ovarian cancer

Address for correspondence:
Prof. Anita M. Chudecka-Głaz
Department of Gynecological Surgery and Gynecological Oncology of Adults and Adolescents, Independent Public Clinical Hospital No. 2,
Pomeranian Medical University in Szczecin
al. Powstańców Wielkopolskich 72,
70–111 Szczecin, Poland
e-mail: anitagl@poczta.onet.pl

Translation: dr n. med. Dariusz Stencel
Oncology in Clinical Practice
DOI: DOI: 10.5603/ocp.99480

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Olaparib-bevacizumab combination therapy has been included in the drug program for the maintenance treatment of patients with newly diagnosed ovarian cancer (B.50). Patients with *BRCA* gene mutation and/or homologous recombination deficiency (HRD) are eligible for the drug program. Both drug products have an acceptable safety profile but have so far been used separately — in monotherapy. Combination therapy appears to be an effective and safe solution and a new option for maintenance treatment of patients with advanced ovarian cancer.

Keywords: PAOLA, olaparib, bevacizumab, ovarian cancer, safety

Oncol Clin Pract

PARP inhibitor – olaparib

Poly-ADP-ribose polymerase (PARP) proteins are enzymes involved in transcription and DNA repair. Olaparib is an inhibitor of PARP1, PARP2, and PARP3. *In vitro* studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage and subsequent cancer cell death. Olaparib has also been shown to inhibit the growth of selected cancer cell lines *in vitro* and reduce tumor growth in mouse xenograft models of human cancer, both as monotherapy and following platinum-based chemotherapy. After treatment with olaparib, increased cytotoxicity and antitumor activity were observed in cell lines and mouse models of cancer with deficiency of *BRCA1/2*, *ATM,* or other genes involved in DNA repair through homologous recombination repair (HRR) and correlated with response to platinum [1].

The introduction of PARP inhibitors (PARPi) into clinical practice has opened a new era in the treatment of patients with ovarian cancers. Olaparib was first PARPi registered by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) in December 2014. The first registered indication was the treatment of patients with recurrent,

Received: 21.02.2024 Accepted: 23.09.2024 Early publication: 24.01.2025

platinum-sensitive ovarian cancer and was based on the Study-19 results [2]. It was a phase II pivotal study conducted in patients with recurrent ovarian cancer after at least two lines of prior platinum-based treatment. The study demonstrated a statistically significant improvement in progression-free survival (PFS) in the olaparib arm compared with the placebo arm, with median PFS of 8.4 months in the olaparib arm versus 4.8 months in the control arm [hazard ratio (HR) = 0.35; $p < 0.00001$]. A trend toward improved overall survival (OS; HR = 0.73; $p = 0.025$) was also demonstrated. Reduced progression risk was constantly observed in all predefined subgroups of patients receiving olaparib [*BRCA* mutation status, age, ethnic group, response to first-line platinum-based chemotherapy — complete response (CR) *vs.* partial response (PR), time from last line of chemotherapy] compared with the placebo arm [2].

The FDA initially registered olaparib for monotherapy in patients with germline *BRCA1/2* mutations who had previously received at least three lines of chemotherapy, while the EMA registration allowed the use of olaparib in the maintenance treatment of patients with recurrent, platinum-sensitive ovarian cancer with either germline or somatic *BRCA1/2* gene mutations. In Poland, olaparib has been included in the list of reimbursed drugs since September 2016, and its use was possible under the drug program B.80 — "Maintenance treatment with olaparib in patients with recurrent, platinum-sensitive advanced ovarian cancer, fallopian tube cancer or primary peritoneal cancer." The drug program included patients with confirmed hereditary and/or somatic mutation in the *BRCA1* and/or *BRCA2* gene who had previously received at least two lines of platinum-based chemotherapy.

The SOLO 2 study [3] was designed to confirm the efficacy of olaparib treatment and the use of its new formulation (tablets). The study included patients with platinum-sensitive, relapsed ovarian cancer with a *BRCA* mutation who achieved CR or PR during the last line of platinum-based chemotherapy. The obtained data confirmed the previous results, showing PFS prolongation in patients receiving olaparib compared with the control arm (PFS 19.1 *vs.* 5.5 months; HR = 0.30; $p < 0.0001$).

According to encouraging results of treatment with olaparib in further treatment lines, studies with its use in first-line therapy were initiated. The randomized phase III SOLO1 study [4] confirmed the clinical importance of PARP inhibitor monotherapy in the maintenance treatment of patients with newly diagnosed ovarian cancer with *BRCA1/2* mutation. A statistically significant PFS improvement was achieved in patients with advanced ovarian cancer and *BRCA1/2* mutation (HR = 0.30; $p < 0.0001$), with median PFS of 56 months in the olaparib group compared to 13.8 months in the placebo group [5]. Based on the results of the SOLO1 study [4], in December 2018, the FDA approved the use of olaparib in the first-line maintenance treatment in patients with *BRCA1/2* mutation, and then the drug was granted a marketing authorization by the EMA in June 2019. Since May 2021, the drug has been approved for use under the B.50 drug program for the maintenance treatment of patients with advanced, newly diagnosed, poorly differentiated ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with a *BRCA* mutation who responded to platinum-based therapy. At the same time, the use of olaparib in recurrent poorly differentiated ovarian, fallopian tube, and peritoneal cancer has also been expanded to include all patients who achieved CR or PR to platinum-based chemotherapy (previously, only treatment of patients with *BRCA* mutation was reimbursed) [6]. Based on the results of clinical studies, it has been confirmee that *BRCA1/2* mutation, loss of heterozygosity in the genome, and homologous recombination deficiency (HRD) are predictors of response to PARP inhibitor therapy (SOLO1 [4], SOLO2 [3], ATHENA [7], NOVA [8], and PRIMA [9] studies).

Treatment with olaparib contributed not only to prolonging PFS but also OS without significantly affecting the quality of life of patients treated with the PARP inhibitor.

Over the years, the product characteristics have changed. Initially, it was available in the form of capsules of 50 mg (as in the pivotal study Study 19 [2]), and the recommended starting dose was 400 mg, which was associated with a large number of capsules to take (16 capsules per day). Based on numerous studies, the bioavailability of the product was improved by changing its form to tablets of 150 and 100 mg. During the Study 24 trial [10], due to the different bioavailability of the drug, the optimal dose of the medicinal product was established for the use of olaparib in the form of tablets at 300 mg (4 tablets per day), which allowed for a reduction in the number of medications taken orally. Due to the different bioavailability and pharmacokinetics of the drug, according to the summary of product characteristics (SmPC), one milligram of olaparib in the form of capsules did not correspond to one milligram of olaparib in the form of tablets; therefore, the dosage was changed [1, 11]. Olaparib is a compound with low solubility in the physiological pH range, and the pH level does not affect its solubility. Studies have shown that taking olaparib with high-fat, high-calorie meals slows down the absorption but does not affect its complete absorption, so the drug can be used regardless of the meal [1].

