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REVIEW ARTICLE

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Niraparib maintenance in newly diagnosed advanced ovarian cancer — review and case series

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ABSTRACT

Introducing PARP inhibitors maintenance therapy into clinical practice significantly improved treatment outcomes in patients with high-grade platinum-sensitive advanced ovarian cancer, the most lethal gynecological malignancy. Niraparib is a potent PARP inhibitor whose safety and efficacy were assessed in the placebo-controlled, randomized clinical trial PRIMA. Niraparib significantly prolonged progression-free survival in the overall population of high-grade advanced ovarian cancer regardless of BRCA and homologous deficiency status compared to placebo. However, the most significant benefit was observed in *BRCA* mutated and homologous recombination deficient subgroups. Niraparib has a manageable toxicity profile and is well-tolerated by patients. Most common toxicities are hematological and can be managed with drug interruption and dose reduction that do not decrease efficacy. Niraparib is recommended for patients who responded to the first-line chemotherapy with platinum compound regardless of homologous recombination status. This review will discuss the use of niraparib in newly diagnosed advanced ovarian cancer patients focusing on its efficacy and tolerability. Additionally, a case series will be presented to further discuss this drug use in clinical practice in Poland.

Key words: ovarian cancer, maintenance therapy, niraparib, PARP inhibitors, synthetic lethality

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Introduction

Epithelial ovarian cancer is the fifth most common type of cancer in women and the fourth most common cause of cancer death. The estimated number of new ovarian cancer cases worldwide in 2020 was 313 959, with 207 252 deaths. Approximately 30% of cases are diagnosed in Europe [1]. The incidence of ovarian cancer in Poland is about 15% higher than in other European Union countries, with 3 734 cases and 2829 deaths in 2018 [2]. In most cases, diagnosis is made at an advanced stage. High-grade serous ovarian cancer (HGSOC), the most common ovarian cancer subtype, is conventionally treated with surgery and paclitaxel/carboplatin combination chemotherapy [3]. Initial response rates are 60–80%, but eventually, the majority of patients relapse. The addition of a third agent to the adjuvant chemotherapy or the use of high-dose sequential therapies increased the toxicity and did not benefit patients. Second and other lines of chemotherapy consisting of a platinum compound in the case of platinum sensitivity or pegylated liposomal doxorubicin, weekly paclitaxel, gemcitabine, etoposide or topotecan in the case of platinum-refractory or resistant relapse are used in clinical practice but usually with poor outcomes. In this landscape, the innovative maintenance treatment with poly (ADP-ribose) polymerase (PARP) inhibitors demonstrated an outstanding activity in ovarian cancer and changed clinical practice. Niraparib is an orally active small-molecule PARP inhibitor.

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Among 733 patients with newly diagnosed advanced ovarian cancer who had a response to platinum-based chemotherapy, those who received niraparib via participation in the PRIMA trial had significantly longer progression-free survival (PFS) than those who received placebo, regardless of the presence or absence of homologous-recombination deficiency (HRD) although the benefit was more significant in the HRD subgroup [4]. This review will discuss the use of niraparib in newly diagnosed advanced ovarian cancer patients focusing on its efficacy and tolerability. Additionally, a case series will be presented to further discuss this drug use in clinical practice in Poland.

