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REVIEW

Advances in the use of PARP inhibitor therapy for breast cancer

Kelly E McCann MD, PhD, Sara A Hurvitz MD

David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA, USA

Abstract

Poly-ADP-ribose polymerase 1 (PARP-1) and PARP-2 are DNA damage sensors that are most active during S-phase of the cell cycle and that have wider-reaching roles in DNA repair than originally described. BRCA1 and BRCA2 (Breast Cancer) proteins are involved in homologous recombination repair (HRR), which requires a homologous chromosome or sister chromatid as a template to faithfully repair DNA double-strand breaks. The small-molecule NAD+ mimetics, olaparib, niraparib, rucaparib, veliparib, and talazoparib, inhibit the catalytic activity of PARP-1 and PARP-2 and are currently being studied in later-stage clinical trials. PARP inhibitor clinical trials have predominantly focused on patients with breast and ovarian cancer with deleterious germline *BRCA1* and *BRCA2* mutations (g*BRCA1/2*+) but are now expanding to include cancers with known, suspected, or more-likely-than-not defects in homologous recombination repair. In ovarian cancer, this group also includes women whose cancers are responsive to platinum therapy. Olaparib was FDA-approved in January 2018 for the treatment of g*BRCA1/2*+ metastatic breast cancers. g*BRCA1*+ predisposes women to develop triple-negative breast cancers, while women with g*BRCA2*+ tend to develop hormone-receptor-positive, human epidermal growth factor receptor 2 negative breast cancers. Although PARP inhibitor monotherapy strategies seem most effective in cancers with homologous recombination repair defects, combination strategies may allow expansion into a wider range of cancers. By interfering with DNA repair, PARP inhibitors essentially sensitize cells to DNA-damaging chemotherapies and radiation therapy. Certainly, one could also consider expanding the utility of PARP inhibitors beyond g*BRCA1/2*+ cancers by causing DNA damage with cytotoxic agents in the presence of a DNA repair inhibitor. Unfortunately, in numerous phase I clinical trials utilizing a combination of cytotoxic chemotherapy at standard doses with dose-escalation of PARP inhibitors, there has generally been failure to reach monotherapy dosages of PARP inhibitors due to myelosuppressive toxicities. Strategies utilizing angiogenesis inhibitors and immune checkpoint inhibitors are generally not hindered by additive toxicities, though the utility of combining PARP inhibitors with treatments that have not been particularly effective in breast cancers somewhat tempers enthusiasm. Finally, there are combination strategies that may serve to mitigate resistance to PARP inhibitors, namely, upregulation of the intracellular PhosphoInositide-3-kinase, AK thymoma (protein kinase B), mechanistic target of rapamycin (PI3K–AKT–mTOR) pathway, or perhaps are more simply meant to interfere with a cell growth pathway heavily implicated in breast cancers while administering relatively well-tolerated PARP inhibitor therapy.

Keywords: *BRCA1*, *BRCA2*, breast cancer, niraparib, olaparib, PARP inhibitor, rucaparib, talazoparib, veliparib.

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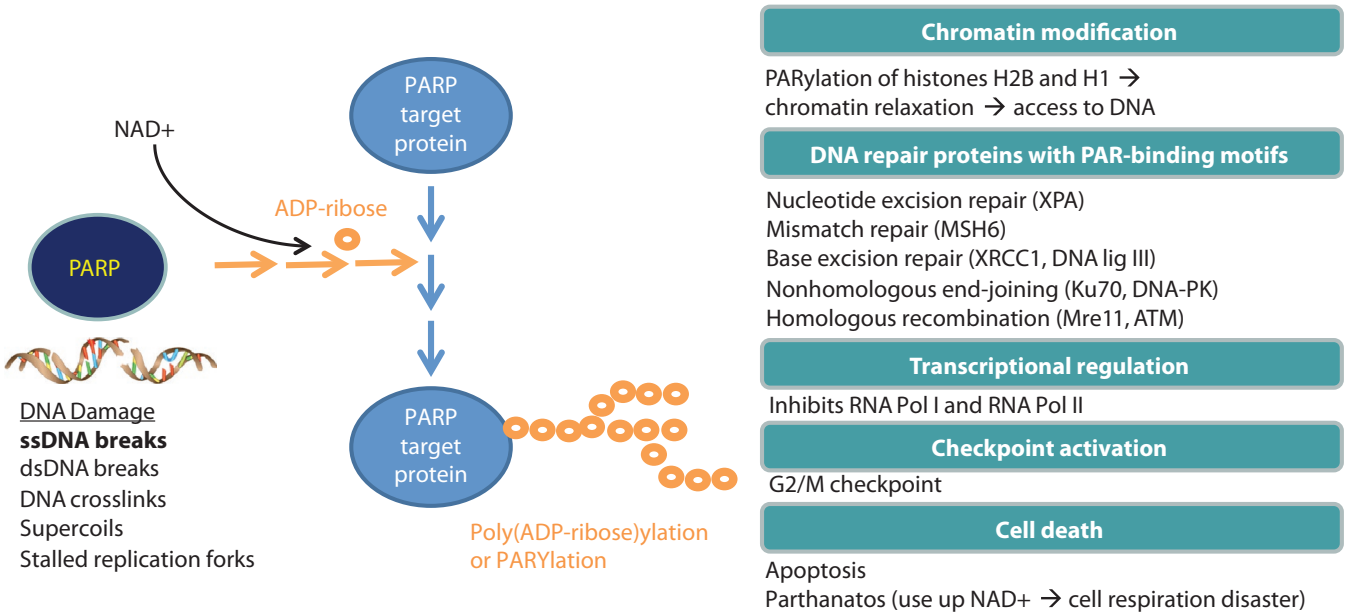
Introduction

In the care of oncology patients, poly-ADP-ribose polymerase (PARP) inhibitors are best known as a semitargeted treatment for *BRCA1*- and *BRCA2*-associated ovarian and breast cancers, but a broader understanding of PARP biology has spurred interest in expanding their clinical utility (see Figure 1). Using NAD+ as a substrate, PARP enzymes catalyze the addition of linear and branching chains of ADP-ribose to aspartic acid, glutamic acid, and/or lysine amino acids on acceptor proteins in a process termed poly-ADP-ribose-ylation ('PARylation').[1] Seventeen PARP enzymes have been discovered, with their functionalities primarily determined by their target-binding domains, cellular compartment localization signals, and tertiary structures.[1,2] PARP-1 and PARP-2 localize to the nucleus and undergo conformational changes to become catalytically activated upon binding to exposed DNA. They effectively act as sensors of DNA damage – including single-strand and double-strand DNA breaks, DNA supercoils, DNA crosslinks, and stalled replication forks – and facilitate DNA repair processes at the

Figure 1. PARP's diverse roles in DNA repair.