According to the SmPC, olaparib is approved for use as monotherapy in patients over 18 years of age with advanced Federation of Gynaecology and Obstetrics (FIGO) stage III/IV high-grade ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, with

BRCA1/2 mutation (germline and/or somatic), who achieved a response (CR or PR) after completing first-line platinum-based chemotherapy. It is also available for maintenance treatment of adult patients with platinum-sensitive, recurrent, high-grade ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who achieved a response (CR or PR) to platinum-based chemotherapy.

Olaparib is also registered as:

— monotherapy for the treatment of adult patients with germline *BRCA1/2*-mutations who have HER2 negative, locally advanced, or metastatic breast cancer, previously treated with an anthracycline and a taxane;

— monotherapy for the maintenance treatment of adult patients with germline *BRCA1/2*-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen;

— monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and *BRCA1/2*-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.

Niraparib, another PARP inhibitor, was also registered for maintenance treatment of patients with newly diagnosed ovarian cancer based on the results of the PRIMA study [9]. Niraparib can be used regardless of the molecular status, including patients without *BRCA1/2* mutations or HRD. Clinical trials have also been conducted with rucaparib [7] and veliparib [12]. Updated results of the SOLO1 study were presented at the European Society of Medical Oncology (ESMO) conference in 2022. Based on 7 years of follow-up, a 45% reduction in the risk of death was demonstrated in the olaparib-treated group (HR = 0.55; p = 0.0004) [13]; 67% of the olaparib-treated group and 46.5% of the control group were still alive during the analysis. The SOLO1 study has the longest follow-up period for patients with newly diagnosed advanced ovarian cancer treated with PARP inhibitors.

Angiogenesis inhibitor — bevacizumab

Angiogenesis is a key process for the formation of new blood vessels that enable tumor growth and the development of metastatic foci. The complex process of angiogenesis is regulated by numerous mechanisms aimed at maintaining homeostasis between proangiogenic processes [including vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF)] and antiangiogenic processes. VEGF activity is controlled by a group of vascular endothelial growth factor receptors (VEGFRs) with tyrosine kinase activity [14].

The use of antiangiogenic therapy in patients with ovarian cancer has been extensively analyzed in recent decades. Numerous studies have been conducted on various angiogenesis inhibitors, including bevacizumab, aflibercept, cediranib, sorafenib, sunitinib, pazonanib, vatalanib, volociximab, and trebananib (AMG 386) [15].

Bevacizumab is an angiogenesis inhibitor that is the most widely studied in the treatment of ovarian cancer. It is a humanized monoclonal antibody targeting VEGF. Initially, studies using bevacizumab were conducted in patients with recurrent ovarian or peritoneal cancer. In the GOG170 study, an objective response to treatment with bevacizumab was achieved by 21% of patients and disease stabilization by 52% of patients [16]. Numerous phase II studies using combined therapy (chemotherapy + bevacizumab) in patients with recurrent ovarian cancer have also been conducted. The studies included different doses of bevacizumab (7.5–15 mg/kg body weight) and treatment schedules (weekly/every three weeks) in combination with different chemotherapeutic agents (cyclophosphamide, paclitaxel, gemcitabine, topotecan, and pegylated liposomal doxorubicin). Phase III studies aimed at assessing the efficacy of treatment in patients with recurrent ovarian cancer, both platinum-sensitive (OCEANS [17] — carboplatin with gemcitabine in combination with bevacizumab) and platinum-resistant (including AURELIA [18] — pegylated liposomal doxorubicin/topotecan/paclitaxel weekly in combination with bevacizumab) demonstrated the efficacy, safety, and good tolerability of bevacizumab in combination with chemotherapy.

In 2011, based on the results of the phase III GOG-0218 study [19], bevacizumab was registered in Europe for the treatment of patients with newly diagnosed advanced ovarian cancer in combination with platinum-based chemotherapy and subsequent maintenance treatment. The initial results of the GOG-0218 study showed increased PFS in patients treated with carboplatin, paclitaxel, and bevacizumab and continuing with bevacizumab as maintenance therapy (HR = 0.72; p < 0.0001) compared to other study groups (chemotherapy *vs.* chemotherapy with bevacizumab) [19]. However, a retrospective analysis of the ICON-7 study, after OS data maturation, demonstrated the benefit of bevacizumab treatment only in high-risk patients (with suboptimal cytoreduction, with stage III or IV, unfavorable KELIM™ score < 1.0, median OS — 29.7 *vs.* 20.6 months; HR = 0.78) [20]. The ICON-7 study also demonstrated prolongation of PFS in patients receiving bevacizumab (median PFS — 21.8 *vs.* 20.3 months; HR = 0.81; p = 0.004) [21]. The final results of the ICON-7 study demonstrated prolonged OS in a predefined high-risk population, including patients with stage IV and stage III disease,

according to FIGO, in whom surgical treatment was not possible or cytoreduction was incomplete with postoperative residual lesions above 1 cm (median OS — 39.3 *vs.* 34.5 months; HR = 0.78).

Combination therapy with PARP and angiogenesis inhibitors — mechanism of action

Promising results of using angiogenesis inhibitors and then PARP inhibitors in maintenance treatment for patients with newly diagnosed ovarian cancer raised the question of the justification and potential efficacy of combined treatment. Combination of antiangiogenic therapy with PARP inhibitors should hypothetically result in increased antitumor activity [22].

By preventing VEGF receptors from binding to cancer cells, bevacizumab inhibits angiogenesis and tumor growth. However, despite the initial response to treatment, cancer cells develop adaptive resistance mechanisms, gradually reducing the response to therapy [23]. One of the resistance mechanisms is hypoxia of cancer cells due to the reduction of tumor vascularization and supply of nutrients using an antiangiogenic agent. The consequence of cell hypoxia is an increase in the amount of cellular DNA damage and genetic instability [23]. Chan and Bristow [24] in their studies noted that cancer cells exposed to chronic hypoxia acquire defects in homologous recombination mechanisms, as well as increased sensitivity to PARP inhibition [24]. Preclinical studies have shown the effect of hypoxia induction on the expression of *BRCA1/2* and *RAD51*, which are the main factors of homologous recombination mechanisms. In cancer cells with HRD, including *BRCA1/2*-mutated cancer cells, the mechanisms of DNA damage repair during replication are not fully understood. Due to the accumulation of errors in DNA repair, as genomic rearrangements accumulate, cells stop functioning properly, which leads to their death [25, 26]. Direct targeting of PARP proteins by olaparib and indirect sensitization of cancer cells to its action by acquiring homologous recombination defects in response to bevacizumab support the use of combination therapy in the treatment of ovarian cancer patients. The exact mechanisms of action of the combination of PARP inhibitors and antiangiogenic drugs are not yet fully understood [27–29]. Other potential mechanisms of action of combination therapy may result from the inhibition of VEGFR3 in ovarian cancer cells (resulting in reduced *BRCA* gene expression as well as induction of cell cycle arrest and chemosensitivity [30]) or the potential involvement of PARP1 in angiogenesis and the antiangiogenic effect of PARP inhibitors (including the upregulation of VEGF-A expression) [31, 32]. Overexpression of PARP1 in human ovarian cancer cells seems to be associated with higher grade and lymph node involvement, suggesting a link between PARP1 and ovarian cancer progression [31].