Homologous recombination and PARP inhibitors

Homologous recombination (HR) is one of six main ways in which cells can repair DNA damage and one of two pathways for repairing double-strand DNA breaks (DSBs) [5]. Cells with homologous recombination deficiency (HRD) rely only on the second mechanism, Non-Homologous End Joining (NHEJ), a pathway that is less exact and more mistake prone, which predisposes for tumorigenesis [6]. In approximately 50% of all ovarian cancers, HRD is present due to mutations or epigenetic changes in HR pathway genes. The most common changes responsible for HRD are *BRCA1* and *BRCA2* germline and somatic mutations that can be found in up to 25% of ovarian cancer patients [7, 8]. Additional changes responsible for HRD are alterations in other genes like *PALB2, FANCA, FANCI, FANCL, FANCC, RAD50, RAD51, RAD51C, RAD54L, ATM, ATR, CHEK1*, and *CHEK2* [5]. *BRCA1* and *BRCA2* are the most widely studied genes which, when mutated, increase the risk of developing various cancers, mainly breast cancer (lifetime risk up to 60–85%) but also ovarian, pancreatic and prostate cancer [9]. Ovarian cancer patients with BRCA1 and BRCA 2 mutations often present at an advanced stage and younger age. In this subgroup of patients, good responses to platinum and generally better outcomes are often observed. PARPs are a family of proteins that allow the transfer of ADP-ribose to various target proteins essential for vital cellular processes like proliferation and apoptosis, but not only. PARP-1 and PARP-2 isoforms are best known because of their role in DNA repair by base excision repair (BER) of the single-stranded DNA breaks (SSBs) and nucleotide excision repair (NER) [10–12]. Originally it was believed that PARP inhibition causes accumulation of SSBs which are converted to DSBs that cannot be repaired in the case of HRD and lead to the process called synthetic lethality resulting in cell death [13]. Recently novel models explaining synthetic lethality between PARPis and HRD focusing on PARP1 trapping at DNA damage sites have been proposed [5]. Regardless of an exact mechanism of synthetic lethality relying on PARP inhibition, it is still the only case when this concept was successfully translated into clinical practice.

Clinical efficacy of niraparib

Niraparib is a potent PARP-1 and PARP-2 inhibitor whose efficacy was first observed in BRCA mutated cell lines and in-vivo models [14]. Finally, the effectiveness in newly diagnosed ovarian cancer was confirmed in the pivotal double-blind, placebo-controlled, multicenter phase III trial PRIMA [4]. Patients aged 18 years and older with histologically confirmed advanced ovarian cancer of high-grade serous or endometrioid histology were offered participation in the study. The advanced disease was classified as the International Federation of Gynecology and Obstetrics (FIGO) stage III with visible residual tumor after primary debulking surgery, inoperable stage III disease or any stage IV disease. Patients who received neoadjuvant chemotherapy were not excluded.

All the patients had to receive six to nine cycles of first-line chemotherapy that included platinum compound and resulted in partial or complete response. Tumor samples were evaluated for HRD defined as a deleterious *BRCA* mutation, 42 out of 100 points on the MyChoice Myriad test (calculated by the presence of the loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions) or both.

The trial was conducted in 20 countries at 181 clinical sites. Within 12 weeks after receiving the last cycle of the platinum-based chemotherapy, the patients were randomly assigned in a 2:1 ratio to receive oral niraparib or placebo. Randomization included stratification according to clinical response after first-line platinum-based chemotherapy, receipt of neoadjuvant chemotherapy, and status regarding tumor homologous recombination. Initially, patients were scheduled to receive a fixed dose of 300 mg once daily for 28-day cycles until disease progression or up to 36 months. However, the dose reduction rate due to a treatment-emergent adverse event (TEAE) was 68.9%, and the discontinuation rate due to TEAE was 14.7%, including 3.3% due to thrombocytopenia. Therefore, after analysis of factors predicting the risk of TEAE development, an amendment in the protocol was made to include an individualized starting dose of 200 mg once daily for patients with a baseline body weight of less than 77 kg, a baseline platelet count of less than 150 000/uL, or both. Importantly PFS in patients with dose reductions was consistent with those who remained on the dose of 300 mg [15]. During the trial, computed tomography (CT) or magnetic resonance (MR) imaging was per-

formed to assess progressive disease according to RECIST 1.1 every 12 weeks until treatment discontinuation.

