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# Diagnostics and treatment of *BRCA*-associated cancers with olaparib — expert position statement

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## ABSTRACT

Protein products of the *BRCA1* and *BRCA2* genes play a key role in DNA repair processes carried out by homologous recombination. Maintaining the correct double-stranded DNA structure is important for genome stability and preventing cancer transformation, including uncontrolled proliferation of tumor cells. The BRCA1 protein also plays an important role in controlling cell cycle progression and gene expression, including those genes responsible for individual phases of the cell cycle and chromatin remodeling. The BRCA2 protein also participates in modulating the immune response, including that induced in response to the appearance of cells expressing neoantigens. Germline or somatic mutations in the *BRCA1* and *BRCA2* genes may be found in many cancers, including in patients diagnosed with breast, ovarian, prostate, or pancreatic cancers. Detection of mutations is an important predictor of response to chemotherapy based on platinum derivatives or poly-ADP ribose polymerase (PARP) inhibitors. This article discusses the most important aspects of molecular diagnostics and indications for olaparib use in the treatment of breast, ovarian, prostate, or pancreatic cancers.

**Keywords**: *BRCA1*, *BRCA2*, HRD, olaparib, PARP inhibitors, ovarian cancer, breast cancer, prostate cancer, pancreatic cancer

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## Introduction

Hereditary (germinal) mutations, occurring initially in reproductive cells may be inherited by the offspring of carriers and, consequently, can be found in all body cells. Non-hereditary (somatic) mutations are present only in cancer cells, and their formation is related to malignant cell transformation [1]. Deoxyribonucleic acid (DNA) isolated from peripheral blood leukocytes constitutes the biological material used for detecting hereditary mutations. An alternative may be a swab from the oral mucosa, whose use should be considered in patients who received blood product transfusions within 2 months before molecular analysis. It should be remembered that the material for analyses to detect germline mutations cannot be used in diagnostics of somatic mutations, which, as mentioned above, occur only in cancer cell DNA. The use of DNA isolated from tumor cells allows the detection of both somatic and germline mutations but without the possibility of distinguishing between them. Therefore, this type of material cannot be used for properly conducted genetic counseling in individual families.

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The most commonly used material for planned molecular analyses is postoperative tissue. Usually, it is a tissue sample fixed in 10% buffered formalin (pH 7.2–7.4) and embedded in paraffin [formalin-fixed paraffin-embedded (FFPE)] [2, 3]. The fixation time should not be shorter than 6 hours and cannot exceed 48 hours [fixing tissue longer than 48 hours significantly increases the risk of DNA and ribonucleic acid (RNA) degradation, limiting its usefulness for diagnosis of gene mutations]. Molecular analyses are preceded by pathological examination of the sample, which allows for selection of tissue material that will contain a sufficient number of cancer cells, thus ensuring that an appropriate amount of DNA can be obtained. The material is submitted for molecular testing in the form of cut and unstained paraffin sections (FFPE), 5–10 mm thick, with tumor mass and percentage of cancer cells in the selected area marked (on one HE-stained slide) [2, 3]. In the case of next generation sequencing (NGS) tests, the percentage of cancer cells in preparation of tissue material cannot be less than 20% [3]. To detect gene number variation [copy number variations (CNV)] and homologous recombination deficiency (HRD), a higher percentage of cancer cells in the sample is necessary, amounting to at least 30% [3, 4]. If tissue material is unavailable or does not meet quantitative and qualitative criteria, molecular tests can be performed based on liquid biopsy, which involves the analysis of circulating tumor cells (CTC) or free DNA/RNA released into the bloodstream by cancer cells. Currently, extracellular circulating tumor DNA (ctDNA) is routinely used in diagnostics [5–7].

## Genetic testing of mutations in the *BRCA1/2* genes and homologous recombination disorders in BRCA-related cancers

### Ovarian cancer

Mutations in the *BRCA1* and *BRCA2* genes are detected in tumor tissue in approximately 25% of ovarian cancer (OC) patients, with germline mutations and somatic mutations accounting for approximately 14–18% and 3–8% findings, respectively [8–10]. A disadvantage of fixed tissue material (FFPE block) is the inability to assess large genomic rearrangements (LGR), which account for approximately 10% of detected abnormalities. Notably, approximately 44% of OC cancer patients have no positive family history, and 25% of carriers of hereditary mutations in the *BRCA1* and *BRCA2* genes are over 60 years of age at diagnosis. Therefore, risk assessment in hereditary *BRCA1*/*BRCA2* gene mutation carriers is difficult [10–12]. To perform a molecular test, the material obtained during core needle biopsy, diagnostic laparoscopy, or laparotomy is used. The last of these is preferred due to its greater representativeness. Surgical material sampled during interval surgery is also useful [3, 4].

Genetic diagnostics in OC begin with examination of entire coding sequences of the *BRCA1* and *BRCA2* genes using the NGS method. If there are no mutations in the tissue material, the next step is assessing the homologous recombination status, which occurs when the cell is unable to repair double-strand breaks in the DNA structure. It is currently known that impaired repair by homologous recombination is found in approximately 50% of women with high-grade serous OC and may be the result of mutations located in gene sequences other than *BRCA1/2* [13, 14]. If there is no access to tissue material, a test using DNA isolated from peripheral blood leukocytes should be performed to detect hereditary (germinal) *BRCA1*/*BRCA2* mutations [9].

### Breast cancer

About 5–10% of breast cancers develop in patients with a hereditary predisposition. Carriers of germline *BRCA1*/*BRCA2* gene mutations have the highest predisposition to the development of breast cancer. Approximately 5–7% of breast cancer patients are carriers of *BRCA1* and *BRCA2* mutations. The risk of developing breast cancer in this population is increased 10-fold and ranges between 56% and 84% throughout life [15, 16]. Among the mutations found in breast cancer patients, so-called founder mutations can be distinguished. They are variants that originated in a given population several hundred years ago and have become widespread and consolidated. Among all mutations detected in the *BRCA1* and *BRCA2* genes in the Polish population, founder mutations account for 48–75% [17, 18], and major rearrangements may constitute approximately 3–5%.

To perform a molecular test, DNA isolated from peripheral blood leukocytes is used. The test of choice is the NGS of entire coding sequences in the *BRCA1* and *BRCA2* genes. Failure to detect mutations using this method may be an indication in the diagnostic algorithm for testing major rearrangements in the *BRCA1* and *BRCA2* genes using the multiplex ligation-dependent probe amplification (MLPA) method. In the case of genetic counseling, detection of mutations associated with breast cancer begins with assessment of founder mutations. If they are not detected, NGS diagnostics should be continued, assessing the entire coding sequences of the *BRCA1* and *BRCA2* genes.

### Prostate cancer

The frequency of germline and somatic mutations in the *BRCA1* gene in prostate cancer patients is approximately 1%. However, their frequency in the *BRCA2* gene is 6–7% and 5.4%, respectively. The preferred material for *BRCA1/2* mutations testing is tissue material (FFPE block) sampled during prostatectomy. If not available, tissue material from a biopsy can be used. The percentage of cancer cells in tissue material selected by the pathologist for molecular examination should not be less than 20%. If tissue material from the primary tumor cannot be used for quality reasons [e.g. due to inappropriate fixation or a long time that has passed since the start of archiving (>10 years)], a biopsy of metastatic lesions to soft tissue or bone may be considered; however, it is more difficult to obtain DNA of appropriate quantity and quality from bone. An alternative is to perform molecular analyses using ctDNA. It is important to collect blood samples at the time of disease progression or metastasizing, which can help to obtain an adequate amount of ctDNA. Additionally, molecular tests can be performed using DNA isolated from peripheral blood leukocytes, which, however, allows only for the detection of hereditary mutations in the *BRCA1* and *BRCA2* genes, accounting for approximately 50% of all mutations in these genes in prostate cancer patients. It should be remembered that this testing requires a highly sensitive method (at least 0.01%, i.e. one DNA molecule with a mutation per 10000 DNA molecules tested in the sample) because the amount of ctDNA is only a small fraction (0.1–5%) [19–22].

### Pancreatic cancer

In pancreatic cancer, hereditary mutations in the *BRCA1* and *BRCA2* genes occur with a frequency of approximately 1% and 5%, respectively. The method of choice is NGS testing covering all coding sequences of the *BRCA1* and *BRCA2* genes [23, 24]. The material tested is DNA isolated from peripheral blood leukocytes [23, 24].

## Clinical implications of determining *BRCA1* and *BRCA2* gene mutations in selected cancers

### Ovarian cancer

Ovarian cancer is the most common cause of death among gynecological cancers. It is a significant public health problem, ranking very high in terms of morbidity and mortality worldwide [25]. Although over the last 5 decades, there has been an improvement in mortality rates due to solid tumors, this trend does not apply to OC [26]. The lifetime risk of developing OC is approximately 0.7% worldwide in the general population and increases significantly among patients with a familial or genetic predisposition [27]. A family history of OC is one of the most important risk factors. So far, at least 16 genes associated with hereditary OC have been identified, and *BRCA1/2* mutations are considered the main cause of OC development [28]. The risk of OC by the age of 70 is 40–50% for *BRCA1* mutation carriers and 10–20% for *BRCA2* mutation carriers [29, 30]. It is estimated that in the general population one in 300–800 people have a *BRCA1* or *BRCA2* mutation [31]. In turn, between 8% and 15% of women diagnosed with OC have an inherited *BRCA1* or *BRCA2* mutation.

