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BRCA mutation in ovarian cancer: testing, implications and treatment considerations

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***Abstract*:** Ovarian cancer is a heterogeneous disease that encompasses a number of different cellular subtypes, the most common of which is high-grade serous ovarian cancer (HGSOC). Still today, ovarian cancer is primarily treated with chemotherapy and surgery. Recent advances in the hereditary understanding of this disease have shown a significant role for the *BRCA* gene. While only a minority of patients with HGSOC will have a germline *BRCA* mutation, many others may have tumor genetic aberrations within BRCA or other homologous recombination proteins. Genetic screening for these *BRCA* mutations has allowed improved preventative measures and therapeutic development. This review focuses on the understanding of *BRCA* mutations and their relationship with ovarian cancer development, as well as future therapeutic targets.

Keywords: BRCA, mutations, ovarian cancer, PARP inhibitor

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Introduction

Ovarian cancer is the most lethal of all gynecologic malignancies in the United States. In 2016 it was estimated that approximately 14,240 patients with ovarian cancer would succumb to their disease.[1] Despite advances in care, for newly diagnosed patients the overall survival at 5 years has only marginally improved to 46% during the last 20 years. The two most important factors for the lack of improvement are a high rate of advanced disease at diagnosis and lack of new therapeutic options. Epithelial ovarian cancer (EOC), which accounts for a majority of diagnoses, is further subdivided into various cell types, grades, and anatomic locations. The most common form is high-grade serous ovarian cancer (HGSOC), which accounts for approximately 70% of all EOC.[2] Historically, the treatment of ovarian cancer has been surgical cytoreduction followed by adjuvant chemotherapy. The concept of improved outcomes in patients for optimal or complete surgical cytoreduction has been explored extensively over the years, with a consistent benefit seen for upfront surgical management.[3–5] The cornerstone of chemotherapy for ovarian cancer is platinum and taxane-based treatment. Advances in the route of administration, including intraperitoneal chemotherapy, have helped to delay progression and increase survival.[6,7] While some more recent gains have been seen from newer targeted therapies (i.e. bevacizumab), moving the field forward in the future is going to depend on a greater understanding of the genetic basis of the disease to identify new targets.

Ovarian carcinoma, especially HGSOC, is a highly mutated cancer. In 2011, a comprehensive analysis performed by The Cancer Genome Atlas (TCGA) found a number of genes to be significantly mutated in ovarian carcinoma; most notably *p53*, which was mutated in nearly 96% of HGSOC.[8] From this work, it was also found that *BRCA1/2* genes play a role in many HGSOC, irrespective of germline status. Further analysis on pathways found nearly half of all tumors tested had a mutation in one gene related to homologous recombination function. These findings point to an important role, as well as therapeutic potential to exploit, for tumors displaying deficiency in homologous recombination.

Hereditary ovarian cancer was first identified by Pierre Paul Broca in 1866 with his documentation of breast and ovary cancer within his wife's

family.[9] Nearly 130 years passed until molecular confirmation of this hereditary cancer syndrome was announced. Mary Claire-King and colleagues first published a linkage analysis of families with early-onset breast cancer and identified the gene locus of *BRCA1* at 17q21.[10] The gene was cloned in 1994, which allowed reproducible testing.[11] Shortly thereafter, the *BRCA2* gene was identified and cloned as well on chromosome 13.[12] Over the last 20 years, research has expanded to improve the understanding of BRCA-related ovarian cancers, specifically how they respond to treatment as well as the expected clinical course. Better characterization of alterations in these genes may enable development of new, targeted therapies, or broadening the clinical application of current therapies.

Understanding the role of BRCA in ovarian cancer development

The process of repairing DNA damage from external or internal sources of derangement is an essential task of the genome in order to prevent cell death. One of the most significant alterations to DNA can occur through a double strand break (DSB), and if left unchecked it is lethal to a cell.[13] DSBs are disruptions in both reading frames of the DNA, often caused by external insults such as ionizing radiation. These breaks are more difficult for DNA repair because there is a lack of a normal reading frame to repair nucleotides to, and for this reason are prone to error. Two main mechanisms allow a cell to repair a DSB: non-homologous end joining (NHEJ) and homologous recombination (HR). NHEJ causes open ends of the DNA to attach binding proteins to stabilize and ultimately reconnect the sides of the DNA, but without regard for the reading frame.[14,15] This induces errors into the DNA. HR allows for repairing an unaltered reading frame. From the open ends, a single strand 3′ opening is created. This allows a series of proteins (including RAD51/BRCA2) to populate to begin searching for a compatible sequence with which to invade and create a D-loop. This process allows both sides to faithfully reconstruct the reading frame.[15] BRCA 1/2 each play multiple, unique roles in HR repair. BRCA1 is thought to be part of a larger complex molecule that helps to survey the DNA for DSB damage.[16] The role of BRCA2 is less clear, but it likely has a more direct role in repair by assisting the *RAD51* complex in attaching to the repair site.[17] Both genes serve as important pieces in a large framework of repair molecules.

