New roles of PARP inhibitors in the treatment of breast cancer

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Introduction

While the development of poly-(ADP-ribose) polymerase inhibitors (PARPi) was initially aimed at the sensitization of tumours to DNA interacting chemotherapeutics the discovery of the synthetic lethal effects of PARPi treatment on cells with defects in homologous recombination (HR)[1,2] has led to the clinical development of PARPi for use in several different tumour subtypes including breast, ovarian, prostate and pancreas with germline *BRCA1* and *BRCA2* mutations or biomarker evidence of HR deficiency. The earliest clinical signal of proof of concept was generated in both breast and ovarian cancer patients[3] but as the principle of synthetic lethal targeting of HR defects extends to those with somatic mutations and epigenetic silencing of expression of HR genes such as *BRCA1* and *RAD51C* there was greatest initial interest in clinical development of PARPi in in High Grade Serous Ovarian Cancer (HGSOC) where the combined prevalence of germline, somatic and epigenetic silencing of HR genes is considered highest.[4] Successful registration trials in advanced HGSOC have now led to licensing of a number of PARP inhibitors not only in those with germline *BRCA*1/2 mutations[5–8] but also biomarker evidence of HR deficiency[9] or the functional measure of HR deficiency represented by platinum sensitivity.[10] The progress to phase 3 studies in breast cancer has been more challenging[11] but much progress has been made in recent years leading to marketing authorizations for two PARPi in advanced disease and evidence of effects on pathological response and survival endpoints in early breast cancer as we outline below.

BRCA1 and *BRCA2* genes and Breast Cancer

Approximately 5% of patients with breast cancer carry germline variants in *BRCA1* or *BRCA2* that are classified as pathogenic or likely pathogenic.[12,13] Following the linkage of the *BRCA1 and BRCA2* gene loci to hereditary breast cancer risk in 1990[14] and the cloning of *BRCA1* and *BRCA2* genes, much work focused on further understanding the role of the *BRCA1* and *BRCA2* genes in the DNA damage response (DDR) (reviewed in Tutt et al. 2002[15]). Carriers of heterozygous germline variants in *BRCA1* and *BRCA2* have significantly higher risk of developing cancer where there is somatic loss of the wild-type (wt) allele in the progenitor cells of a tumour leading to loss of function. Compared to sporadic cancers, patients with *BRCA1/2* mutation associated breast cancer are usually younger, they are at increased risk of developing ovarian cancer and are likely to have a strong family history of breast cancer.[16] Interestingly, whilst germline *BRCA1* mutation carriers typically develop basal-like triple negative breast cancers (TNBC), *BRCA2* mutation carriers predominantly develop luminal subtypes[17–19] while patients with *BRCA1/2* mutations do develop breast cancers with pathological features associated with higher risks of recurrence the presence of germline mutation is not itself an adverse prognostic factor in those who receive

chemotherapy[20] perhaps related to an increased sensitivity of tumours to the DNA intercalating chemotherapy drugs.[21,22] It does however highlight the need for novel therapies that can target the tumour cell restricted defect in HR in such patients. Recent evidence has suggested that there is an approximate prevalence of HR deficiency of 60% in TNBC that is caused by both genetic and epigenetic dysregulation of HR gene function in TNBC in particular.[23]

Homologous recombination

HR is a critical pathway of DNA repair in mammalian cells; it is a highly conserved process which utilizes a homologous strand of DNA to act as a template for repair of a double stranded DNA break (DSB), often occurring in the context of an arrested or collapsed DNA replication fork – leading to restoration of the original DNA sequence. BRCA1 and BRCA2 play crucial roles in HR; Upon the development of a DSB the checkpoint kinase ataxia telangiectasia mutant (ATM) recruits BRCA1 to the site of DSB. BRCA1 recruits the MRE11, RAD50 and NBN (MRN) complex in order to promote DNA end resection. This results in the generation of single strands of DNA with 3' projections. BRCA2*,* and another gene associated with hereditary breast cancer risk *PALB2,* assist in the loading of RAD51 on single stranded DNA filaments that search and invade a strand of homologous DNA (most usually in the post replication sister chromatid) to use as a template for DNA synthesis and error free repair.

HR also plays a key role in the mediation of replication fork progression; stalled replication forks are detected by the checkpoint kinase ataxia telangiectasia mutant-rad3 related (ATR) protein kinase and subsequent down-stream effector proteins induce HR, controlling this vital step in DNA replication.[24] When cells become HR deficient due to loss of function of these genome caretaker DNA tumour suppressors, *BRCA1, BRCA2* and PALB2, they seek other methods of DNA repair which are typically error prone including non-homologous end joining (NHEJ) and microhomology-mediated end joining (MMEJ). This leads to accelerated and distinctive forms of mutagenesis and early acquisition of the somatic genome required for tumourigenesis.[25,26]

The role of *PARP1/2*

DDR proteins mediate DNA damage sensing, cell cycle checkpoint responses and DNA repair effector mechanisms – on recognition of DNA damage they halt the cell cycle and allow DNA repair to take place, therefore having a key role in the maintenance of genomic stability. The DDR enzymes PARP1 and 2 are vital to the DDR process and play an important part in base excision repair (BER).[27] Upon sensing single stranded DNA breaks

(SSB) PARP1 is recruited to the site of damaged DNA; it undergoes allosteric changes at this interaction which activate its catalytic function. The PARP enzymes then act as signal transducers in the DDR pathway. Upon binding DNA PARP1 uses nicotinamide adenine dinucleotide (NAD+) to undergo PARylation – a process involving the synthesis of negatively charged PAR chains on target proteins, and recruitment of DNA repair proteins. Following the successful formation of a scaffold for DNA repair, PARP1 autoPARylates releasing itself from the strand of DNA.[28,29]

Synthetic lethality and the preclinical development of PARPi

After discovering the role of PARP1 and PARP2 in the DDR pathway small molecule inhibitors of PARP1 and PARP2 were developed (reviewed in Zaremba et al. in 2007[30]). It was thought that PARPi induce persistent SSBs, leading to stalled replication forks and subsequent replication fork collapse; however more recently studies have shown that most PARPi both inhibit catalytic activity and trap PARP1 onto DNA to varying degrees, preventing PARylation and PARP1 dissociation from the site of DNA damage.[31,32]

Early preclinical models tested PARPi in combination with cytotoxic chemotherapy – based on the rationale that PARPi would offer both chemopotentiation and enhance radiosensitivity.[33–36] The first combination treatment entered the clinic in 2003, and was associated with heightened toxicity, most notably myelosuppression.[37] In 2005 pre-clinical data from two research groups showed that *BRCA* deficient cells were many times more sensitive to PARPi than *BRCA* wild type cells *in vitro* and *in vivo.*[1,2] Synthetic lethality was initially described in 1922 and describes a phenomenon where a defect in one of two genes has no effect but a defect in both genes leads to cell death,[38] this was a first illustration of its use with selective therapeutic intent. In breast cancer cells harboring biallelic mutations in *BRCA1* or *BRCA2*, HR cannot take place whereas normal tissues retain a functioning wt*BRCA* allele and functional HR. As a result the cancer cells undergo cell death and normal cells are spared – leading to selective tumour cell kill.[39]

Early clinical development of PARPi involving breast cancer patients.

After the demonstration of *BRCA1/2* tumour selective synthetic lethality in the pre-clinical setting, and its extension to mutations in DDR genes relevant to familial breast cancer[40] the first exploration of PARPi monotherapy was conducted in a phase 1 trial to evaluate the pharmacokinetics and pharmacodynamics of olaparib. The study included 60 patients, 23 of whom had a *BRCA1/2* mutation; 3 of these patients had breast cancer. Clinical benefit was reported in 63% of *BRCA* carriers treated with olaparib but no objective responses were

seen in patients without *BRCA* mutations providing an early signal that the concept of tumour selective synthetic lethality held true in the clinic.[3] Different properties of PARPi are outlined in figure 1.