The combination of both classes of drugs — PARP inhibitors and antiangiogenic drugs — aroused particular interest due to the exceptional efficacy of both therapies with relatively non-overlapping toxicity profiles. The characteristics of both drugs are presented in Table 1 [1, 33, 34].

The use of anti-VEGF plus PARP inhibitor combination therapy in the treatment of ovarian cancer patients was first investigated in patients with relapsed, platinum-sensitive ovarian cancer in the phase II NCT01116648 study with cediranib plus olaparib [35]. The study showed improved PFS in the olaparib plus cediranib arm compared with olaparib monotherapy (17.7 *vs.* 9 months; $p = 0.005$). The next studies using combination therapy were the phase II AVANOVA2 study of niraparib in combination with bevacizumab, also conducted in patients with relapsed, platinum-sensitive ovarian cancer (PFS 11.9 *vs.* 5.5 months; HR = 0.35; $p < 0.001$) [36] and the phase III PAOLA-1 study of first-line combination treatment with olaparib and bevacizumab in patients with newly diagnosed advanced ovarian [37].

Table 1. Characteristics of olaparib and bevacizumab [1, 33, 34]

	Olaparib	Bevacizumab
Mechanism of action	PARP1, PARP2, and PARP3 inhibitor	Binds VEGF and prevents VEGF from interacting with its receptors (Flt-1, KDR) on the surface of endothelial cells
Metabolism	Hepatic, partially *via* CYP3A, renal	Major route of elimination is whole body proteolytic catabolism (linear, nonspecific clearance), not hepatic metabolism or renal excretion [34]
Interactions	With CYP3A inhibitors; possible interaction with other myelosuppressive drugs resulting in increased and prolonged myelotoxicity	No clinically significant effect on use with other drugs
Mean half-life	14.9 hours	19–20 days
Administration route	Tablets	Injection (100 mg or 400 mg vials)

Flt-1 — fetal liver kinase 1; KDR — kinase insert domain receptor; PARP — poly-ADP-ribose polymerase; VEGF — vascular endothelial growth factor

PAOLA-1 study

The PAOLA-1 study [37] was the first prospective phase III clinical trial to examine the combination of a PARP inhibitor (olaparib) with antiangiogenic therapy (bevacizumab). The control arm of the study was an active comparator cohort receiving maintenance therapy with bevacizumab. The study included patients with advanced ovarian cancer, regardless of molecular status or surgical outcome in terms of residual disease. Patients who achieved CR or PR to first-line platinum-based chemotherapy and antiangiogenic therapy with bevacizumab were enrolled. The *BRCA1/2* mutations and HRD were assessed in the PAOLA-1 study using the Myriad MyChoice test. The study showed statistically significant prolongation of median PFS in the combination arm compared with bevacizumab monotherapy (22.1 *vs.* 16.6 months; HR = 0.59; $p < 0.001$). The greatest reduction in the risk of disease progression or death was observed in HRD patients with coexisting *BRCA* mutation (HR = 0.33). In HRD patients without *BRCA* mutations, HR was 0.43. The PAOLA-1 study did not show a PFS or OS benefit in patients without homologous recombination proficiency (HRP).

Based on the results of the PAOLA-1 study, the FDA and the EMA, registered, in May 2020 and September 2020, respectively, the combination therapy of olaparib with bevacizumab for the maintenance treatment of adult patients with advanced high-grade epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, who achieved a response to first-line platinum-based chemotherapy in combination with bevacizumab and with HRD and/or *BRCA1/2* mutations in cancer cells. In Poland, the B.50 drug program for patients with newly diagnosed advanced ovarian cancer, fallopian tube cancer, or primary peritoneal cancer has been expanded since November 1, 2022, to include the possibility of using combination therapy with olaparib and bevacizumab in patients with *BRCA1/2* genes mutations or confirmed HRD.

Drug dosage in the PAOLA-1 study

In the PAOLA-1 study, bevacizumab had to be administered at least in the three last cycles of platinum-based chemotherapy [in the case of interval debulking surgery (IDS) at least in the two last cycles]. According to the study design, treatment with olaparib was continued for 24 months or until disease progression or unacceptable toxicity. Patients who achieved CR according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 after 24 months were required to discontinue olaparib, whereas patients with CR were allowed to continue olaparib beyond 24 months if, in the opinion of the treating physician, they would derive further benefit from continued therapy. Maintenance therapy with bevacizumab in the PAOLA-1 study was recommended at a dose of 15 mg/kg body weight every 3 weeks for a total treatment period of 15 months, including chemotherapy and maintenance therapy. The recommended daily dose of olaparib was 300 mg (two 150 mg tablets) taken orally, twice daily, with or without food.

Side effects of olaparib

The most common adverse effects of olaparib are fatigue and gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea, constipation, taste disturbances, or decreased appetite). The most common hematological adverse effects are anemia, occurring in approximately 38% of patients, and neutropenia (17%). Most adverse effects occurring during treatment with olaparib can be effectively treated by dose modification or interruption therapy. A small number of adverse events require treatment discontinuation [38, 39].

The principles of management of the most common adverse events and possible treatment modifications related to the use of olaparib are described below.

Side effects of bevacizumab

The safety profile of bevacizumab in the first-line maintenance treatment of patients with ovarian cancer was evaluated in the GOG-218 study. Grade 3 and higher adverse events occurring at a higher frequency (≥ 2%) in the bevacizumab-treated population, compared with the control arm, were fatigue, hypertension, thrombocytopenia, and leukopenia [21]. The most common adverse events observed in patients treated with bevacizumab (at a frequency of > 10% and occurring at least twice as often as in the control arm) included epistaxis, headache, hypertension, rhinitis, proteinuria, taste changes, dry skin, rectal hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis. Adverse events of treatment were usually grade 1 or 2. In all clinical trials conducted with bevacizumab, its administration was discontinued due to adverse events in 8.4–21% of patients [33].

Adverse events in the PAOLA-1 study

The safety profiles of combined PARP inhibitor therapy with antiangiogenic drugs and reported adverse events were consistent with those previously observed in studies with each drug used as monotherapy [40].