PARP-1 and PARP-2 recognize DNA damage, including single-strand and double-strand DNA breaks, DNA crosslinks, supercoils, and stalled replication forks. Upon binding to DNA, PARP-1 and PARP-2 become catalytically active, utilizing nicotinamide as a substrate to add ADP-ribose chains to target proteins in a process termed 'PARylation.' PARylation of histones H2B and H1 relaxes the chromatin to allow access to DNA for repair, the G2/M checkpoint is activated to allow time to repair DNA, DNA repair proteins are recruited to the site of damage, and transcription is temporarily halted via PARylation of RNA Pol I and RNA Pol II. PARP-1 also has roles to play in cell death if DNA cannot be repaired, both as an active participant in apoptosis and indirectly by draining the cell of its nicotinamide resources, which is necessary for normal cell respiration.
ATM, Ataxia telangiectasia mutated serine/threonine kinase; dsDNA, double-stranded DNA; NAD+, nicotinamide; PARP-1, poly-ADP-ribosyl polymerase 1; PARylation, poly(ADP-ribose)ylation; ssDNA, single-stranded DNA.

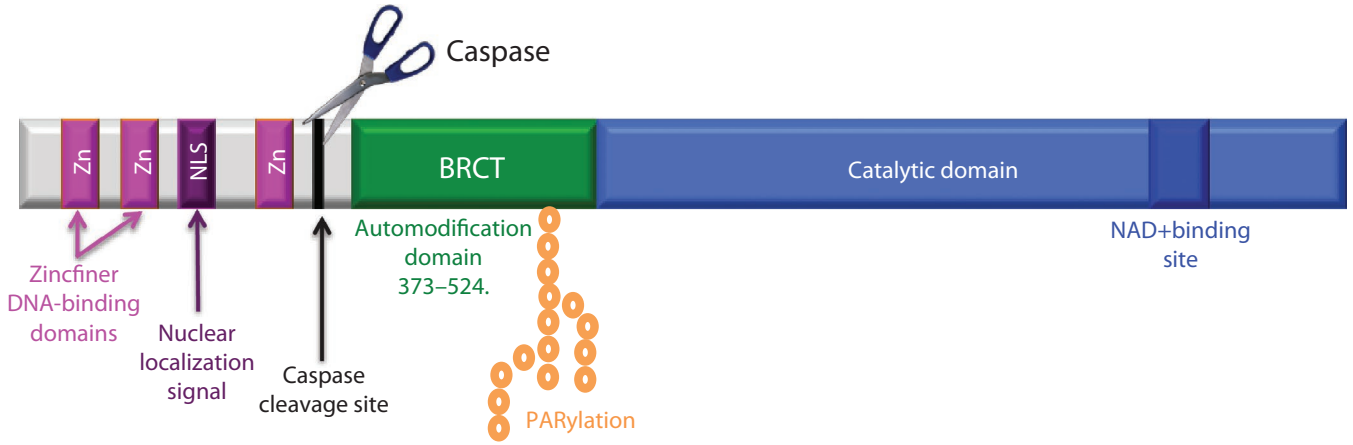
site of damage.[3] PARP-1 self-PARylates its automodification domain to release itself from DNA, a process that is inhibited in the presence of PARP inhibitors (PARPi) and has been termed 'PARP-trapping.'[2,4,5]

PARP-1 and PARP-2 are the primary targets of PARPi in clinical development due to their roles in the repair of DNA, but the understanding of PARP-1's role in DNA repair has shifted over time. PARP-1 was originally described as part of the base excision repair (BER) pathway based on genetic studies, but PARP-1 and PARylation are now known to have much wider-reaching roles in all major DNA repair pathways. PARP-1 has been implicated in chromatin relaxation by histone modification, recruitment of repair proteins to the site of DNA damage, inhibition of transcription through PARylation of Ribonucleic acid (RNA) polymerases I and II, cell cycle arrest, and apoptosis.[2,6–8] During apoptosis, caspase-mediated cleavage of PARP-1 releases the N-terminal nuclear localization signal and DNA-binding domains from the C-terminal catalytic and auto-PARylation domains, uncoupling DNA repair and DNA binding (Figure 2).[2,3,9] The N-terminal fragment of 'cleaved PARP' binds DNA in a natural form of PARP-trapping to prevent DNA repair, replication, and transcription in a dying cell.[9]

PARPi are molecular mimics of nicotinamide that compete with NAD+ at the catalytic site of PARP enzymes and thus prevent PARylation. Their specificity for one or more of the PARP enzymes varies, as does their potency.[10–12] By interfering with its ability to PARylate itself but not its ability to bind DNA, PARP-1 inhibitors also result in PARP-trapping.[4,5] In addition to interfering with DNA repair, transcription, and replication, PARP-trapping can itself cause lethal DNA double-strand breaks during S-phase by collapse of stalled replication forks.[13] The most well-represented PARPi in clinical trials include olaparib, veliparib, niraparib, rucaparib, and talazoparib.[14–18] Although iniparib was found to inhibit PARP-1 function *in vitro* and was tested in clinical trials, it was eventually found to bind to PARP-1's zinc-finger domain rather than the catalytic domain and is no longer considered to be a PARP inhibitor for the purposes of clinical trial research.[19,20]

Early clinical trials were designed to use PARPi in patients with germline *BRCA1* or *BRCA2* mutations with breast and ovarian cancers deficient in DNA repair by HRR due to acquired loss of *BRCA1/2* heterozygosity.[21–23] With an understanding of PARP as a BER enzyme, the PARPi were thought to contribute to a type of 'synthetic lethality' by

Figure 2. PARP-1 protein domains.



PARP-1 and PARP-2's protein domains include zing finger DNA-binding domains and a nuclear localization signal on the N-terminus. Their catalytic domain with NAD+ binding site is located on the C-terminus. Unique to PARP-1 is a BRCT domain upon which PARP-1 auto-PARylates itself, undergoing a conformational change that frees the protein from its DNA target, and a caspase cleavage site that separates the DNA-binding domains from PARP-1's DNA repair functions.[2,3]
BRCT, BRCA1 C-terminus domain; NAD+, Nicotinamide adenine dinucleotide; NLS, nuclear localization signal; PARP-1, poly-ADP-ribosyl polymerase 1; PARylation, poly(ADP-ribose)ylation; Zn, zinc finger DNA-binding domains.

which inhibition of two DNA repair pathways contributes to preferential cell kill in HRR-deficient cancerous cells over normal cells. As knowledge of PARP-1's roles and the mechanisms by which PARPi exert their efficacy has expanded, an updated basic science understanding also considers PARPi as 1) interfering with the identification of DNA damage and multiple types of repair, 2) predominantly exerting their effects during S-phase when dependence on PARP-1 and PARP-2 is highest, DNA is exposed for replication, and HRR is preferred over nonhomologous end-joining (NHEJ) for repair of DNA double-strand breaks, and[3] likely to be strongly dose-dependent if PARP-trapping is a clinically relevant *in vivo* mechanism.[1,4–6,8] These concepts drive some of the PARPi combination trials, as is most evident in the plethora of combination clinical trials for ovarian cancer.[24]

Current PARPi clinical trials registered with the National Institutes of Health's United States National Library of Medicine in ClinicalTrials.gov which include patients with breast cancer are listed in Table 1, which is headed by monotherapy trials followed by combination trials, organized by type of combination (e.g. PARPi + chemotherapy) and clinical trial phase from I to III within each category, and includes trial characteristics, patient population (with gBRCA1/2 bolded if a requirement for a particular trial), trial interventions with the PARPi bolded for easy reference, and outcome measures. Search terms were 'breast cancer' and 'PARP.' Data for individual trials were garnered using the Google and Google Scholar search engines to identify published manuscripts and oncology conference abstracts.