Overall, 70% of OCs are of serous subtype, accounting for 16–21% of *BRCA1* or *BRCA2* mutations [32, 33]. Poorly differentiated OCs are extremely genetically unstable and are characterized by the presence of mutations in the *TP53* gene in 96% of patients, accompanied by impaired function of the *BRCA1*, *BRCA2*, *RAD51C,* and other genes encoding DNA repair proteins [34, 35]. The distribution of molecular abnormalities in poorly differentiated serous OC is shown in Figure 1 [34–36]. Most cases of OC in women with hereditary *BRCA1/2* mutations are poorly differentiated serous carcinomas [37, 38]. This group of cancers also includes tumors without a germline *BRCA1/2* mutation but with somatic mutations

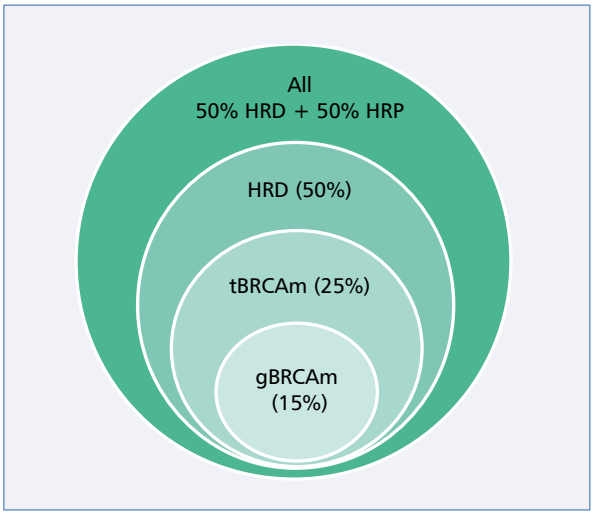



**Figure 1.** Distribution of molecular abnormalities in serous poorly differentiated ovarian cancer (OC); gBRCAm — germline *BRCA* mutation; HRD — homologous recombination deficiency; HRP — homologous recombination proficiency; tBRCAm — *BRCA* mutation present in tumour tissue

or methylation in the *BRCA1*/*BRCA2* genes and other genes related to the homologous recombination pathway, such as *RAD51*, *CHK1*, *CHK2*, *ATM*, *ATR,* and *FANCF* [39–43]. It is worth emphasizing that homologous recombination abnormalities occur in as many as 50% of cases [34].

Previous studies have shown that OCs developing in patients with *BRCA1/2* mutations have different clinical and pathological characteristics. The most important features include a younger age at onset [44], a poorly differentiated serous histological type [37, 38, 45], and an advanced clinical stage at diagnosis. However, what is extremely important, they are associated with a high probability of permanent remission and a better prognosis [46, 47], which results from their greater sensitivity to platinum derivatives and poly-ADP ribose polymerase (PARP) inhibitors. Recent studies have also shown that OCs with *BRCA1/2* mutations develop distant metastases more often than OCs with wild-type *BRCA1/2* [48].

The majority of studies that assessed the relationship between *BRCA1/2* mutations and clinical/pathological features analyzed *BRCA1* and *BRCA2* mutation carriers as one population [47, 49–52]. However, a comparative analysis between patients with *BRCA1* and *BRCA2* mutations was performed in several studies [46, 53–56]. The first studies conducted on relatively small groups of OC patients showed a tendency for a different clinical disease course depending on whether the mutation occurred in the *BRCA1* or *BRCA2* gene [53, 55, 57]. It provided the basis for larger analyses aimed at establishing final conclusions regarding the clinical differences related to *BRCA1* and *BRCA2* mutations in OC. In one of the recently published studies, the authors conducted integrated analyses of multidimensional genomic and clinical data collected as part of The Cancer Genome Atlas (TCGA) project from 316 patients with poorly differentiated serous OC and showed different clinical tumor characteristics depending on the type of mutation (*BRCA1 vs. BRCA2*). Patients with *BRCA1* gene mutations were younger at diagnosis [55.9 *vs.* 61.8 years compared to the wild-type ($p = 0.006$) and 55.9 *vs.* 60.9 years compared to the *BRCA2* mutation ($p = 0.03$)]. All *BRCA2* mutation carriers were sensitive to platinum-based chemotherapy, while in the group of patients with the *BRCA1* mutation, the sensitivity rate was 80% ($p = 0.05$). Progression-free survival (PFS) was also longer in *BRCA2* mutation carriers. The result of this analysis led to the conclusion that OC patients with the *BRCA2* gene mutations show a more pronounced "mutator phenotype", defined as the total number of mutations in the entire exome. Tumors with mutations in the *BRCA1* gene did not show a significant increase in mutations [58].

The results of the quantitative analysis of the relationship between *BRCA1* and *BRCA2* mutations and genomic instability in OC suggest that the protein product of the *BRCA2* gene plays a more important role, compared to *BRCA1*, in the DNA double-strand break repair pathway. Therefore, shutting off *BRCA2* gene activity leads to extensive gene mutations in cancer cells, making them susceptible to DNA-damaging cytostatics. It is important to note that the TCGA dataset provides a more representative range of *BRCA* mutations in the general population than previous studies, given that only 7% of patients in the TCGA dataset are from the Ashkenazi Jewish population [58]. The observational study conducted by Bolton et al. [52] included a total of 3739 patients with OC (909 *BRCA1* mutation carriers, 304 *BRCA2* mutation carriers, and 2666 women without the mutation). The patients came from the USA, Europe, Israel, Hong Kong, Canada, Australia and the UK. It was shown that *BRCA2* mutation carriers had the best prognosis. There was a particularly noticeable trend in 5-year survival, which was 36% for non-carriers, 44% for *BRCA1* mutation carriers, and 52% for *BRCA2* mutation carriers.

The presence of homologous recombination disorders in patients without *BRCA1/2* mutations is also of prognostic importance. The results of many randomized trials show a clear difference in the course of disease and treatment outcomes depending on the status of homologous recombination, with a clear tendency towards a better prognosis in patients with a deficit of this repair mechanism.

Due to significant differences between poorly differentiated serous OCs developing on the basis of molecular abnormalities (germinal and somatic *BRCA1/2* mutations and homologous recombination disorders), compared to patients with a properly functioning homologous recombination repair (HRR) mechanism, treatment in this group of patients should be planned very precisely. The results of recent studies even suggest the possibility of complete recovery in quite a significant percentage of cases in this population [59, 60].

Poly-ADP ribose polymerase inhibitors are particularly effective in the population of patients with the *BRCA1*/2 mutation and other molecular abnormalities that disrupt the DNA repair process by homologous recombination. All published study results demonstrated an improvement in PFS, and in some cases also in overall survival (OS), in patients receiving maintenance therapy based on PARP inhibitors compared to placebo [61–67]. The SOLO1 study was the first randomized clinical trial assessing the effectiveness of olaparib monotherapy as maintenance

treatment in patients with newly diagnosed, advanced, and platinum-sensitive OC with a *BRCA1/2* mutation [61–63]. It included 391 patients with mainly germline *BRCA1/2* mutations, the majority of whom were in clinical stage III (84.6%), after primary cytoreductive surgery (61.9%), without residual disease (78%), with complete radiological response to first-line chemotherapy (81.9%). Patients received olaparib 300 mg twice daily [62, 63]. Three analyses of the study results were performed, after 3, 5, and 7 years. The last analysis was carried out in 2022, and the results were presented at the European Society for Medical Oncology (ESMO) congress [59]. The primary endpoint of the study was PFS. A statistically significant reduction in the risk of progression or death was achieved in the third year of follow-up [by 70%; hazard ratio (HR) = 0.30; $p < 0.001$) [62]. After 5 years, the PFS benefit was maintained (HR = 0.33); 48% of women had no progression or death, and the risk of these events was reduced by 67% [63]. For the first time in the studies using PARP inhibitors in OC, the SOLO1 trial demonstrated a significant clinical benefit from the use of these drugs in terms of OS — median OS was not reached in the olaparib study group. In total, 67% of women in the study group remained alive, as compared to 46.5% in the placebo group, despite the possibility of subsequent use of PARP inhibitors (used by as many as 44.3% of women in the control group). The most common reasons for treatment discontinuation were disease progression (19.6%) and side effects (11.5%). The most frequently observed adverse events (AEs) included gastrointestinal disorders, fatigue, and anemia. After 7 years of observation, the incidence of myelodysplastic syndromes and new cases of malignant tumors remained low, and the incidence was balanced between the analyzed groups. The most important finding from the 7-year observation is the fact that in the study group receiving olaparib, as many as 45.3% of patients did not require any anticancer therapy. The authors concluded that disease in this group of patients could be curable; however, this is still a tentative statement [59].

According to the Summary of Product Characteristics (SmPC), "olaparib as monotherapy is indicated for the maintenance treatment of adult patients with advanced [International Federation of Gynecology and Obstetrics (FIGO) stages III and IV] *BRCA1/2* mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy".

The PAOLA-1/ENGOT-ov45 study is the first trial demonstrating the effectiveness of maintenance therapy based on bevacizumab in combination with olaparib in patients with newly diagnosed, advanced, and platinum-sensitive OC [66]. The study included 806 women with advanced, poorly differentiated, serous, and endometrial OCs, regardless of molecular abnormalities [patients with *BRCA1/2* mutations, HRD, and homologous recombination proficiency (HRP)]. The patients received bevacizumab at a dose of 15 mg/m$^2$ for 15 cycles and olaparib 300 mg twice daily for 2 years. In total 70% of the patients included in the study had clinical stage III disease, 42% received neoadjuvant chemotherapy and 50% had undergone primary cytoreductive surgery. There was no residual disease in 60.1% of patients, with a very good radiological response to treatment [no evidence of disease (NED) + complete response (CR) = 74%]. The results were analyzed after 2 and 5 years of follow-up [60, 66]. The reduction in the risk of progression or death in the 2-year follow-up was 67% for the entire HRD group (HR = 0.33), 68% for women with somatic *BRCA1/2* mutations (HR = 0.31), 56% for the HRD group excluding the *BRCA1/2* mutations (HR = 0.43), and 8% for the HRP population (HR = 0.92). The benefit of such a combined treatment regimen in terms of PFS has been demonstrated for both low-risk patients (in clinical stage III after primary cytoreductive surgery without residual disease, HR = 0.15) and the high-risk recurrence group (patients in clinical stage III, after primary cytoreductive surgery and with residual disease, patients in stage IV, and patients after neoadjuvant chemotherapy, HR = 0.39). After 5 years of follow-up, the previously observed clinical benefit in terms of reducing the risk of progression or death was maintained for the entire HRD group (HR = 0.41); 46.1% of patients had no events compared to the control group, in which only 19.2% of patients lived progression-free. However, after 5 years of follow-up, the most important conclusions concern the clinical benefits in terms of overall survival. It has been shown that the combination of olaparib with bevacizumab as maintenance therapy in patients with advanced OC and homologous recombination disorders brings a clinical benefit in the form of a 5-year survival rate in 65% of patients in the study group compared to 48.4% in the control group (HR = 0.62). Such benefits have not been demonstrated in patients without a DNA repair system deficiency.