Almost all patients enrolled in the PAOLA-1 study experienced adverse events regardless of the treatment

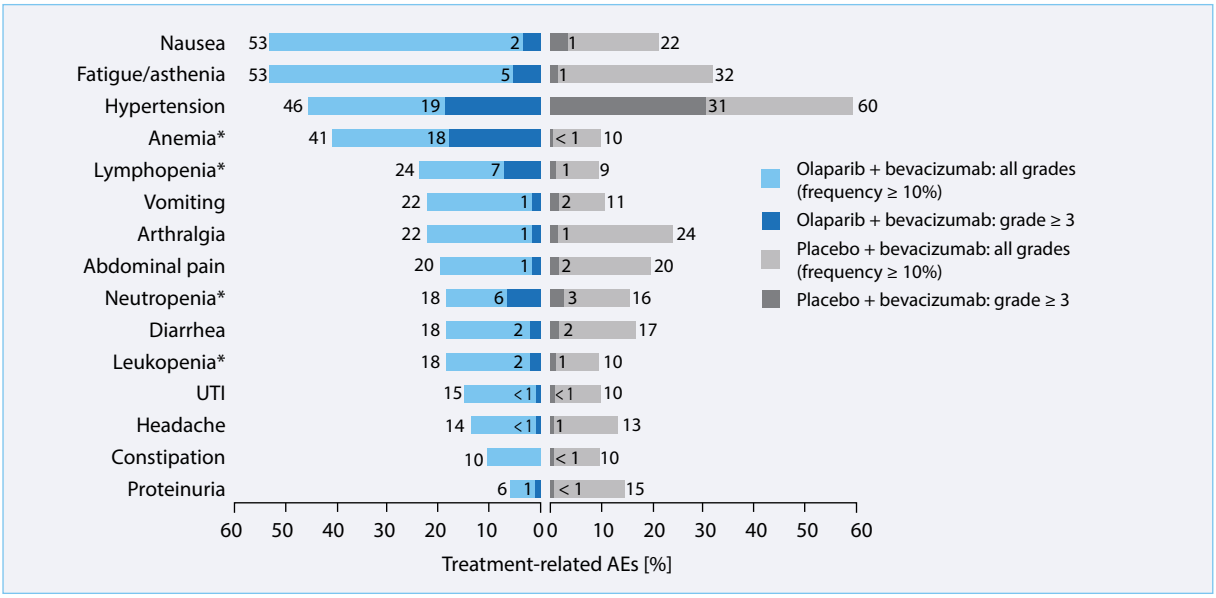

Figure 1. Safety profile of combination therapy in the PAOLA-1 study [38]; AE — adverse event; UTI — urinary tract infection

arm (99% of patients receiving combination therapy *vs.* 96% receiving bevacizumab alone), and grade 3 or higher adverse events occurred in approximately half of patients (57% *vs.* 51% in the treatment and control arms, respectively). The most common adverse events in patients receiving combination therapy, compared with the control group receiving bevacizumab monotherapy, included nausea (53%), fatigue (including asthenia; 53%), vomiting (22%), and hematologic disorders [anemia (41%), lymphopenia (24%), leukopenia (18%)]. Venous thromboembolic events occurred more frequently in patients receiving combination therapy (5%) than in those receiving bevacizumab alone (1.9%). The most common adverse events are shown in Figure 1.

In the PAOLA-1 study, a significantly lower incidence of symptoms such as hypertension and proteinuria was observed in patients receiving the combination therapy with olaparib and bevacizumab compared to bevacizumab monotherapy.

Among the hematologic abnormalities in the PAOLA-1 study, the most common was anemia, which occurred significantly more frequently in patients receiving combination therapy compared with bevacizumab (41 *vs.* 10%). The Common Terminology Criteria for Adverse Events (CTCAE) grade of toxicity was also significantly higher in the combination therapy group (18 *vs.* < 1% of patients with grade ≥ 3 anemia). Similarly, neutropenia was observed significantly more frequently in patients treated with olaparib in combination with bevacizumab compared with the control arm (24 *vs.* 9%).

Temporary treatment interruption was required in 54% of patients receiving combination therapy compared with 24% in the group receiving bevacizumab alone. In the PAOLA-1 study, 41% of patients receiving combination therapy required olaparib dose reduction, and 20% prematurely discontinued treatment due to adverse events. The most common toxicities leading to treatment discontinuation were anemia (4%) and nausea (3%). The most common adverse events leading to dose interruption in the combination group were anemia (21%), nausea (7%), vomiting (3%), and fatigue (3%). Reasons for dose reduction included anemia (19%), nausea (7%), and fatigue (4%) [41]. The PAOLA-1 study demonstrated comparable tolerability and safety profile compared with previous studies using PARP inhibitor monotherapy in the first-line treatment of patients with advanced ovarian disease. The overall percentage of patients discontinuing maintenance therapy due to adverse events, patient decision, or other reasons not related to disease progression was similar in the SOLO-1 (24% in the olaparib arm) [4], PRIMA (18% in the niraparib arm) [8], and ATHENA-MONO (18% in the rucaparib arm) [6] studies. The comparison of adverse event profiles between olaparib monotherapy and olaparib plus bevacizumab combination therapy is presented in Table 2 [38, 40, 41].

The 5-year follow-up analysis of the PAOLA-1 study showed no new safety signals. In the final OS analysis, there were 9 (1.7%) cases of myelodysplastic syndrome, acute myeloid leukemia, or aplastic anemia in the combined group, compared with 6 (2.2%) cases in the control group. There were 22 (4.1%) new cases of primary malignancy in the olaparib plus bevacizumab group and 8 (3.0%) in the bevacizumab alone group [42].

Table 2. Comparison of adverse events of combined therapy in the PAOLA-1 study [40, 41] and olaparib monotherapy in the SOLO-1 study [38]

	PAOLA-1		SOLO-1
Adverse Event	**Olaparib + bevacizumab**	**Bevacizumab + placebo**	**Olaparib**
Fatigue, asthenia			
Grade 1–4	53%	32%	67%
Grade 3–4	5%	1.5%	4%
Nausea			
Grade 1–4	53%	22%	77%
Grade 3–4	2.4%	0.7%	1%
Vomiting			
Grade 1–4	22%	11%	40%
Grade 3–4	1.7%	1.9%	0%
Anemia			
Grade 1–4	41%	10%	38%
Grade 3–4	17%	0.4%	21%
Lymphopenia			
Grade 1–4	24%	9%	No data
Grade 3–4	7%	1.1%	No data
Leukopenia			
Grade 1–4	18%	10%	13%
Grade 3–4	1.9%	1.5%	3%
Hypertension			
Grade ≥ 3	19%	30%	No data
Proteinuria			
Grade ≥ 3	1%	15%	No data
Pulmonary embolism	1%	< 1%	No data
Venous thrombosis	< 1%	0%	No data
Bowel perforation	< 1%	1%	No data
Postoperative wound dehiscence	< 1%	0%	No data

Considering the adverse events resulting from the use of bevacizumab in patients participating in the PAOLA-1 study, there were no significant differences in the occurrence of adverse events between patients receiving combination therapy and those receiving bevacizumab alone [37]. The most common adverse event, most likely related to the use of bevacizumab, was arterial hypertension and proteinuria.

