PARP Inhibitors as a Novel Treatment Strategy for Patients with *BRCA*-Mutated Metastatic Breast Cancer

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Abstract

Inhibitors of poly(ADP-ribose) polymerase (PARP), such as olaparib and talazoparib, have recently been approved as therapies for *BRCA*-mutated human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (BC). In addition, olaparib, as well as rucaparib and niraparib, have received approval for treatment of patients with *BRCA*-mutated or platinum-sensitive recurrent ovarian cancer.

The treatment efficacy of PARP inhibitors is higher in case of malignancies that harbour deleterious germline or somatic *BRCA* mutations compared to *BRCA* wild-type tumours. Consequently, *BRCA* mutations or intrinsic tumour sensitivity to platinum therapy are considered indicators of impaired ability to repair DNA double-strand breaks via homologous recombination.

However, not all *BRCA*-mutated cancer patients benefit from PARP inhibitors. In contrast, for some patients with wild-type *BRCA* or platinum-resistant tumours, the PARP inhibitors may still offer some therapeutic advantages. Therefore, there is a need to determine additional biomarkers to more precisely select patients without deleterious *BRCA* mutations, who may be eligible for treatment with PARP inhibitors.

The main objective of this mini-review is to present the main mechanisms of action of PARP inhibitors and briefly summarise the clinical trials leading to their approval in treatment of *BRCA*-mutated, HER2-negative metastatic BC. In addition, this article discusses the efficacy, safety, and resistance to PARP inhibitors in women with metastatic BC.

INTRODUCTION

Physiologically, cells are equipped with DNA damage repair systems that can correct various errors. However, congenital defects in DNA repair mechanisms may cause accumulation of DNA mutations and elevated risk of malignancy. Certain genes that are involved in DNA damage repair pathways play a key role in neoplastic development. For instance, an elevated susceptibility to inherited breast cancer (BC)

and ovarian cancer (OC) has been reported in women harbouring germline mutations of *BRCA1* and *BRCA2* (both tumour suppressor genes).[1,2] Despite their structural differences, these genes perform similar cellular actions and are instrumental for genome protection.[1,2] The *BRCA1* gene is located on the long arm of chromosome 17, and *BRCA2* gene on the long arm of chromosome 13.[3] Currently, >2,000 mutations have been detected in both *BRCA* genes (e.g., deletions, insertions, or duplications) that result in various aberrant transcriptional outcomes (e.g., missense, nonsense, silent, and splice-site).[3] From a clinical point of view, *BRCA* changes that augment cancer susceptibility have been recognised as deleterious mutations, and usually result in nonfunctional proteins.[3] As a consequence, such mutations interfere with the repair of the damaged DNA. For instance, a large study on *BRCA1* or *BRCA2* mutation carriers has revealed a significant cumulative risk of BC and OC, in regard to both the *gBRCA1m* mutation (72% for BC and 44% for OC) and *gBRCA2m* mutation (69% for BC and 17% for OC).[4] In contrast, in the general population of women the cumulative risk is only 12.0% for BC, and 1.3% for OC.[5] Furthermore, malignancy risk differs depending on various predictors (e.g., family history) and the location of mutations within the *BRCA1* and *BRCA2* genes.[4] It should be emphasised that deleterious *BRCA1* or *BRCA2* mutations can also augment the risk of breast and prostate cancer in men,[6] as well as pancreatic and stomach cancers,[7,8] or colorectal cancer, in both women and men.[9]

Poly(ADP-ribose) polymerases (PARP) are a family of enzymes that transfer adenosine diphosphate (ADP) ribose parts to surrounding proteins in response to different cellular stimuli. PARP1 and PARP2 participate in the cellular response to single-strand DNA breaks.[10] Inhibition of the ability of PARP to repair single-strand DNA breaks results in double-strand breaks (DSB) and subsequent replication fork collapse, which can lead to cell death. DSB can be repaired via different mechanisms, including the predominate means homologous recombination (HR) repair, which depends on *BRCA1* and *BRCA2* functionality.[10] Recent evidence has shown that PARP inhibitors (e.g., olaparib and talazoparib) are effective in treatment of malignancies that harbour deleterious g*BRCA*m compared to *BRCA* wild-type tumours (e.g., metastatic BC).[11,12]

The objective of this mini-review is to present the mechanisms of action of PARP inhibitors and briefly summarise the clinical trials leading to the approval of olaparib, talazoparib, rucaparib, and niraparib for treatment of *BRCA*-mutated, human epidermal growth factor receptor 2 (HER2)-negative metastatic BC. It should be noted that PARP inhibitors (which are well tolerated oral agents) are providing some reasonable hope for better outcomes and quality of life in a vulnerable population of patients with metastatic BC. In addition, this article discusses the efficacy, safety, and resistance to PARP inhibitors, focussing on women with metastatic BC.