These promising findings led to two simultaneous proof-of-concept phase 2 trials involving patients with germline *BRCA* mutations and breast cancer or ovarian cancer[41,42] where approximately 40% of patients achieved objective responses when treated with olaparib despite extensive prior chemotherapy. These results were confirmed with activity restricted to patients with *BRCA* mutations in a succeeding trial with olaparib in breast cancer.[43] Signals of efficacy were also seen in other *BRCA*1/2 mutation associated malignancies such as prostate and pancreatic cancers.[44] Since these initial early phase studies,[3,42–44] phase 1 and 2 trials of other PARPi have included cohorts of patients with HR gene mutations including those with breast cancer[45,46](Table 1).

PARPI in the locally/advanced and/or metastatic breast cancer setting

Monotherapy

Olaparib

Following evidence of activity of olaparib in phase 2 trials,[42–44] a phase 3 open label randomized controlled trial (RCT) (OlympiAD) compared olaparib maintenance treatment with physician choice of standard breast cancer chemotherapy therapy in patients with advanced germline variant *BRCA* associated HER-2 negative breast cancer. Median progression free survival (PFS) was significantly prolonged in the olaparib group compared to chemotherapy (7.0 months vs. 4.2 months), with a hazard ratio (HR) for disease progression or death of 0.58 (95% CI 0.43-0.80; P<0.0001). There was also significantly better preservation of quality of life in the olaparib arm[47] (table 1). Following publication of this data olaparib was approved by regulators in 2018 for use in patients with deleterious or suspected deleterious variants in germline *BRCA1* and/or *BRCA2* and HER-2-negative metastatic breast cancer, who had received prior chemotherapy. Patients with hormone receptor positive breast cancer should have been offered, or been considered for, hormone therapy prior to olaparib. More recently overall survival (OS) analysis in OlympiaD was updated showing median OS was 19.3 months in the olaparib group vs. 17.1 months in the physician's choice group. They noted an OS benefit in the subgroup of patients who had not

received prior chemotherapy for metastatic disease (HR 0.51 95%CI 0.29-0.90).[48] Tung et al. have recently reported a study testing an extension of the approach assessing olaparib response in patients with metastatic breast cancer with somatic mutations in *BRCA1/2* or germline mutations in HR genes beyond *BRCA1/2*. Interestingly, confirmed responses were seen in those with germline PALB2 mutations (overall response rate (ORR), 82%; PFS 13.3months) and somatic *BRCA1/2* mutations (ORR,50%; PFS 6.3 months). This proof of principle trial highlights the importance of genomic profiling of the germline and tumour to determine patients who may benefit from PARPi treatment. Moreover, this trial confirmed that the cohort of patients with genetic forms of *BRCA*ness who might be considered for PARPi in breast cancer is broader than initially hypothesized.[49]

Talazoparib

The EMBRACA phase 3 trial, very similar in design to OlympiaD but using the most potent of the PARPi Talazoparib, reported efficacy in patients who may have received no more than three prior lines of chemotherapy including a taxane and/or anthracycline and were assigned to talazoparib or physician's choice. Median PFS was significantly longer in the talazoparib group compared with standard of care (8.6 months vs 5.6 months, HR for disease progression or death was 0.54 (95%CI 0.41-0.71; p<0.001). Talazoparib also offered improved preservation of quality of life compared to standard of care chemotherapy. It has subsequently been approved by the global regulatory agencies in advanced HER-2 negative breast cancer in germline *BRCA1/2* mutation carriers following the publication of EMBRACA (table 1).[50]

Niraparib

The randomized open label phase 3 trial BRAVO has recently reported the activity of niraparib monotherapy in patients with germline *BRCA1/2* mutated advanced breast cancer. Patients were randomized 2:1 to receive niraparib or physician's choice of chemotherapy. The BRAVO trial reported substantial discordance between local and central review, with the direction of discordance being different for each study arm. This resulted in informative censoring, where many patients considered to have progressed by local assessment were censored for the primary endpoint of PFS by central review, resulting in inflation of the centrally-determined PFS in the physician's choice control arm preventing robust comparison between arms. After a pre-planned interim analysis the investigators halted recruitment. PFS was the primary end point, and at median follow up of 19.9 months the median centrally assessed PFS in the niraparib arm was 4.1 months vs 3.1 months in the physician's choice arm.[51]

The OlympiAD, EMBRACA and BRAVO trial participants had differing baseline characteristics. In particular the proportion of patients treated in the “first line” metastatic setting but in addition, per eligibility criteria, first line patients in BRAVO, but not OlympiAD nor EMBRACA, must have relapsed within 12 months of adjuvant chemotherapy. Cross-trial comparisons are therefore inappropriate. Both OlympiAD and EMBRACA reported patients treated with olaparib or talazoparib had a significant improvement in health-related quality of life and delay in time to deterioration in function and symptoms.

All three trials allowed prior exposure to platinum-based chemotherapy in adjuvant therapy after a 6- or 12-month disease free interval or in advanced disease as long as no progression had occurred on platinum. No trial compared platinum-based chemotherapy to PARPi in germline *BRCA* variant cancers;[47,50] this remains an untested comparison in this indication. There are many ongoing PARPi monotherapy trials summarized in table 2.

Selection of cross-resistance by prior chemotherapy to PARPi monotherapy

In *BRCA*-associated breast cancer, exploitation of the critical weakness in HR repair through use DNA intercalating agents such as platinums has been shown to be advantageous over taxane based chemotherapy. Platinum agents form bulky DNA adducts through inter- and intrastrand DNA crosslinks that would usually be repaired by HR, involving *BRCA2* and *RAD51.*[52,53]

Unlike in ovarian cancer platinums have not been the standard of care in early or advanced breast cancers. However, the Phase 3 TNT Trial evaluated the role of carboplatin vs. the standard of care taxane docetaxel in advanced TNBC testing the hypothesis that subgroups with germline *BRCA* mutations and those with TNBC and epigenetic ‘*BRCA*ness’ might specifically benefit from platinum therapy as a result of a shared phenotypic loss of HR function. While patients with a deleterious *BRCA1* or *2* germline pathogenic variant had a significantly improved PFS in the carboplatin group over the docetaxel group (6.8 months vs 4.4 months, p=0.002) and improved ORR, the study highlighted the biological heterogeneity within TNBC and the differential impacts of genetic and epigenetic HR deficiency in breast cancer. This study raises the hypothesis that epigenetic *BRCA*ness may be a more plastic and reversible HR deficiency target in breast cancer limiting the application of PARPi in advanced breast cancer if selected based on mutational signatures of HR deficiency.[21]

The TNT study[21] and other studies in advanced and early forms of TNBC have led to an increase in the use of platinum agents in patients who have *BRCA1/2* mutations.[54–57] The

selective pressure and potential for consequent selection of cross-resistance has raised the question of impact of increased use of prior platinums on the activity of PARPi in breast cancer. While PARPi have activity in patients with germline *BRCA* mutation and prior platinum exposure there are signals suggesting that response rate may be lower in the setting of recent progression following platinum based therapy.[46] Known mechanisms of resistance to both platinums and PARPi include somatic mutations close to the germline mutation in *BRCA1/2* genes (so called 'reversion mutations') – which may restore the open reading frame of the *BRCA* gene. This leads to *BRCA1/2* driven restoration of HR removing the selective HR deficiency target in these tumours.[58] Other potential mechanisms of resistance include *BRCA1/2* independent mechanisms of HR restoration such as loss of 53BP1 protein,[59] point mutations in PARP1[60] and mutations in the REV7/shieldin complex (proteins which regulate 53BP1 chromatin complex, a vital component of DSB repair pathway).[59,61,62] The study of the prevalence of distinct mechanisms of resistance and cross-resistance to platinums and PARPi in breast cancer that may inform therapy choices appears an urgent need. It is hoped that combining PARPi with cytotoxic chemotherapeutic agents, molecularly targeted agents or immunomodulatory agents may potentiate their effect and reduce the rates of resistance.