PARP inhibitor monotherapy

Olaparib, rucaparib, and niraparib are approved for use in ovarian cancer as monotherapy.[104–110] Efficacy data for PARP inhibitor monotherapy in breast cancer patients primarily come from early stage clinical trials. However, two phase III studies evaluating single agent PARP inhibition (olaparib and talazoparib) in advanced breast cancer have recently been reported, resulting in the first regulatory approval of a PARP inhibitor for breast cancer. The results of monotherapy studies are reviewed later.

Olaparib

In 2009, Fong et al. published the results of a phase I clinical trial (NCT00516373) of olaparib in patients with advanced solid tumors followed by an expansion cohort enriched for g*BRCA1/2*+ patients with ovarian and breast cancers.[27] One of the nine breast cancer patients – g*BRCA2*+ with extensive pulmonary metastases and progression on anthracycline-based chemotherapy – had a complete response (CR) that lasted over 60 months. An additional 3/9 breast cancer patients, one g*BRCA2*+ and two *BRCA* wild-type (*BRCA*-wt), had stable disease (SD) for 4 months or more.

The nature of phase I clinical trials with cytotoxic therapies is to dose-escalate to a maximum tolerated dose (MTD) based on dose-limiting toxicities (DLTs) to establish a recommended phase II dose (RP2D). The minimal effective dose is not usually determined, though in clinical practice cytotoxic therapies are often dose-reduced from standard doses according to an

Table 1. Breast cancer clinical trials with PARP inhibitors registered with clinicaltrials.gov as on April 2018.

NCT number (Trial name)	Trial phase, design	Eligible population*	Interventions	Primary outcomes	Secondary outcomes
PARP inhibitor monotherapy					
NCT03329937[25] *Recruiting*	I NR SG O **Neoadj**	Women **gBRCA1/2+** HER2– breast carcinoma >1 cm in neoadjuvant setting	• **Niraparib**	MRI RadR	pCR, TRR, S/T
NCT00749502[26]	I NR SG O Adv	All genders Advanced malignancies including HER2– breast cancer after ≤1 cytotoxic regimen	• **Niraparib**	DLT, MTD, PD	Not given
NCT00516373[27]	I NR SG O Adv	All genders Advanced solid tumors, incurable. Expansion cohort with gBRCA1/2+ enriched population, primarily ovarian	• **Olaparib**	DLT, MTD, RP2D	ORR
NCT00777582[28]	I R X O Adv	All genders Stage I: Advanced solid tumors refractory to standard therapies Stage II: Solid tumors, particularly gBRCA1/2+ breast or ovarian cancer	• **Olaparib**, 300 mg tablet po bid • **Olaparib**, 400 mg capsule po bid • **Olaparib**, 400 mg tablet po bid	PK, RP2D	PD, S/T
NCT02210663[29,30]	I NR SG O Adv	All genders, 20 yo and up **gBRCA1/2+** advanced breast cancer after anthracyclines and/or taxane (in Japanese patients)	• **Veliparib**	DLT	PK, AEs, SD, PR, CR
NCT00892736[31,32]	I NR SG O Adv	All genders, 19 yo and up gBRCA1/2+ cancers, ovarian cancer, and HER2– basal-like breast cancer with progression after standard therapies	• **Veliparib**	MTD, DLT, RP2D	PK, CR, PR, SD, AEs, PD

(*Continued*)

Table 1. (*Continued*)

NCT01989546[33] *Recruiting*	I/II NR SG O Met	All genders **gBRCA1/2+** metastatic breast cancer after ≥1 cytotoxic treatment	• **Talazoparib**, 1 mg po daily	PD	CR, PR
NCT01286987[34,35]	I/II NR SG O Adv	All genders Ph I: Inoperable locally advanced or metastatic solid tumor Ph II: **gBRCA1/2+** breast cancer after ≤4 cytotoxic regimens	• **Talazoparib**	MTD	AEs, PK, RP2D, ORR
NCT00494234 (**ICEBERG 1**)[36,37]	II NR P O Adv	Women **gBRCA1/2+** advanced breast cancer after failure of ≥1 cytotoxic	• **Olaparib**, 100 mg bid • **Olaparib**, 400 mg bid	ORR	CBR, PFS, DOR, ECOG
NCT00679783[38,39]	II NR P O Adv	All genders Advanced, recurrent **gBRCA1/2+** breast cancer or TNBC. Also included ovarian cancer patients	• **Olaparib**, 400 mg po bid	ORR	DCR, DOR, PFS
NCT03344965[40] *Recruiting*	II NR P O Met	All genders gBRCA1/2 wild-type, metastatic breast cancer with genetic HRD or deleterious somatic BRCA1/2 mutation	• **Olaparib**	ORR	CBR, PFS, SD, AEs
NCT02681562 (**OLTRE**)[41]	II R P O **Neoadj**	Women Locally advanced TNBC (arm A) or gBRCA1/2+ breast cancer (arm B)	• **Olaparib**	Correlate gene expression and protein with clinical response	ORR, S/T, QoL

(*Continued*)

Table 1. (*Continued*)

NCT number (Trial name)	Trial phase, design	Eligible population*	Interventions	Primary outcomes	Secondary outcomes
NCT02299999 (**SAFIR02_ Breast**)[42] *Recruiting*	II R P O Met	All genders Metastatic HER2– breast cancer after ≤2 cytotoxic regimens	• Targeted therapy** (including **olaparib**, 300 mg po bid) • Chemotherapy or bevacizumab • Immunotherapy with PDL1 inhibitor durvalumab	PFS	PFS, OS, ORR, PR, CR, SD, S/T
NCT00664781[43]	II NR SG O Adv	All genders **gBRCA1/2+** inoperable locally advanced or metastatic breast cancer or ovarian cancer	• **Rucaparib**, 600 mg po bid	ORR, S/T	TTP, OS, PK
NCT02505048 (**RUBY**)[44] *Recruiting*	II NR SG O Met	Women Metastatic gBRCA1/2 wild-type, HER2– breast cancer after ≥1 chemo with 'BRCAness' by Clovis genomic signature or BRCA1/2 somatic mutation	• **Rucaparib**, 600 mg po bid	CBR	CR, PR, SD, PFS, OS, AEs
NCT02034916 (**ABRAZO**)[45,46]	II NR P O Adv	All genders **gBRCA1/2+** locally advanced or metastatic breast cancer with a documented PR or CR to platinum for metastatic disease or ≥2 nonplatinum regimens in the metastatic setting	• **Talazoparib**, 1 mg, after exposure to platinum • **Talazoparib**, 1 mg, without prior exposure to platinum in metastatic setting	ORR	CBR, DOR, PFS, OS, AEs, S/T, PK, QoL
NCT02286687[47] *Recruiting*	II NR SG O Adv	All genders Advanced or metastatic solid tumors with HRD due to somatic mutations	• **Talazoparib**, 1 mg po daily	CBR, CR, PR, SD	Not given
NCT02401347[48] *Recruiting*	II NR P O Adv	All genders Advanced BRCA1/2 wild-type TNBC with HRD by Myriad's HRD assay or HER2– cancer with HR gene deficiency excluding BRCA1/2+ after ≥1 cytotoxics	• **Talazoparib**, 1 mg po daily	ORR	CBR, PFS, AEs

(*Continued*)

Table 1. (*Continued*)