THE ROLE OF POLY(ADP-RIBOSE) POLYMERASE ENZYMES IN DNA REPAIR AND THE INSIGHTS INTO TARGETED SYNTHETIC LETHALITY OF THE TUMOUR

To ensure genomic integrity, cells can apply different mechanisms that identify and repair DNA injuries caused by exogenous or endogenous factors via highly coordinated DNA damage response systems.[13] Several 'sensors' of DNA lesions are located in the cell nucleus, which communicate with effectors at the different cell sites.[14] In particular, PARP1 (a member of the superfamily of ADP-ribosyl transferases that transfer poly[ADP-ribose] [PAR] or mono-ADP-ribose) is one such nuclear protein that is activated by DNA breaks.[15] PARP1 is able to synthesise PAR chains, which are signals for the mobilisation of DNA repair proteins.[16] Similarly, PARP2 and PARP3 display DNA-dependent (ADP-ribose) transferase activity.[16] Poly-ADP-ribosylation (PARylation) relates to the covalent binding of negatively charged PAR on target proteins.[16,17] It should be underscored that PARylation may destabilise or stabilise protein-DNA interactions, activate target proteins, and induce protein degradation by the proteasome.[17] In addition, PARP proteins can regulate various cellular functions (e.g., DNA transcription and DNA damage response) via PARylation.[15-17]

At different points of the cell cycle, cells can apply several mechanisms for DNA repair. For instance, if single-stranded break repair is blocked and that cell tries to divide, the break can become double-stranded. At this point, if the cell has HR deficiency (HRD) it cannot survive. Moreover, cells that do not have BRCA1 or BRCA2 proteins (resultant of deleterious *BRCA* mutations) are very sensitive to PARP inhibition because they are unable to repair the DSB. This leads to synthetic lethality and cellular apoptosis.[10,13] The concept of synthetic lethality has initiated the development of an innovative, genomically targeted therapy for patients with cancers that harbour g*BRCA*m (e.g., metastatic BC and OC).[11,14] This therapeutic strategy is possible because the genomic instability of some cancer cells allows a novel class of medications, PARP inhibitors, to act specifically on tumour cells and spare healthy cells. In fact, many tumour cells with HRD are more susceptible to PARP inhibitors because

of the fact that if DNA DSB are formed, and HR is the predominant repair mechanism in those cells, the unrepaired breaks are lethal. As a consequence, the patients with tumours harbouring deleterious *BRCA* mutations (e.g., germline or somatic, resulting in defective DSB repair by HR) can achieve the greatest clinical benefits.[13,16]

POLY(ADP-RIBOSE) POLYMERASE INHIBITORS: AN OVERVIEW OF THE MAIN CLINICAL TRIALS LEADING TO THEIR APPROVAL IN THE METASTATIC BREAST CANCER SETTING

Recently, the following PARP inhibitors have received approval by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA): olaparib, talazoparib, rucaparib, and niraparib (Table 1).[11,12,18-24]

Table 1: Poly(ADP-ribose) polymerase inhibitors for the treatment of patients with advanced breast and ovarian cancer (based on the main clinical trials leading to their approval).

PARP inhibitor	Clinical trial	*BRCA* mutation	1. FDA approval [month/year] - Treatment indications 2. EMA approval [month/year] - Treatment indications	Reference
Olaparib	OlympiAD, Phase III NCT02000622 Study 42, Phase II NCT01078662 Study 19, Phase II NCT00753545	Deleterious germline or somatic *BRCA* mutations.	1.FDA [January 2018] - g*BRCA*m, HER2-negative metastatic BC (previously treated with CHT) in the neoadjuvant, adjuvant, or metastatic setting. FDA [December 2014] - g*BRCA*m, advanced OC (treated with ≥3 prior lines of CHT). 2.EMA [October 2014] - maintenance treatment of relapsed, platinum-sensitive high-grade OC with mutations (germline or somatic) in *BRCA* genes.	11 20 19

Table 1 continued.