The primary endpoint was PFS in patients who had tumors with HRD and in those in the overall population. Progression-free survival was defined as the time from randomization to the earliest date of objective disease progression on imaging or death from any cause. Overall survival was a key secondary endpoint. In total, 733 patients underwent randomization, and 728 received treatment.

Patient characteristics at baseline were well-balanced between the two trial groups. Of the 733 patients, 373 (50.9%) had tumors with HRD based on myChoice testing, including 223 tumors with *BRCA* mutations.

In the overall population, niraparib treatment significantly prolonged the median duration of PFS to 13.8 months compared to 8.2 months with placebo ($p < 0.001$). Niraparib significantly prolonged the median duration of PFS in the HRD group [21.9 months with niraparib and 10.4 months with placebo ($p < 0.001$)]. Within this population, the median duration of PFS for $BRCA_{mut}$ patients was slightly more prominent compared to patients with HRD but not $BRCA_{mut}$ (Tab. 1). The overall survival data are not mature yet, but the interim analysis showed that niraparib significantly increased the chance for survival of 24 months in the overall population and the HRD group.

Niraparib efficacy was recently confirmed in PRIME trial comparing niraparib maintenance therapy with placebo in a larger population of patients with advanced serous or endometroid high grade ovarian cancer patients that responded to the chemotherapy with platinum. In this study niraparib maintenance significantly prolonged the PFS for the whole population regardless of BRCA status or cytoreductive surgery outcome (24.8 months with niraparib vs. 8.3 months with placebo; $p < 0.001$) [16].

Regarding the combination maintenance therapy of niraparib with bevacizumab, its safety in newly diagnosed advanced ovarian cancer was assessed in the OVARIO study which was a phase II, single-arm, open-label trial that showed promising results and safety profiles consistent with those known from bevacizumab and niraparib monotherapy [17]. The phase III trial, which aims to compare the efficacy of the niraparib monotherapy maintenance with combined niraparib and bevacizumab maintenance therapy in patients with FIGO III/IV (except FIGO stage IIIA2 without nodal involvement) ovarian cancer regardless of BRCA status and debulking surgery outcome, is about to start recruitment (NCT05009082).

Safety and tolerability

In the PRIMA trial, TEAEs, especially of grades 3 and 4, were more frequently reported in the niraparib group compared to placebo, which was consistent with the class effects of PARP inhibitors (Tab. 2).

The most common complaints from the patients were slight nausea, constipation, and fatigue. The most frequent adverse effects of grade 3 and higher were hematological: anemia in 31 % of patients, neutropenia in 12.8%, and thrombocytopenia in 28.7%. Dose reduction due to the TEAEs occurred in 70.9% of patients receiving niraparib, and 12% discontinued the treatment. In the PRIMA trial, there were no treatment-related deaths reported.

Recommendations on ovarian cancer and the use of niraparib in ovarian cancer treatment in Poland

Several guidelines recommend niraparib as a maintenance treatment option for newly diagnosed ovarian cancer. According to National Comprehensive Cancer Network (NCCN), niraparib is a recommended post-primary treatment option in patients with FIGO II–III ovarian cancer with complete response (CR) or partial response (PR) according to RECIST 1.1 after chemother-

Table 1. Efficacy of niraparib in the PRIMA trial

	PFS (months)		HR
	Niraparib (n)	Placebo (n)	
Overall population	13.8 (487)	8.2 (246)	0.62 95% CI, 0.50 to 0.76;
HRD	21.9 (247)	10.4 (126)	0.43 95% CI, 0.31 to 0.59;
$BRCA_{mut}$	22.1 (152)	10.9 (71)	0.40 95% CI, 0.27 to 0.62
HRD but not $BRCA_{mut}$	19.6 (95)	8.2 (55)	0.50 95% CI, 0.31 to 0.83
HRp	8.1 (169)	5.4 (80)	0.68 95% CI, 0.49 to 0.94