Patients who have germline mutations in either *BRCA1/2* are at a higher risk for certain cancers compared to the general public. In rational terms, this would mean many tissues would be at a higher risk of tumor development. However, the majority of cancers developing from *BRCA* mutations are of either breast or ovarian origin. Some research suggests that menstrual cycle oxidative stress may play a role in ovarian tumorigenesis.[18] Also, hormone regulation, especially estrogen, appears to increase DSB, which may explain tissue specificity.[19]

Germline mutations in *BRCA1/2* have been extensively studied in the population to ascribe a risk associated to carriers for the development of breast and ovarian carcinoma. In a seminal paper analyzing over 8000 unselected cases of breast or ovarian cancer, the average cumulative risk of developing ovarian cancer with a *BRCA1/2* mutation was 39% and 11% respectively.[20] The authors also found convincing evidence of an age discrepancy for onset of disease between *BRCA1*/2, with *BRCA1* patients having an increased risk after age 40 and *BRCA2* patients after age 50. This becomes important when counseling patients regarding options for risk reduction. Of all patients who are diagnosed with serous ovarian carcinoma, over 15% will have a germline *BRCA* mutation (gBRCAmut) present.[21] Particularly noteworthy is that these patients are the incident case in the family over 40% of the time.[22] Ethnic minorities, in some instances, are affected with *BRCA* mutation more frequently. Ashkenazi Jewish descendants have a 1–2% chance of harboring a *BRCA1/2* mutation compared to the general public, which has a rate of 1/400.[23]

The role of germline *BRCA* mutation screening for ovarian cancer in clinical practice

Female and male relatives may harbor germline mutations in the *BRCA* genes. This point is crucial to understand for an adequate assessment of genetic history. The risk of breast cancer (up to 80% lifetime) in *BRCA 1/2*, along with risks for ovarian cancer, usually dominates the discussion. It is important when counseling patients, however, to note the increased risk of pancreatic cancer, melanoma, as well as breast and prostate cancers in men.[24–27] Given the implications for treatment and cancer risk determination, there is widespread agreement among professional organizations like the Society of Gynecologic Oncology

(SGO) and the National Comprehensive Cancer Network (NCCN) that all women diagnosed with epithelial ovarian, fallopian tube, and/or peritoneal cancers should be offered cancer genetic counseling and testing for germline *BRCA1/2* mutations. Genetic counseling should include the collection of a three-generation pedigree and involves comprehensive risk assessment based on the patient's personal and family histories.[28]

The US Supreme Court's 2013 ruling to dismiss gene patents[29] was a landmark case in the field of molecular genetics. The case allowed for a competitive availability of next-generation sequencing technology for the genetic screening of *BRCA* mutations. In addition to single-gene/syndrome testing, multi-gene panel tests, from various distributors, have been adopted by clinicians as affordable and efficient alternatives. Clinical use of multi-gene panels is not without controversy, particularly when less-studied moderate-risk susceptibility genes are included. The NCCN advises that in patients who have a personal and/or family history suggestive of more than one potential hereditary cancer syndrome, it may be appropriate to consider multi-gene panel testing but does not provide guidance for deciding which of the many available testing options should be offered in specific clinical situations. Fortunately, several studies have described the spectrum of gene mutations identified in patients with EOC. Norquist and colleagues recently reported multigene panel testing outcomes from 1915 unselected patients with EOC and found that 3.3% of patients had mutations in genes other than *BRCA1, BRCA2*, or the Lynch syndrome-associated mismatch repair genes. Derangements in genes like *BRIP1, PALB2, RAD51C, RAD51D*, and *BARD1* made up 20% of the mutations identified in this study, and each confer an estimated 5–15% lifetime risk of ovarian cancer.[30] It is important to note that these genes are not often referred to as 'moderate-risk genes'. The most recent version of the NCCN Guidelines for Genetic/Familial High-Risk Assessment includes interventions for individuals with mutations in these genes, with the exception of *BARD1*, perhaps making multi-gene panel testing for women with ovarian cancer less controversial. It should also be noted that given the added complexities inherent to multi-gene panel testing it is generally recommended that these tests be ordered by providers with specific cancer genetics expertise. Expertise is required to give the essential elements of informed consent necessary for any cancer genetic test. During the consent process, special attention should be paid to the potential limitations of result interpretation, the application to clinical management, as well as the possibility of receiving an uncertain test result.[31]

Genetic testing in clinical practice should always begin with the affected individual. This allows for accurate interpretation of the results, either positive for mutation or negative. Cascade testing begins with an affected relative, and then progresses to unaffected patients. Only in situations of patients who meet high-risk criteria, and have no known living affected relative should testing occur in an unaffected individual first. Testing in these situations can lead to confusion of results, and may require broadening the scope of screening (i.e. multi-gene panel testing).

Implications of BRCA testing in ovarian cancer

Hereditary cancer syndromes, such as the one associated with *BRCA* mutation, provide an opportunity to screen family members earlier, and in some cases carry out preventative measures to greatly reduce the risk of developing cancer. The NCCN has compiled a list of guidelines for providers to use when counseling for genetic risk evaluation. The SGO and American College of Obstetrician and Gynecologists have joined in a consensus statement regarding genetic counseling as well.[32] Notably, all patients with EOC are recommended to receive genetic counseling and testing for *BRCA* mutations. In addition, patients who have been diagnosed with early-onset breast cancer (age <45) and patients diagnosed with triple negative breast cancer prior to age 60.

Testing positive for BRCA: understanding the role of ovarian cancer screening

Breast cancer screening, with mammograms, remains one of the most effective tools to date in reducing the risk of breast cancer mortality. The recommendations for breast cancer screening in a high-risk population have been extensively studied and covered in various publications.[33–35] Unfortunately, ovarian cancer screening has a long history of relatively poor outcomes with regard to early detection or prevention. Ovarian cancer screening on trial has been performed with pelvic ultrasonography and CA-125 measurement. The relative short interval from early disease to advanced-stage disease in ovarian cancer

makes surveillance particularly difficult. The large US-based Prostate, Lung, Colorectal and Ovarian (PLCO) cancer trial, which evaluated screening for ovarian cancer among other diseases, failed to show reduction in ovarian cancer mortality among a non-selected population.[36] These results were further reiterated in the randomized UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).[37] Unfortunately, even in high-risk populations, no screening modality has been shown to be effective at reducing mortality or detecting early disease.[38,39] NCCN guidelines state that although the data on screening have been inconclusive, it is reasonable to consider in patients who are unwilling to go through a risk-reducing salpingo-oophorectomy (RRSO) at a young age (<35 years old). Table 1 outlines the recommendations from national organizations for ovarian cancer surveillance and risk-reducing management for the high-risk population.