NCT01905592 (**BRAVO**)[49]	III R P O Adv	All genders **gBRCA1/2+**, HER2– metastatic or incurable locally advanced breast cancer after ≤2 cytotoxic regimens	• **Niraparib**, 300 mg po daily • Physician's choice of cytotoxic chemotherapy	PFS	OS, QoL
NCT02000622 (**OlympiAD**)[50–52]	III R P O Met	All genders **gBRCA1/2+** metastatic breast cancer after anthracycline + taxane in adjuvant or metastatic setting or after endocrine therapy for ER/PR+	• **Olaparib**, 300 mg po bid • Physician's choice of capecitabine, vinorelbine, or eribulin	PFS	PFS2, OS, ORR, CR, PR, SD, QoL, TFST, TSST
NCT01945775 (**EMBRACA**)[53]	III R P O Adv	All genders **gBRCA1/2+** inoperable locally advanced or metastatic breast cancer with ≤3 cytotoxic regimens	• **Talazoparib**, 1 mg po daily • Physician's choice of capecitabine, eribulin, gemcitabine, or vinorelbine	PFS	ORR, OS, AEs, PK, DOR, QoL
PARP inhibitors + chemotherapy					
NCT00782574[54]	**I** NR SG O Met	All genders Metastatic, incurable ovarian, pancreatic, or breast cancer	• **Olaparib** + cisplatin ⇒ olaparib, 300 mg po bid maintenance	S/T	PK, ORR
NCT01445418[55]	**I** NR P O Adv	All genders **gBRCA1/2+** unresectable or metastatic TNBC or ovarian cancer	• **Olaparib** + carboplatin on day 1 of a 21-day cycle	S/T	ORR, PD
NCT01237067[56]	**I** NR P O Adv	All genders Recurrent/refractory inoperable or metastatic breast cancer, particularly if gBRCA1/2+, and gynecological cancers	• **Olaparib** + carboplatin ⇒ olaparib, 300 mg po bid maintenance	PD, S/T	Not given

(*Continued*)

Table 1. (*Continued*)

NCT number (Trial name)	Trial phase, design	Eligible population*	Interventions	Primary outcomes	Secondary outcomes
NCT02418624 (**REVIVAL**)[57]	**I** R P O Adv	All genders gBRCA1/2+ HER2– advanced breast cancer treated with ≤1 prior cytotoxic therapy in metastatic setting	• **Olaparib** + carboplatin ×2 cycles ⇒ olaparib, 300 mg po bid maintenance • Capecitabine	MTD olaparib in combination	PK, PD, ORR
NCT00516724[58]	**I** NR P O Met	All genders Metastatic solid tumors	• **Olaparib** + carboplatin • **Olaparib** + paclitaxel • **Olaparib** + paclitaxel + carboplatin	MTD of olaparib in combination	DLT
NCT00819221[59]	**I** NR SG O Adv	All genders Advanced incurable solid tumors, ≤3 cytotoxic therapies	• **Olaparib** + liposomal doxorubicin	RP2D, MTD	PK, S/T, AEs, PD
NCT01009190[60]	**I** NR P O Adv	All genders Advanced solid tumors, including breast	• **Rucaparib** IV + carboplatin • **Rucaparib** IV + carboplatin + paclitaxel • **Rucaparib** IV + premetrexed + cisplatin • **Rucaparib** IV + epirubicin + cyclophosphamide • **Rucaparib** po + carboplatin	DLT, MTD of rucaparib	PK, PD, QTc
NCT01251874[61]	**I** NR SG O Adv	All genders Inoperable locally advanced or metastatic TNBC, gBRCA1/2+, or FANC-associated HER2– breast cancers; ≤3 cytotoxic regimens in metastatic setting	• **Veliparib** po bid + carboplatin	AEs, S/T, RP2D	CR, PR, SD, CBR, PD, exploratory biology
NCT02033551[62]	**I** NR P O Met	All genders Metastatic malignancy; must be gBRCA1/2+ for monotherapy arm	• **Veliparib** monotherapy • **Velaparib** + carboplatin + paclitaxel • **Velaparib** + FOLFIRI	AEs	ORR, OS, TTP, PFS, EKG, PK

(*Continued*)

Table 1. (*Continued*)

NCT00535119[63]	**I** NR SG O Adv	All genders A. Advanced solid malignancy B: gBRCA1/2+ breast cancer	• **Velaparib** + carboplatin + paclitaxel	RP2D	DLT, PR, CR, SD, TTP, AEs, PD
NCT01281150[64]	**I** NR SG O Adv	All genders Inoperable locally advanced or metastatic HER2– breast cancer	• **Veliparib** + carboplatin + paclitaxel	MTD	PD, DLT, AEs, CR, PR, SD
NCT01366144[65] *Recruiting*	**I** NR SG O Adv	All genders Inoperable locally advanced or metastatic solid tumors in patients with liver or kidney disease	• **Velaparib** + carboplatin + paclitaxel	PK, PD, MTD in pts with liver or renal dysfunction	AEs, DLT, SD, PR, CR, ORR, TTP
NCT01104259[66]	**I** NR SG O Met	All genders Recurrent or metastatic TNBC or gBRCA1/2+ associated	• **Veliparib** po bid + cisplatin + vinorelbine ⇒ velaparib maintenance	MTD veliparib	S/T, PK, PD, PFS, CR, PR, ORR, DOR, ECOG, TTP
NCT01351909[67]	**I** NR SG O Adv	All genders Inoperable locally advanced or metastatic HER2– breast cancer after ≥1 hormonal or chemo treatment unless gBRCA1/2+	• Cyclophosphamide + **veliparib**	RP2D	PFS, CBR, CR, PR, OS, biomarkers
NCT01145430[68]	**I** NR SG O Met	All genders Metastatic TNBC after ≤2 cytotoxic regimens	• Pegylated liposomal doxorubicin + **veliparib**	RP2D	AEs, OS, PFS

(*Continued*)

Table 1. (*Continued*)

NCT number (Trial name)	Trial phase, design	Eligible population*	Interventions	Primary outcomes	Secondary outcomes
NCT01063816[69]	**I** NR SG O Adv	All genders Inoperable locally advanced or metastatic solid tumors, ≤2 cytotoxic regimens	• **Veliparib** + carboplatin + gemcitabine for up to ten cycles ⇒ optional veliparib maintenance	MTD veliparib, RP2D	PK, S/T, PR, CR, SD
NCT00576654[70] *Recruiting*	**I** NR P O Adv	All genders Inoperable locally advanced or metastatic TNBC; **gBRCA1/2+** required for dose expansion phase	• **Veliparib** D1–15 + irinotecan (21-day cycle) • **Veliparib** D1–4, 8–11 + irinotecan (21-day cycle)	OBD, MTD, RP2D, DLT	AEs, PR, SD, CR, PD PK
NCT00526617[71]	**I** NR SG O Adv	All genders Unresectable or metastatic nonheme malignancies Expansion cohort must be **gBRCA1/2+**	• **Velaparib** + temozolomide	MTD, S/T, PK	Not given
NCT01618136[72]	**I/II** NR (I) SG (I) O Met	All genders Ph I: Metastatic breast cancer Ph II : TNBC after one cytotoxic regimen (but excluded if given carboplatin or paclitaxel)	• PARP1/2 and tankyrase 1/2 inhibitor **E7449** • **E7449** + temozolomide • **E7449** + carboplatin + paclitaxel	Ph I: MTD of E7449	Ph II: ORR
NCT00707707[73]	**I/II** NR SG O Met	Women Metastatic TNBC, ≤1 cytotoxic regimen in the metastatic setting	• **Olaparib**, 200 mg po bid continuously + paclitaxel, 90 mg/m^2 weekly ×3 weeks of a 28-day cycle (n=19)	RP2D, AEs, S/T	Not given
NCT01074970 (**BRE09-146**)[74]	**II** R P O Adj	All genders gBRCA1/2+ and TNBC who received neoadjuvant chemotherapy (anthracyclines 57% and taxanes 91%) and surgery with curative intent	• Cisplatin, 75 mg/m^2 day 1 of a 21-day cycle ×4 cycles • Cisplatin, 75 mg/m^2 day 1 + **rucaparib**, 30 mg IV days 1–3 of a 21-day cycle ×4 cycles Both arms followed by **rucaparib**, 30 mg IV or 100 mg po maintenance ×24 weeks	2 year DFS	1 year DFS, S/T, OS, PK