PARPi and chemotherapy in advanced breast cancer

Olaparib and Taxanes

Olaparib in combination with chemotherapy agents in the treatment of advanced breast cancer has been studied in phase 1 and 2 trials since 2013, a selection can be found in tables 3&4.[63–68] A phase 1 trial evaluated the toxicity profile of olaparib in combination with paclitaxel in patients with metastatic TNBC. They reported significant neutropenia in the first cohort, leading to enrolment of a second cohort of patients who were given granulocyte-colony stimulating factor (G-CSF) if they developed neutropenia grade ≥2 in first cycle. An encouraging response rate was observed leading to recommendation of alternative dose and schedule to address the high rates of neutropenia.[63]

Olaparib and Platinum agents

A number of early phase trials set out to determine the safety of PARPi in combination with platinum agents. Although platinum and PARPi are not synergistic, in contrast to topoisomerase 1 inhibitors,[69] the fact that both agents create adducts on DNA predicted a likely increase in bone marrow toxicity of the combination. In 2014 a phase 1 trial reported an ORR of 87.5% in patients with germline *BRCA* mutations receiving olaparib and

carboplatin in combination, followed by maintenance olaparib. In the small breast cancer cohort (n=8), 1 achieved complete response (CR) via the Response Evaluation in Solid Tumours (RECIST) version 1.1 criteria, 6 patients achieved partial response (PR) as best response. Toxicity was significant with reports of G3/4 hematological toxicity, with 42.5% of cases suffering from G3 neutropenia.[68] Further phase 1 trials assessing the combination of olaparib with a platinum agent confirmed efficacy but with similar safety signals suggesting that regimen optimization may be required and assessed in phase 2 trials ahead of phase 3 trial assessments.[70]

Rucaparib and Platinum agents

A phase 1 trial published in 2017 reported the safety of oral rucaparib given on days 1-14 combined with carboplatin on day 1 of a 21-day cycle. The majority of patients in the trial had breast cancer, but most had no *BRCA1/2* mutation testing done prior to treatment.[64] They reported 63.6% of patients in the rucaparib and carboplatin group achieved disease control >12 weeks when treated with carboplatin dosed at AUC5. Neutropenia (27.1%) and thrombocytopenia (18.8%) were the most common grade ⩾3 toxicities across combinations and were dose limiting toxicities (DLTs) with this combination. The authors hypothesized that PARPi monotherapy may be sufficiently active in patients with defects in HR but for a wider population of patients without HR defects the combination of PARPi and platinums was both feasible and might be required for activity (table 3).

Veliparib and platinum agents + taxanes

Veliparib is a significantly less potent PARPi with significantly less PARP1 trapping activity than other PARPi in the clinic and that may affect not only single agent activity but also the toxicity of combinations with chemotherapy (reviewed by Tutt in Annals of Oncology[71]). BROCADE was a randomized phase 2 study which included patients with locally recurrent or metastatic breast cancer and a deleterious *BRCA1/2* germline variant. Patients were randomized 1:1:1 to receive veliparib, carboplatin + paclitaxel (VCP), veliparib and temozolomide (VT) or placebo, carboplatin + paclitaxel (PCP). For VCP vs PCP median PFS was 14.1 months vs 12.3 months (HR 0.789; 95%CI 0.536-1.162 p=0.227). ORR was greater in the VCP group (77.8%) vs PCP (61.3%; p=0.027). VT median PFS was 7.4 months (HR 1.858; 95%CI 1.278-2.702, p=0.001) with a far inferior ORR of 28.6% (p<0.001). VT was deemed inferior to PCP and VCP and the weak signal of enhanced effect of VCP was taken into a phase 3 comparison[67] (Table 2). BROCADE 3 randomized similar gBRCA1/2 patients to VCP or PCP, allowing patients to continue with veliparib after failure to tolerate continued chemotherapy in the absence of progression. The trial has reported a modest but significant effect with improved PFS in the veliparib group of 14.5 months vs 12.6

months (HR 0.71; 95%CI 0.57-0.88); p=0.0016) (Table 3). Interestingly this separation of the PFS curves only becomes apparent at the point where chemotherapy has stopped in a majority in both arms of the study. Data on OS has not yet been reported.[72,73]

PARPi and cell cycle checkpoint inhibitor therapies

Preclinical studies have provided a rationale for combination of PARPi with inhibitors of the S and G2/M cell cycle checkpoint kinases Wee1[74] ((Wee1i) or ATR[75] (ATRi). It has also been shown that olaparib resistant models may be re-sensitized to olaparib when combined with Wee1i or ATRi.[76–79] Simultaneous combination treatment of Wee1i plus olaparib revealed significant toxicity in mouse models but toxicity was reduced when delivered sequentially.[80] As TNBC has a high prevalence of signatures of HR Deficiency[23] and replication stress a phase 2 trial has assessed the safety and efficacy of olaparib monotherapy vs. olaparib in combination with the Wee1i AZD 1775 or olaparib in combination with the ATRi AZD6738 in 2 cohorts of patients with advanced TNBC who have a qualifying *BRCA1/2* or other HR gene mutation or a cohort without any HR mutation found in tumour tissue (VIOLETTE trial; NCT03330847). This trial has closed to recruitment, and will provide interesting insights into the relative activity of single agent olaparib and feasibility and toxicity of these combinations in molecularly stratified patient cohorts within TNBC.

Phosphoinositide 3-kinases (PI3K) are oncogenes involved in many cell signaling pathways which control proliferation and differentiation of cells; as such PI3K inhibitors (PI3Ki) are well established in the treatment of many cancers including breast cancer.[81] In 2012 Ibrahim et al. suggested PI3K inhibition results in downregulation of *BRCA1* and *BRCA2* and inhibition of HR leading to sensitization to PARPi in *BRCA* mutant TNBC cell lines.[82,83] Recent data has shown that the oncogenes RAS and PI3K may induce HR, and that inhibition of these key signaling proteins may induce a chemical *BRCA*ness and an HR deficient phenotype.[84] A phase 1 study of PI3Ki BKM120 in combination with olaparib (300mg BD) included 24 breast cancer patients, 18 of whom had germline *BRCA* variants;[85] results were encouraging in that of the 18 patients included, 5 (28%) had partial response and 8 (44%) had stable disease. Known toxicities associated with BKM120 are depression, anxiety and hepatotoxicity. When BKM120 was taken in combination with olaparib 36% of patients suffered from depressive symptoms, with one patient suffering from severe symptoms requiring dose reduction. Transaminase elevation was seen in 20% of patients, with 2 patients suffering severe toxicity requiring dose reduction; a summary of the trials published and ongoing involving small molecule inhibitors in combination with PARPi are found tables 5&6.[86]

The establishment of a role for CDK4/6 inhibitors in the treatment of advanced ER positive HER2 negative breast cancer has been a major advance in recent years (reviewed in the lancet[87] and may have a role in adjuvant therapy. The assessment of the toxicity and efficacy of CDK4/6 inhibitors in combination with PARPi is now an important but understudied area and will be of particular importance in *BRCA2* and *PALB2* germline mutation carriers who more commonly develop Luminal ER positive breast cancers than *BRCA1* carriers. An ongoing Phase 1/2 trial reporting on the safety and efficacy of olaparib when taken in combination with the CDK4/6i palbociclib and selective estrogen receptor down-regulator fulvestrant is still recruiting (HOPE, NCT03685331) (table 5). In addition, a phase 1 trial recently opened for recruitment and will report on the MTD, safety and clinical response in patient's receiving niraparib and abemaciclib (CDK4/6i) in the neoadjuvant setting (NCT0448113)(table 11).