Role of prophylactic surgery in BRCA*-positive patients for ovarian cancer risk reduction*

Prophylactic surgery in patients with gBRCA-mut has been shown to be beneficial in prevention of ovarian cancer. RRSO was analyzed in two separate studies that were released in 2002. Kauff and colleagues showed that in patients that chose RRSO, who were at high risk for a breast or a *BRCA*-related gynecologic malignancy, had a 75% decreased risk of developing ovarian cancer following surgery.[41] Overall, patients who underwent an RRSO had <1% chance of developing a primary fallopian tube or ovarian malignancy. Rebbeck and colleagues showed essentially the same results, but over a longer follow-up period. In that study, RRSO conferred a 96% reduction in *BRCA*-related gynecologic cancer.[42] A large meta-analysis confirmed the significant reduction in ovarian cancer risk among patients with *BRCA* who undergo an RRSO (HR = 0.21). The authors reported a continued small risk of developing a primary peritoneal cancer after RRSO. In addition, a statistically significant decrease in the risk of breast cancer in patients undergoing RRSO (HR = 0.47) was also seen.[43] The ages recommended for consideration of RRSO are also based on these studies. Currently, NCCN and SGO recommend consideration of RRSO following completion of childbearing and after age 35. This is based on the relative increase in risk of a gynecologic malignancy in a *BRCA1* carrier after age 40. It is reasonable to consider a delay of RRSO in patients who have a *BRCA2* mutation, since their age-adjusted risk for ovarian cancer does not start to increase until age 50.[41]

There are some early data regarding the role of prophylactic salpingectomy only in younger patients who do not desire or are unwilling to pursue oophorectomy. The risk reduction for ovarian cancer is 35–50% with a salpingectomy alone in a non-selected population.[44] This hypothesis is based on the theory that a majority of epithelial ovarian carcinoma (serous in particular) actually originates in the fallopian tube. The serous tubal intraepithelial carcinoma (STIC) theory originated in the late 1990s when pathologists noted occult lesions on the fallopian tubes of women with *BRCA1/2* mutations following prophylactic surgery.[45] The concept is that these serous carcinomas more closely resembled the cells of the fallopian tube fimbria, and STICs are found in high numbers of patients with HGSOC.[46–48] While the data are thought-provoking, it is still too early to formally recommend this for all patients at high risk of *BRCA*-related gynecologic malignancy.

Oral contraceptives and BRCA mutation carriers

Patients who are diagnosed at a younger age with a *BRCA* mutation often question what can be done to reduce their risk for ovarian cancer prior to definitive surgical intervention. Oral contraceptive pills (OCPs) have been studied as a type of 'chemoprophylaxis' for ovarian carcinoma. Narod and colleagues found that patients who had taken OCPs for any length of time saw a reduction in risk of ovarian cancer by about 50%.[49] Further, as the timing of OCP use extended past 6 years, the risk reduction was up to 60%. A meta-analysis confirmed this finding, and showed that the benefit of OCP use among patients with a *BRCA* mutation may be similar or better than the general population.[50] However, the use of OCPs has to be weighed against the theoretical risk of or impact on breast cancer and the impact of hormonal manipulation. Whether OCP use increases the risk of breast cancer in *BRCA* mutation carriers is conflicting.[51,52] Based on the current data disparity, *BRCA* carriers should be counseled on the potential benefits and perils of OCP use and it should be considered a cautious choice when seeking an alternative way to reduce their risk of ovarian cancer.

Table 1. Professional guidelines in support of genetic counseling and testing for patients with epithelial ovarian cancer.

Organization	Guideline	Year	Recommendation for ovarian cancer risk management	
National Comprehensive Cancer Network (NCCN)	Breast and/or ovarian cancer genetic assessment	2017	• No evidence to support screening • Discuss oral contraceptive for risk reduction • Prophylactic BSO age 35–40 (after childbearing); can delay to 45 with *BRCA2* mutation if breast risk minimized	www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf
American College of Obstetricians and Gynecologists (ACOG)	Committee on Genetics Opinion and Guidelines for Managing Hereditary Breast and Ovarian Cancer Syndrome	2009/2015	• No evidence to support screening • Discuss oral contraceptive for risk reduction • Prophylactic BSO by age 40 (after childbearing)	www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Genetics/Hereditary-Cancer-Syndromes-and-Risk-Assessment www.ncbi.nlm.nih.gov/pubmed/19305347
Society of Gynecologic Oncology (SGO)	Clinical Practice Statement: Genetic Testing for Ovarian Cancer and Recommendations for the Prevention of Ovarian Cancer	2014/2015	• Discuss oral contraceptive for risk reduction • Prophylactic BSO by age 40 (after childbearing) • Consider salpingectomy if menopause not desired with plan for BSO by age 40	Lancaster *et al.*[32] Walker *et al.*[40]

BSO, bilateral salpingo-oophorectomy.