Multiple safety assessments of the PAOLA-1 study were performed using post-hoc analyses, including stratification of patients by risk of disease progression. The group with a higher risk of disease progression included patients with stage III disease and residual disease after primary surgery or after neoadjuvant chemotherapy and with FIGO stage IV disease. The group with a lower risk of progression included patients with FIGO stage III disease who underwent primary debulking surgery (PDS) and achieved complete cytoreduction (R0). The tolerability and safety profile of olaparib in combination with bevacizumab was similar in the subgroups of patients with both higher and lower risk of progression. There were no clinically significant changes or differences in quality of life between the two groups [43].

The study population was also stratified by age (≥ 65 *vs.* < 65 years). The frequency of treatment discontinuation and/or dose reduction due to treatment-related adverse events was similar in older and younger women (46.6% *vs.* 41.4% and 37.7% *vs.* 37.8%, respectively). The most common adverse event leading to dose reduction in the elderly population was anemia (23.5%). Treatment was discontinued due to olaparib-related adverse events in 21.1% of patients aged 65 and over, compared with 15.7% of those under 65 years of age. The most common adverse events leading to treatment discontinuation in both age groups were anemia (4.9%), nausea (3.4%), and fatigue/asthenia (1.5%). Grade 3 or higher adverse events were observed in 64.7% of older patients receiving olaparib compared with 51.7% in the younger group ($P = 0.0031$). In patients receiving bevacizumab alone, the incidence was 45.9% and 61.6%,

respectively. The incidence of grade 3 or higher olaparib-related adverse events was similar in both age subgroups (36.8% in older patients compared with 31.7% in younger patients; $P = 0.23$). During the study, one treatment-related fatal adverse event was observed in the younger group treated with olaparib. However, no deaths resulting from treatment-related adverse events were reported in the older patients. Myelodysplastic syndrome was diagnosed in one older patient and two younger patients in the olaparib group [44].

Montegut et al. [45] analyzed the safety, quality of life, and efficacy of the treatment used in the PAOLA-1 study, allocating patients to age groups ≥ 70 and < 70 years [45]. A moderately increased frequency of grade 3 and higher treatment-related adverse events was observed in older patients (in particular, anemia 21.2% *vs.* 16.5% and neutropenia 9.7% *vs.* 5.1%, respectively). The most common non-hematological adverse event was hypertension, which is consistent with the results presented in the post-hoc analysis of the PAOLA-1 study. Fujivara et al. [46] showed a similar safety profile in a post hoc analysis of the Japanese subpopulation of patients enrolled in the PAOLA-1 study.

Treatment monitoring

According to the drug program B.50, to monitor the possible occurrence of treatment-related adverse effects and toxicity during combined therapy, it is recommended to closely monitor the results of laboratory tests both at the time of qualification for maintenance treatment and during this therapy. The tests should include a complete blood count (CBC) with a differential, creatinine and bilirubin serum level and transaminase activity level, general urinalysis (during cycles with bevacizumab), or other tests if clinically indicated before starting each subsequent therapy cycle.

Management of the most common olaparib-related adverse events

In the case of adverse reactions, it is recommended to discontinue therapy or reduce the dose. The recommended reduced dose of olaparib is 250 mg twice daily. If further reduction is necessary, the dose can be reduced to 200 mg twice daily.

Hematologic toxicity

It is not recommended to start olaparib until the hematologic toxicity from prior chemotherapy has resolved or has returned to a maximum of grade 1. CBC should be monitored for cytopenias, particularly at the beginning of treatment, and then monthly for clinically significant changes. If prolonged hematologic toxicity occurs, olaparib should be discontinued and CBC monitored weekly until improvement. If CBC parameters do not return to grade 1 or less after 4 weeks, the patient should be referred to a hematologist for further evaluation, including bone marrow biopsy and blood sampling for cytogenetic testing. If myelodysplastic syndrome/acute myeloid leukemia is confirmed, the drug should be discontinued.

Respiratory system

If patients have any new or worsening respiratory symptoms (such as dyspnea, cough, and fever) or abnormal radiological findings, olaparib should be discontinued, and diagnostic tests should be extended to identify the cause of the symptoms. If pneumonia is confirmed, olaparib should be temporarily discontinued, and appropriate treatment should be introduced.

Nausea and vomiting

Nausea and vomiting are among the most common adverse events in patients receiving combination maintenance therapy with olaparib and bevacizumab. Similar adverse events were observed in studies with PARP inhibitor monotherapy in over 75% of patients with ovarian cancer, but grade 3 or 4 events occurred in only 1–2% [47]. Nausea usually occurs within the first few days to weeks after starting olaparib. It is usually mild and decreases with the duration of therapy. In patients who experience increasing nausea and vomiting lasting more than three months after starting treatment, disease progression should be excluded [47]. The SOLO-1 study showed that the first nausea occurred in patients approximately 4 days after starting therapy, and the median duration was 1.4 months [38]. To prevent discontinuation of PARP inhibitor therapy due to nausea or vomiting, prophylactic measures should be taken. No clinical studies have been conducted to assess the efficacy and safety of antiemetics in patients treated with PARP inhibitors. The SmPC does not recommend the use of antiemetic prophylaxis, but nausea and vomiting can be effectively managed by drug interruption, dose reduction, and/or antiemetic therapy [1, 38]. In the SOLO-1 study, nausea and vomiting were managed with supportive care or dose modification of the antineoplastic drug, and few patients discontinued treatment with olaparib. In this study, metoclopramide was used to reduce nausea/vomiting in 32.7% of patients receiving olaparib compared with 13.7% of patients receiving placebo. Serotonin receptor antagonists (5-HT3) were used in 23.8% of patients receiving olaparib compared with 16.0% of patients receiving placebo. The treatment resulted in the resolution of adverse symptoms [38].

Use of olaparib in specific populations and treatment modifications

Liver failure

In patients with advanced cancer, coexisting different stages of liver failure are possible, sometimes resulting from the presence of metastases. Olaparib is metabolized in the liver via cytochrome P450 isoenzymes 3A4/5. Rolfo et al. [48] conducted a study on the pharmacokinetics and safety of olaparib in patients with advanced liver tumors and mild-to-moderate liver failure. They demonstrated no significant differences in exposure to olaparib in patients with liver failure compared to patients with normal liver function. Furthermore, they demonstrated that patients with liver failure did not require any dosage adjustments for either tablets or capsules. According to the SmPC, there is no need to adjust the initial olaparib dose in patients with mild-to-moderate hepatic impairment (Child-Pugh class A and B). There is currently no data on patients with severe hepatic impairment (Child-Pugh class C).