(*Continued*)

Table 1. (*Continued*)

NCT01149083[75]	**II** NR SG/X O Adv	Women **gBRCA1/2+**, inoperable locally advanced or metastatic breast cancer after progression on at least one cytotoxic regimen excluding platinums	• **Veliparib**, 400 mg po bid (n=44) ⇒ progression ⇒ Veliparib, 150 mg po bid + carboplatin AUC 5–6 every 3 weeks (n=30)	ORR	PFS, S/T, CBR at 24 weeks, OS
NCT01506609 (**BROCADE**)[76]	**II** R P DM Adv	All genders **gBRCA1/2+** inoperable locally recurrent or metastatic breast cancer after ≤2 cytotoxic regimens in the metastatic setting; patients who received taxane in the metastatic setting were excluded	• Temozolomide, 150–200 mg/m^2 D1–5 + **veliparib**, 40 mg po bid D1–7 of 28-day cycle (n=94) • Carboplatin AUC6 + paclitaxel, 175 mg/m^2 q3 weeks + **veliparib**, 120 mg po bid D1–7 (n=97) • Carboplatin + paclitaxel + placebo (n=99)	PFS	OS, CBR, ORR, CR, PR, SD, CIPN
NCT01042379 (**I-SPY 2**)[77]	**II** R P O **Neoadj**	All genders Stage II–III or regional IV (supraclavicular lymph nodes only) with operable breast cancer and tumors ≥2.5 cm	• Paclitaxel, 80 mg/m^2 weekly ⇒ doxorubicin + cyclophosphamide (standard of care) • Paclitaxel, 80 mg/m^2 weekly + carboplatin AUC6 on day 1 + **veliparib,** 50 mg po bid continuously of a 21-day cycle ⇒ doxorubicin + cyclophosphamide	Probability of pCR over standard neoadjuvant	pCR, RCB, RFS, OS, AEs, MRI volume
NCT02595905[78] *Recruiting*	**II** R P O Adv	All genders Locally recurrent or metastatic TNBC or gBRCA1/2+ breast cancer treated with ≤1 cytotoxic regimen	• Cisplatin + **velaparib** • Cisplatin + placebo	PFS	OS, CBR, CR, PR, SD
NCT01306032[79]	**II** R X O Met	All genders Metastatic TNBC	• **Veliparib**, 60 mg po continuously + cyclophosphamide, 50 mg po daily ×21 days • Cyclophosphamide, 50 mg po daily ×21 days	ORR, CR, PR, PFS	AEs, PD, biomarkers
NCT01009788[80]	**II** NR SG O Met	All genders Metastatic BC after ≥1 cytotoxic regimen with expansion cohort of **gBRCA1/2+** metastatic breast cancer	• **Veliparib**, 30–40 mg po bid + temozolomide, 150 mg/m^2 po daily days 1–5 on a 28-day cycle	ORR, S/T	PFS, CBR

(*Continued*)

Table 1. (*Continued*)

NCT number (Trial name)	Trial phase, design	Eligible population*	Interventions	Primary outcomes	Secondary outcomes
NCT03150576 (**PARTNER**)[81] *Recruiting*	**II/III** R P O Neoadj	All genders, 16–70 yo TNBC or gBRCA1/2+ HER2– tumors	• Paclitaxel, 80 g/m^2, on days 1, 8, 15 + carboplatin AUC5 day 1 of a 21-day cycle • Paclitaxel, 80 g/m^2, on days 1, 8, 15 + carboplatin AUC5 day 1 + **olaparib**, 150 mg po bid day 2–10 of a 21-day cycle • Paclitaxel, 80 g/m^2, on days 1, 8, 15 + carboplatin AUC5 day 1 + **olaparib**, 150 mg po bid day 3–14 of a 21-day cycle	AE, pCR, TCR	RFS, BCSS, DDFS, LRFS, OS, RCB, RadR, QoL
NCT02032277 (**BrighTNess**)[82]	**III** R P DM **Neoadj**	Women Operable stage II–III TNBC (T1N1-2 or T2-4N0-2), gBRCA1/2+ or gBRCA1/2 wild-type	• Paclitaxel, 80 mg/m^2 weekly + carboplatin AUC6 on day 1 + **veliparib**, 50 mg bid of a 21-day cycle ×4 cycles ⇒ surgery ⇒ adjuvant AC (n=316) • Paclitaxel + carboplatin + po placebo ⇒ surgery ⇒ AC (n=160) • Paclitaxel + IV placebo + po placebo ⇒ surgery ⇒ AC (n=158)	pCR	EFS, CBR OS, S/T, BCS, QoL, ECOG, RCB
NCT02163694 (**BROCADE 3**)[83]	**III** R P DM Adv	All genders **gBRCA1/2+** HER2– inoperable locally advanced or metastatic breast cancer with ≤2 cytotoxic regimens	• Paclitaxel, 80 mg/m^2 on days 1,8, and 15 + carboplatin AUC6 on day 1 + **veliparib**, 120 mg po bid days 2–5 of a 21-day cycle ⇒ maintenance veliparib, 300–400 mg po bid continuously • Paclitaxel + carboplatin + placebo	PFS	DOR, PFS2, ORR, OS, CBR, ECOG, QoL
PARP inhibitors + angiogenesis inhibitors					
NCT03075462[84] *Recruiting*	**I** NR SG O Adv	Women Inoperable locally advanced or metastatic TNBC after ≤1 cytotoxic regimen	• **Fluzoparib** + VEGFR inhibitor apatinib	AEs	ORR, DOR, TTP, OS, PK
NCT01116648[85]	**I/II** R P O Met	Women Ph I only: recurrent ovarian or metastatic TNBC	• **Olaparib**, 100–400 mg po bid + VEGF inhibitor cediranib maleate 20–30 mg po bid • **Olaparib**, 300 mg po bid	DLT, MTD, PFS	Ph I: S/T

(*Continued*)

Table 1. (*Continued*)