*Risk-reducing surgery and non-*BRCA *gene mutations*

The advent of multi-gene panel testing for hereditary breast and ovarian cancer has increased the finding of germline genetic mutations in genes associated with an increased risk of these cancers. Walsh and colleagues found that approximately 6% of patients with ovarian cancer had a mutation that was a non-*BRCA* loss of function.[53] *BRCA* mutations are highly penetrant, while other genes have variable penetrance. *RAD51C* and *RAD51D* mutant carriers have been shown to have a relative risk of ovarian cancer of 5.88 and 6.30 respectively.[54,55] Furthermore, a more recent case-control study of over 3000 patients with ovarian cancer found a significantly higher proportion of patients with mutations in *RAD51C* and *RAD51D* compared to controls. The researchers noted that by age 70, the risk of ovarian cancer for *RAD51C* and *RAD51D* was 5.2% and 12% respectively.[56] Though other mutations have yet to yield compelling evidence for preemptive surgical management, with careful counseling regarding the early nature of the research, patients carrying alterations in the *RAD51* genes, in context with family history, can be considered for RRSO.[57]

Treatment considerations in germline *BRCA* mutation carriers for ovarian caner

Germline BRCA *mutations and ovarian cancer prognosis*

The presence of a germline *BRCA* mutation (gBRCAmut) in a patient with HGSOC confers a survival benefit when compared to patients without the mutation. In 1996, the first study analyzing outcomes among patients with a *BRCA* mutation showed that *BRCA* mutant patients lived longer than non-*BRCA* patients (77 *versus* 29 months).[58] Further studies have confirmed that these patients have a better response to platinum therapy compared to patients without *BRCA* mutations.[22,59,60] gBRCAmut carriers appear to also be more sensitive to the benefits of intraperitoneal chemotherapy.[61] In a large pooled analysis of 26 observational studies, *BRCA1/2* germline mutations were shown to have a definitive improvement in overall survival compared to

patients without a mutation. For *BRCA2* mutation carriers, the mean 5-year overall survival was 52% compared to 36% in non-carriers.[62] *BRCA2* mutations, in particular, carry a higher survival rate. This may be due to its mechanism of action; BRCA2 protein more closely regulates the process by which crosslink damage repair occurs, thus making these patients more sensitive to DNA-damaging chemotherapy.[63] Unfortunately, when analyzing survival out to 10 years, the protective effect of a *BRCA* mutation seems to diminish.[64]

PARP inhibitors

Poly (ADP-ribose) polymerase (*PARP*) was first discovered as a molecule in 1963.[65] *PARP* is a member of the collection of proteins that aides in the HR repair of DSBs. The first inhibitor of *PARP* was discovered in 1980 and was originally designed for possible use in chemotherapy sensitization.[66] Originally, these molecules were not thought to be a single-agent therapy choice for patients with cancer due to its mechanism of action, which was thought to only slow down cancer cell growth, but not induce lethality. In 2005, two published reports showed that combining a *PARP* inhibitor with cells that were deficient in *BRCA1* caused significant cellular death compared to cells with *BRCA* intact.[67,68] Independent researchers had identified a new term called 'synthetic lethality', where either endogenous or exogenous depletion of two molecules in a DNA repair pathway becomes lethal to a cell. This exploitative function for *PARP* inhibitors became especially noteworthy for cancers such as breast and ovary related to germline *BRCA* mutations.

PARP inhibitors in treatment of ovarian cancer

The first trials in *PARP* inhibitors for patients with solid tumors with a gBRCAmut were published in 2009. The population studied was enriched with patients who had a known mutation in *BRCA* and included patients with ovarian tumors. Other tumors included were breast, colon, melanoma, prostate, and sarcomas. In patients with known *BRCA1/2* mutations, single-agent treatment with olaparib showed a 63% clinical benefit (including disease stabilization).[69] These results were followed up with an expansion cohort (phase IB) looking at recurrent ovarian/fallopian tube/primary peritoneal cancer patients only. The expansion included only known germline *BRCA* mutation carriers and heavy pre-treatment. The results showed an overall response rate of 40%, with a subanalysis showing a 62% response rate in patients who had been platinum sensitive with their last platinum treatment.[70] Following a trial by Kaye and colleagues [ClinicalTrials.gov identifier: NCT00628251] in which olaparib showed comparable efficacy to a standard of care option (pegylated liposomal doxorubicin),[71] a larger phase II randomized study was opened with olaparib. This trial (study 19) was the first to enroll patients with recurrent disease who may or may not have a gBRCAmut. This trial was specifically studying whether patients who display a *BRCA*-like phenotype respond similarly to those with an actual *BRCA* mutation. Inclusion in the study did not require *BRCA 1/2* mutation status to be known. Patients were required to be platinum sensitive to most recent platinum chemotherapy, showing an objective response. Olaparib or placebo was provided in a maintenance setting. Overall, the progression free survival (PFS) with olaparib was 8.4 months *versus* 4.8 months compared to placebo.[72] In a second paper updating overall survival, the authors presented pre-planned subanalysis on *BRCA* status. The two arms were well balanced with over 50% of patients having either a germline or a tumor somatic mutation of *BRCA* (the majority were gBRCAm). In this population, the PFS was 11.2 *versus* 4.3 months (HR 0.18; $p < 0.0001$) comparing olaparib and placebo.[73] The results of this study led to the European Medicines Agency granting approval for olaparib in the maintenance setting for patients with recurrent HGSOC who are platinum sensitive.

A second pivotal study, by Kaufman and colleagues (study 42), was a multicenter phase II trial that enrolled patients with a *BRCA1/2* mutation who had recurrent cancer. The majority of the tumor types were ovarian; however, other solid tumors such as pancreatic and prostate were enrolled. In this trial, patients who had ovarian cancer had to be resistant to platinum therapy. All patients received olaparib 400 mg twice daily. The primary outcome was tumor response rate (TRR). The overall TRR was 26%; however, for patients with ovarian cancer the TRR was 31%. In addition, ovarian cancer patients showed a stable disease rate of 40%. The PFS and overall survival (OS) for ovarian cancer patients were 7 months and 16.6 months respectively, with over 64% of patients alive at 12 months.[74] On the basis of this trial, the Food and Drug Administration (FDA) approved use of olaparib as monotherapy in patients with a gBRCAm who have received $\geqslant$3 lines of chemotherapy in the United States.