Olaparib	SOLO2, Phase III NCT01874353	No requirement for deleterious germline or somatic *BRCA* mutations.	1.FDA [August 2017] - maintenance treatment of recurrent OC (in a complete or partial response to platinum-based CHT).	18
	Study 19, Phase II NCT00753545		2.EMA [May 2018] - maintenance treatment of platinum-sensitive relapsed high-grade OC (in complete or partial response to platinum-based CHT), regardless of *BRCA* status.	19
Talazoparib	EMBRACA, Phase III NCT01945775	Deleterious germline or somatic *BRCA* mutations.	1.FDA [October 2018] - g*BRCA*m, HER2-negative locally advanced or metastatic BC.	12
Rucaparib	ARIEL3, Phase III NCT01968213	No requirement for deleterious germline or somatic *BRCA* mutations.	1.FDA [April 2018] - maintenance treatment of recurrent OC (in a complete or partial response to platinum-based CHT).	21
Rucaparib	ARIEL2, Phase II NCT01891344	Deleterious germline or somatic *BRCA* mutations.	2.EMA [May 2018] - platinum-sensitive, relapsed or progressive, gBRCAm, high-grade OC (previously treated with ≥2 lines of platinum-based CHT, and unable to tolerate further platinum-based CHT).	22
	Study 10, Phase I/II NCT01482715		1.FDA [December 2016] - g*BRCA*m OC (previously treated with ≥2 CHT lines).	23

Niraparib	NOVA study, Phase III NCT01847274	No requirement for deleterious germline or somatic *BRCA* mutations.	1.FDA [March 2017] - maintenance treatment of recurrent OC (in a complete/ partial response to platinum-based CHT). 2.EMA [November 2017] - maintenance treatment of platinum-sensitive relapsed high-grade OC, in response (complete/partial) to platinum-based CHT.	24

BC: breast cancer; CHT: chemotherapy; EMA: European Medicines Agency; FDA: U.S. Food and Drug Administration; g*BRCA*m: germline *BRCA*-mutation; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; OC: ovarian cancer (i.e., serous epithelial ovarian, fallopian tube, or primary peritoneal cancer); PARP: poly (ADP-ribose) polymerase.

Olaparib was the first PARP inhibitor approved for the treatment of BC, based on the OlympiAD, Phase III randomised controlled trial, which has demonstrated that PARP inhibition was superior in the metastatic setting (e.g., third-line therapy), in terms of efficacy and safety, to chemotherapy (CHT).[11] The CHT choices in OlympiAD included capecitabine, eribulin, and vinorelbine.[11] As a consequence, olaparib has been indicated for deleterious or suspected deleterious g*BRCA*m, in women with HER2-negative metastatic BC, who have been treated with CHT (e.g., in the neoadjuvant, adjuvant, or metastatic setting).[11] In addition, olaparib has been approved as maintenance therapy in patients with platinum-sensitive high-grade OC (with or without BRCA mutations) (Table 1).[18,19] Likewise, talazoparib has been approved for the treatment of women with deleterious g*BRCA*m, HER2-negative locally advanced, or metastatic BC (based on the EMBRACA, Phase III randomised control trial).[12] From a clinical point of view, the findings of the OlympiAD and EMBRACA trials appear encouraging; however, it should be pointed out that the efficacy of PARP inhibitors was not compared to that of platinum CHT, and thus, the OlympiAD and EMBRACA studies could not evaluate the relative benefits of PARP inhibitors and platinum-based CHT in BC patients with gBRCAm.[11,12]