If strong or moderate CYP3A inhibitors should be used, it is recommended to reduce the olaparib dose to 100 mg twice daily if a strong CYP3A inhibitor is used or 150 mg twice daily if a moderate CYP3A inhibitor is used.

Kidney failure

Olaparib metabolites are excreted via the urinary system (44%) and the digestive system (42%). The safety and pharmacokinetics of the drug were compared in patients with renal impairment in a multicenter, prospective phase I study. The pharmacokinetics of a single dose of olaparib (300 mg tablet) in patients with mild-to-moderate renal impairment were compared to those in patients with normal renal function based on creatinine clearance (CLcr). A slight, clinically insignificant increase in olaparib exposure was observed in patients with a mild reduction in glomerular filtration rate (GFR), and the safety profile of this group was similar to that observed in patients with normal renal function. In the group of patients with moderate renal impairment, an increase of olaparib exposure by 44% was observed. Despite this, no new safety signals were detected. It was noted that it is necessary to monitor patients with moderate renal impairment and to adjust the appropriate treatment dose in the range of 300 to 200 mg twice daily [49]. According to the SmPC, no dose adjustment is recommended in patients with mild renal impairment (CLcr 51–80 mL/min according to the Cockcroft-Gault equation), while in the group with moderate impairment (CLcr 31–50 mL/min), the dose of olaparib should be reduced to 200 mg twice daily. There is no data for patients with severe renal impairment or end-stage renal disease (CLcr ≤ 30 mL/min) [1].

Use of bevacizumab in specific populations and treatment modifications

In patients with advanced ovarian cancer, the question remains: at what point in therapy is it appropriate to start combination therapy with bevacizumab — before or after attempting radical surgical treatment? According to the SmPC, bevacizumab may cause impaired healing of postoperative wounds. Therapy with its use should be completed at least 28 days before surgical treatment, and its re-administration in patients after IDS should be started at least 28 days after the surgical procedure or after the postoperative wound has fully healed.

According to the SPC, there is no indication for bevacizumab dose reduction, and maintenance treatment with its use should be continued until disease progression. Bevacizumab should be discontinued in the case of gastrointestinal perforation, intestinal fistula or intraabdominal abscess, postoperative wound dehiscence or wound healing complications requiring medical intervention, necrotizing fasciitis, massive bleeding or hemoptysis, severe arterial thromboembolic complications, life-threatening (grade IV) thromboembolic disease (including pulmonary embolism), severe arterial hypertension (which cannot be controlled pharmacologically), hypertensive crisis or hypertensive encephalopathy, and nephrotic syndrome. Conditions in which bevacizumab treatment can be temporarily discontinued are presented in Table 3.

Quality of life of patients treated with olaparib-bevacizumab combination therapy

In the PAOLA-1 study, the patient quality of life was analyzed using the Quality of Life Questionnaire (EORTC QLQ-C30) and QLQOV28 forms of the European Organization for Research and Treatment of Cancer. No significant differences in quality of life were found between the group receiving combined therapy and bevacizumab alone [50]. Analysis of the time until definitive deterioration (TUDD) — defined as the time from the patient's enrollment to the first clinically significant symptoms of deterioration in quality of life by at least 10 points and persisting over time — did not show any differences between patients receiving combined therapy and the control arm. However, in HRD patients, the benefit of combined therapy was confirmed by extending the TUDD in the aspect of global health-related quality of life (G-HRQoL) [50]. In both groups, clinically significant deterioration in emotional and social functioning was observed at the time of disease progression.

Table 3. Modification of bevacizumab treatment according to the summary of product characteristics [33]

Adverse Event	Grade	Treatment modification
Wound healing complications	Any	Treatment interruption until adequate wound healing
	Necrotizing fasciitis	Treatment discontinuation
Bleeding	Grade 3 or 4	Treatment discontinuation
	Hemoptysis (2.5 mL or more)	Treatment interruption
Hypertension	Hypertensive crisis Hypertensive encephalopathy	Treatment discontinuation
	Severe hypertension (Grade 3)	Treatment interruption
Renal failure/proteinuria	Nephrotic syndrome	Treatment discontinuation
	Proteinuria ≥ 2 g/day	Treatment interruption; continue after proteinuria < 2 g/day
Side effects related to drug administration	Severe	Treatment discontinuation
	Clinically significant	Infusion interruption; should be resumed at a slower rate after clinical symptoms have resolved
	Mild, clinically insignificant	Infusion rate should be slowed down

Similar data were obtained in the analysis performed by the GINECO group, which conducted the TWiST (Time without symptoms or toxicity) study, which included the time without symptoms and/or treatment toxicity after randomization until the start of treatment in the PAOLA-1 study [51]. Maintenance therapy with olaparib in combination with bevacizumab did not have a negative impact on G-HRQoL [50]. This observation is particularly important considering that almost 50% of patients who achieved a response to platinum-based chemotherapy in the PAOLA-1 study had no disease symptoms at the time of enrollment. The use of effective maintenance therapy, prolonging PFS, in patients with advanced high-grade ovarian cancer may delay the clinically significant deterioration of emotional and social functioning, which was observed among patients with disease progression in the PAOLA-1 study.

A study by Montegut et al. [45] also analyzed the safety profile, quality of life, and treatment efficacy in patients participating in the PAOLA-1 study. Among others, the quality of life of patients ≥ 70 years of age was assessed using the EORTC QLQ-C30 forms. The global health status during the first two years of maintenance treatment in this age group was similar in both therapeutic arms, regardless of the treatment used, despite an increased incidence of grade 3 or higher adverse events in patients receiving combined therapy.

Conclusions

The PAOLA-1 study demonstrated the efficacy of the combination of olaparib with bevacizumab in the maintenance treatment of patients with advanced ovarian cancer who responded to platinum-based therapy. The adverse events reported in the study are typical complications of each of the drugs used in monotherapy. No new, additional adverse events were identified resulting from the use of combination therapy. Taking into account the risk of therapy interruption or discontinuation, the safety profile of that treatment is acceptable.

Article Information and Declarations

Author contributions

K.M.: conception, manuscript writing; A.M. C.-G.: conception, manuscript writing, supervision.

Funding

The article was commissioned by the Publisher.

Acknowledgments

None.

Conflict of interest

The authors declare honoraria for lectures and advisory board membership from Astra Zeneca.

Supplementary material

None.