The results of the aforementioned studies have led to an increase in the number of phase III trials for multiple *PARP* inhibitors. This includes trials in the upfront setting with primary therapy as well as trials in maintenance therapy following initial adjuvant treatment [GOG-9923 (ClinicalTrials.gov identifier: NCT02470585) and SOLO-1 (ClinicalTrials.gov identifier: NCT1844986)]. Rucaparib, a *PARP-1/2* inhibitor, has shown promise in a similar population of recurrent HGSOC patients. In a trial, now closed to accrual [ARIEL-2 (ClinicalTrials.gov identifier: NCT01891344)], rucaparib was tested in a population with recurrent HGSOC. The trial was conducted in two parts. ARIEL2 Part 1 looked at patients with recurrent, platinum-sensitive disease, who had at least one prior platinum-based therapy. Patients could enroll as known gBRCAm; however, all tissue was tested for *BRCA* mutations, and confirmed as germline with blood testing. In addition, a molecular signal from the tumor is also being studied to determine if high levels of HRD (homologous recombination deficiency) is present. Testing focused on determining the amount of genomic scarring that is present in the cancer genome, which was quantified by analyzing loss of heterozygosity (LOH) in the tumor. A high amount of LOH indicates genomic instability.[75] Recently published results show that in patients with either a germline *BRCA* mutation or a *BRCA* wildtype with high LOH on tumor testing, the response is significantly greater than patients with *BRCA* wildtype and a low LOH. Specifically, the PFS was 12.8 months *versus* 5.2 months comparing *BRCA* mutation and *BRCA* wildtype low-LOH score.[76] This trial highlights the understanding that somatic *BRCA* mutations are not only present in high percentages, but also can be exploited with *PARP* inhibitors. Based on the results of ARIEL2, as well as a smaller phase I/II by Kristeleit and colleagues (study 10) in Europe,[77] rucaparib was recently approved for use in germline or somatic *BRCA* mutation patients who have had $\geq$2 lines of therapy.[78] This marked the first *PARP* inhibitor to receive approval for use in ovary cancers with somatic *BRCA* mutations in the United States.

Niraparib is a third *PARP* inhibitor that involves inhibition of *PARP-1, PARP-2*, and *PARP-3*. Recently a phase III trial (NOVA/ENGOT-OV16 trial) of recurrent HGSOC patients receiving niraparib *versus* placebo was published. All patients were platinum sensitive and the trial was conducted with two main objectives: (1) efficacy of the drug over placebo; and (2) identify a biologic marker for HRD (through MyChoice Myriad™ testing). The results demonstrated that the PFS for patients with a gBRCAm was 21 *versus* 5.5 months. The authors also found there was a significant improvement in PFS in patients with a high HRD score who did not have a gBRCAm. Perhaps most surprising, though, was that patients who had a low HRD score and did not have a germline/somatic *BRCA* mutation also had a significant PFS advantage.[79] The FDA, as a result of this data, just recently approved niraparib to be used in the maintenance setting for platinum-sensitive HGSOC, regardless of *BRCA* status. *PARP* inhibitors are also being explored with other targeted therapies as well. A phase II trial looking at combining olaparib and cediranib (VEGF inhibitor) found a significant improvement in PFS compared to olaparib alone.[80] The study population in this trial combined those with and without gBRCAmut. *PARP* inhibitor use will continue to expand in ovarian cancer with the promising results seen so far. Defining optimal patient populations as well as optimal timing for these therapies are key questions going forward in *PARP* inhibitor development. Table 2 provides a succinct review of the major clinical trials in PARP inhibitors for the treatment of ovarian cancer.

Conclusions

Understanding the role *BRCA* mutations play in the development, treatment response, and prognosis is an exciting and developing area in the treatment of ovarian cancer. Since its discovery in 1990, research has led to understanding the role of *BRCA* in tumorigenesis and, more recently, as a therapeutic potential. Identification of a *BRCA* mutation may not only help the afflicted patient, but also allows for genetic testing to be performed on relatives, allowing for the potential to prevent ovarian cancer. Furthermore, *PARP* inhibition has an opportunity to significantly improve outcomes in women who harbor germline or somatic *BRCA* mutations, as well as tumors that display a high degree of HRD. As we continue to advance our understanding of *BRCA* and its role in the development and outcomes of ovarian cancer, there is great potential to not only prevent many cases through improved access to genetic screening, but also revolutionize the long-term treatment of patients with this insidious disease.

Table 2. *PARP* inhibitors and major published trials.