ASSOCIATIONS BETWEEN GERMLINE *BRCA* MUTATIONS AND TRIPLE-NEGATIVE BREAST CANCER

BRCA1 and *BRCA2* play an important role in repairing DNA injuries.[25] It should be highlighted that the *BRCA1* mutations are strongly associated with triple-negative breast cancer (TNBC) (oestrogen receptor-negative, progesterone receptor-negative, and HER2-negative BC).[26] Conversely, the *BRCA2* mutations are mostly associated with hormone receptor-positive/HER2-negative BC.[26] TNBC is the predominant subtype in women with a g*BRCA*m.[26,27] However, the majority of basal-like BC are not in the *BRCA1* carriers group, and 20% of genomic instability in TNBC can be explained by *BRCA1* or *BRCA2* inactivation.[28] For instance, 5–10% of BC, and 80% of *BRCA1*-related BC, are TNBC.[26,27] It should be noted that in TNBC, the *BRCA*ness phenotype can be related to *BRCA* mutations, *BRCA1* promoter methylation, or low BRCA1 mRNA or protein expression.[27] Most *BRCA1* carriers have basal-like BC. Among patients

with TNBC, 14.6% have germline DNA repair gene mutations (e.g., 8.5% in *BRCA1*, 2.7% in *BRCA2*, and 3.7% in the *PALB2* [partner and localiser of *BRCA2*], BARD1 [*BRCA1* associated RING domain 1], *RAD51* [RAD51 recombinase], or *BRIP1* [(*BRCA1* interacting protein C-terminal helicase 1]).[25,28]

In a recent clinical trial, conducted among women with metastatic TNBC (with abnormal changes in DNA repair that were similar to those of *BRCA*-mutated tumours), 50% of the patients were treated with carboplatin, and the other 50% with docetaxel.[29] It was shown in this unselected study population, that carboplatin and docetaxel revealed similar efficacy. It should be underscored that in women with g*BRCA*m, carboplatin doubled the response rate compared to those from the docetaxel group (68% versus 33%). However, this clinical advantage was not reported in patients with *BRCA1* mRNA-low tumours, *BRCA1* methylation, or HRD.[29] It should be noted that with regard to olaparib, the reported response rate of 68% and the median progression-free survival (PFS) of 6.8 months were similar to those observed with carboplatin in metastatic TNBC.[11] Since platinum sensitivity is associated with tumour susceptibility to PARP inhibitors, hopefully future large scale trials will compare the platinum-based CHT with the PARP inhibitors and show the application of carboplatin in TNBC.

RESISTANCE TO POLY(ADP-RIBOSE) POLYMERASE INHIBITORS: CHALLENGES AND CONSIDERATIONS

PARP inhibitor resistance can develop via multiple mechanisms because BRCA1/2-deficient tumour cells can restore HR repair and stabilise their replication forks.[30] In addition, it should be noted that there is some cross-resistance between platinum-based CHT and PARP inhibitors; however, this cross-resistance is incomplete, and it is still unclear to what degree the platinum compounds and the PARP inhibitors 'operate' on the same pathway. For instance, a study in women with OC has shown that patients who have platinum-sensitive cancers have also higher overall response rates to single-agent PARP

inhibition. Conversely, patients with platinum-resistant or refractory tumours have revealed lower response rates.[31] Unfortunately, not all patients with *BRCA* mutations are responsive to PARP inhibitors, indicating a potential role of the primary resistance to such a therapy. This may be attributable to the possibility that certain changes in the *BRCA* genes could have different functional influences on the individual response to PARP inhibitors. Moreover, an analysis of tumour biopsies has revealed some molecular mechanisms that can be 'in charge' of the primary and acquired resistance to PARP inhibitors. The most common acquired resistance mechanisms to PARP inhibitors consist of secondary mutations restoring the BRCA1 or BRCA2 protein functionality. Such mechanisms have been studied in patients with OC and BC (i.e., metastatic TNBC), who were resistant to platinum compounds.[32,33]

In a recent study, secondary somatic mutations that restored the open reading frame of *BRCA* or HR-related genes (e.g., *RAD51C* and *RAD51D*) were identified in patients with OC, who progressed during treatment with rucaparib.[34] Furthermore, in patients with *BRCA* somatic heterozygous disruption, tumour progression was related to a recovery of *BRCA* activity. In contrast, patients with a single-copy loss of chromosome 17 and a somatic nonsense *BRCA1* mutation (in the remaining allele) had a long-term response (>7 years) to olaparib. In this case, deletion of the wild-type allele resulted in the restoration to a functional gene.[35] Some other clinically relevant resistance mechanisms can involve mutations or downregulation of PARP enzymes.[36] It should be highlighted that HR gene sequencing, HR deficiency, genomic loss of heterozygosity tests, or some genetics scoring systems can allow detection of several patients as possible candidates for therapy with PARP inhibitors. However, such testing may still overlook some patients for whom the treatment with PARP inhibitors might be beneficial. Therefore, in the future, clinical studies should integrate all the data derived from DNA sequence and gene copy number variation that are relevant to other DNA repair mechanisms, such as nonhomologous end joining, alternative-nonhomologous end joining, and DNA damage regulatory gene processes.[34] In the meantime, g*BRCA*m can be considered

as an indicator for targeted therapy with PARP inhibitors.