CI — confidence interval; HRD — homologous recombination deficiency; $BRCA_{mut}$ — *BRCA mutated*; HR — hazard ratio; HRp — homologous recombination proficiency; N — number of patients; PFS — progression-free survival

Table 2. Treatment-related adverse events of special interest in the PRIMA trial

Adverse Events	Niraparib (n = 484)	Placebo (n = 244)
	n (%)	
Any	478 (98.8%)	224 (91.8)
Grade ≥ 3	341 (70.5)	46 (18.9)
Leading to dose reduction	343 (70.9)	20 (8.2)
Leading to discontinuation	58(12)	6 (2.5)
Adverse events of special interest		
Anemia		
Any grade	307 (63.4)	43 (17.6)
Grade ≥ 3	150 (31.0)	4 (1.6)
Nausea		
Any grade	278 (57.4)	67 (27.5)
Grade ≥ 3	6 (1.2)	2 (0.8)
Thrombocytopenia		
Any grade	222 (45.9)	9 (3.7)
Grade ≥ 3	139 (28.7)	1 (0.4)
Neutropenia		
Any grade	128 (27.5)	16 (6.6)
Grade ≥ 3	62 (12.8)	3 (1.2)

apy with a platinum compound who did not receive bevacizumab regardless of BRCA and HRD status. In patients with BRCA mutation, after treatment with bevacizumab, niraparib is an option if a combination of bevacizumab and olaparib is not available [18]. According to European Society for Medical Oncology (ESMO), niraparib for 36 months is recommended for FIGO III and the IV HRD population with CR or PR after primary chemotherapy without bevacizumab. In the case of negative or unknown HRD status, a decision on niraparib treatment should be made individually as long-term outcome data in this setting are not available [19]. American Society of Clinical Oncology (ASCO) guidelines state that all patients with newly diagnosed stage III–IV high-grade serous or endometrioid epithelial ovarian cancer with CR or PR after first-line platinum-based chemotherapy should be offered maintenance therapy with niraparib while the subgroup of patients with *BRCA1/2* mutations should be treated with olaparib [20].

Since the 1st of January 2022, niraparib has been available in Poland for the patients with advanced (FIGO III and IV) high-grade ovarian or fallopian tube and primary peritoneal cancer irrespective of BRCA or HRD status who responded to platinum-based chemotherapy. Detailed inclusion and exclusion criteria are listed in Table 3. Treatment in a maximal dose of 300 mg daily must be initiated within 12 weeks after the last dose of chemotherapy and can last up to 36 months.

Table 3. Inclusion and exclusion criteria for the niraparib prescription program in Poland

Inclusion criteria	Exclusion criteria
High grade ovarian, fallopian tube or primary peritoneal cancer of stage:	Hypersensitivity to the active substance or to any of the excipients
— FIGO III with *BRCA1/2* mutation regardless of the status of primary debulking surgery	Breastfeeding
or	
— FIGO III after primary debulking surgery	Progresive disease
or	
— FIGO III or IV after neoadjuvant chemotherapy	Persistent grade 3 adverse events
or	
— FIGO IV	Any medical condition making the treatment unfeasible as per physician decision
PR or CR according to RECIST 1.1 after 1st line chemotherapy with platinum	
PS 0–1	
> 18 years old	
Hemoglobin level >/10g/dL	
WBC >/3000/uL	
Platelets >/100 000/uL	
Bilirubin level < 1.5 × UNL (excluding patients with Gilbert syndrome)	
ALT and AST < 2.5 × UNL (< 5 when liver metastasis present)	
Creatinine level < 1.5 × UNL	
Patient is not pregnant	

AST — aspartate transaminase; ALT — alanine transaminase; CR — complete response; FIGO — The International Federation of Gynecology and Obstetrics staging system; PR — partial response; WBC — white blood cells; UNL — upper normal limit