PARP inhibitor	Study year	Design	Inclusion criteria	Number of patients	PFS	ORR	Citation
Olaparib	2010	Phase IB (ovarian cancer expansion cohort)	gBRCAm; at least one prior line of chemotherapy	50		40% (platinum-sensitive patients: 61.5%)	Fong *et al.*[70]
	2010	Phase II (two dose cohorts: 400 mg BID and 100 mg BID)	gBRCAm and recurrent ovarian cancer	57	5.9 *versus* 1.9 months	33% *versus* 16%	Audeh *et al.*[81]
	2011	Phase II (400 mg BID)	gBRCAm with any histology and/or recurrent/metastatic TNBC or HGSOC	90 (64 ovary and 26 breast)		Ovary: 29% (41% in patients with gBRCAm) Breast: 0%	Gelmon *et al.*[82]
	2012	Randomized phase II (200 mg BID *versus* 400 mg BID *versus* PLD 50 mg/m^2 q28d)	Recurrent ovarian cancer and platinum sensitive and gBRCAm	97	6.5 *versus* 8.8 *versus* 7.1 months (ns)	25% *versus* 31% *versus* 18% (ns)	Kaye *et al.*[71]
	2012	(Study 19) Randomized phase II (400 mg BID *versus* placebo) (maintenance therapy)	Recurrent HGSOC; platinum-sensitive disease; +/– *BRCA* mutation	265	8.4 *versus* 4.8 months (HR 0.35)*		Ledermann *et al.*[72]
	2014	Pre-planned OS and *BRCA* mutation analysis of study 19			+gBRCAm: 11.2 *versus* 4.3 months –gBRCA m: 7.4 *versus* 5.5 months OS: 29.8 *versus* 27.8 months		Ledermann *et al.*[73]
	2015	Phase II (400 mg BID) Study 42	Advanced solid tumors; platinum resistant; +gBRCAm	298	Ovary: 7.9 months	Ovary: 31.1%	Kaufman *et al.*[74]
	2017	Randomized double-blind phase III (300 mg BID *versus* placebo)	Recurrent HGSOC; platinum sensitive; +gBRCAm; CR or PR to most recent platinum	295	19.1 months *versus* 5.5 months (HR 0.30)*		Pujade-Lauraine *et al.*[83]

Table 2. (Continued)

PARP inhibitor	Study year	Design	Inclusion criteria	Number of patients	PFS	ORR	Citation
Rucaparib	2016	Phase II (IV up to 18 mg/m^2 dose-escalation and PO up to 600 mg BID)	Locally advanced/metastatic breast cancer and advanced ovary cancer; IV cohort – must have gBRCAm; PO cohort – HGSOC patients could enroll then test for gBRCAm	78		IV: 2% PO: 15% SD (IV): 41% SD (PO): 66%	Drew *et al.*[84]
	2017	Phase I/II (dose-escalation phase I and 600 mg BID phase II)	Recurrent HGSOC; gBRCAM+; platinum sensitive	Phase I: 56 and Phase II: 42		Phase II: 59.5%; median duration response: 7.8 months	Kristeleit *et al.*[77]
	2017	Phase II, Part I(ARIEL2): 600 mg BID	Recurrent platinum-sensitive HGSOC: +/–gBRCAm or somatic mutation; LOH high and LOH low	206	BRCAm + (germline or somatic): 12.8 months; 5.7 months LOH high; 5.2 months LOH low		Swisher *et al.*[76]
Niraparib	2013	Phase I (dose-escalation)	Recurrent solid tumors	100		Ovary (gBRCAm): platinum sensitive 50%; platinum resistant 33%	Sandhu *et al.*[85]
	2016	Phase III: randomized, placebo-controlled (NOVA)- 300 mg daily	Recurrent HGSOC; platinum-sensitive disease; allowed gBRCAm and non-gBRCAm (tested non-gBRCA for HRD)	553 (201 gBRCAm and 345 non-gBRCA)	gBRCA: 21 months *versus* 5.5 months (HR 0.27)*; HRD-positive subgroup: 12.9 months *versus* 3.8 months (HR 0.38)*; non-gBRCAm: 9.3 months *versus* 3.9 months (HR 0.45)*		Mirza *et al.*[79]
Veliparib	2015	Phase II: 400 mg BID	Recurrent HGSOC; gBRCAm +; ⩾3 lines chemo	52	8.18 months	ORR: 26%; SD: 48%	Coleman *et al.*[86]

BID, twice daily; gBRCAm, germline *BRCA* mutation; HGSOC, high-grade serous ovarian cancer; HR, hazard ratio; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; ns, not significant; ORR, objective response rate; PFS, progression free survival; PLD, pegylated liposomal doxorubicin; PO, oral; SD, stable disease; TNBC, triple negative breast cancer.
*$p < 0.05$.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

References

1. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; 66: 7–30.
2. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. *Pathology* 2011; 43: 420–432.
3. Bristow RE, Tomacruz RS, Armstrong DK, *et al.* Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* 2002; 20: 1248–1259.
4. Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *Natl Cancer Inst Monogr* 1975; 42: 101–104.
5. Hoskins WJ, McGuire WP, Brady MF, *et al.* The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am J Obstet Gynecol* 1994; 170: 974–979; discussion 9–80.
6. Armstrong DK, Bundy B, Wenzel L, *et al.* Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006; 354: 34–43.
7. Wright AA, Cronin A, Milne DE, *et al.* Use and effectiveness of intraperitoneal chemotherapy for treatment of ovarian cancer. *J Clin Oncol* 2015; 33: 2841–2847.
8. Network CGAR. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011; 474: 609–615.
9. Broca PP. *Traite des tumeurs*. Paris: P. Asselin, 1866.
10. Hall JM, Lee MK, Newman B, *et al.* Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 1990; 250: 1684–1689.
11. Miki Y, Swensen J, Shattuck-Eidens D, *et al.* A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 1994; 266: 66–71.
12. Wooster R, Neuhausen SL, Mangion J, *et al.* Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12–13. *Science* 1994; 265: 2088–2090.
13. Huertas P. DNA resection in eukaryotes: deciding how to fix the break. *Nat Struct Mol Biol* 2010; 17: 11–16.
14. Pardo B, Gomez-Gonzalez B and Aguilera A. DNA repair in mammalian cells: DNA double-strand break repair – how to fix a broken relationship. *Cellular Mol Life Sci* 2009; 66: 1039–1056.
15. Hartlerode AJ and Scully R. Mechanisms of double-strand break repair in somatic mammalian cells. *Biochemical J* 2009; 423: 157–168.
16. Gudmundsdottir K and Ashworth A. The roles of BRCA1 and BRCA2 and associated proteins in the maintenance of genomic stability. *Oncogene* 2006; 25: 5864–5874.
17. Yang H, Jeffrey PD, Miller J, *et al.* BRCA2 function in DNA binding and recombination from a BRCA2–DSS1–ssDNA structure. *Science* 2002; 297: 1837–1848.
18. Hamada J, Nakata D, Nakae D, *et al.* Increased oxidative DNA damage in mammary tumor cells by continuous epidermal growth factor stimulation. *J Natl Cancer Inst* 2001; 93: 214–219.
19. Savage KI, Matchett KB, Barros EM, *et al.* BRCA1 deficiency exacerbates estrogen-induced DNA damage and genomic instability. *Cancer Res* 2014; 74: 2773–2784.
20. Antoniou A, Pharoah PD, Narod S, *et al.* Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003; 72: 1117–1130.
21. 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: 700–710.
22. 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: 2654–2663.
23. Struewing JP, Hartge P, Wacholder S, *et al.* The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 1997; 336: 1401–1408.
24. Castro E, Goh C, Olmos D, *et al.* Germline BRCA mutations are associated with higher risk