POLY(ADP-RIBOSE) POLYMERASE INHIBITORS: CLINICAL IMPLICATIONS, CONCERNS, AND FUTURE DIRECTIONS

PARP inhibitors are generally well tolerated, and their adverse effects (AE) are mostly related to haematologic and digestive tract toxicity (Table 2).[37,38] Such AE can be successfully managed by adjusting doses, and using symptomatic medications or transfusions, if necessary.[37,38] Although PARP inhibitors have revealed therapeutic efficacy mostly in women with advanced BC who harbour g*BRCA*m, their effectiveness outside of g*BRCA*m carriers (e.g., in case of somatic *BRCA* mutations or other genetic mutations) is an important area of future studies. Furthermore, novel predictive biomarkers of responsiveness (beyond g*BRCA*m) are needed in patients with metastatic BC. In addition, exploring the use of PARP inhibitors in combination with other anticancer therapies presents an ongoing challenge. In practice, the PARP inhibitors can be used as single agents, according to the concept of synthetic lethality (because of the defects in HR).[39] Moreover, the PARP inhibitors can be used in combination with other treatments (e.g., CHT or radiotherapy) because PARP inhibitors augment DNA damage and contribute to an increase in overall DNA damage in tumour cells, even without the presence of HRD.[39]

Olaparib, applied as a single agent, has been beneficial in patients with advanced BC and OC, and the median PFS in the case of BC is approximately 6 months.[33] Similarly, talazoparib, which is the most potent PARP inhibitor, has been used as a single agent in women with BC harbouring g*BRCA*m, in which the median PFS was almost 9 months.[40] It should be underscored that for patients with advanced and metastatic BC, *BRCA* testing is very important, together with possible testing for other germline mutations since PARP inhibition is an effective targeted therapy for g*BRCA*m. However, some important questions, which will hopefully be answered in the future trials, involve the following issues:

> Which therapies are most optimal for combination with PARP inhibitors?

> Should PARP inhibitors be introduced into the early-stage BC treatment?

> How effective are PARP inhibitors in BC patients with prior exposure to platinum-based CHT?

> Can intermittent therapeutic dosing of PARP inhibitors be used?

CONCLUSION

For many patients with metastatic BC, treatment with PARP inhibitors can be more effective and less toxic than that of CHT. Because of the underlying defects in DNA repair, cancer cells with *BRCA* mutations are vulnerable to therapies that target PARP. In particular, for malignant tumours with HRD, PARP inhibitors induce synthetic lethality.

Some subtypes of BC with g*BRCA*m or functional (nonmutational) defects in BRCA proteins represent therapeutic targets for PARP inhibitors. Clinical benefits of PARP inhibitors have mostly been accomplished in *BRCA*-associated cancers (such as advanced BC and OC). BC with defects in a specific DNA damage repair pathway is particularly sensitive to targeted therapy with PARP inhibitors. For instance, olaparib (the first PARP inhibitor approved by the FDA) has currently been indicated for the treatment of patients with HER2-negative metastatic BC previously treated with CHT and who harbour deleterious g*BRCA*m. The recent OlympiAD trial has revealed a significant PFS benefit of olaparib compared with the CHT. In addition, PARP inhibitors may offer an effective and safe therapeutic option for women with TNBC. The most common AE of PARP inhibitors include anaemia, neutropenia, nausea, and vomiting.

It should be highlighted that identifying possible predictors of response to PARP inhibitors and strategies to overcome various mechanisms of resistance merit investigation in the future clinical trials. In particular, the HRD assays attempt to use chromosomal instability as a marker. Also, there are many candidate genes beyond *BRCA1/2* that are involved in HR (e.g., *RAD51D*). Advances in genome-sequencing of tumour DNA, combined with modern

bioinformatics, will hopefully contribute to defining a more precise panel of genes that will be helpful in determining profiles of individual patients who may favourably respond to the therapy with PARP inhibitors.