Case series

Before the year 2022, our department was participating in an expanded access program (EAP) offering niraparib to patients with advanced platinum-sensitive ovarian cancer. Inclusion criteria were age 18 and older, diagnosis of advanced high-grade ovarian, fallopian tube or primary peritoneal cancer, PR or CR after first-line platinum-based chemotherapy, ANC ≥ 1500/μL, platelets ≥ 100.000/μL, hemoglobin level ≥ 9 g/dL, sufficient liver and renal function. Exclusion criteria were severe, uncontrolled medical condition, hematological toxicity of grade ≥ 3 lasting for more than four weeks, uncontrolled hypertension, hypersensitivity to the active substance or any of the excipients, diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leucemia (AML), qualification or participation in a clinical trial involving niraparib, pregnancy and breastfeeding.

Between January and April 2021, four patients were enrolled in the program. All patients were diagnosed with advanced high-grade serous ovarian cancer (FIGO IIIA

to FIGO IVB), one was BRCA 1 mutated, and one was diagnosed with HRD. All patients underwent primary cytoreductive surgery and 6 to 8 cycles of adjuvant carboplatin-paclitaxel chemotherapy that resulted in PR or CR. All the patients initiated the niraparib treatment with an individualized starting dose of 200 mg once daily. To avoid nausea, they were instructed to take the medication at bedtime. Two patients underwent dose reduction, one due to grade 2 thrombocytopenia during the first cycle and one due to grade 3 anemia that required blood transfusion after completing the ninth cycle. The last patient also complained of double vision and moderate headaches lasting for a few days. Similar symptoms occurred twice in the past years. The patient underwent a detailed ophthalmologist evaluation that did not reveal the underlying cause. The consulting neurologist ordered a brain MR that did not show any signs of metastasis, bleeding or posterior reversible encephalopathy syndrome (PRES). Double vision resolved without causative treatment during one week break from niraparib. The patient was rechallenged with a reduced dose of 100 mg, and we did not observe the symptoms' recurrence. Our patients were monitored weekly during the first cycle with complete blood count and later on monthly with complete blood count, liver and kidney function and Ca-125 blood tests. CT was performed every 3–6 months. At the time of publication, all of the patients were stable on niraparib treatment (treatment time 16–18 months).

Details on patient characteristics and treatment are listed in Table 4.

Discussion

Along with other PARPi, niraparib has shown a great benefit in patients with advanced ovarian cancer in the first-line maintenance treatment and should be considered in every patient that responded to first-line platinum-based chemotherapy. Niraparib shows a good tolerability profile with patient-reported outcomes. In PRIMA trial there were no decrease in health-related quality-of-life scores, including Functional Assessment of Cancer Therapy — Ovarian Symptom Index (FOSI), EuroQol-5 Dimensions (EQ-5D), and European Organisation for Research and Treatment of Cancer quality of life questionnaire for ovarian cancer patients EORTC-QLQ-C30/OV28 questionnaires [4]. Our experience with niraparib shows excellent tolerability, and our patients did not complain of drug-related symptoms.

The biggest concern during niraparib treatment is hematological toxicity leading to dose reduction. Post-hoc analysis from the preceding NOVA trial assessing the niraparib efficacy in recurrent ovarian cancer showed lower body weight and platelet count as predictive factors for hematologic toxicities and dose reductions. Based on these findings, the PRIMA trial protocol was amended to include individualization of the starting dose. Furthermore, the efficacy was not decreased in the group with an individualized starting dose [21].