Despite the use of combined treatment, no new safety signals were identified. The most common reasons for treatment discontinuation were radiologically confirmed disease progression (34%) and AEs (20%), occurring mainly in older people. The dominant symptoms were fatigue, hypertension, nausea, and hematological disorders. The percentage of myelodysplastic

syndromes as well as new cases of malignant tumors remained low after 5 years; this percentage was similar between analyzed groups. Patients' quality of life during combination therapy with bevacizumab and olaparib was good. During the first 96 weeks of follow-up, the global health score (GHS) did not exceed 10 points in the study group [60, 66]. The results of the PAOLA-1 study show the great importance of personalized medicine, in which detailed analysis of biomarkers has prognostic and predictive value.

According to the SmPC, "olaparib in combination with bevacizumab is indicated for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with HRD 3 positive status defined by either a *BRCA1/2* mutation and/or genomic instability".

The presented clinical trials clearly and unequivocally demonstrate enormous progress that has been made in the treatment of OC in recent years thanks to the introduction of maintenance therapy with PARP inhibitors. Although in most studies a beneficial clinical effect is visible regardless of molecular abnormalities, the greatest benefit from maintenance therapy with PARP inhibitors is observed in patients with OC that developed as a result of *BRCA1/2* mutations and homologous recombination disorders. Therefore, the diagnosis of molecular abnormalities is necessary for proper planning of first-line treatment in patients with advanced OC. Such recommendations are increasingly included in guidelines of scientific societies [68, 69]. A simplified algorithm of molecular diagnostics in newly diagnosed OC is presented in Figure 2.

The first clinical trial assessing the effectiveness of olaparib in patients with platinum-sensitive, poorly differentiated, recurrent OC who achieved a complete or partial response to platinum-based chemotherapy was phase II Study 19 [70]. The study included 265 patients (136 receiving olaparib and 129 receiving placebo). Olaparib was administered until disease progression or unacceptable toxicity. The presence of *BRCA1/2* mutations was assessed retrospectively. The use of olaparib prolonged median PFS in the entire population (8.4 months *vs.* 4.8 months, $p < 0.00001$). In the group of patients with *BRCA1/2* mutations, median PFS was 11.2 months, as compared to 4.3 months in the placebo group ($p < 0.00001$). In the group of patients without mutations, increased mPFS was also observed (7.4 months *vs.* 5.5 months, $p = 0.0075$). There was no significant increase in OS (34.9 months *vs.* 31.9 months, $p = 0.192$). The treatment was well tolerated. A long-term benefit from olaparib was observed: prolonged time to progression (TTP) as well as time to first subsequent therapy or death (TFST) and second subsequent therapy [time to second subsequent therapy (TSST) or death]. In patients with *BRCA1/2* mutations, median TFST was 15.6 months in the olaparib group compared to 6.2 months in the placebo group (HR = 0.32; $p < 0.0001$), and median TSST was 22 months and 15.3 months, respectively (HR = 0.41; $p < 0.0001$). The SOLO2 clinical trial, whose results were published in 2017, included only patients with recurrent, poorly differentiated, serous, or endometroid OCs with a mutation in the *BRCA1/2* genes [71]. The study involved 295 patients (196 patients in the olaparib group and 99 in the placebo group). The median time to progression was longer in the olaparib group (19.1 months compared to 5.5 months in the placebo group; $p < 0.0001$). A significant prolongation of median TFST ($p < 0.0001$), median time to second progression ($p < 0.0002$), and median TSST ($p < 0.0001$) was observed in the group treated with olaparib, compared to the placebo group. Final analyses of the SOLO2 trial showed that the use of olaparib numerically extended overall survival by 12.9 months [72]. Median OS was 57.1 months in the olaparib-treated group and 38.8 months in the placebo group, respectively (HR = 0.74; $p = 0.054$). It should be noted that 38% of patients in the placebo group and 10% in the olaparib group received PARP inhibitors after disease progression.

According to the SmPC, "olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy".

Olaparib is available in Poland under the B.50 Drug Program for patients:

a) with newly diagnosed OC, fallopian tube cancer, or peritoneal cancer in monotherapy (patients with confirmed *BRCA1/2* mutation) or in combination with bevacizumab (patients with mutations in the *BRCA1/2* genes or confirmed HRD), and
b) in the treatment of recurrent OC, fallopian tube cancer, or primary peritoneal cancer in monotherapy in patients with mutations in the *BRCA1/2* genes, after prior use of at least two lines of platinum-based chemotherapy (disease recurrence no earlier than 6 months after platinum-based chemotherapy cessation) (Tab. 1).

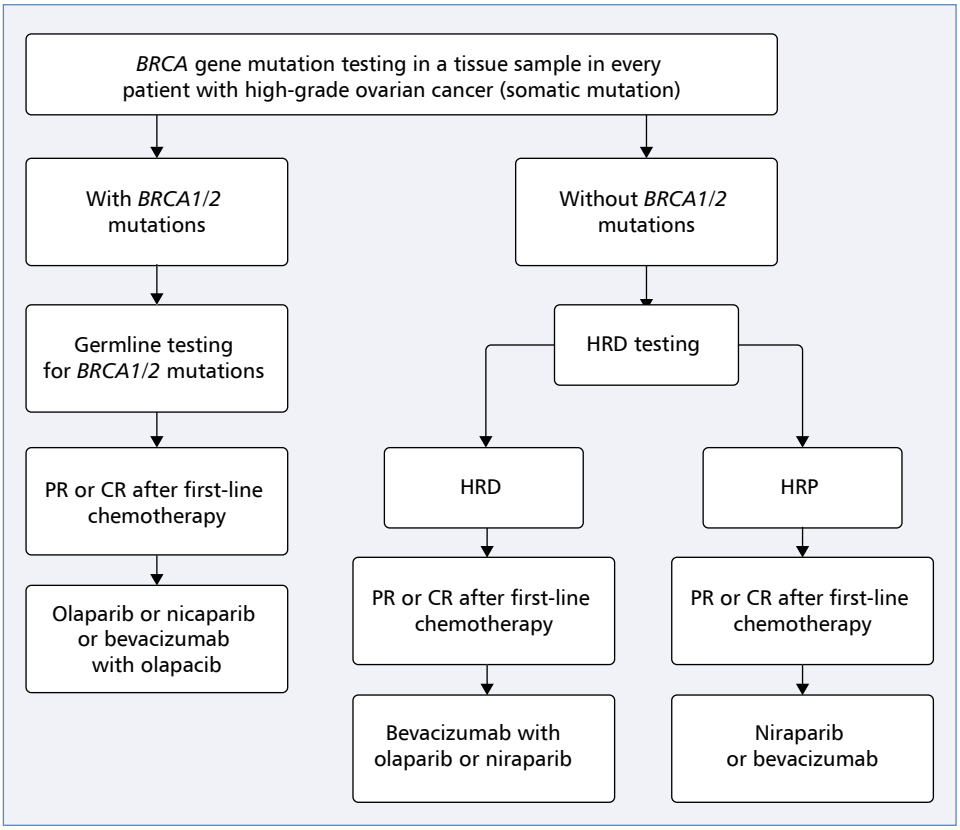



**Figure 2.** Simplified algorithm for molecular diagnostics in newly diagnosed ovarian cancer; CR — complete response; HRD — homologous recombination deficiency; HRP — homologous recombination proficiency; PR — partial response

## Breast cancer

Breast cancer is the most common female cancer in Poland and worldwide. It is the second cause of cancer-related deaths after lung cancer in women. There is a constant increase in the incidence of breast cancer, which is mainly related to environmental factors and changes in women's lifestyles. The vast majority of breast cancers are sporadic, and genetic abnormalities cause the disease in 5–10% of women (most often pathogenic variants in the *BRCA1/2* genes) [73]. These genetic abnormalities are associated with over 60% risk of developing breast cancer, 40–60% risk of OC in patients with *BRCA1* mutation, and 13–30% in patients with *BRCA2* mutation. There is also an increased risk of other neoplasms (melanoma, prostate, and pancreatic cancer). Breast cancer is more often diagnosed at a young age. In women with a mutation in the *BRCA1* gene, the highest risk occurs between the ages of 30 and 40, and in women with the *BRCA2* gene variant, between the ages of 40 and 50. In a significant proportion of patients, these tumors are triple-negative, with a high degree of histological malignancy, and neither estrogen or progesterone receptor expression nor *HER2* gene amplification [74].

Carriers of *BRCA1/2* gene mutations require special multidisciplinary care due to the need for genetic counseling for family members, the possibility of implementing surgical treatment reducing the risk of cancer, the use of bilateral mastectomy in the case of breast cancer diagnosis, the possibility of including targeted systemic treatment into radical therapy and palliative care, as well as fertility protection before oncological treatment or before risk-reducing bilateral salpingo-oophorectomy (RRSO), or using *in vitro* fertilization combined with preimplantation diagnosis.

Reducing costs has significantly improved access to genetic testing (especially — NGS). This resulted in an increased number of patients and their family members who were diagnosed with breast cancer. Recognition of a pathogenic variant in the *BRCA1/2* genes is often the beginning of actions aimed at reducing the risk of cancer or implementing appropriate therapeutic procedures.

*BRCA1/2* genes are involved in the repair of double-strand DNA breaks by homologous recombination. Poly-ADP ribose polymerase inhibitors block the PARP enzyme activity which is responsible for activating alternative pathways for repairing genetic material and protecting the cell against irreversible damage.