Table 2: Poly(ADP-ribose) polymerase inhibitors: Dosing schedules, adverse effects, and special precautions.

PARP inhibitor	Olaparib (Lynparza)[11,37,38]	Talazoparib (Talzenna)[12]	Rucaparib (Rubraca)[21-23]	Niraparib (Zejula)[24]
Dosing schedule	300 mg PO bid	1 mg PO qd	600 mg PO bid	300 mg PO bid or qd
Adverse effects	Anaemia, leukopenia, fatigue, nausea, vomiting, diarrhoea, abdominal pain.	Fatigue, nausea, headache, alopecia, anaemia, neutropenia, thrombocytopenia, vomiting, diarrhoea, decreased appetite.	Anaemia, leukopenia, fatigue, increased sensitivity to sunburn, nausea, vomiting, diarrhoea, abdominal pain.	Nausea, thrombocytopenia, fatigue, anaemia, constipation, vomiting, abdominal pain, neutropenia.
Special precautions	**Pneumonitis -** interrupt treatment if pneumonitis is suspected, discontinue if it is confirmed; **MDS/AML (rare)** - if confirmed, discontinue olaparib; combination of olaparib with other DNA damaging agents can increase **myelosuppressive toxicity;** coadministration of CYP3A4 inhibitors can increase olaparib plasma concentrations (CYP3A inhibitors should be avoided, or the dose of olaparib has to be reduced, e.g., to 100 mg PO bid).	Coadministration with amiodarone, carvedilol, verapamil, clarithromycin, or itraconazole should be avoided; however, if these agents have to be used, the dose of talazoparib should be reduced (e.g., to 0.75 mg qd).	**MDS/AML (rare)** - if confirmed, discontinue rucaparib; advise patients to use sun protection.	**MDS/AML (rare) -** if it is confirmed, discontinue niraparib; **Hypertension and hypertensive crisis -** use antihypertensive medications and adjust dose of niraparib; **Haematologic adverse reactions** (e.g., if platelet count is ≤10,000/mcL - consider platelet transfusion, or if other agents, such as anticoagulant or antiplatelet agents are used, interrupt anticoagulants or antiplatelet agents or transfuse if necessary).
Monitoring tests	CBC count for cytopenia - at baseline and then monthly; patients have to recover from haematological toxicity (e.g., because of previous therapy) before starting a PARP inhibitor.	CBC count for cytopenia at baseline and then monthly; patients have to recover from haematological toxicity (e.g., because of previous therapy) before starting a PARP inhibitor.	CBC count for cytopenia at baseline and then monthly; patients have to recover from haematological toxicity (e.g., because of previous therapy) before starting a PARP inhibitor.	Monitor BP and pulse monthly for the first year and periodically thereafter during treatment.

AML: acute myeloid leukaemia; bid: twice a day; BP: blood pressure; CBC: complete blood count; CHT: chemotherapy; ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; MDS: myelodysplastic syndrome; PARP: poly (ADP-ribose) polymerase; PO: per os (orally); qd: once a day.

References

1. Miki Y et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science. 1994;266(5182):66-71.

2. Wooster R et al. Identification of the breast cancer susceptibility gene BRCA2. Nature. 1995;378(6559):789-92.

3. Karami F, Mehdipour P. A comprehensive focus on global spectrum of BRCA1 and BRCA2 mutations in breast cancer. Biomed Res Int. 2013;2013:928562.

4. Kuchenbaecker KB et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA. 2017;317(23):2402-16.

5. Howlader N et al. SEER cancer statistics review (CSR) 1975-2014. 2018. Available at: https://seer.cancer.gov/archive/csr/1975_2014/. Last accessed: 09 August 2019.

6. Lecarpentier J et al. Prediction of breast and prostate cancer risks in male BRCA1 and BRCA2 mutation carriers using polygenic risk scores. J Clin Oncol. 2017;35(20):2240-50.

7. Lucas AL et al. BRCA1 and BRCA2 germline mutations are frequently demonstrated in both high-risk pancreatic cancer screening and pancreatic cancer cohorts. Cancer. 2014;120(13):1960-7.

8. Cavanagh H, Rogers KMA. The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers. Hered Cancer Clin Pract. 2015;13:16.