NCT02484404[86] *Recruiting*	**I/II** NR P O Met	All genders Ph I: metastatic solid tumors Ph II: **gBRCA1/2+** recurrent TNBC after ≤3 cytotoxic regimens	• **Olaparib** + PDL1 inhibitor durvalumab • VEGFR inhibitor cediranib + durvalumab • **Olaparib** + durvalumab + cediranib	Ph I: RP2D Ph II: ORR	Not given
NCT02498613[87] *Recruiting*	**II** NR SG O Adv	All genders Unresectable or metastatic TNBC after cytotoxic chemotherapy	• **Olaparib** + cediranib maleate	ORR	AEs, PFS, biomarkers
PARP inhibitors + protein chaperone inhibitors					
NCT02898207[88] *Recruiting*	**I** NR SG O Met	All genders Metastatic TNBC after ≤4 cytotoxic regimens	• **Olaparib** + HSP90 inhibitor onalespib	MTD	PD
PARP inhibitors + immune checkpoint inhibitors					
NCT02657889 (**KEYNOTE-162**)[89]	**I/II** NR SG O Adv	All genders Advanced or metastatic TNBC Ph I: ≤4 cytotoxic therapies in metastatic setting Ph II: ≤2 cytotoxic therapies in metastatic setting	• **Niraparib**, 200 mg po bid + PD1 inhibitor pembrolizumab, 200 mg IV on day 1 of a 21-day cycle	DLT, ORR	S/T, DOR, ORR, DCR, PFS, OS, PK, biomarkers
NCT02734004 (**MEDIOLA**)[90,91]	**I/II** NR SG O Met	All genders Ph II **gBRCA1/2+** HER2– metastatic breast cancer patients who have received anthracycline/taxane therapy	• Ph I: **Olaparib**, 300 mg po bid + PDL1-inhibitor durvalumab • Ph II: **Olaparib**, 300 mg po bid ×4 weeks, ⇒ olaparib, 300 mg po bid + durvalumab, 1500 mg IV every 4 weeks	CBR, CR, PR, SD, S/T	Biomarkers, TDT, DOR, PFS, OS, ADA, PK, PD
NCT03330405 (**JAVELIN PARP MEDLEY**)[92] *Recruiting*	**Ib/II** NR S O Adv	All genders Inoperable locally advanced or metastatic gBRCA1/2+ or ATM-deficient TNBC or HR+ breast cancer	• **Talazoparib** + PD-L1 inhibitor avelumab	DLT, OR	PK, ADA, biomarkers, TTR, DOR, PFS, OS
NCT02484404	Olaparib + durvalumab + cediranib (see angiogenesis section above)				

(*Continued*)

Table 1. (*Continued*)

NCT number (Trial name)	Trial phase, design	Eligible population*	Interventions	Primary outcomes	Secondary outcomes
NCT03167619 (**DORA**)[93]	**II** R P O Adv	Women, 21 yo and up Inoperable locally advanced or metastatic TNBC after ≥4 cycles of platinum-based therapy with documented clinical benefit	• **Olaparib**, 300 mg po bid • **Olaparib**, 300 mg po bid + durvalumab	PFS	OS, S/T, ORR
Not yet recruiting					
NCT02849496[94]	**II** R X O Adv	All genders Stage III–IV **gBRCA1/2+** TNBC after ≤3 cytotoxic chemotherapy regimens	• **Veliparib** po bid continuously • Atezolizumab • **Veliparib** po bid continuously + atezolizumab	PFS	ORR, DOR, biomarkers
PARP inhibitors + intracellular signaling inhibitors					
NCT01623349[95,96]	**I** NR P O Met	All genders Metastatic TNBC after failure of ≥1 cytotoxic	• **Olaparib** + PI3K inhibitor BKM120 • **Olaparib** + PI3K inhibitor BYL719	MTD, RP2D	S/T, PK, ORR, exploratory biology
NCT03162627[97]	**I** NR P O Met	All genders Metastatic solid tumors	• **Olaparib** + MEK1/2 inhibitor selumetinib	MTD	PK, ORR, PD
Recruiting					
NCT02208375[98,99]	**I/II** NR P O Met	Women Metastatic TNBC, ovarian cancer, and endometrial cancer	• **Olaparib**, 300 mg po bid + mTORC1/2 inhibitor AZD2014 (continuous dosing) • **Olaparib**, 300 mg po bid + mTORC1/2 inhibitor AZD2014 (intermittent dosing) • **Olaparib**, 300 mg po bid + AKT inhibitor AZD5363 (intermittent)	MTD, RP2D	ORR, biomarkers

(*Continued*)

Table 1. (*Continued*)

PARP inhibitors + radiation therapy					
NCT03109080 (**RadioPARP**)[100] *Recruiting*	**I** NR SG O Met, Adj	Women Inoperable advanced disease, residual disease after neoadjuvant therapy and surgery, or metastatic TNBC	• **Olaparib** + radiation therapy	MTD of olaparib	AEs, ORR, CR, PR, LRFS, DDFS, OS, BCSS, biomarkers
NCT02227082[101] *Recruiting*	**I** NR SG O Adv	Women Inoperable local recurrence and/or metastatic breast cancer	• **Olaparib** + radiation therapy	DLT	S/T
NCT01477489[102]	**I** NR SG O Adj, Adv	All genders, 19 yo and up Locoregional recurrence after mastectomy or inflammatory BC after mastectomy in adjuvant setting.	• **Veliparib** + radiation therapy	MTD of veliparib	S/T
PARP inhibitors + HER2 inhibitors					
NCT03368729[103] *Not yet recruiting*	**I/II** NR SG O Met	Women Metastatic HER2+ breast cancer	• **Niraparib** + HER2 inhibitor trastuzumab	Ph I: DLT Ph II: ORR	Ph I: PK Ph II: AEs, PFS

Table 1 is organized by category (e.g. monotherapy trials), followed by clinical trial phase, then alphabetized by PARP inhibitor. The PARP inhibitor utilized is bolded. If germline *BRCA1* or *BRCA2* mutation (or strong suspicion of such) is a requirement for enrollment, g*BRCA1/2*+ is bolded. Clinical trials with iniparib are not included, as iniparib is no longer considered as a PARP inhibitor. In clinical trials performed after this came to light, use of iniparib was not considered as prior use of a PARP inhibitor and therefore not a barrier to enrollment.
*18 years old and older unless otherwise mentioned.
**Therapy targeted to deleterious mutations discovered by comparative genomic hybridization and next generation sequencing, including olaparib, antiandrogen bicalutamide, VEGFR and EGFR inhibitor vandetanib, MEK inhibitor selumetinib, pan-HER inhibitor sapitinib, AKT inhibitor AZD5363, EGFR inhibitor AZD4547, and mTORC1/2 inhibitor vistusertib.
ADA, antidrug antibodies; Adj, adjuvant therapy = after definitive resection with curative intent; Adv, advanced breast cancer = inoperable, locally invasive or metastatic disease; AEs, adverse events as defined by the Common Terminology Criteria for Adverse Events (CTCAE); BCS, breast conservation surgery; BCSS, breast cancer-specific survival = time from enrollment to death from breast cancer; BICR, blinded-independent central review; bid, *bis in die* (twice a day); CBR, clinical benefit rate = CR + PR + SD; CIPN, chemotherapy-induced neuropathy; CR, complete response rate = proportion of patients with no measurable disease; CTCAE, Common Terminology Criteria for Adverse Events = definitions for severity of organ toxicity for patients receiving antineoplastic agents per the National Cancer Institute; DCR, disease control rate = CR + PR + SD; DDFS, distant disease-free survival = time from study enrollment to distant relapse or date of death from all causes; DLT, dose-limiting toxicity = drug-related grade 3–5 adverse