**Table 1. The use of olaparib based on the provisions of drug programs**

| | Drug program | Molecular target | Tested material | Method | Indication for treatment with olaparib in the drug program; dosage/duration of treatment in the program |
|---|---|---|---|---|---|
| Ovarian cancer | B.50 | *BRCA1/2* (somatic and/or germline mutations) | Tumor tissue | NGS | **Newly diagnosed advanced ovarian cancer** (stage III–IV according to FIGO) with high grade (G2 or G3), fallopian tube cancer, or primary peritoneal cancer<br>Olaparib given as monotherapy (**maintenance treatment**): daily dose of 600 mg/treatment for 2 years in the case of CR or until progression in the case of PR detected after 2 years of treatment, or:<br>Olaparib in combination with bevacizumab (maintenance treatment): daily dose of olaparib 600 mg + bevacizumab 15 mg/kg body weight (up to 22 cycles)<br>Treatment with olaparib should be initiated no later than 12 weeks after the last dose of chemotherapy<br>Only patients who achieved CR or PR after treatment with platinum-based chemotherapy may be qualified for treatment<br>**Recurrent ovarian cancer**, fallopian tube cancer, or primary peritoneal cancer<br>Olaparib administered as monotherapy (**maintenance treatment**): daily dose of 600 mg/treatment until progression<br>Treatment with olaparib should be initiated no later than 12 weeks after the last dose of chemotherapy<br>Only patients who achieved CR or PR after treatment with the last line of platinum-based chemotherapy may be qualified for treatment |
| | | HRD if no *BRCA1/2* mutations | Tumor tissue | NGS | **Newly diagnosed advanced ovarian cancer** (stage III–IV according to FIGO) with high grade (G2 or G3), fallopian tube cancer, or primary peritoneal cancer, **regardless of residual disease and/or cytoreduction procedure**<br>Daily dose of olaparib 600 mg + bevacizumab 15 mg/kg body weight (up to 22 cycles);<br>Olaparib treatment (**maintenance treatment**): 2 years in the case of CR or until progression in the case of PR diagnosed after 2 years of treatment<br>Treatment with olaparib should be initiated no earlier than 3 weeks after and no later than 12 weeks after the last dose of chemotherapy combined with bevacizumab |
| Breast cancer | B.9 | *BRCA1/2* germline mutations | Blood | NGS | Adjuvant treatment of patients with germline *BRCA1/2* mutations who have hormone-dependent HER2-negative or triple-negative high-risk early breast cancer previously receiving neoadjuvant or adjuvant chemotherapy<br>Second- or third-line treatment of patients with germline *BRCA1/2* mutations after previous hormone therapy with or without CDK4/6 inhibitors in palliative treatment (prior use of 1–2 lines of palliative chemotherapy or perioperative chemotherapy with anthracycline and taxoid and 1 line of palliative chemotherapy is acceptable)<br>First-, second-, or third-line treatment of metastatic or locally advanced triple-negative breast cancer with germline *BRCA 1/2* mutations, when local treatment is ineffective or not feasible; patients must have previously received chemotherapy containing a taxoid or anthracycline<br>For perioperative or palliative treatment, it is acceptable to a prior application of no more than two lines of chemotherapy palliative chemotherapy or perioperative chemotherapy and one line of palliative chemotherapy<br>Recommended maximum daily dose of olaparib: 600 mg/day (daily).<br>It is possible to use olaparib concurrently with hormone therapy |

→

**Table 1.cont. The use of olaparib based on the provisions of drug programs**

| | Drug program | Molecular target | Tested material | Method | Indication for treatment with olaparib in the drug program; dosage/duration of treatment in the program |
|---|---|---|---|---|---|
| Prostatic cancer | B.56 | *BRCA1/2* (somatic and/or germline mutations) | Tumor tissue | NGS; in the case of non-diagnostic tissue or in the absence of tissue — ctDNA | Metastatic castration-resistant prostate cancer (mCRPC)<br>Olaparib administered as monotherapy: daily dose of 600 mg/treatment until progression.<br>Use only in patients previously receiving NHA |
| Pancreatic cancer | B.85 | *BRCA1/2* germline mutation | Blood | NGS<br>or<br>if the test was performed earlier, it is possible to use a test performed using a method other than NGS | Metastatic or locally advanced pancreatic adenocarcinoma<br>Olaparib administered as monotherapy (maintenance therapy): daily dose of 600 mg/treatment until progression<br>Treatment possible in patients with SD, PR, or CR after completion of first-line platinum-based chemotherapy lasting at least 16 weeks<br>Treatment with olaparib should be initiated no later than 8 weeks after the last dose of platinum-based chemotherapy |

CR — complete response; ctDNA — circulating tumor DNA; FIGO — International Federation of Gynecology and Obstetrics; HRD — homologous recombination deficiency; NGS — next generation sequencing; NHA — new hormonal agent; PR — partial response; SD — stable disease

The effectiveness of PARP inhibitors was first shown in patients with metastatic and locally advanced breast cancer and then in patients with early breast cancer with a germline mutation in the *BRCA1/2* genes. The risk of transmitting a germline mutation to offspring is 50%.

Due to the lack of proven effectiveness of PARP inhibitors in patients with breast cancer with a somatic mutation, genetic diagnostics in this area are rarely carried out in daily clinical practice, but also in clinical trials and scientific research. Available data indicate a low frequency of somatic mutations in an unselected population of breast cancer patients [75].

Genetic diagnostics should be performed based on genetic material isolated from peripheral blood cells. It is also possible to use tissue samples while taking into account certain limitations of this procedure. If a genetic variant is detected, it is necessary to confirm the nature of the abnormality (germinal/somatic) in a peripheral blood test. Another serious limitation is the possibility that approximately 10% of genetic variants, such as deletions or duplications, may not be diagnosed in the tumor tissue.

Due to the large diversity of diagnosed variants, genetic diagnostics should be based on next-generation sequencing, taking into account point variants, large rearrangements, deletions and duplications, and, if necessary, it should also be supplemented with analysis using the MLPA technique.

Recommendations on the treatment of breast cancer patients and genetic diagnostics from different scientific societies define the groups that should be tested differently. Experts from the ESMO suggest the following patient populations:

— patients with a family history of breast cancer, OC, pancreatic cancer, and/or prostate cancer with high risk of recurrence or metastasis in multiple relatives;
— patients with a diagnosis of breast cancer before the age of 50;
— patients with a diagnosis of triple-negative breast cancer before the age of 60;
— male patients with a history of OC or cancer of the contralateral breast or breast cancer [76].

The National Comprehensive Cancer Network (NCCN) proposes the following criteria:

— age of breast cancer onset ≤ 50;
— bilateral breast cancer (synchronous or metachronous);
— triple-negative breast cancer at any age;
— patients treated with cyclin-dependent kinase 4 and 6 inhibitors (iCDK4/6), alpelisib with fulvestrant due to advanced disease;
— breast cancer in men;
— lobular cancer and a family history of diffuse gastric cancer [77].

The most important step is to carry out molecular diagnostics immediately after cancer diagnosis, but selection of patients remains to be considered. Contrary to the postulates to diagnose all breast cancer patients, the NCCN recommendations suggest limiting molecular diagnostics to the population at increased risk, which enhances the chance of diagnosing carriers of mutations in genes that increase the risk of developing specific cancers.

Both OlympiAD and EMBRACA studies, with talazoparib and olaparib in the treatment of patients with advanced breast cancer, showed an increase in the time to cancer progression and an improvement in the quality of life as compared to systemic treatment based on investigator decision [7.0 *vs.* 4.2 months; HR = 0.58; 95% confidence interval (CI) 0.43–0.8; $p < 0.001$] and (8.6 *vs.* 5.6 months; HR = 0.54; 95% CI 0.41–0.71; $p < 0.001$). However, those treatments did not extend OS [78, 79].

In breast cancer patients with a high risk of recurrence treated radically, it is necessary to seek therapies that improve their prognosis. In the OlympiA study, patients after surgery, perioperative chemotherapy, and adjuvant radiotherapy were administered olaparib or placebo for one year in combination with hormone therapy and zoledronic acid therapy [80]. There was a statistically significant reduction in the risk of death by approximately 30% (HR = 0.68; 98.5% CI 0.47–0.97; $p = 0.009$) and an improvement in 4-year invasive-disease-free survival (82.7% *vs.* 75.4%; Δ 7.3%; 95% CI 3.0–11.5%) and 4-year distant metastasis-free survival (86.5% *vs.* 79.1%; Δ 7.4%; 95% CI 3.6–11.3%). The benefits of olaparib treatment in the study were confirmed in patients regardless of previous platinum-based therapy based on platinum derivatives (Fig. 3).

Treatment tolerance and duration were similar in both groups. Early treatment discontinuation, including due to disease relapse, was observed in approximately 26% of patients treated with olaparib and in almost 21% of patients receiving placebo. In patients in the experimental arm, the most common grade ≥ 3 AEs were anemia (8.7%), neutropenia (4.8%), leukopenia (3.0%), fatigue (1.8%), and lymphopenia (1.2%). No grade ≥ 3 AEs were observed in the control arm. Fatal heart failure occurred in 1 patient treated with olaparib. Acute myeloid leukemia and OC resulted in death in 2 patients receiving placebo. Serious adverse events of special interest (pneumonia, radiation pneumonitis, myelodysplastic syndrome, acute myeloid leukemia, and others) did not occur more often in the experimental arm than in the control arm [79].

Olaparib is available in Poland from November 1, 2023 under the B.9 Drug Program in accordance with the registration indications for patients with breast cancer with a confirmed germline mutation in the *BRCA1/2* genes, both in adjuvant treatment and in metastatic disease (Tab. 1).

Early NGS diagnostics in patients at risk, genetic counseling, and cascade diagnostics of their family members are basic elements of care for patients diagnosed with early and advanced breast cancer. Therefore, after mutation detection in the blood sample, the patient should be referred to the Genetic Clinic to carry out the family members screening.