References

1. Astra Zeneca Phrarmaceuticals, Lynparza Tablets Digital Presciber Information Placeholder, last accessed January 8th, 2024. https://www.lynparza.co.uk/content/dam/open-digital/lynparza/en/landing-page/ni-pi-lynparza-tablets.pdf.
2. Ledermann J, Harter P, Gourley C, et al. Olaparib Maintenance Therapy in Patients With Platinum-Sensitive Relapsed Serous

Ovarian Cancer. Obstet Gynecol Surv. 2014; 69(10): 594–596, doi: 10.1097/ogx.0000000000000107.
3. Pujade-Lauraine E, Ledermann JA, Selle F, et al. SOLO2/ENGOT-Ov21 investigators. 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(9): 1274–1284, doi: 10.1016/S1470-2045(17)30469-2, indexed in Pubmed: 28754483.
4. 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, indexed in Pubmed: 30345884.
5. Agencja Oceny Technologii Medycznych i Taryfikacji.
6. 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. Lancet Oncol. 2021; 22(12): 1721–1731, doi: 10.1016/S1470-2045(21)00531-3, indexed in Pubmed: 34715071.
7. Monk BJ, Coleman RL, Fujiwara K, et al. ATHENA (GOG-3020/ENGOT-ov45): a randomized, phase III trial to evaluate rucaparib as monotherapy (ATHENA-MONO) and rucaparib in combination with nivolumab (ATHENA-COMBO) as maintenance treatment following frontline platinum-based chemotherapy in ovarian cancer. Int J Gynecol Cancer. 2021; 31(12): 1589–1594, doi: 10.1136/ijgc-2021-002933, indexed in Pubmed: 34593565.
8. 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(32): 2968–2973, doi: 10.1200/JCO.18.02238, indexed in Pubmed: 31173551.
9. González-Martín A, Pothuri B, Vergote I, et al. PRIMA/ENGOT--OV26/GOG-3012 Investigators. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019; 381(25): 2391–2402, doi: 10.1056/NEJMoa1910962, indexed in Pubmed: 31562799.
10. Mateo J, Moreno V, Gupta A, et al. An Adaptive Study to Determine the Optimal Dose of the Tablet Formulation of the PARP Inhibitor Olaparib. Target Oncol. 2016; 11(3): 401–415, doi: 10.1007/s11523-016-0435-8, indexed in Pubmed: 27169564.
11. Charakterystyka Produktu Leczniczego, Pfizer Aneks i Charakterystyka Produktu Leczniczego 1 BioNTech Comirnaty Pfizer. 2AD, 1–156.
12. Coleman RL, Fleming GF, Brady MF, et al. Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. N Engl J Med. 2019; 381(25): 2403–2415, doi: 10.1056/NEJMoa1909707, indexed in Pubmed: 31562800.
13. DiSilvestro P, Banerjee S, Colombo N, et al. 517O Overall survival (OS) at 7-year (y) follow-up (f/u) in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm) who received maintenance olaparib in the SOLO1/GOG-3004 trial. Ann Oncol. 2022; 33: S779, doi: 10.1016/j.annonc.2022.07.645.
14. Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. Nat Rev Cancer. 2008; 8(8): 579–591, doi: 10.1038/nrc2403, indexed in Pubmed: 18596824.
15. Han ES, Wakabayashi M, Leong L. Angiogenesis inhibitors in the treatment of epithelial ovarian cancer. Curr Treat Options Oncol. 2013; 14(1): 22–33, doi: 10.1007/s11864-012-0220-6, indexed in Pubmed: 23288484.
16. Burger RA, Sill MW, Monk BJ, et al. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2007; 25(33): 5165–5171, doi: 10.1200/JCO.2007.11.5345, indexed in Pubmed: 18024863.
17. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012; 30(17): 2039–2045, doi: 10.1200/JCO.2012.42.0505, indexed in Pubmed: 22529265.
18. Pujade-Lauraine E, Hilpert F, Weber B, et al. AURELIA: A randomized phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT)-resistant recurrent ovarian cancer (OC). J Clin Oncol. 2012; 30(15_suppl): LBA5002–LBA5002, doi: 10.1200/jco.2012.30.15_suppl.lba5002.
19. Burger RA, Brady MF, Bookman MA, et al. Gynecologic Oncology Group. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011; 365(26): 2473–2483, doi: 10.1056/NEJMoa1104390, indexed in Pubmed: 22204724.
20. Colomban O, Tod M, Peron J, et al. Bevacizumab for Newly Diagnosed Ovarian Cancers: Best Candidates Among High-Risk Disease Patients (ICON-7). JNCI Cancer Spectr. 2020; 4(3): pkaa026, doi: 10.1093/jncics/pkaa026, indexed in Pubmed: 32596636.
21. Perren TJ, Swart AM, Pfisterer J, et al. ICON7 Investigators. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011; 365(26): 2484–2496, doi: 10.1056/NEJMoa1103799, indexed in Pubmed: 22204725.
22. McCann KE. Novel poly-ADP-ribose polymerase inhibitor combination strategies in ovarian cancer. Curr Opin Obstet Gynecol. 2018; 30(1): 7–16, doi: 10.1097/GCO.0000000000000428, indexed in Pubmed: 29251678.
23. Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. Nat Rev Cancer. 2008; 8(8): 592–603, doi: 10.1038/nrc2442, indexed in Pubmed: 18650835.
24. Chan N, Bristow RG. „Contextual" synthetic lethality and/or loss of heterozygosity: tumor hypoxia and modification of DNA repair. Clin Cancer Res. 2010; 16(18): 4553–4560, doi: 10.1158/1078-0432.CCR-10-0527, indexed in Pubmed: 20823145.
25. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017; 355(6330): 1152–1158, doi: 10.1126/science.aam7344, indexed in Pubmed: 28302823.
26. Pommier Y, O'Connor MJ, de Bono J. Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. Sci Transl Med. 2016; 8(362): 362ps17, doi: 10.1126/scitranslmed.aaf9246, indexed in Pubmed: 27797957.
27. Bindra RS, Crosby ME, Glazer PM. Regulation of DNA repair in hypoxic cancer cells. Cancer Metastasis Rev. 2007; 26(2): 249–260, doi: 10.1007/s10555-007-9061-3, indexed in Pubmed: 17415527.
28. Bindra RS, Schaffer PJ, Meng A, et al. Down-regulation of Rad51 and decreased homologous recombination in hypoxic cancer cells. Mol Cell Biol. 2004; 24(19): 8504–8518, doi: 10.1128/MCB.24.19.8504-8518.2004, indexed in Pubmed: 15367671.
29. Alvarez Secord A, O'Malley DM, Sood AK, et al. Rationale for combination PARP inhibitor and antiangiogenic treatment in advanced epithelial ovarian cancer: A review. Gynecol Oncol. 2021; 162(2): 482–495, doi: 10.1016/j.ygyno.2021.05.018, indexed in Pubmed: 34090705.
30. Lim JJ, Yang K, Taylor-Harding B, et al. VEGFR3 inhibition chemosensitizes ovarian cancer stemlike cells through down-regulation of BRCA1 and BRCA2. Neoplasia. 2014; 16(4): 343–53.e1, doi: 10.1016/j.neo.2014.04.003, indexed in Pubmed: 24862760.
31. Wei W, Li Y, Lv S, et al. PARP-1 may be involved in angiogenesis in epithelial ovarian cancer. Oncol Lett. 2016; 12(6): 4561–4567, doi: 10.3892/ol.2016.5226, indexed in Pubmed: 28101214.
32. Tentori L, Lacal PM, Muzi A, et al. Poly(ADP-ribose) polymerase (PARP) inhibition or PARP-1 gene deletion reduces angiogenesis. Eur J Cancer. 2007; 43(14): 2124–2133, doi: 10.1016/j.ejca.2007.07.010, indexed in Pubmed: 17714938.
33. Genentech I. Highlights of Prescribing Information for Avastin. 2019, 43.
34. Panoilia E, Schindler E, Samantas E, et al. A pharmacokinetic binding model for bevacizumab and VEGF165 in colorectal cancer patients. Cancer Chemother Pharmacol. 2015; 75(4): 791–803, doi: 10.1007/s00280-015-2701-3, indexed in Pubmed: 25687989.
35. Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol. 2014; 15(11): 1207–1214, doi: 10.1016/S1470-2045(14)70391-2, indexed in Pubmed: 25218906.
36. Mirza MR, Åvall Lundqvist E, Birrer MJ, et al. AVANOVA investigators. Niraparib plus bevacizumab versus niraparib alone for platinum--sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. Lancet Oncol. 2019; 20(10): 1409–1419, doi: 10.1016/S1470-2045(19)30515-7, indexed in Pubmed: 31474354.
37. Ray-Coquard I, Pautier P, Pignata S, et al. PAOLA-1 Investigators. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med. 2019; 381(25): 2416–2428, doi: 10.1056/NEJMoa1911361, indexed in Pubmed: 31851799.
38. Colombo N, Moore K, Scambia G, et al. Tolerability of maintenance olaparib in newly diagnosed patients with advanced ovarian cancer and a BRCA mutation in the randomized phase III SOLO1 trial. Gynecol Oncol. 2021; 163(1): 41–49, doi: 10.1016/j.ygyno.2021.07.016, indexed in Pubmed: 34353615.
39. Colombo N, Moore K, Scambia G, et al. Adverse events (AEs) with maintenance olaparib in newly diagnosed patients (pts) with advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): Phase III SOLO1 trial. J Clin Oncol. 2019; 37(15_suppl): 5539–5539, doi: 10.1200/jco.2019.37.15_suppl.5539.
40. LYNPARZA® (Olaparib) [Prescribing Information]. Wilmington, AstraZeneca Pharm. LP; 2022.