of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol* 2013; 31: 1748–1757.

25. Evans DG, Susnerwala I, Dawson J, *et al.* Risk of breast cancer in male BRCA2 carriers. *J Med Gen* 2010; 47: 710–711.
26. Ginsburg OM, Kim-Sing C, Foulkes WD, *et al.* BRCA1 and BRCA2 families and the risk of skin cancer. *Fam Cancer* 2010; 9: 489–493.
27. Iqbal J, Ragone A, Lubinski J, *et al.* The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers. *Br J Cancer* 2012; 107: 2005–2009.
28. Berliner JL, Fay AM, Cummings SA, *et al.* NSGC practice guideline: risk assessment and genetic counseling for hereditary breast and ovarian cancer. *J Genet Couns* 2013; 22: 155–163.
29. Association for Molecular Pathology *et al. v.* Myriad Genetics, Inc.: Supreme Court of the United States, 2013.
30. Norquist BM, Harrell MI, Brady MF, *et al.* Inherited mutations in women with ovarian carcinoma. *JAMA Oncol* 2016; 2: 482–490.
31. Robson ME, Bradbury AR, Arun B, *et al.* American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol* 2015; 33: 3660–3667.
32. Lancaster JM, Powell CB, Chen LM, *et al.* Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol* 2015; 136: 3–7.
33. Kriege M, Brekelmans CT, Boetes C, *et al.* Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med* 2004; 351: 427–437.
34. Saslow D, Boetes C, Burke W, *et al.* American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin* 2007; 57: 75–89.
35. Warner E, Plewes DB, Hill KA, *et al.* Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA* 2004; 292: 1317–1325.
36. Buys SS, Partridge E, Black A, *et al.* Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening randomized controlled trial. *JAMA* 2011; 305: 2295–2303.
37. Jacobs IJ, Menon U, Ryan A, *et al.* Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet* 2016; 387: 945–956.
38. Lacey JV Jr., Greene MH, Buys SS, *et al.* Ovarian cancer screening in women with a family history of breast or ovarian cancer. *Obstet Gynecol* 2006; 108: 1176–1184.
39. Woodward ER, Sleightholme HV, Considine AM, *et al.* Annual surveillance by CA125 and transvaginal ultrasound for ovarian cancer in both high-risk and population risk women is ineffective. *BJOG* 2007; 114: 1500–1509.
40. Walker JL, Powell CB, Chen LM, *et al.* Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. *Cancer* 2015; 121: 2108–2120.
41. Kauff ND, Satagopan JM, Robson ME, *et al.* Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med* 2002; 346: 1609–1615.
42. Rebbeck TR, Lynch HT, Neuhausen SL, *et al.* Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med* 2002; 346: 1616–1622.
43. Rebbeck TR, Kauff ND and Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst* 2009; 101: 80–87.
44. Falconer H, Yin L, Gronberg H, *et al.* Ovarian cancer risk after salpingectomy: a nationwide population-based study. *J Natl Cancer Inst* 2015; 107.
45. Piek JM, Verheijen RH, Kenemans P, *et al.* BRCA1/2-related ovarian cancers are of tubal origin: a hypothesis. *Gynecol Oncol* 2003; 90: 491.
46. Kindelberger DW, Lee Y, Miron A, *et al.* Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: evidence for a causal relationship. *Am J Surg Pathol* 2007; 31: 161–169.
47. Przybycin CG, Kurman RJ, Ronnett BM, *et al.* Are all pelvic (nonuterine) serous carcinomas of tubal origin? *Am J Surg Pathol* 2010; 34: 1407–1416.
48. Tone AA, Begley H, Sharma M, *et al.* Gene expression profiles of luteal phase fallopian tube epithelium from BRCA mutation carriers resemble high-grade serous carcinoma. *Clin Cancer Res* 2008; 14: 4067–4078.
49. Narod SA, Risch H, Moslehi R, *et al.* Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *N Engl J Med* 1998; 339: 424–428.

50. Moorman PG, Havrilesky LJ, Gierisch JM, *et al.* Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. *J Clin Oncology* 2013; 31: 4188–4198.

51. Lee E, Ma H, McKean-Cowdin R, *et al.* Effect of reproductive factors and oral contraceptives on breast cancer risk in BRCA1/2 mutation carriers and noncarriers: results from a population-based study. *Cancer Epidemiol Biomarkers Prev* 2008; 17: 3170–3178.