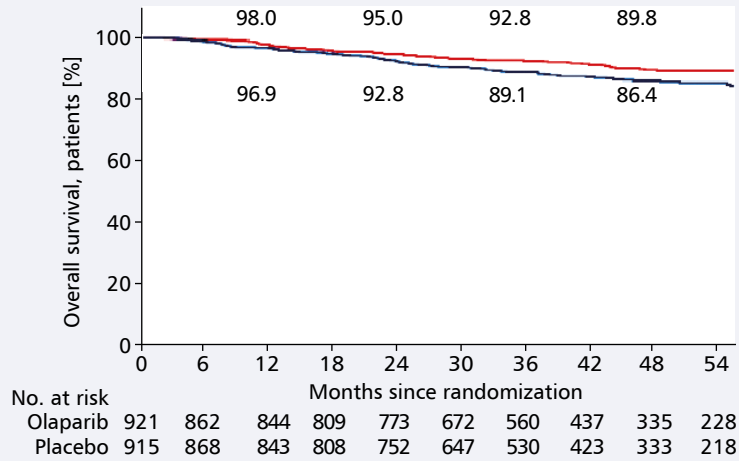
## Prostate cancer

Recommendations for genetic and genomic testing in prostate cancer patients were only introduced in the last two decades, although besides age, a history of advanced prostate cancer and prostate cancer diagnosed at an early age in close family members were recognized as important risk factors a long time ago. In a 2015 publication of the TCGA Research Network, mutations in DNA repair genes were found in 19% of evaluated 333 primary prostate cancers [81]. The next research project done by the Prostate Cancer Foundation/American Association for Cancer Research, based on metastatic tissue biopsies collected from patients with castration-resistant disease, documented about 23% alterations in DNA repair pathway genes, most commonly within the *BRCA2, ATM*, and *BRCA1* genes [82].

Currently tumor-based molecular assays and germline genetic testing according to the NCCN guidelines are recommended as standard procedures for men with family history of first- or second-degree relative with metastatic prostate cancer, OC, breast cancer diagnosed at age ≤ 45 years, colorectal or endometrial cancer at ≤ 50 years, or pancreatic cancer, or two or more first- or second-degree relatives with breast, prostate (no GG1, grade group 1), colorectal, or endometrial cancers at any age [83].

Somatic tumor testing may influence treatment decision-making, including eligibility for biomarker-directed treatments with PARP inhibitors, and it is recommended in all patients with metastatic prostate cancer. Alterations in homologous recombination genes occur early in the tumorigenesis of prostate cancer. At the same time, archival tissue that is used for molecular diagnostics mass degrades over time. Therefore, it is recommended to perform genetic testing on the archival tissue as early as possible.

Confirmatory germline testing may provide information for assessment of the patient's family members' cancer risk. Genomic biomarkers are increasingly used in clinical decision-making in metastatic castration-resistant prostate cancer (mCRPC) patients, but challenges of tissue analysis slow down integration of biomarkers into routine practice. Otherwise, metastatic tissue biopsy is difficult to perform, from the patient's perspective and technical point of view; it also has high failure rates (16–40%), especially in the case of bone lesions. In addition, archival tissues can be difficult to

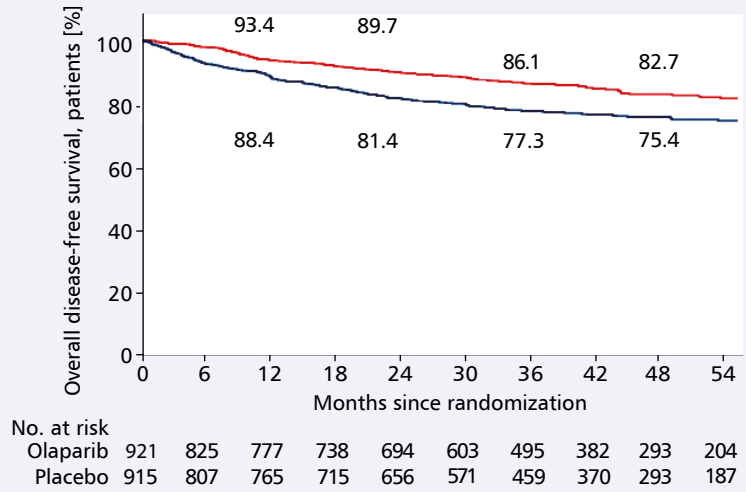



Olaparib: 75 deaths
Placebo: 109 deaths

Difference: 4-year OS rate
3.4% (95% CI –0.1% to 6.8%)

Difference: 3-year OS rate
3.8% (95% CI 0.9% to 6.6%)

Stratified hazard ratio: 0.68
(98.5% CI 0.47–0.97)
p = 0.009

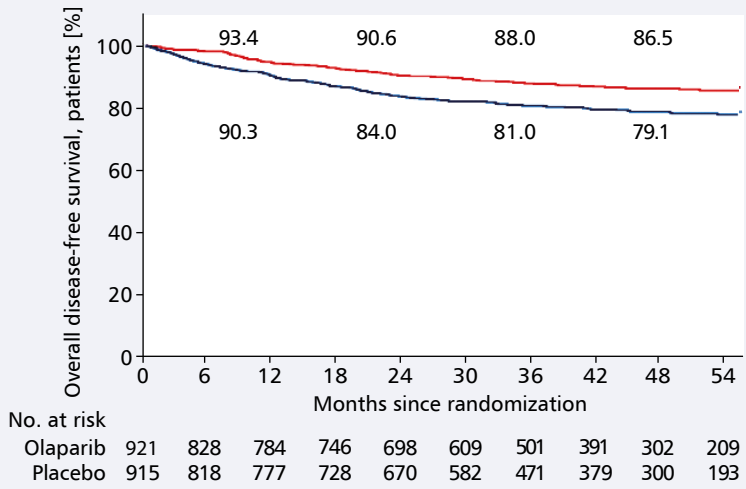



Olaparib: 134 events
Placebo: 207 events

Difference: 4-year IDFS rate
7.3% (95% CI –3.0% to 11.5%)

Difference: 3-year IDFS rate
8.8% (95% CI 5.0% to 12.6%)

Stratified hazard ratio: 0.63
(95% CI 0.50–0.78)




Olaparib: 107 events
Placebo: 172 events

Difference: 4-year DDFS rate
7.4% (95% CI 3.6% to 11.3%)

Difference: 3-year DDFS rate
7.0% (95% CI 3.5% to 10.6%)

Stratitied hazard ratio: 0.61
(95% CI 0.48–0.77)

**Figure 3.** Effect of olaparib therapy on overall survival (OS) (**A**), invasive disease-free survival (IDFS) (**B**), and distant metastasis-free survival (DDFS) (**C**); CI — confidence interval

retrieve and may no longer molecularly reflect contemporaneous mCRPC that has been influenced by previous long-lasting systemic therapy. Plasma ctDNA is a new and established minimally invasive test of predictive and prognostic biomarkers, overcoming many of the limitations of tissue-only testing. So far ctDNA testing, used mostly in clinical trials, can provide easy access to precision oncology since blood samples can be drawn outside specialized cancer treatment centers and sent for centralized testing [84]. However liquid biopsy is a less sensitive technology, and the result of the testing strongly depends on the stage of the disease. So, testing based on liquid biopsy is recommended for patients with disseminated and advanced disease.

Patients with prostate cancer with either somatic or germline pathogenic *BRCA1/2* mutation have an increased risk of higher Gleason grade ≥ 8, T3/T4 stage, nodal involvement, and metastases at initial diagnosis. A more aggressive course of disease leads to shorter cancer-specific survival and metastasis-free survival (MFS) after curative intent therapy, and there is some rationale for intensified early cancer therapy [85, 86].

Poly-ADP ribose polymerase inhibitors are the first targeted drug class developed for metastatic prostate cancer patients. The first drug used was olaparib assessed in the single-arm, phase II, TOPARP-A study, where patients with alterations in DNA damage response genes *BRCA2*, *ATM*, and *BRCA1* achieved significantly higher response rates to olaparib than biomarker-negative patients. In the phase III PROfound study patients with mCRPC harboring DNA repair alterations who had progressed on at least one androgen receptor-pathway inhibitor (ARPi) had improved PFS and OS compared to second ARPi. In the population with *BRCA1/2* mutations, median PFS was 9.79 months for olaparib *vs.* 2.96 months for ARPi (HR = 0.22, 95% CI 0.15–0.32), and median OS was 20.1 months for olaparib *vs.* 14.4 months for ARPi (HR = 0.63 95% CI 0.42–0.95). This led to olaparib being the first Food and Drug Administration (FDA) and European Medicines Agency (EMA) — approved PARP inhibitor for prostate cancer in 2020. Toxicities reported in the PROfound trial were generally consistent with those observed in other olaparib clinical trials, with anemia being the most common AE (50%). Other frequent AEs were fatigue or asthenia (42%) and gastrointestinal toxicities: nausea (43%), decreased appetite (31%), diarrhea (21%), vomiting (20%), and constipation (19%) [87–89].

Currently, multiple phase III studies have investigated the combination of PARPi with ARPi for mCRPC in unselected or genetically selected populations. All results have consistently shown the greatest PARPi benefit in patients whose tumors have germline or somatic DNA damage response defects [90–92].

In Poland, olaparib is reimbursed by the B.56 Drug Program as a treatment option for patients diagnosed with mCRPC who harbor somatic and/or germline mutations in *BRCA1/2* genes and who progressed on new hormonal agent (NHA) (Tab. 1).