PARPi and immunotherapy

Recent studies have shown an interaction between the DDR and the immune system,[88,89] and patients with defects in DDR genes may have heightened sensitivity to immunotherapy[90,91] There are number studies underway reviewing the safety and efficacy of immunotherapy in conjunction with PARPi and these are outlined in table 7.[92,93] A key phase I/II basket trial (MEDIOLA) reported the 12-week disease control rate (DCR) as the primary endpoint as well as ORR in a group of patients with advanced solid tumours who received olaparib twice daily (300mg oral) in addition to durvalumab (1.5g IV) once every 4 weeks. The 12-week DCR was 80% for the combination and exceeded the prespecified target of 75%.[92] The TOPACIO/KEYNOTE-162 trial reported the use of niraparib in combination with pembrolizumab in patients with advanced TNBC or recurrent ovarian cancer.[93] Although the phase I component involved TNBC patients, the phase 2 trial solely reported on patients with platinum resistant advanced ovarian cancer. Their primary endpoint of ORR was 18% with a disease control rate of 65%.[93]

PARPi in HER-2 positive breast cancer

Ongoing early phase trials are reviewing the dose response and toxicity of niraparib in combination with trastuzumab in patients with metastatic HER-2 positive breast cancer with *BRCA* mutations (clinical trial NCT03368729). While there is no reason to believe that PARPi would be inactive in those with BRCA mutations and HER-2 positive breast cancer, and the toxicity of combination of PARPi with anti-HER-2 antibodies is not expected to be challenging, this subset of patients has been studied in less detail than the HER-2 negative cohort and so reports from future clinical studies will be very helpful.

PARPi in the adjuvant breast cancer setting

Monotherapy

Olaparib

There remained no data for the use of PARPi monotherapy in the adjuvant setting until the recent publication of the OlympiA trial (NCT02032823). An interim analysis drove early reporting, at a median follow up of 2.5 years, of the this phase-3 double blind randomized trial that included patients with high recurrence risk HER-2 negative breast cancer with pathogenic or likely pathogenic *BRCA1* and *BRCA2* variants. All participants had received local treatment and at least six cycles of standard NACT or adjuvant chemotherapy. Patients were randomized to receive olaparib or placebo. The primary end point was invasive disease-free survival (IDFS); at the event driven pre-specified interim analysis IDFS the hazard ratio (HR) was 0.58 (99.5%CI 0.41-0.81; p<0.001) and 3-year IDFS was 85.9% in the olaparib group versus 77.1% in the placebo group. Distant-disease free survival was also significantly improved with an HR of 0.57 (99.5% CI, 0.39 to 0.83; P<0.001).[94] This first trial of PARPi as an adjuvant therapy strategy has changed treatment guidelines[95,96] and is likely to change practice. A limitation of the interpretation of this study is the inability to compare the effects of olaparib with those of second adjuvant capecitabine which has since become part of standard practice in such patients[97] in the sub-population of those with residual disease after NACT for non-biomarker selected sporadic forms of TNBC.

The SUBITO trial has already set out to test a comparison of intensive high dose alkylator chemotherapy and autologous stem cell rescue compared to standard platinum containing NACT followed by a year of olaparib as the standard of care comparator (NCT02810743). A phase 3 RCT reviewing the safety and efficacy of niraparib in patients with stage I-III invasive breast cancer following standard chemotherapy, is due to open for recruitment. Participants must have either HER2- breast cancer with a tumour *BRCA* mutation or have TNBC with wtBRCA tumour but have evidence of circulating tumour DNA (ctDNA) following adjuvant chemotherapy. The ZEST trial (NCT04915755) could offer vital insight into the subgroup of patients with invasive disease without a *BRCA1/2* germline mutation who may benefit from adjuvant PARPi using plasma cell free DNA presence as a risk of recurrence prediction biomarker for patient selection.

Combination therapy

There have been very few trials testing PARPi in combination with other agents in the adjuvant setting; a randomized phase II trial with a small safety “run in” phase was carried out by Kalra et al. who reported the use of cisplatin either alone or in combination with

rucaparib in 128 patients with TNBC or a deleterious *BRCA1/2* pathogenic germline variant and who had significant residual disease after NACT. Twenty-two patients had *BRCA1/2* mutations. This group of patients with residual cancer burden (RCB) II-III have a high-risk of recurrence and poorer prognosis, with only around 35% remaining disease free at 2 years,[98] and so there is a need for the development of more effective treatment regimens. The combination regimen was challenging to deliver due to bone marrow toxicity and did not show an improvement in 2-year DFS compared to cisplatin alone in this phase II study largely conducted in non-biomarker selected TNBC. They acknowledge limitations to their study, notably the lack of a standard of care control arm which at the time the study was conducted would have been placebo.[99]

PARPi in neoadjuvant breast cancer setting

Monotherapy

Olaparib

Data for olaparib treatment as a single agent preceding surgery in early breast cancer is limited. A pioneering presurgical "window of opportunity" study in 2013 assessed the pharmacokinetics and pharmacodynamics of olaparib monotherapy in patients preceding elective breast surgery. Interestingly the study revealed 50% lower plasma olaparib exposure than seen in advanced disease studies – but they reported a mean maximal PARP inhibition in peripheral blood mononuclear cells (PBMCs) and tumour tissue of 51% and 70% respectively;[100] currently there are no neoadjuvant monotherapy trials with olaparib ongoing.

Talazoparib

Pre-clinical data shows talazoparib has highly potent PARP1 trapping capacity, which has been correlated with cytotoxicity.[101] This suggests that talazoparib may have significant single agent efficacy in HR deficient breast cancer. A feasibility study was set up in 2017, to investigate single agent talazoparib in patients with pathogenic germline *BRCA* variants and HER-2 negative primary cancer with tumour sizes over 1cm.[102] The study accrued 13 patients within 8 months and the regimen was considered feasible; given the rapid accrual rate the study was modified into a phase II expansion study determining response rates after 6 months of talazoparib monotherapy.[103] This study enrolled patients with stage II-III HER-2 negative breast cancer with a germline *BRCA* variant. Participants received neoadjuvant talazoparib for 4-6 months without chemotherapy and response was assessed on the surgical specimen. Safety and tolerability were also assessed. Twenty patients enrolled, 19 of whom completed 6 months treatment; ten of these patients had a pathological complete response (pCR); the rate of RCB 0-1 was 100% in patients with germline *BRCA2* variants.

Talazoparib was generally well tolerated in this cohort, with side effects consistent with previous studies and included a significant incidence of anemia and fatigue. Although a small study size, results are striking in reporting pCR in a majority after PARPi monotherapy in *BRCA1/2* mutation associated breast cancer. A second larger study focused on patients with germline *BRCA1* and *BRCA2* mutations and TNBC has recently reported at ASCO2021 showing similarly encouraging efficacy with pCR again being reported in over 50% of patients.[103] Limitations of these studies are the lack of control arms allowing comparison with standard of care chemotherapy but these data suggest that some patients with germline mutations and small tumours might avoid chemotherapy if pCR is achieved. Further information on NACT trials can be found in Tables 8&9.