52. Narod SA, Dube MP, Klijn J, *et al.* Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Instit* 2002; 94: 1773–1779.

53. Walsh T, Casadei S, Lee MK, *et al.* Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc Natl Acad Sci USA* 2011; 108: 18032–18037.

54. Loveday C, Turnbull C, Ramsay E, *et al.* Germline mutations in RAD51D confer susceptibility to ovarian cancer. *Nat Genet* 2011; 43: 879–882.

55. Loveday C, Turnbull C, Ruark E, *et al.* Germline RAD51C mutations confer susceptibility to ovarian cancer. *Nat Genet* 2012; 44: 475–476; author reply 6.

56. Song H, Dicks E, Ramus SJ, *et al.* Contribution of germline mutations in the RAD51B, RAD51C, and RAD51D genes to ovarian cancer in the population. *J Clin Oncol* 2015; 33: 2901–2907.

57. Tung N, Domchek SM, Stadler Z, *et al.* Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol* 2016; 13: 581–588.

58. Rubin SC, Benjamin I, Behbakht K, *et al.* Clinical and pathological features of ovarian cancer in women with germ-line mutations of BRCA1. *N Engl J Med* 1996; 335: 1413–1416.

59. Tan DS, Rothermundt C, Thomas K, *et al.* 'BRCAness' syndrome in ovarian cancer: a case-control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations. *J Clin Oncol* 2008; 26: 5530–5536.

60. Yang D, 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: 1557–1565.

61. Lesnock JL, Darcy KM, Tian C, *et al.* BRCA1 expression and improved survival in ovarian cancer patients treated with intraperitoneal cisplatin and paclitaxel: a Gynecologic Oncology Group Study. *Br J Cancer* 2013; 108: 1231–1237.

62. Bolton KL, Chenevix-Trench G, Goh C, *et al.* Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. *JAMA* 2012; 307: 382–390.

63. Cipak L, Watanabe N and Bessho T. The role of BRCA2 in replication-coupled DNA interstrand cross-link repair in vitro. *Nat Struct Molec Biol* 2006; 13: 729–733.

64. Kotsopoulos J, Rosen B, Fan I, *et al.* Ten-year survival after epithelial ovarian cancer is not associated with BRCA mutation status. *Gynecol Oncol* 2016; 140: 42–47.

65. Chambon P, Weill JD and Mandel P. Nicotinamide mononucleotide activation of new DNA-dependent polyadenylic acid synthesizing nuclear enzyme. *Biochem Biophys Res Commun* 1963; 11: 39–43.

66. Purnell MR and Whish WJ. Novel inhibitors of poly(ADP-ribose) synthetase. *Biochem J* 1980; 185: 775–777.

67. Farmer H, McCabe N, Lord CJ, *et al.* Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 2005; 434: 917–921.

68. Bryant HE, Schultz N, Thomas HD, *et al.* Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* 2005; 434: 913–917.

69. Fong PC, Boss DS, Yap TA, *et al.* Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med* 2009; 361: 123–134.

70. Fong PC, Yap TA, Boss DS, *et al.* Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol* 2010; 28: 2512–2519.

71. Kaye SB, Lubinski J, Matulonis U, *et al.* Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. *J Clin Oncol* 2012; 30: 372–379.

72. Ledermann J, Harter P, Gourley C, *et al.* Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012; 366: 1382–1392.

73. 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: 852–861.

74. Kaufman B, Shapira-Frommer R, Schmutzler RK, *et al*. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol* 2015; 33: 244–250.
75. Korpanty G, Timms K, Abkevich V, *et al*. Loss of heterozygosity (LOH) as a measure of whole-genome instability in ovarian cancer correlates with clinical outcomes. *J Clin Oncol* 2011; 29: 5027.
76. Swisher EM, Lin KK, Oza AM, *et al*. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *The Lancet Oncol* 2017; 18: 75–87.
77. Kristeleit R, Shapiro GI, Burris HA, *et al*. A phase I–II study of the oral poly(ADP-ribose) polymerase inhibitor rucaparib in patients with germline BRCA1/2-mutated ovarian carcinoma or other solid tumors. *Clin Cancer Res* 2017.
78. Release FN. FDA grants accelerated approval to new treatment for advanced ovarian cancer, www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm533873.htm2016.
79. Mirza MR, Monk BJ, Herrstedt J, *et al*. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med* 2016; 375: 2154–2164.
80. Liu JF, Barry WT, Birrer M, *et al*. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. *Lancet Oncol* 2014; 15: 1207–1214.
81. Audeh MW, Carmichael J, Penson RT, *et al*. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet* 2010; 376: 245–251.
82. Gelmon KA, Tischkowitz M, Mackay H, *et al*. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol* 2011; 12: 852–861.
83. Pujade-Lauraine E, Ledermann JA, Penson RT, *et al*. Treatment with olaparib monotherapy in the maintenance setting significantly improves progression-free survival in patients with platinum-sensitive relapsed ovarian cancer: Results from the Phase III SOLO2 study. *Society of Gynecologic Oncology – Annual Meeting on Women's Cancer*. National Harbor, Maryland, 2017.
84. Drew Y, Ledermann J, Hall G, *et al*. Phase 2 multicentre trial investigating intermittent and continuous dosing schedules of the poly(ADP-ribose) polymerase inhibitor rucaparib in germline BRCA mutation carriers with advanced ovarian and breast cancer. *Br J Cancer* 2016; 114: 723–730.
85. Sandhu SK, Schelman WR, Wilding G, *et al*. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. *Lancet Oncol* 2013; 14: 882–892.
86. Coleman RL, Sill MW, Bell-McGuinn K, *et al*. A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation: an NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol* 2015; 137: 386–391.