41. Ray-Coquard I, Leary A, Pignata S, et al. PAOLA-1/ENGOT-ov25 investigators. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. Ann Oncol. 2023; 34(8): 681–692, doi: 10.1016/j.annonc.2023.05.005, indexed in Pubmed: 37211045.
42. Ray-Coquard IL, Leary A, Pignata S, et al. LBA29 Final overall survival (OS) results from the phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance olaparib (ola) plus bevacizumab (bev) in patients (pts) with newly diagnosed advanced ovarian cancer (AOC). Ann Oncol. 2022; 33: S1396–S1397, doi: 10.1016/j.annonc.2022.08.025.
43. Harter P, Mouret-Reynier MA, Pignata S, et al. Efficacy of maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed, advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. Gynecol Oncol. 2022; 164(2): 254–264, doi: 10.1016/j.ygyno.2021.12.016, indexed in Pubmed: 34952708.
44. Sabatier R, Rousseau F, Joly F, et al. Efficacy and safety of maintenance olaparib and bevacizumab in ovarian cancer patients aged ≥65 years from the PAOLA-1/ENGOT-ov25 trial. Eur J Cancer. 2023; 181: 42–52, doi: 10.1016/j.ejca.2022.11.029, indexed in Pubmed: 36634389.
45. Montégut C, Falandry C, Cinieri S, et al. 167 Safety and quality of life of first-line maintenance olaparib plus bevacizumab in older patients with advanced ovarian cancer in the PAOLA-1 trial. Int J Gynecol Cancer. 2021; 31: A201–A202.
46. Fujiwara K, Fujiwara H, Yoshida H, et al. Olaparib plus bevacizumab as maintenance therapy in patients with newly diagnosed, advanced ovarian cancer: Japan subset from the PAOLA-1/ENGOT-ov25 trial. J Gynecol Oncol. 2021; 32(5): e82, doi: 10.3802/jgo.2021.32.e82, indexed in Pubmed: 34378365.
47. Friedlander M, Lee YC, Tew WP. Managing Adverse Effects Associated With Poly (ADP-ribose) Polymerase Inhibitors in Ovarian Cancer: A Synthesis of Clinical Trial and Real-World Data. Am Soc Clin Oncol Educ Book. 2023; 43: e390876, doi: 10.1200/EDBK_390876, indexed in Pubmed: 37285556.
48. Rolfo C, Isambert N, Italiano A, et al. Pharmacokinetics and safety of olaparib in patients with advanced solid tumours and mild or moderate hepatic impairment. Br J Clin Pharmacol. 2020; 86(9): 1807–1818, doi: 10.1111/bcp.14283, indexed in Pubmed: 32227355.
49. Rolfo C, de Vos-Geelen J, Isambert N, et al. Pharmacokinetics and Safety of Olaparib in Patients with Advanced Solid Tumours and Renal Impairment. Clin Pharmacokinet. 2019; 58(9): 1165–1174, doi: 10.1007/s40262-019-00754-4, indexed in Pubmed: 30877569.
50. Kurtz J, Anota A, Cropet C, et al. Quality of life in patients with advanced high-grade ovarian cancer (HGOC) receiving maintenance therapies after first-line (1L) chemotherapy in the randomized phase III PAOLA-1/ENGOT-ov25 trial (NCT02477644). J Clin Oncol. 2022; 40(16_suppl): 5560–5560, doi: 10.1200/jco.2022.40.16_suppl.5560.
51. Joly F, Chabaud S, Cropet C, et al. Time without symptoms or toxicity (TWiST) in patients with newly diagnosed advanced ovarian cancer receiving maintenance olaparib or placebo plus bevacizumab: Analysis of PAOLA-1/ENGOT-ov25 phase III trial. J Clin Oncol. 2022; 40(16_suppl): 5562–5562, doi: 10.1200/jco.2022.40.16_suppl.5562.