## Pancreatic cancer

Pancreatic cancer remains a malignancy with an extremely poor prognosis. Only approximately 20% of patients are diagnosed at an early stage, which allows for surgical treatment and adjuvant systemic therapy. Despite this, most patients experience local recurrence or dissemination of the disease. Median OS, depending on the stage of the disease at diagnosis, ranges from 25–28 months in patients with early cancer to 6–11 months in the group of patients with advanced disease. The 5-year OS rate is 37% and 3% of patients, respectively. This status, which has not changed for years, results, among others, from the limited sensitivity of cancer cells to systemic chemotherapy based mainly on regimens containing 5-fluorouracil, oxaliplatin or irinotecan (FOLFIRINOX, FOLFOX, CAPOX), or gemcitabine administered either as monotherapy or in combination with cisplatin or nab-paclitaxel, as well as from resistance to chemotherapy acquired at relatively early stages of treatment. This results from desmoplastic changes occurring during treatment and surrounding the primary tumor located in the pancreas and modulation of the tumor microenvironment, which, consequently, inhibits the anti-tumor immune response, intensifies neoangiogenesis, and increases the ability of cancer cells to infiltrate surrounding tissues, form distant metastases, and create functional barriers preventing penetration of cytotoxic agents into the tumor [93]. The dynamic development of molecular biology techniques allowed for the detection of several leading mutations during neoplastic transformation in the DNA of pancreatic adenocarcinoma cells, among which the most important mutations are located in the *CDKN2A*, *TP53*, *BRCA1*, *BRCA2*, *ATM,* and *MLH1* genes. In relation to a normal cell, the occurrence of mutations in the genes of the repair system (*BRCA1*, *BRCA2*, *ATM*), whose protein products participate in the removal, by homologous recombination, of double-stranded DNA breaks, leads to the accumulation of abnormalities in cellular DNA and, consequently, cell death [93, 94]. In patients with pancreatic adenocarcinoma, mutations in the *BRCA1* or *BRCA2* genes are found in 0.6% and 1.9% of patients, respectively, and

the frequency of germline mutations is twice (*BRCA1*) or six times higher (*BRCA2*) compared to the general population [95]. In families with a confirmed aggregation of pancreatic adenocarcinoma cases, the frequency of mutations in the *BRCA2* gene is up to 15% [96]. As demonstrated by numerous observations, patients with pancreatic adenocarcinoma with germline mutations in the *BRCA1* or *BRCA2* genes were characterized by longer overall survival as a result of platinum-based chemotherapy compared to patients with normal function of the repair system genes [97]. The explanation for this observation is the inability to remove double-strand breaks from DNA generated by the action of platinum derivatives in patients with impaired function of the protein product of the *BRCA1* or *BRCA2* gene, which results from the presence of a germline mutation in these genes. Therefore, the use of PARP inhibitors in patients with mutations in the *BRCA1* or *BRCA2* genes led to increased destruction of cancer cells.

The clinical effect and safety of olaparib in maintenance treatment in patients with advanced pancreatic adenocarcinoma were assessed in the POLO study [93]. This study included patients diagnosed with advanced pancreatic adenocarcinoma with a germline mutation in the *BRCA1* or *BRCA2* genes, achieving at least disease stabilization after platinum-based first-line chemotherapy lasting at least 16 weeks. In total, the study included 154 patients who were randomized in a 3:2 ratio to the group receiving oral olaparib at a dose of 300 mg twice daily or to the control arm with placebo. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint of the study was PFS prolongation as assessed by an independent committee, and secondary endpoints included OS and PFS prolongation in the investigator's assessment, response rate, and disease control rate. Moreover, this study assessed the safety of therapy and its impact on patients' quality of life. In total, 72.6% of patients included in the study had a germline mutation in the *BRCA2* gene, and the median duration of first-line chemotherapy before enrollment was 5 months in the olaparib arm and 5.1 months in the placebo arm. The most frequently used chemotherapy regimen was FOLFIRINOX or its modifications, administered in 87% of patients receiving olaparib maintenance therapy and 81% of patients receiving placebo. Data analysis presented in 2019 showed a statistically significant extension of median PFS (7.4 *vs.* 3.8 months) and a 47% reduction in the risk of cancer progression (HR = 0.53; p = 0.004) as a result of the use of maintenance therapy with Olaparib. Moreover, in the olaparib arm, there was an increase in the percentage of patients remaining progression-free at follow-up after 6, 12, 18, and 24 months (53% *vs.* 23%, 33.7% *vs.* 14.5%, 27.6% *vs.* 9.6%, and 22.1% *vs.* 9.6%, respectively) [98]. Subgroup analysis showed a consistent clinical benefit from olaparib maintenance therapy in all analyzed subgroups; however, it should be remembered that the statistical power of the study was insufficient to demonstrate differences between individual subgroups. However, this study did not show the impact of the analyzed therapy on overall survival. The results of the next interim analysis presented in 2022 confirmed previous observations — median OS in the olaparib or placebo arms was 19.2 and 19.0 months, respectively (HR = 0.83; p = 0.3487). It should be remembered, however, that 26% of patients in the placebo arm received olaparib and subsequent lines of treatment upon disease progression, which may have significantly affected the final OS outcomes. Analysis of median times to start the first and subsequent treatment lines (median TFST 9.0 *vs.* 5.4 months; HR = 0.44; p < 0.0001), second and subsequent treatment lines (median TSST 14.9 *vs.* 9.6 months; HR = 0.61; p = 0.0111), or median times to treatment completion or death due to cancer (HR = 0.43; p < 0.0001) indicated a significant benefit from maintenance therapy with a PARP inhibitor [99]. Importantly, 20% of patients receiving olaparib as maintenance therapy did not require another treatment line during the 3-year follow-up. A similar observation occurred only in 3.6% of patients receiving placebo [100]. The analysis of treatment toxicity and safety showed good tolerance, with only 5% of patients requiring early treatment discontinuation due to toxicity. The main grade 3 AEs reported in the study were anemia (12.2%), fatigue (5.6%), abdominal pain (3.3%), vomiting (2.2%), and nausea, diarrhea, and joint pain observed in approximately 1% of patients receiving olaparib [100]. It is also worth emphasizing the lack of impact of olaparib therapy on patients' quality of life.

Olaparib has been available in Poland since November 1, 2022 under the B85 Drug Program for patients with locally advanced and metastatic pancreatic adenocarcinoma. According to the current provisions of the program, in patients qualified for maintenance therapy with olaparib, the presence of a pathogenic or probably pathogenic germline mutation in the *BRCA1* or *BRCA2* gene should be demonstrated, based on the NGS technique. The program provisions also allow for the use of previous results, confirming the presence of mutations based on techniques other than NGS (Tab. 1). Taking into account the dynamic course of the disease and its poor prognosis, genetic analyses should be performed at the stage of cancer diagnostics.

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### Author contributions

All authors contributed equally to the article.

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### Supplementary material

None.

## References

1. Hennessy BTJ, Timms KM, Carey MS, et al. Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. J Clin Oncol. 2010; 28(22): 3570–3576, doi: 10.1200/JCO.2009.27.2997, indexed in Pubmed: 20606085.
2. Capoluongo E, Ellison G, López-Guerrero JA, et al. Guidance Statement On BRCA1/2 Tumor Testing in Ovarian Cancer Patients. Semin Oncol. 2017; 44(3): 187–197, doi: 10.1053/j.seminoncol.2017.08.004, indexed in Pubmed: 29248130.
3. Grafodatskaya D, O'Rielly DD, Bedard K, et al. Practice guidelines for tumour testing in ovarian cancer. J Med Genet. 2022; 59(8): 727–736, doi: 10.1136/jmedgenet-2021-108238, indexed in Pubmed: 35393334.
4. van Dijk EL, Jaszczyszyn Y, Thermes C. Library preparation methods for next-generation sequencing: tone down the bias. Exp Cell Res. 2014; 322(1): 12–20, doi: 10.1016/j.yexcr.2014.01.008, indexed in Pubmed: 24440557.
5. Corcoran RB, Chabner BA. Application of Cell-free DNA Analysis to Cancer Treatment. N Engl J Med. 2018; 379(18): 1754–1765, doi: 10.1056/NEJMra1706174, indexed in Pubmed: 30380390.
6. Pantel K, Alix-Panabières C. Liquid biopsy and minimal residual disease - latest advances and implications for cure. Nat Rev Clin Oncol. 2019; 16(7): 409–424, doi: 10.1038/s41571-019-0187-3, indexed in Pubmed: 30796368.
7. Kowalik A, Kowalewska M, Góźdź S. Current approaches for avoiding the limitations of circulating tumor cells detection methods-implications for diagnosis and treatment of patients with solid tumors. Transl Res. 2017; 185: 58–84.e15, doi: 10.1016/j.trsl.2017.04.002, indexed in Pubmed: 28506696.
8. Chandrasekaran D, Sobocan M, Blyuss O, et al. Implementation of Multigene Germline and Parallel Somatic Genetic Testing in Epithelial Ovarian Cancer: SIGNPOST Study. Cancers (Basel). 2021; 13(17), doi: 10.3390/cancers13174344, indexed in Pubmed: 34503154.
9. Kowalik A, Zalewski K, Kopczyński J, et al. Somatic mutations in BRCA1&2 in 201 unselected ovarian carcinoma samples - single institution study. Pol J Pathol. 2019; 70(2): 115–126, doi: 10.5114/pjp.2019.82905, indexed in Pubmed: 31556562.
10. Pennington KP, Walsh T, Harrell MI, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res. 2014; 20(3): 764–775, doi: 10.1158/1078-0432.CCR-13-2287, indexed in Pubmed: 24240112.
11. 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.
12. Mavaddat N, Barrowdale D, Andrulis I, et al. Pathology of Breast and Ovarian Cancers among *BRCA1* and *BRCA2* Mutation Carriers: Results from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA). Cancer Epidemiol Biomarkers Prev. 2012; 21(1): 134–147, doi: 10.1158/1055-9965.epi-11-0775, indexed in Pubmed: 22144499.
13. Wen H, Feng Z, Ma Y, et al. Homologous recombination deficiency in diverse cancer types and its correlation with platinum chemotherapy efficiency in ovarian cancer. BMC Cancer. 2022; 22(1): 550, doi: 10.1186/s12885-022-09602-4, indexed in Pubmed: 35578198.
14. Miller RE, Leary A, Scott CL, et al. ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. Ann Oncol. 2020; 31(12): 1606–1622, doi: 10.1016/j.annonc.2020.08.2102, indexed in Pubmed: 33004253.
15. Davies H, Glodzik D, Morganella S, et al. HRDetect is a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures. Nat Med. 2017; 23(4): 517–525, doi: 10.1038/nm.4292, indexed in Pubmed: 28288110.
16. Winter C, Nilsson MP, Olsson E, et al. Targeted sequencing of BRCA1 and BRCA2 across a large unselected breast cancer cohort suggests that one-third of mutations are somatic. Ann Oncol. 2016; 27(8): 1532–1538, doi: 10.1093/annonc/mdw209, indexed in Pubmed: 27194814.
17. Kowalik A, Siołek M, Kopczyński J, et al. BRCA1 founder mutations and beyond in the Polish population: A single-institution BRCA1/2 next-generation sequencing study. PLoS One. 2018; 13(7): e0201086, doi: 10.1371/journal.pone.0201086, indexed in Pubmed: 30040829.
18. Wojcik P, Jasiowka M, Strycharz E, et al. Recurrent mutations of BRCA1, BRCA2 and PALB2 in the population of breast and ovarian cancer patients in Southern Poland. Hered Cancer Clin Pract. 2016; 14: 5, doi: 10.1186/s13053-016-0046-5, indexed in Pubmed: 26843898.
19. Gonzalez D, Mateo J, Stenzinger A, et al. Practical considerations for optimising homologous recombination repair mutation testing in patients with metastatic prostate cancer. J Pathol Clin Res. 2021; 7(4): 311–325, doi: 10.1002/cjp2.203, indexed in Pubmed: 33630412.
20. Chi KN, Barnicle A, Sibilla C, et al. Detection of BRCA1, BRCA2, and ATM Alterations in Matched Tumor Tissue and Circulating Tumor DNA in Patients with Prostate Cancer Screened in PROfound. Clin Cancer Res. 2023; 29(1): 81–91, doi: 10.1158/1078-0432.CCR-22-0931, indexed in Pubmed: 36043882.
21. Matsubara N, de Bono J, Olmos D, et al. Olaparib Efficacy in Patients with Metastatic Castration-resistant Prostate Cancer and BRCA1, BRCA2, or ATM Alterations Identified by Testing Circulating Tumor DNA. Clin Cancer Res. 2023; 29(1): 92–99, doi: 10.1158/1078-0432.CCR-21-3577, indexed in Pubmed: 36318705.
22. Hiemenz MC, Graf RP, Schiavone K, et al. Real-World Comprehensive Genomic Profiling Success Rates in Tissue and Liquid Prostate Carcinoma Specimens. Oncologist. 2022; 27(12): e970–e972, doi: 10.1093/oncolo/oyac181, indexed in Pubmed: 36069892.
23. Wong W, Raufi AG, Safyan RA, et al. BRCA Mutations in Pancreas Cancer: Spectrum, Current Management, Challenges and Future Prospects. Cancer Manag Res. 2020; 12: 2731–2742, doi: 10.2147/CMAR.S211151, indexed in Pubmed: 32368150.
24. Vietri MT, D'Elia G, Caliendo G, et al. Pancreatic Cancer with Mutation in BRCA1/2, MLH1, and APC Genes: Phenotype Correlation and Detection of a Novel Germline BRCA2 Mutation. Genes (Basel). 2022; 13(2), doi: 10.3390/genes13020321, indexed in Pubmed: 35205366.
25. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019; 69(1): 7–34, doi: 10.3322/caac.21551, indexed in Pubmed: 30620402.
26. Lisio MA, Fu L, Goyeneche A, et al. High-Grade Serous Ovarian Cancer: Basic Sciences, Clinical and Therapeutic Standpoints. Int J Mol Sci. 2019; 20(4), doi: 10.3390/ijms20040952, indexed in Pubmed: 30813239.