PARPi in combination with chemotherapy

Veliparib combination with carboplatin in standard of care NACT regimens

As discussed above progress in development of combinations of PARPi with chemotherapies in advanced breast cancer has been limited due to hematological toxicities but, possibly as a result in differences in potency and PARP trapping activity, this has been proven more feasible with veliparib than other PARPi. The ISPY-2 trial was a phase II randomized trial with an Bayesian adaptive design evaluating different therapeutic compounds in the neoadjuvant setting. Patients were randomized to receive a backbone chemotherapy regime containing paclitaxel with or without veliparib-carboplatin, followed by adriamycin and cyclophosphamide for 4 cycles. The primary outcomes were pCR and tolerability and the study met the adaptive designs criterion for “graduation”. This suggested a large-scale phase 3 randomized controlled trial in the TNBC subgroup where a predicted benefit was seen for the carboplatin-veliparib arm in comparison to the control (predicted pCR 51% vs 26% pCR).[104] A significant limitation of the design was the inability to determine if the activity was due to veliparib or carboplatin or the combination. A further phase 3 trial, BrightNEss, compared veliparib and carboplatin in combination with paclitaxel in standard sequential NACT ahead of standard adriamycin and cyclophosphamide for 4 cycles. In this study the experimental arm was also compared with paclitaxel and carboplatin alone and with paclitaxel alone also followed by adriamycin and cyclophosphamide for 4 cycles. The pCR rate in carboplatin containing regimes was significantly greater than paclitaxel alone, but there was no difference between the veliparib-carboplatin group and the carboplatin alone group,the trial was not powered to detect differences in survival endpoints between groups but suggests that differences in treatment effect assessed by pCR is driven by carboplatin rather than the addition of veliparib. There is as yet no available survival data[105] (table 10).

Olaparib in combination with paclitaxel in standard of care NACT regimens

The GeparOLA trial has tested a reduced but continuous dosing of olaparib in combination with paclitaxel in comparison to the standard of care combination of paclitaxel with carboplatin in the neoadjuvant setting. Patient selection included breast cancers with a germline *BRCA1/2* mutation or a mutational signature of HR deficiency. The olaparib group achieved similar pathological response as the carboplatin arm and less toxicity but failed to reach its primary endpoint of exclusion of a pCR rate lower than an ambitious 55%. The hormone receptor subgroups showed a signal of greater efficacy for olaparib over carboplatin with 53% HR+ patients achieving pCR in comparison to 20% in the carboplatin arm but this observation requires validation in larger study. The study suggests that this paclitaxel olaparib regimen is feasible and might improve tolerability while optimizing activity in some subgroups of HR deficient breast cancer.[106]

Olaparib in combination with carboplatin in standard of care NACT regimen

The PARTNER trial is an ongoing 3 stage phase 2/3 trial evaluating the addition of intermittent dose reduced olaparib to carboplatin based neoadjuvant chemotherapy in triple negative and/or *BRCA* mutated breast cancer patients (Table 11). This study has shown the challenges of this combination but has now selected the more tolerable dose and exposure combination and is ongoing.[107]

PARPi and radiotherapy

Pre-clinical studies into the use of PARPi in conjunction with radiotherapy are underway. A study published in 2019 reports PARP1 inhibition with olaparib radiosensitizes models of inflammatory breast cancer to ionizing radiation.[108] This has since been expanded into a phase 2 trial to examine invasive DFS in patients with early inflammatory breast cancer (NCT03598257); there are several trials ongoing involving combination treatment of radiotherapy with PARPi which are outlined in table 12.

Future thoughts

Despite the ability of PARPi to elicit profound and sustained effects among *BRCA*-mutated breast cancer patients, intrinsic and acquired resistance is commonly seen. Understanding resistance mechanisms is vital and will help inform combination therapies to be explored; having an understanding of the patient's germline and their tumours genetic, epigenetic and

transcriptomic profile will help guide us to the most appropriate personalised treatment option. As much important DNA damage response biology is determined by complex post-translation modifications of protein function and dynamic changes in protein localization it will be important to develop methods that can analyze this in breast cancer tissue before, during and after selective pressures of therapy including PARPi. It is clear that both germline and biallelic somatic mutations in the *BRCA* genes are a predictive biomarker for response to PARPi in breast cancer patients. With greater understanding of differential effects of chemotherapy induced selection of resistance mechanisms such as pathogenic *BRCA* reversion mutations,[109] inactivation of key DNA repair pathway proteins such a 53BP1 and REV7[62] and effects on PARPi trapping,[110] we will be better placed to choose which patients are likely to have benefit from adjuvant PARPi use, durable responses to PARPi in advanced disease, benefit from platinums after PARPi and who might benefit from a different or novel targeted therapy approaches.[111,112]

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Figures:

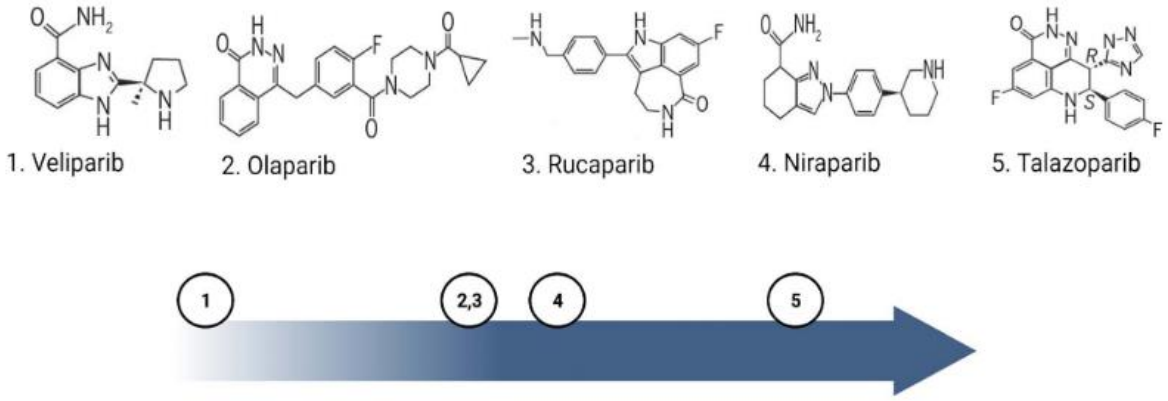

FIGURE 1. PARP1 trapping potency of PARPi (from low to high). Chemical structures of the 5 clinical PARPi discussed are arranged in their
increasing ability to trap PARP1 correlating with their cytotoxic potency. Veliparib is the least potent, whereas talazoparib is the most potent.
Adapted with permission from The American Association for the Advancement of Science, Lord and Ashworth.

Tables:

TABLE 1. Published Advanced Monotherapy Trials

Study Name/ NCT Number	PARPi	Study Phase	Study Population	Treatment Arms	Outcomes	Results	Safety	Reference
NCT00516373	Olaparib	I	Advanced solid tumors n = 60, breast cancer n = 9	Olaparib 400 mg BD oral 28-day cycle	ORR and safety	1 CR, 1 SD (in gBRCA cohort)	At 400 mg BD G3 mood alteration and fatigue 12.5%	Fong et al.,[3] 2009
ICEBERG-1/ NCT00494234	Olaparib	II	*gBRCA1/2m* advanced breast cancer n = 54	Olaparib 400 mg BD oral (n = 27) or 100 mg BD oral (n = 27) 28-d cycle	ORR and safety	In the group receiving 400 mg BD: ORR 41%, 1 CR 10PR; 100 mg BD group: ORR 22%	At 400 mg BD G3/4 nausea 15%; G3 /4 anemia 11%	Tutt et al.,[42] 2010
NCT00679783	Olaparib	II	Advanced HGSOC or TNBC, with or without *BRCAm*. Total n = 91, TNBC n = 26 (10 BRCA carriers)	Olaparib 400 mg BD oral 28-d cycle	ORR and safety	BC group—ORR 0%, PFS 3.6 mo in gBRCAm group vs. wt*BRCA* 1.8 m	G1/2 nausea and vomiting 50% (breast cancer patients)	Gelmon et al.,[43] 2011
NCT01078662	Olaparib	II	Solid tumors with *gBRCA1/2m*; BC treated with >3 lines chemotherapy. Total enrolled n = 298, *gBRCA1/2m* BC n = 62	Olaparib 400 mg BD oral 28-d cycle or SOC chemotherapy	ORR and safety	BC group—ORR 12.9%, PR n = 8, SD > 8 wk = 47%	G3 AEs in 54%; G3 anemia 17%	Kaufman et al.,[44] 2015
NCT00749502	Niraparib	I	Advanced solid tumors enriched for *BRCA* mutations	Part A: niraparib daily 30 mg–400 mg escalation doses in a 21-d cycle (n = 60) Part B: MTD investigated in sporadic platinum-resistant HGSOC and sporadic prostate cancer (n = 100)	MTD, safety, ORR	50% of *BRCA1* or *BRCA2* mutation carriers with breast cancer had PR	G4 thrombocytopenia at dose 400 mg OD	Sandhu et al.,[45] 2013
ABRAZO/ NCT02034916	Talazoparib	II	Advanced breast cancer with *gBRCAm* Cohort 1: after platinum-based therapy (n = 49) Cohort 2: after >3 platinum-free cytotoxic regimens (n = 35)	Talazoparib 1 mg OD oral 28-d cycle	ORR	Cohort 1: ORR 21% Cohort 2: ORR 37%	G1–4 anemia 52%, fatigue 45%, nausea 42%	Turner et al.,[46] 2017
OLYMPIAD/ NCT02000622	Olaparib	III	HER2-ve advanced breast cancer with *gBRCAm*	Olaparib 300 mg BD oral 28-d cycle (n = 205) vs. SOC chemotherapy (physicians' choice)(n = 97)	ORR, PFS	Olaparib vs. SOC: ORR 59.9% vs28.8%; PFS 7 mo vs. 4.2 mo ($P < 0.001$)	Olaparib vs. SOC: G3 toxicities 36.6% vs. 50.5%	Robson et al.,[47] 2017
EMBRACA/ NCT01945775	Talazoparib	III	Metastatic HER2-ve breast cancer with *gBRCAm*—Talazoparib vs. SOC chemotherapy	Talazoparib 1 mg OD oral 28-d cycle (n = 287) vs. SOC chemotherapy (n = 144) (physician's choice)	ORR, PFS	Talazoparib vs. SOC: ORR 62.2% vs. 27.2%, PFS 8.6 mo vs. 5.6 mo ($P < 0.001$)	G3/4 anemia 38%, non-hematologic G3 33%	Litton et al.,[48] 2018

ORR indicates objective response rate; SD, stable disease; TNBC, triple-negative breast cancer; SOC, standard of care.

TABLE 2. Advanced Breast Cancer Monotherapy Trials

Study Name/NCT Number	PARPi	Study Phase	Study Population	Treatment Arms	Outcomes
NCT03990896	Talazoparib	II	Metastatic breast cancer with somatic *BRCA1/2m*; either TNBC with PD after one prior palliative chemotherapy; ER+ HER2-ve with one prior palliative endocrine treatment	Talazoparib 1 mg oral OD 28-d cycle	PFS, ORR and safety profile
COMETA-Breast/ NCT03205761	Olaparib	II	Metastatic TNBC with somatic *BRCA1/2* promoter region methylation in the absence of germline mutations	Olaparib 300 mg BD oral 28-d cycle	ORR, CBR, DOR, PFS, OS and toxicity
NCT04892693	Talazoparib	II	Metastatic breast cancer, with defects in HR genes (including somatic or germline mutations in *BRCA1/2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPPR2A, RAD51B, RAD51C, RAD51D* and *RAD54L*	Talazoparib 1 mg OD oral 28-d cycle	RR, PFS, DOR, CBR, OS and safety profile
NCT02401347	Talazoparib	II	*BRCA1/2* wild type HER2-ve metastatic breast cancer Cohort A: TNBC with HRD score >42 on tumor biopsy; COHORT B HER2-ve with a deleterious germline or somatic mutation in HR pathway genes excluding *BRCA1/2* Cohort B: HER2-ve solid tumors with deleterious hereditary or somatic mutations in the following genes: *PTEN, PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD50, RAD51C, RAD51D, MRE11, ATR,* Fanconi anemia complementation group of genes	Talazoparib 1 mg OD oral 28-d cycle	ORR, CBR, PFS and safety profile
NOBROLA/ NCT03367689	Olaparib	II	Non *BRCAm* metastatic breast cancer Stage 1: TNBC with deficiency in HR Stage 2: ER+ HER2-ve with deficiency in HR	Olaparib 300 mg BD oral 28-d cycle	CBR, safety profile, PFS, ORR, OS
NCT03344965	Olaparib	II	Metastatic breast cancer without *gBRCAm* Cohort 1: germline HR gene mutations; 1a: *gPALB2m* Cohort 2: somatic HR gene mutations; 2a: somatic *BRCAm*	Olaparib 300 mg BD oral 28-d cycle	ORR, CBR, PFS and safety profile
NCT01905592	Niraparib	III	Metastatic HER2-ve breast cancer with *gBRCAm*	Niraparib 300 mg OD oral 28-d cycle vs. SOC chemotherapy (physician's choice)	PFS, OS, safety profile

CBR indicates clinical benefit rate; DOR, duration of response; ER, estrogen receptor; OS, overall survival; RR, response rate; HRD, homologous recombination deficiency; HR, homologous recombination.

TABLE 3. Advanced Breast Cancer Published Trial Combination PARPi and Chemotherapy