(*Continued*)

Table 1. (*Continued*)

events using CTCAE; DM, double masking; DOR, duration of response = time from initial response to first documented tumor progression; g*BRCA1/2*+, germline-mutated *BRCA1* or *BRCA2*; HER2, human epidermal growth factor; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency (as defined by a deleterious mutation in *BRCA1*, *BRCA2*, PTEN, PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD50, RAD51C, RAD51D, MRE11, ATR, or FANC genes or by a high score on Myriad's HRD assay); irRC, Immune-Related Response Criteria = rules defining tumor response, stabilization, or progression for immuno-oncology drugs, which can result in an inflammatory response that appears to be progression; LRFS, local recurrence-free survival = time from enrollment to first local recurrence or death from all causes; Met, metastatic disease; MTD, maximum tolerated dose = one dose level below the highest dose at which 1/3 of the patients at that dose level experience a dose-limiting toxicity as defined by NCI CTCAE; NCI, National Cancer Institute; Neoadj, neoadjuvant = pre-operative chemotherapy; NR, nonrandomized; O, open label; OBD, optimal biologic dose = dose of complete PARP inhibition; ORR, objective response rate = CR + PR; OS, overall survival = time from study enrollment until death from all causes; P, parallel assignment; pCR, pathological complete response = no tumor remaining in breast or lymph nodes after neoadjuvant therapy as determined by pathological evaluation; PD, pharmacodynamics = drug effect on physiology; PFS, progression-free survival = time from study enrollment to determination of tumor progression or death due to any cause; PFS2, progression-free survival 2 = time from first PFS to second PFS or death; PK, pharmacokinetics = study of the absorption, bodily distribution, metabolism, and excretion of drugs; po, *per os* (by mouth); PR, partial response rate = proportion of patients with favorable but incomplete response of a predefined amount for a predefined minimum time period; QoL, quality of life = impact of health status on physical, mental, emotional, social functioning; R, randomized; RadR, radiological response rate; RCB, residual cancer burden = pathological diagnosis of residual cancer burden after neoadjuvant chemotherapy at time of surgical resection; RECIST, Response Evaluation Criteria in Solid Tumors = rules defining tumor response, stabilization, or progression for antineoplastic agents; RFS, relapse-free survival; RP2D, recommended phase 2 dose = highest oncology drug dose with acceptable toxicity, usually defined in reference to DLT and MTD established in phase I clinical trials; S, sequential assignment; SD, stable disease rate = proportion of patients without disease shrinkage or progression by RECIST criteria; SG, single group; S/T, safety and tolerability = number and grade of adverse events; TCR, therapy completion rate; TFST, time to first subsequent therapy = time from enrollment to the first subsequent therapy start date or death date; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer; TRR, tumor response rate = CR + PR; TSST, time to second subsequent therapy = time from enrollment to the second subsequent therapy start date or death date; TTD, time to treatment discontinuation = time from enrollment to treatment discontinuation for any reason; TTF, time to treatment failure = time from enrollment to documentation of progression, unacceptable toxicity, or patient refusal to continue participation; TTP, time to progression = time from study enrollment to determination of tumor progression; TTR, time to tumor response; TTSC, time to second cancer; VEGFR, Vascular endothelial growth factor receptor; X, crossover study; yo, years old.

individual patient's toxicities. It could be argued that PARP inhibitors are a novel cytotoxic therapy, as they do essentially perpetuate DNA damage and have myelosuppression as the DLT. Olaparib was originally FDA-approved at a dosage of 400 mg by mouth twice daily, which required patients to take eight 50 mg capsules twice a day. The phase II trial ICEBERG 1 (NCT00494234) investigated dosage levels of 100 mg by mouth twice daily (n=27) compared with 400 mg by mouth twice daily (n=27) in women with g*BRCA1/2* mutations with advanced breast cancers after a minimum of one cytotoxic regimen in the metastatic setting. The 100 mg dosage was grossly inferior in terms of median progression free survival (mPFS), overall response rate (ORR), and clinical benefit rate (CBR).[36] Women in the olaparib, 100 mg by mouth twice daily (*p.o. b.i.d.*), arm had a mPFS of 122 days (n=24) compared with 193 days (n=26), ORR of 22% (n=27; 95% CI: 11–41) compared with 41% (n=27; 95% CI: 25–59), and CBR 62.5% (n=24; 95% CI: 42.7–78.8) compared with 84.6% (n=26; 95% CI: 66.5–93.9).[37]

Disappointingly, there were no confirmed partial or CRs in the phase II trial NCT00679783 with olaparib, 400 mg *p.o. b.i.d.*, in patients with advanced g*BRCA1/2*+ breast cancer or triple-negative breast cancer (TNBC) (n=26 with 4 g*BRCA1*+, 6 g*BRCA2*+, 16 *BRCA*-wt).[38] Five of the ten *gBRCA1/2*+ breast patients did actually have decrease in the size of target lesions by >30%, but three were not confirmed at the next follow up visit and two were taken off study for progression of nontarget lesions or new lesions. Of the 23 breast cancer patients evaluable for response, almost 1/3 had SD at 8 weeks, including 2 of 3 g*BRCA1*+, 3 of 5 g*BRCA2*+, and 2 of 14 *BRCA*-wt patients.[39]

A tablet formulation of olaparib was developed in part to reduce the 16-capsule/day pill burden on patients. Pharmacokinetic parameters for capsule versus tablet formulations were compared in the first stage of phase I trial NCT00777582 with the determination that the olaparib, 300 mg *p.o. b.i.d.*, tablet formulation matched or exceeded drug exposure at steady state compared to the 400 mg *p.o. b.i.d.* capsule form.[28] In the expansion phase, patients with advanced solid tumors refractory to standard therapies were randomly assigned to receive olaparib, 400 mg *p.o. b.i.d.*, in capsule formulation, 400 mg *p.o. b.i.d.* in tablet form, or 300 mg *p.o. b.i.d.* in tablet form. Efficacy was similar in all three arms, but the 300 mg *p.o. b.i.d.* tablet dosing was more tolerable. In fact, almost 2/3 of patients taking 400 mg *p.o. b.i.d.* tablets required dose reduction to 300 mg *p.o. b.i.d.* The olaparib monotherapy dose for phase II and III clinical trials thereafter was set at 300 mg *p.o. b.i.d.* tabs, which reduced the pill burden from 16 capsules a day to four tablets a day.[28]

The phase III OlympiAD trial randomized patients with g*BRCA1/2*+ metastatic breast cancer to olaparib, 300 mg *p.o. b.i.d.*, compared with physician's choice of capecitabine, vinorelbine, or eribulin.[51] The primary outcome measure was mPFS with ORR and overall survival (OS) as secondary endpoints. mPFS in the olaparib arm (n=205) was 7.0 months (95% CI: 5.7–8.3 months) based on investigator analysis and 7.4 months based on blinded-independent central review (BICR) compared to the chemotherapy arm (n=97) with mPFS of 4.2 months (95% CI: 2.8–4.3 months) by investigator analysis and 4.2 months (95% CI: 2.8–4.3 months) on BICR (hazard ratio [HR] 0.58, 95% CI: 0.43–0.80, $p<0.001$). Of the patients with measurable disease, 59.9% (100/167) on olaparib had an objective response compared to 28.8% (19/66) of the patients given chemotherapy. OS was not significantly different between the arms at 19.3 months in the PARP inhibitor arm and 19.6 months in the chemotherapy arm (HR 0.90, 95% CI: 0.63–1.29, $p=0.57$). The rate of grade 3 and 4 adverse events was lower in the olaparib arm at 36.6% compared to 50.5% in the chemotherapy arm. The most common grade 3/4 toxicities were anemia (16.1%), neutropenia (9.3%), and leukopenia (3.4%). Low-grade gastrointestinal side-effects were also common, including nausea (58.0%), vomiting (29.8%), and diarrhea (grade 1/2 20.0%, grade 3/4 0.5%). Olaparib was FDA-approved in January 2018 for g*BRCA1/2*+ HER2– breast cancers in the metastatic setting.