27. Control U. Epithelial ovarian cancer. Rev Cancer Med WHO Lists Essent Med. 2014; 42(2010): 1–9.
28. Pennington KP, Swisher EM. Hereditary ovarian cancer: beyond the usual suspects. Gynecol Oncol. 2012; 124(2): 347–353, doi: 10.1016/j.ygyno.2011.12.415, indexed in Pubmed: 22264603.
29. King MC, Marks JH, Mandell JB, et al. New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003; 302(5645): 643–646, doi: 10.1126/science.1088759, indexed in Pubmed: 14576434.
30. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007; 25(11): 1329–1333, doi: 10.1200/JCO.2006.09.1066, indexed in Pubmed: 17416853.
31. Whittemore AS, Gong G, Itnyre J. Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: results from three U.S. population-based case-control studies of ovarian cancer. Am J Hum Genet. 1997; 60(3): 496–504, indexed in Pubmed: 9042908.
32. Risch HA, McLaughlin JR, Cole DE, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet. 2001; 68(3): 700–710, doi: 10.1086/318787, indexed in Pubmed: 11179017.
33. Pal T, Permuth-Wey J, Betts JA, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer. 2005; 104(12): 2807–2816, doi: 10.1002/cncr.21536, indexed in Pubmed: 16284991.
34. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011; 474(7353): 609–615, doi: 10.1038/nature10166, indexed in Pubmed: 21720365.
35. Bowtell DDL. The genesis and evolution of high-grade serous ovarian cancer. Nat Rev Cancer. 2010; 10(11): 803–808, doi: 10.1038/nrc2946, indexed in Pubmed: 20944665.
36. Abkevich V, Timms KM, Hennessy BT, et al. Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer. Br J Cancer. 2012; 107(10): 1776–1782, doi: 10.1038/bjc.2012.451, indexed in Pubmed: 23047548.
37. Gilks CB, Prat J. Ovarian carcinoma pathology and genetics: recent advances. Hum Pathol. 2009; 40(9): 1213–1223, doi: 10.1016/j.humpath.2009.04.017, indexed in Pubmed: 19552940.
38. Piek JMJ, Torrenga B, Hermsen B, et al. Histopathological characteristics of BRCA1- and BRCA2-associated intraperitoneal cancer: a clinic-based study. Fam Cancer. 2003; 2(2): 73–78, doi: 10.1023/a:1025700807451, indexed in Pubmed: 14574155.
39. Geisler JP, Hatterman-Zogg MA, Rathe JA, et al. Frequency of BRCA1 dysfunction in ovarian cancer. J Natl Cancer Inst. 2002; 94(1): 61–67, doi: 10.1093/jnci/94.1.61, indexed in Pubmed: 11773283.
40. Hilton JL, Geisler JP, Rathe JA, et al. Inactivation of BRCA1 and BRCA2 in ovarian cancer. J Natl Cancer Inst. 2002; 94(18): 1396–1406, doi: 10.1093/jnci/94.18.1396, indexed in Pubmed: 12237285.
41. Lim SL, Smith P, Syed N, et al. Promoter hypermethylation of FANCF and outcome in advanced ovarian cancer. Br J Cancer. 2008; 98(8): 1452–1456, doi: 10.1038/sj.bjc.6604325, indexed in Pubmed: 18414472.
42. Wang Z, Li M, Lu S, et al. Promoter hypermethylation of FANCF plays an important role in the occurrence of ovarian cancer through disrupting Fanconi anemia-BRCA pathway. Cancer Biol Ther. 2006; 5(3): 256–260, doi: 10.4161/cbt.5.3.2380, indexed in Pubmed: 16418574.
43. D'Andrea AD. The Fanconi Anemia/BRCA signaling pathway: disruption in cisplatin-sensitive ovarian cancers. Cell Cycle. 2003; 2(4): 290–292, indexed in Pubmed: 12851475.
44. Soegaard M, Kjaer SK, Cox M, et al. BRCA1 and BRCA2 mutation prevalence and clinical characteristics of a population-based series of ovarian cancer cases from Denmark. Clin Cancer Res. 2008; 14(12): 3761–3767, doi: 10.1158/1078-0432.CCR-07-4806, indexed in Pubmed: 18559594.
45. Shaw PA, McLaughlin JR, Zweemer RP, et al. Histopathologic features of genetically determined ovarian cancer. Int J Gynecol Pathol. 2002; 21(4): 407–411, doi: 10.1097/00004347-200210000-00011, indexed in Pubmed: 12352190.
46. Vencken PM, Kriege M, Hoogwerf D, et al. Chemosensitivity and outcome of BRCA1- and BRCA2-associated ovarian cancer patients after first-line chemotherapy compared with sporadic ovarian cancer patients. Ann Oncol. 2011; 22(6): 1346–1352, doi: 10.1093/annonc/mdq628, indexed in Pubmed: 21228333.
47. Gallagher DJ, Konner JA, Bell-McGuinn KM, et al. Survival in epithelial ovarian cancer: a multivariate analysis incorporating BRCA mutation status and platinum sensitivity. Ann Oncol. 2011; 22(5): 1127–1132, doi: 10.1093/annonc/mdq577, indexed in Pubmed: 21084428.
48. Gourley C, Michie CO, Roxburgh P, et al. Increased incidence of visceral metastases in scottish patients with BRCA1/2-defective ovarian cancer: an extension of the ovarian BRCAness phenotype. J Clin Oncol. 2010; 28(15): 2505–2511, doi: 10.1200/JCO.2009.25.1082, indexed in Pubmed: 20406939.
49. Hyman DM, Zhou Q, Iasonos A, et al. Improved survival for BRCA2-associated serous ovarian cancer compared with both BRCA-negative and BRCA1-associated serous ovarian cancer. Cancer. 2012; 118(15): 3703–3709, doi: 10.1002/cncr.26655, indexed in Pubmed: 22139894.
50. Bolton KL, Chenevix-Trench G, Goh C, et al. EMBRACE, kConFab Investigators, Cancer Genome Atlas Research Network. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA. 2012; 307(4): 382–390, doi: 10.1001/jama.2012.20, indexed in Pubmed: 22274685.
51. Liu J, Cristea MC, Frankel P, et al. Clinical characteristics and outcomes of BRCA-associated ovarian cancer: genotype and survival. Cancer Genet. 2012; 205(1-2): 34–41, doi: 10.1016/j.cancergen.2012.01.008, indexed in Pubmed: 22429596.
52. Reitsma W, de Bock GH, Oosterwijk JC, et al. Clinicopathologic characteristics and survival in BRCA1- and BRCA2-related adnexal cancer: are they different? Int J Gynecol Cancer. 2012; 22(4): 579–585, doi: 10.1097/IGC.0b013e31823d1b5c, indexed in Pubmed: 22274543.
53. Cass I, Baldwin RL, Varkey T, et al. Improved survival in women with BRCA-associated ovarian carcinoma. Cancer. 2003; 97(9): 2187–2195, doi: 10.1002/cncr.11310, indexed in Pubmed: 12712470.
54. Lacour RA, Westin SN, Meyer LA, et al. Improved survival in non-Ashkenazi Jewish ovarian cancer patients with BRCA1 and BRCA2 gene mutations. Gynecol Oncol. 2011; 121(2): 358–363, doi: 10.1016/j.ygyno.2010.12.354, indexed in Pubmed: 21276604.
55. Pal T, Permuth-Wey J, Kapoor R, et al. Improved survival in BRCA2 carriers with ovarian cancer. Fam Cancer. 2007; 6(1): 113–119, doi: 10.1007/s10689-006-9112-x, indexed in Pubmed: 17160431.
56. Pharoah PD, Easton DF, Stockton DL, et al. Survival in familial, BRCA1--associated, and BRCA2-associated epithelial ovarian cancer. United Kingdom Coordinating Committee for earch (UKCCCR) Familial Ovarian Cancer Study Group. Cancer Res. 1999; 59(4): 868–871, indexed in Pubmed: 10029077.
57. Chetrit A, Hirsh-Yechezkel G, Ben-David Y, et al. Effect of BRCA1/2 mutations on long-term survival of patients with invasive ovarian cancer: the national Israeli study of ovarian cancer. J Clin Oncol. 2008; 26(1): 20–25, doi: 10.1200/JCO.2007.11.6905, indexed in Pubmed: 18165636.
58. Yang Da, Khan S, Sun Y, et al. Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. JAMA. 2011; 306(14): 1557–1565, doi: 10.1001/jama.2011.1456, indexed in Pubmed: 21990299.
59. DiSilvestro P, Banerjee S, Colombo N, et al. Overall survival at 7-year follow up in patients with newly diagnosed advanced ovarian cancer and BRCA mutation who received maintenance Olaparib in the SOLO1/GOG 3004 trial. ESMO Congress Paris, 2022.
60. Ray-Coquard IL, Leary A, Pignata S, et al. Final overall survival results from the phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance Olaparib plus bevacizumab in patients with newly diagnosed advanced ovarian cancer. ESMO Congress Paris, 2022.
61. 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.
62. 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.
63. Bradley W, Moore K, Colombo N, et al. Maintenance olaparib for patients with newly diagnosed, advanced ovarian cancer and a BRCA mutation: 5-year follow-up from SOLO1. Gynecol Oncol. 2021; 162: S25–S26, doi: 10.1016/s0090-8258(21)00694-6.
64. 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). Gynecol Oncol. 2022; 166: S50–S51, doi: 10.1016/s0090-8258(22)01298-7.
65. 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.
66. 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.