Since the introduction of niraprab into the clinical practice, some concerns regarding an increased risk of developing secondary MDS and AML have been discussed but with scarce data. In the PRIMA trial, one patient was diagnosed with MDS in the niraparib group [4]. Beyond the PRIMA trial, cases of AML and MDS were seen in patients receiving niraparib in monotherapy or combined therapy from 0.5 months to more than 4.9 years (in total, 15 cases in 1785 patients). All cases were secondary MDS/AML in patients receiving chemotherapy, including platinum compounds and others resulting in DNA changes [22]. The latest meta-analysis of 28 randomized clinical trials from 2021 showed that PARPi treatment significantly increased the risk of

Table 4. Niraparib EAP patients and treatment characteristics

Age	48	44	64	57
HRD	Yes	No	Yes	No
$BRCA_{mut}$	Yes	No	No	No
FIGO stage	IVA	IIIA	IIIC	IIIC
Surgical intervention	Primary debulking surgery — R1	Primary debulking surgery — R0	Primary debulking surgery — R1	Primary debulking surgery — R1
Chemotherapy	6 cycles of CBDCA + PXL	6 cycles of CBDCA + PXL	8 cycles of CBDCA + PXL	6 cycles of CBDCA + PXL
Starting dose	200 mg	200 mg	200 mg	200 mg
Serious adverse events	Thrombocytopenia G3	No	Anemia G3	No
Dose reduction	Yes	No	Yes	No
Treatment time (months)	19	17	17	16

HRD — homologous recombination deficiency; $BRCA_{mut}$ — *BRCA mutation;* CBDCA — carboplatin; PXL — paclitaxel

developing MDS and AML with an incidence of 0.73% compared to 0.47% in the placebo group [23]. Another concern voiced by the European Medicine Agency (EMA) is the risk of hypertension, as grade 3 or 4 hypertension was reported in 6% of the niraparib group in the PRIMA trial. Therefore, weekly blood pressure monitoring is recommended for the first two months and later monthly for the first year [22].

In our patient, symptoms of double vision raised concerns about PRES syndrome, a rare reversible neurological disorder presenting with rapidly evolving symptoms including headache, seizures, visual disturbance or cortical blindness, with or without hypertension. Its etiology is complex, but it was observed after treatment with many oncological agents like bevacizumab, kinase inhibitors, gemcitabine and cisplatin. When clinically suspected, diagnosis is confirmed by MR. PRES during niraparib treatment was reported in clinical trials and post-marketing sources as early as within the first month. However, the total incidence is expected to be lower than 0.1%, and no patient was diagnosed with PRES in the PRIMA trial [22].