Study Name/ NCT Number	PARPi	Study Phase	Study Population	Treatment Arms	Outcomes	Results	Safety	Reference
NCT000707707	Olaparib + paclitaxel	I	Metastatic TNBC after <1 cytotoxic regimen chemotherapy (cohort 1: n = 9, cohort 2: n = 10)	Olaparib 200 mg BD oral 28-d cycle + weekly paclitaxel 90 mg/m2 for 3 wk per 4-wk cycle: Adjustments made: if >G1 neutropenia after C1 added granulocyte colony-stimulating factor	ORR and safety	ORR 37%	Cohort 1: G3/4 neutropenia 44%, Cohort 2: G3/4 neutropenia 20%	Dent et al.,[63] 2013
NCT01009190	Rucaparib + carboplatin	I	Advanced solid tumors including those with breast cancer (n = 22), with *gBRCAm* (n = 7)	Initially IV rucaparib 12–24 mg and chemotherapy (carboplatin, carboplatin/paclitaxel, cisplatin/ pemetrexed or epirubicin/cyclophosphamide) but amended to oral 80–360 mg rucaparib + carboplatin	BRR and safety	1 CR, 1 PR for 3 mo	G3/4 neutropenia 27.1%, thrombocytopenia 18.8%	Wilson et al.,[64] 2017
NCT00782574	Olaparib + cisplatin	I	Advanced solid tumors including those with *gBRCAm* breast cancer: total n = 42, *gBRCAm* n = 17	Olaparib 50–200 mg BD oral and cisplatin 60 mg/m2 IV	ORR and safety	ORR in *gBRCAm* BC 71%	G3/4 neutropenia 16.7% and anemia 9.3%	Balmaña et al.,[65] 2014
NCT01149083	Veliparib + carboplatin	I/II	Metastatic breast cancer with *gBRCAm* n = 71. Phase I n = 27, phase II n = 44	Veliparib BD oral in combination with carboplatin AUC5–6 Phase I: dose escalation of veliparib BD oral 28-d cycle and carboplatin AUC 5–6 on day 1 of 21-d cycle to determine MTD Phase II: single-agent veliparib 400 mg BD PO and combination (veliparib and carboplatin) at progression	ORR and safety	Phase I: MTD veliparib 150 mg BD with carboplatin AUC 5, RR 56% Phase II: ORR = *gBRCA1m* 14%, *gBRCA2m* 36%	Combination therapy G3/4 myelosuppression	Somlo et al.,[66] 2017
BROCADE/ NCT01506609	Veliparib + carboplatin/ paclitaxel	II	Metastatic breast cancer *gBRCAm* n = 290	Veliparib 120 mg BD oral (days 1–7) + temozolomide (VT), or veliparib + carboplatin/paclitaxel (VCP) vs. placebo + carboplatin/paclitaxel (PCP)	PFS, OS, ORR	VCP vs. PCP median PFS 14.1 mo vs. 12.3 mo VT vs. PCP median PFS 7.4 mo vs. 12.3 m	G1–4 neutropenia VT 49.5%, VCP 74.2%	Han et al.,[67] 2018
NCT01445418	Olaparib + carboplatin	I/Ib	Metastatic breast (n = 8) and ovarian cancer (n = 37) with *gBRCAm*	Olaparib 400 mg BD oral on days 1–7, carboplatin (AUC5) IV every 3 wk for 5 cycles	ORR and safety	ORR 87.5% (1 CR and 6PR)	Veliparib vs. control: G3/4 neutropenia/ anemia 81% vs. 86%	Lee et al.,[68] 2014
BROCADE3/ NCT02163694	Veliparib + carboplatin/ paclitaxel	III	Metastatic HER2-ve *gBRCAm* breast cancer: veliparib + carboplatin/ paclitaxel (n = 337) vs. placebo + carboplatin/ paclitaxel (n = 172)	Veliparib + carboplatin/paclitaxel (veliparib group) 1 vs. carboplatin/paclitaxel + placebo (placebo group)	PFS, safety	PFS 14.5 mo (veliparib) vs. 12.6 mo (placebo); $P = 0.0016$	G3 myelosuppression	Diéras et al.,[69] 2020

BRR indicates best radiological response.

TABLE 4. Advanced Breast Cancer Trials With Combination PARPi and Chemotherapy

Study Name/NCT Number	PARPi	Study Phase	Study Population	Treatment Arms	Outcomes
NCT00516724	Olaparib (KU-0059436) +/− carboplatin +/− paclitaxel	I	Advanced solid tumors	1. Carboplatin + olaparib, 2. paclitaxel + olaparib, 3. paclitaxel, carboplatin + olaparib	MTD safety
NCT03641755	Olaparib + sapacitabine	Ib/II	Metastatic breast cancer with *gBRCAm*	Oral olaparib + oral sapacitabine	MTD, ORR
NCT04039230	Talazoparib + sacituzumab govitecan	I	Metastatic TNBC	Oral talazoparib + IV sacituzumab govitecan	DLT, time to tumor response DOR, PFS, OS

TABLE 5. PARPi + Small Molecule Inhibitors/Hormone Treatment/HER2-Directed Therapy

Study Name/ NCT Number	PARPi	Study Phase	Study Population	Treatment Arms	Outcomes
HOPE/ NCT03685331	Olaparib + palbociclib + fulvestrant	I	*gBRCAm* associated HER2-ve, ER+ metastatic breast cancer	Dose incrementation of olaparib 300 mg BD oral, fulvestrant 500 mg IM 1–2× monthly, palbociclib 100 mg oral to MTD	MTD, ORR, CBR
NCT04090567	Olaparib + cediranib (VEGFRi), olaparib + ceralasertib (ATRi)	II	*gBRCAm* HER2-ve metastatic breast cancer	Arm 1. Olaparib BD oral days 1–28, + oral cediranib QDS days 1–28 Arm 2. Olaparib BD oral days 1–28 + ceralasertib oral	ORR, PFS, DOR
NCT03162627	Olaparib + selumetinib (selective inhibitor of MEK)	I	Advanced solid tumors	Dose escalation olaparib oral + selumetinib oral	MTD, determination of drug concentration, anti-tumor activity
NCT04586335	Olaparib + CYH3 (PI3Ki)	I	Advanced solid tumors with DDR mutations and/or PIK3CA mutations, in patients who have progressed on a PARPi	Olaparib 300 mg BD oral 28-d cycle with dose escalation of CYH3 20–40 mg oral	DLT and ORR
NCT03911973	Talazoparib + gedatolisib (PI3Ki)	II	Metastatic TNBC +/− *gBRCAm* breast cancer	Talazoparib 0.75 mg–1 mg OD oral with gedatolisib 150 mg–180 mg IV	MTD, ORR
NCT04703920	Talazoparib + belinostat (HDACi)	I	Metastatic breast cancer, metastatic castrate-resistant prostate cancer and metastatic ovarian cancer	Talazoparib 1 mg OD oral and belinostat up to 1000 mg/m2 IV	DLT
NCT03368729	Niraparib + trastuzumab	I	Metastatic HER2+ve breast cancer	Niraparib 100 mg −200 mg OD oral with trastuzumab 6 mg/kg IV	DLT, ORR
NCT04240106	Niraparib + aromatase inhibitors	II	Metastatic HER2-ve breast cancer with *gBRCAm* or wt*BRCA* + HRD	Niraparib 100 mg–300 mg OD oral + AI (not specified) oral	CBR, PFS, ORR
NCT03154281	Niraparib + everolimus	I	Metastatic HER2-ve breast cancer or metastatic ovarian cancer	Niraparib 100 mg–300 mg OD oral + everolimus 5 mg OD oral	MTD, toxicity and ORR
NCT04764084	Niraparib + anlotinib (EGFR inhibitor)	I	Metastatic HER2-ve solid cancers with germline HR gene mutations	Niraparib 100–200 mg OD oral + anlotinib 12 mg QDS oral	DLT, ORR, PFS
NCT03742245	Olaparib + vorinostat (HDACi)	I	Metastatic HER2-ve breast cancer	Olaparib dose escalation oral + vorinostat dose escalation oral	MTD, DLTs, ORR
OPHELIA/ NCT03931551	Olaparib + trastuzumab	II	Metastatic HER2+ve breast cancer with *gBRCAm*	Olaparib 300 mg BD oral with trastuzumab 4 mg/kg IV	CBR, ORR, PFS

ATRi indicates ataxia telangiectasia mutated Rad3 related protein kinase inhibitor; HDACi, histone deacetylase inhibitor; EGFR, epidermal growth factor receptor; PI3Ki, phosphoinositide-3 kinase inhibitor; VEGFR, vascular endothelial growth factor receptor inhibitor.

importance in *BRCA2* and *PALB2* germline mutation carriers who more commonly develop Luminal ER–positive breast cancers than *BRCA1* carriers. An ongoing phase I/II trial reporting on the safety and efficacy of olaparib when taken in combination with the CDK4/6i palbociclib and selective ER down-regulator fulvestrant is still recruiting (HOPE, NCT03685331) (Table 5). In addition, a phase

TABLE 6. Published Trials of PARPi + Small Molecule Inhibitors/Hormone Treatment/HER2-Directed Therapy

Study Name/ NCT Number	PARPi	Study Phase	Study Population	Treatment Arms	Outcomes	Results	Reference
—	Olaparib + AKTi	I	Advanced solid tumors, 18 BC 7 *gBRCAm* and 1 *gPALB2m*	Arm 1: Olaparib 300 mg BD oral + capivasertib (4 days on–3 days off) Arm 2: Olaparib 300 mg BD oral + capivasertib (2 days on–5 days off)	Clinical benefit	44% achieved clinical benefit, 71.4% of *gBRCAm* patients achieved clinical benefit	Yap et al.,[86] 2020

AKTi indicates protein kinase B inhibitor.