67. Monk BJ, Parkinson C, Lim MC, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/ /GOG-3020/ENGOT-ov45). J Clin Oncol. 2022; 40(34): 3952–3964, doi: 10.1200/JCO.22.01003, indexed in Pubmed: 35658487.
68. Gonzalez-Martin A, Harter A, Leary D, et al. Newly diagnose and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow up. Annnc2023.07.011.
69. Vergote I, González-Martín A, Ray-Coquard I, et al. European experts' consensus group. European experts consensus: BRCA/homologous recombination deficiency testing in first-line ovarian cancer. Ann Oncol. 2022; 33(3): 276–287, doi: 10.1016/j.annonc.2021.11.013, indexed in Pubmed: 34861371.
70. 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. Lancet Oncol. 2014; 15(8): 852–861, doi: 10.1016/S1470-2045(14)70228-1, indexed in Pubmed: 24882434.
71. Pujade-Lauraine E, Ledermann JA, Selle FI, et al. Olaprib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21); a double-blind, randomized, placebo-controlled, phase 3 trial. Lancet Oncol. 2017; 18: 1274–1284, doi: 10.1016/S1470-2045(17)30469-2, indexed in Pubmed: 28754483.
72. Poveda A, Floquet A, Ledermann JA, 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 final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2021; 22(5): 620–631, doi: 10.1016/S1470-2045(21)00073-5, indexed in Pubmed: 33743851.
73. Budny A, Starosławska E, Budny B, et al. [Epidemiology and diagnosis of breast cancer]. Pol Merkur Lekarski. 2019; 46(275): 195–204, indexed in Pubmed: 31152530.
74. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. BRCA1 and BRCA2 Cohort Consortium. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017; 317(23): 2402–2416, doi: 10.1001/jama.2017.7112, indexed in Pubmed: 28632866.
75. Cortesi L, Rugo HS, Jackisch C. An Overview of PARP Inhibitors for the Treatment of Breast Cancer. Target Oncol. 2021; 16(3): 255–282, doi: 10.1007/s11523-021-00796-4, indexed in Pubmed: 33710534.
76. Cardoso F, Kyriakides S, Ohno S, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2019; 30(8): 1194–1220; Erratum in: Ann Oncol. 2021;32(2): 284, doi: 10.1093/annonc/mdz173, indexed in Pubmed: 31161190.
77. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf.
78. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018; 379(8): 753–763, doi: 10.1056/NEJMoa1802905, indexed in Pubmed: 30110579.
79. Tutt ANJ, Garber JE, Kaufman B, et al. OlympiA Clinical Trial Steering Committee and Investigators. Adjuvant Olaparib for Patients with - or -Mutated Breast Cancer. N Engl J Med. 2021; 384(25): 2394–2405, doi: 10.1056/NEJMoa2105215, indexed in Pubmed: 34081848.
80. Geyer CE, Garber JE, Gelber RD, et al. OlympiA Clinical Trial Steering Committee and Investigators. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. Ann Oncol. 2022; 33(12): 1250–1268, doi: 10.1016/j.annonc.2022.09.159, indexed in Pubmed: 36228963.
81. Abeshouse A, Ahn J, Akbani R, et al. The Molecular Taxonomy of Primary Prostate Cancer. Cell. 2015; 163(4): 1011–1025, doi: 10.1016/j.cell.2015.10.025, indexed in Pubmed: 26544944.
82. Robinson D, Van Allen E, Wu YM, et al. Integrative Clinical Genomics of Advanced Prostate Cancer. Cell. 2015; 161(5): 1215–1228, doi: 10.1016/j.cell.2015.05.001, indexed in Pubmed: 26000489.
83. NCCN Guidelines Prostate Cancer Early Detection ver. 1.2023, Prostate Cancer ver. 3.2023.
84. Herberts C, Wyatt AW, Nguyen PL, et al. Genetic and Genomic Testing for Prostate Cancer: Beyond DNA Repair. Am Soc Clin Oncol Educ Book. 2023; 43: e390384, doi: 10.1200/EDBK_390384, indexed in Pubmed: 37207301.
85. Taneja SS. Re: Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Urol. 2013; 190(6): 2093, doi: 10.1016/j.juro.2013.08.101, indexed in Pubmed: 24209519.
86. Castro E, Goh C, Leongamornlert D, et al. Effect of BRCA Mutations on Metastatic Relapse and Cause-specific Survival After Radical Treatment for Localised Prostate Cancer. Eur Urol. 2015; 68(2): 186–193, doi: 10.1016/j.eururo.2014.10.022, indexed in Pubmed: 25454609.
87. Mateo J, Carreira S, Sandhu S, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med. 2015; 373(18): 1697–1708, doi: 10.1056/nejmoa1506859, indexed in Pubmed: 26510020.
88. Bono Jde, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020; 382(22): 2091–2102, doi: 10.1056/nejmoa1911440, indexed in Pubmed: 32343890.
89. Hussain M, Mateo J, Fizazi K, et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020; 383(24): 2345–2357, doi: 10.1056/nejmoa2022485, indexed in Pubmed: 32955174.
90. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. NEJM Evid. 2022; 1(9): EVIDoa2200043, doi: 10.1056/EVIDoa2200043, indexed in Pubmed: 38319800.
91. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Lancet. 2023; 402(10398): 291–303, doi: 10.1016/S0140-6736(23)01055-3, indexed in Pubmed: 37285865.
92. Chi K, Rathkopf D, Smith M, et al. Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. J Clin Oncol. 2023; 41(18): 3339–3351, doi: 10.1200/jco.22.01649, indexed in Pubmed: 36952634.
93. Chi J, Chung SuY, Parakrama R, et al. The role of PARP inhibitors in mutated pancreatic cancer. Therap Adv Gastroenterol. 2021; 14: 17562848211014818, doi: 10.1177/17562848211014818, indexed in Pubmed: 34025781.
94. Lord CJ, Ashworth A. BRCAness revisited. Nat Rev Cancer. 2016; 16(2): 110–120, doi: 10.1038/nrc.2015.21, indexed in Pubmed: 26775620.
95. Hu C, Hart SN, Polley EC, et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. JAMA. 2018; 319(23): 2401–2409, doi: 10.1001/jama.2018.6228, indexed in Pubmed: 29922827.
96. Couch FJ, Johnson MR, Rabe KG, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2007; 16(2): 342–346, doi: 10.1158/1055-9965.EPI-06-0783, indexed in Pubmed: 17301269.
97. Golan T, Kanji ZS, Epelbaum R, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer. 2014; 111(6): 1132–1138, doi: 10.1038/bjc.2014.418, indexed in Pubmed: 25072261.
98. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline -Mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019; 381(4): 317–327, doi: 10.1056/NEJMoa1903387, indexed in Pubmed: 31157963.
99. Kindler HL, Hammel P, Reni M, et al. Overall Survival Results From the POLO Trial: A Phase III Study of Active Maintenance Olaparib Versus Placebo for Germline BRCA-Mutated Metastatic Pancreatic Cancer. J Clin Oncol. 2022; 40(34): 3929–3939, doi: 10.1200/JCO.21.01604, indexed in Pubmed: 35834777.
100. Golan T, Hammel P, Reni M, et al. Overall survival from the phase 3 POLO trial: Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. J Clin Oncol. 2021; 39(3_suppl): 378–378, doi: 10.1200/jco.2021.39.3_suppl.378.