Conflict of interest

Authors declare no conflict of interest.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3): 209–249, doi: 10.3322/caac.21660, indexed in Pubmed: 33538338.
2. Didkowska J, Wojciechowska U, Michalek IM, et al. Cancer incidence and mortality in Poland in 2019. Sci Rep. 2022; 12(1): 10875, doi: 10.1038/s41598-022-14779-6, indexed in Pubmed: 35760845.
3. Ledermann JA, Raja FA, Fotopoulou C, et al. ESMO Guidelines Working Group. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013; 24 Suppl 6: vi24–vi32, doi: 10.1093/annonc/mdt333, indexed in Pubmed: 24078660.
4. 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.
5. 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.
6. Kim H, Ahn S, Kim H, et al. The prevalence of homologous recombination deficiency (HRD) in various solid tumors and the role of HRD as a single biomarker to immune checkpoint inhibitors. J Cancer Res Clin Oncol. 2022; 148(9): 2427–2435, doi: 10.1007/s00432-021-03781-6, indexed in Pubmed: 34510272.
7. Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 2012; 30(21): 2654–2663, doi: 10.1200/JCO.2011.39.8545, indexed in Pubmed: 22711857.
8. Ratajska M, Koczkowska M, Żuk M, et al. Detection of mutations in circulating tumor DNA from patients with ovarian cancer. Oncotarget. 2017; 8(60): 101325–101332, doi: 10.18632/oncotarget.20722, indexed in Pubmed: 29254167.
9. Mavaddat N, Peock S, Frost D, et al. EMBRACE. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst. 2013; 105(11): 812–822, doi: 10.1093/jnci/djt095, indexed in Pubmed: 23628597.
10. Amé JC, Spenlehauer C, Murcia Gde. The PARP superfamily. BioEssays. 2004; 26(8): 882–893, doi: 10.1002/bies.20085.
11. Caldecott KW, Aoufouchi S, Johnson P, et al. XRCC1 polypeptide interacts with DNA polymerase beta and possibly poly (ADP-ribose) polymerase, and DNA ligase III is a novel molecular 'nick-sensor' in vitro. Nucleic Acids Res. 1996; 24(22): 4387–4394, doi: 10.1093/nar/24.22.4387, indexed in Pubmed: 8948628.
12. Flohr C, Bürkle A, Radicella JP, et al. Poly(ADP-ribosyl)ation accelerates DNA repair in a pathway dependent on Cockayne syndrome B protein. Nucleic Acids Res. 2003; 31(18): 5332–5337, doi: 10.1093/nar/gkg715, indexed in Pubmed: 12954769.
13. O'Neil NJ, Bailey ML, Hieter P. Synthetic lethality and cancer. Nat Rev Genet. 2017; 18(10): 613–623, doi: 10.1038/nrg.2017.47, indexed in Pubmed: 28649135.
14. Jones P, Altamura S, Boueres J, et al. Discovery of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (MK-4827): a novel oral poly(ADP-ribose)polymerase (PARP) inhibitor efficacious in BRCA-1 and -2 mutant tumors. J Med Chem. 2009; 52(22): 7170–7185, doi: 10.1021/jm901188v, indexed in Pubmed: 19873981.
15. Berek JS, Matulonis UA, Peen U, et al. Safety and dose modification for patients receiving niraparib. Ann Oncol. 2018; 29(8): 1784–1792, doi: 10.1093/annonc/mdy181, indexed in Pubmed: 29767688.
16. Li N, Zhu J, Yin R, et al. Efficacy and safety of niraparib as maintenance treatment in patients with newly diagnosed advanced ovarian cancer using an individualized starting dose (PRIME Study): A randomized, double-blind, placebo-controlled, phase 3 trial (LBA 5). Gynecologic Oncology. 2022; 166: S50–S51, doi: 10.1016/s0090-8258(22)01298-7.
17. Hardesty M, Krivak T, Wright G, et al. OVARIO phase II trial of combination niraparib plus bevacizumab maintenance therapy in advanced ovarian cancer following first-line platinum-based chemotherapy with bevacizumab. Gynecol Oncol. 2022; 166(2): 219–229, doi: 10.1016/j.ygyno.2022.05.020, indexed in Pubmed: 35690498.
18. https://www.nccn.org/guidelines/guidelines-detail.
19. Colombo N, Ledermann JA. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Updated treatment recommendations for newly diagnosed epithelial ovarian carcinoma from the ESMO Clinical Practice Guidelines. Ann Oncol. 2021; 32(10): 1300–1303, doi: 10.1016/j.annonc.2021.07.004, indexed in Pubmed: 34293462.
20. Tew WP, Lacchetti C, Kohn EC, et al. PARP Inhibitors in the Management of Ovarian Cancer Guideline Expert Panel. PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020; 38(30): 3468–3493, doi: 10.1200/JCO.20.01924, indexed in Pubmed: 32790492.
21. Mirza M, Martin AG, Graybill W, et al. Evaluation of an individualized starting-dose of niraparib in the PRIMA/ENGOT-OV26/GOG-3012 study. J Clin Oncol. 2020; 38(15_suppl): 6050–6050, doi: 10.1200/jco.2020.38.15_suppl.6050.
22. https://www.ema.europa.eu/en/documents/variation-report/zejula-h-c-004249-x-0029-epar-assessment-report-variation_en.pdf.
23. Morice PM, Leary A, Dolladille C, et al. Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database. Lancet Haematol. 2021; 8(2): e122–e134, Erratum in: Lancet Haematol. 2021;8(2): e105, doi: 10.1016/s2352-3026(20)30360-4, indexed in Pubmed: 33347814.