9. Yurgelun MB et al. Cancer susceptibility gene mutations in individuals with colorectal cancer. J Clin Oncol. 2017;35(10):1086-95.

10. Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: Clearing up the misunderstandings. Mol Oncol. 2011;5(4):387-93.

11. Robson M et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med. 2017;377:523-33.

12. Litton JK et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med. 2018;379:753-63.

13. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017;355(6330):1152-8.

14. Liu JF et al. PARP inhibitors in ovarian cancer: Current status and future promise. Gynecol Oncol. 2014;133(2):362-9.

15. Gibson BA, Kraus WL. New insights into the molecular and cellular functions of poly(ADP-ribose) and PARPs. Nat Rev Mol Cell Biol. 2012;13(7):411-24.

16. Pines A et al. Touching base with PARPs: Moonlighting in the repair of UV lesions and double-strand breaks. Trends Biochem Sci. 2013;38(6):321-30.

17. Golia B et al. Poly-ADP-ribosylation signaling during DNA damage repair. Front Biosci Landmark Ed. 2015;20:440-57.

18. Pujade-Lauraine E et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): A double-blind, randomised, placebo-controlled, Phase 3 trial. Lancet Oncol. 2017;18(9):1274-84.

19. Ledermann J 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):852-61.

20. Kaufman B et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33(3):244-50.

21. Coleman RL et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): A randomised, double-blind, placebo-controlled, Phase 3 trial. Lancet. 2017;390(10106):1949-61.

22. Swisher EM et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): An international, multicentre, open-label, Phase 2 trial. Lancet Oncol. 2017;18(1):75-87.

23. Kristeleit R et al. A Phase I-II study of the oral PARP inhibitor rucaparib in patients with germline BRCA1/2-mutated ovarian carcinoma or other solid tumors. Clin Cancer Res. 2017;23(15):4095-106.

24. Mirza MR et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375:2154-64.

25. Winter C 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):1532-8.

26. Mavaddat N 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):134-47.

27. Turner N et al. Hallmarks of the 'BRCAness' in sporadic cancers. Nat Rev Cancer. 2004;4(10):814-9.

28. Couch FJ et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol. 2015;33(4);304-11.

29. Tutt A et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: The TNT Trial. Nat Med. 2018;24(5):628-37.

30. D'Andrea AD. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst). 2018;71:172-6.

31. Balmaña J et al. Phase 1 trial of olaparib in combination with cisplatin for the treatment of advanced breast, ovarian and other solid tumors. Ann Oncol. 2014;25(8):1656-63.

32. Norquist B et al. Secondary somatic mutations restoring BRCA1/2 predict chemotherapy resistance in hereditary ovarian carcinomas. J Clin Oncol. 2011;29(22):3008-15.

33. Tutt A et al. Oral poly (ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: A proof of concept trial. Lancet. 2010;376(9737):235-44.

34. Kondrashova O et al. Secondary somatic mutations restoring RAD51C and RAD51D associated with acquired resistance to the PARP inhibitor rucaparib in high-grade ovarian carcinoma. Cancer Discov. 2017;7(9):984-98.

35. Lheureux S et al. Somatic BRCA1/2 recovery as a resistance mechanism after exceptional response to poly (ADP-ribose) polymerase inhibition. J Clin Oncol. 2017;35(11):1240-9.

36. Pettitt SJ et al. Genome-wide and high-density CRISPR-Cas9 screens identify point mutations in PARP1 causing PARP inhibitor resistance. Nat Commun. 2018;9(1):1849.

37. Le D, Gelmon KA. Olaparib tablets for the treatment of germ line BRCA-mutated metastatic breast cancer. Expert Rev Clin Pharmacol. 2018;11(9):833-9.

38. Domchek SM et al. Efficacy and safety of olaparib monotherapy in germline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more prior therapies. Gynecol Oncol. 2016;140(2):199-203.

39. Murai J et al. Stereospecific PARP trapping by BMN 673 and comparison with olaparib and ruaparib. Mol Cancer Ther. 2014;13(2):433-43.

40. de Bono J et al. Phase 1, dose-escalation, two-part trial of PARP inhibitor talazoparib in patients with advanced germline BRCA1/2 mutations and selected sporadic cancers. Cancer Discov. 2017;7(6):620-9.