TABLE 7. Immunotherapy + PARPi Published and Ongoing Trials

Study Name/ NCT Number	PARPi	Study Phase	Study Population	Treatment Arms	Outcomes	Results	Reference
NCT03025035	Olaparib + pembrolizumab	II	Advanced breast cancer with *gBRCAm*	Olaparib 300 mg BD oral with pembrolizumab 200 mg IV on D1 of each 3-wk cycle	ORR, PFS, OS	Ongoing	
MEDIOLA/ NCT02734004	Olaparib + durvalumab	I/II	Basket trial: 4 cohorts; 1. *gBRCAm* advanced breast cancer, 2. *gBRCAm* advanced ovarian cancer, 3. advanced ovarian cancer, 4. advanced gastric cancer and relapsed SCLC Total n = 34	Olaparib 300 mg BD oral with durvalumab 1.5 g IV on D1 of each 4-wk cycle until disease progression	Disease control at 12 wk, ORR, OS	12-wk DCR 80%, median OS 21.5 mo, ORR63%.	Domchek et al.,[92] 2020
PHOENIX/ NCT03740893	DDR AGENT AZD6738 monotherapy, or olaparib monotherapy or durvalumab monotherapy	IIa	Presurgical window of opportunity (WOP) and postsurgical adjuvant biomarker study in patients with high residual disease TNBC	Part 1: preoperative exposure of 160 mg AZD6738 BD on days 5–14 of the WOP or 300 mg olaparib PO BD days 1–14 of the WOP or 1.5 g durvalumab IV on day 1 of WOP Part 2: 12 mo post-operative exposure to 160 mg AZD6738 BD PO on days 1–14 of a 28 day cycle or 300 mg BD PO continuous of days 1–28 of a 28-d cycle or 1.5 g durvalumab IV on day 1 of a 28-d cycle	Change in mean proliferation index, change in gene expression signatures, change in $CD8^-$ TILS and interferon $-\gamma^+$ post immunotherapy	Ongoing	
TOPACIO/ NCT02657889	Niraparib + pembrolizumab	I/II	Phase I: n = 14; 9 with recurrent ovarian cancer, 5 with TNBC Phase II: n = 53 (all with ovarian carcinoma)	Phase I: dose escalation of niraparib + 200 mg pembrolizumab IV Phase II: RP2D niraparib 200 mg OD oral + pembrolizumab 200 mg IV on day 1 of each 21-d cycle	Phase I: DLT, establish RP2D Phase II: ORR	ORR 18%, 12 wk DCR 65%	Konstantinopoulos et al.,[93] 2019
NCT03801369	Olaparib + durvalumab	II	Metastatic TNBC	Olaparib 300 mg BD oral +1.5 g durvalumab IV every 4 wk	ORR, safety, CBR, PFS	Ongoing	
NCT02849496	Olaparib + atezolizumab	II	Metastatic HER2-ve breast cancer with HRD	Olaparib 300 mg BD oral compared vs. Olaparib 300 mg BD oral + atezolizumab IV every 21 d	PFS, ORR, DOR	Ongoing	
I-SPY2/ NCT01042379	Olaparib + durvalumab	II	Invasive breast cancer	Olaparib 300 mg BD oral with 1.5 g durvalumab IV every 4 wk	Pathological response in surgical specimen	Ongoing	

RP2D indicates recommended phase II dose.

TABLE 8. NACT Monotherapy PARPi Published Data

Study Name/ NCT Number	PARPi	Study Phase	Study Population	Treatment Arms	Outcomes	Results	Safety	Reference
NCT02282345	Talazoparib	II	Stage I–III *gBRCAm* HER2-ve breast cancer n = 20	Talazoparib 1 mg OD oral—for 6 mo preceding surgery	Pathological response in surgical specimen	RCB 0/1 63%	40% G3 anemia	Litton et al.,[102] 2017

TABLE 9. NACT Monotherapy PARPi Ongoing Trials

Study Name/NCT Number	PARPi	Study Phase	Study Population	Treatment Arms	Outcomes	Results
NCT03499353	Talazoparib	II	Stage I–III HER2-ve, *gBRCAm*	Talazoparib 1 mg OD oral—for 6 mo preceding surgery	Pathological response in surgical specimen	Ongoing
NCT03329937	Niraparib	II	Stage II–III HER2-ve, *gBRCAm*	Niraparib 200 mg OD oral—for 2 mo preceding surgery	Tumor response by MRI	Ongoing

TABLE 10. NACT Combination PARPi + Chemotherapy Published Data

Study Name/ NCT Number	PARPi	Study Phase	Study Population	Treatment Arms	Outcomes	Results	Reference
I-SPY 2/ NCT01042379	Veliparib + NACT	II	Stage II or III TNBC	Group 1: veliparib + standard NACT (n = 39) Group 2: standard NACT alone (n = 21)	Pathological response in surgical specimen	pCR = 51% (veliparib) vs. 26% (control)	Rugo et al.,[104] 2016
BrighTNess NCT01818063	Veliparib + carboplatin/ paclitaxel	III	Stage II or III TNBC	Weekly paclitaxel +/− carbo +/− veliparib	Pathological response in surgical specimen	pCR 53% (veliparib/carbo) vs. 58% (carbo alone)vs. 31% (paclitaxel group)	Loibl et al.,[105] 2018
GeparOLA/ NCT02789332	Olaparib + weekly paclitaxel	II	Stage I–III HER2$^-$ HRD breast cancer	Group 1: olaparib + paclitaxel Group 2: carboplatin + paclitaxel	Pathological response in surgical specimen	pCR 55.1% (olaparib) vs. 48.6% (carbo)	Fasching et al.,[106] 2019

TABLE 11. NACT Combination PARPi + Chemotherapy/Hormone Treatment Ongoing Trials

Study Name/NCT Number	PARPi	Study Phase	Study Population	Treatment Arms	Outcomes	Results
NCT03150576/ PARTNER	Olaparib	II/III	Stage I–III TNBC +/– *gBRCAm* breast cancer	Carboplatin/paclitaxel +/− olaparib	Feasibility, safety	Ongoing
NCT04481113	Niraparib	I	Stage II–III ER+, HER2-ve breast cancer	Dose escalation niraparib OD oral with abemaciclib BD oral for 2–4 cycles preceding surgery	MTD, clinical response, pathological response in surgical specimen	Ongoing

TABLE 12. PARPi + Radiotherapy Ongoing Trials

Study Name/NCT Number	PARPi	Study Phase	Study Population	Treatment Arms	Outcomes	Results
NCT04683679	Olaparib	II	Recurrent or metastatic TNBC with one site requiring palliative RT	Arm 1: pembrolizumab, RT + olaparib, Arm 2: pembrolizumab + RT	ORR	Ongoing
NCT03598257	Olaparib	II	Inflammatory breast cancer without metastases, must have completed NACT prior to mastectomy	Arm 1: RT + olaparib 300 mg BD throughout RT. Arm 2: RT alone	Invasive disease-free survival, locoregional recurrence-free survival	Ongoing
RadioPARP/ NCT03109080	Olaparib	II	Inflammatory, locoregionally advanced or metastatic TNBC	1 wk of olaparib alone, followed by 5 wk of olaparib + RT	MTD of olaparib	Ongoing
NCT03945721	Niraparib	II	Nonmetastatic TNBC, for PORT	Postoperative concurrent RT with niraparib	MTD, locoregional relapse	Ongoing

PORT indicates postoperative radiotherapy; RT, radiotherapy.