Talazoparib

In phase I/II trial NCT01286987 with talazoparib, 50% (7/14) of g*BRCA1/2*+ breast cancer patients had an objective response at the 1.0 mg *p.o.* daily dose.[35] The phase II ABRAZO trial (NCT02034916) investigated talazoparib in patients with gBRCA1/2+ locally advanced or metastatic breast cancers with or without prior exposure to platinum agents.[46] Those enrolled in the platinum-exposed arm were required to have had a documented PR or CR and could not have had progression of their disease on a platinum agent. Those who had not been exposed to platinum were required to have had two or more nonplatinum regimens in the metastatic setting. The primary outcome measure was ORR with CBR, PFS, and OS among the secondary outcome measures. Response rates to talazoparib were higher in patients who had not had prior platinum exposure, suggesting some degree of cross-resistance. The ORR was 20.8% (95% CI: 10.47–34.99) with a CBR of 27.1% (95% CI: 15.28–41.85) in the platinum-exposed cohort (n=48). In those without prior platinum exposure (n=35), the ORR was 37.1% (95% CI: 21.49–55.08) with CBR 45.7% (95% CI: 28.83–63.35). mPFS was 4.0 months (95% CI: 2.8–5.4 months) with a median overall survival (mOS) of 11.8 months (95% CI: 8.8–15.0) in those with prior platinum exposure (n=49), but 5.6 months (95% CI: 5.5–7.8 months) with mOS 16.5 months in the nonplatinum-exposed arm (n=35). As with all PARPi, myelosuppression was the predominant toxicity.

EMBRACA (NCT01945775) is a recently reported phase III study comparing talazoparib, 1 mg *p.o.* daily.[46,49,53,111] to physician's choice chemotherapy (eribulin, vinorelbine, capecitabine, or gemcitabine) in patients with advanced breast cancer and germline *BRCA1 or BRCA2* mutations.[112] Patients were randomly assigned in a 2:1 ratio to talazoparib (n=287) or chemotherapy (n=144). The primary endpoint was PFS (assessed by BICR) with secondary endpoints being safety, OS, ORR, CBR at 24 weeks, and quality of life measurements. mPFS was 8.6

months in the talazoparib arm compared to 5.6 months in the chemotherapy arm (HR 0.54, $p<0.0001$) with an ORR of 62.6% (n=219) with talazoparib (including 12 CRs) compared to 27.2% (n=144; no CRs) with chemotherapy. Although grade 3/4 myelosuppressive toxicities were higher with talazoparib than chemotherapy (55 versus 39%), patients experienced fewer grade 3/4 gastrointestinal side-effects (5.6 versus 11.9%) and had a much slower decline in overall health (as assessed by the questionnaire EORTC QLQ-C30) compared to the chemotherapy arm.[113,114] The Food and Drug Administration (FDA) granted priority review designation for talazoparib based on the results of EMBRACA.

Niraparib

In the phase I trial NCT00749502 evaluating niraparib in patients with advanced malignancies, the ORR was 2 of 4 g*BRCA1/2*+ breast cancer patients with one achieving PR at 150 mg/day for 132 days and the second with PR at 210 mg/day for 133 days. The RP2D was declared at 300 mg *p.o.* daily.[26] The BRAVO study (NCT01905592) is a randomized phase III clinical trial investigating niraparib, 300 mg *p.o.* daily, compared to physician's choice of chemotherapy with a primary outcome measure of PFS.

Rucaparib

Rucaparib has been predominantly studied in ovarian cancer, but the phase II 'RUBY' trial (NCT02505048) is currently recruiting patients with metastatic g*BRCA*-wt, HER2-negative breast cancers with a '*BRCA*ness' phenotype as determined by Clovis genomic signature testing or *BRCA1/2* somatic mutation.[115]

Veliparib

Veliparib was studied in cancers associated with g*BRCA1/2*+, ovarian cancers, or basal-like HER2-negative breast cancers in NCT0089736.[31,116] Of the 52 *BRCA*+ patients (13 with breast cancer) evaluated for response (all dose levels included), the ORR was 23%, and the CBR was 58%. At the MTD of 400 mg *p.o. b.i.d.,* 28 g*BRCA1/2*+ patients were evaluated with an ORR of 40% and CBR 68%. Twenty-four *BRCA*-wt patients (21 breast and 3 ovarian) had an ORR of 4% and CBR of 38%.[32]

Combination strategies

Chemotherapy

Recommended monotherapy dosages of PARP inhibitors are as follows: niraparib, 300 mg *p.o.* daily,[26] olaparib, 300 mg *p.o. b.i.d.,*[28] rucaparib, 600 mg *p.o. b.i.d.*,[117] talazoparib, 1 mg *p.o.* daily,[35] and veliparib 400 mg *p.o. b.i.d.*[32] Myelosuppression is the primary DLT for PARPi, which has made combination of PARPi with cytotoxic chemotherapies problematic (see Table 2).

The majority of phase I clinical trials using chemotherapy–PARPi combination approaches has understandably prioritized the use of standard dosages of chemotherapy over maximum doses of PARP inhibitor. In combination with myelosuppressive chemotherapies with efficacy in ovarian and breast cancers with HRR defects, namely, platinum agents in combination with taxane therapy, the RP2Ds of PARPi are a fraction of that required for efficacy as a monotherapy. In the phase II adjuvant BRE09-146 trial (NCT01074970), patients with g*BRCA1/2*+ breast cancers or TNBC were randomized to cisplatin, 75 mg/m^2 on day 1 of a 21-day cycle +/– rucaparib, 30 mg intravenously (IV) on days 1–3, after completion of neoadjuvant chemotherapy and surgery with curative intent. For reference, rucaparib, 24 mg IV, is approximately equivalent to 57 mg by mouth, and the monotherapy dose of rucaparib is 600 mg by mouth twice a day.[122] At 2 years, the disease-free survival was 58.3% in the cisplatin arm compared with 63.1% in the cisplatin + rucaparib arm ($p=0.43$).[126,127] It is not currently clear if maximizing the PARPi dose at the expense of the cytotoxic chemotherapy is a more viable therapeutic strategy, but the results of the phase III BrighTNess trial (discussed later) suggests that using a grossly subtherapeutic dose of PARPi in combination with standard dosages of chemotherapy does not significantly improve clinical outcomes.[128]

Strategies to mitigate the myelosuppressive effects of PARPi have mirrored strategies utilized for myelosuppressive cytotoxic chemotherapies, including intermittent dosing schedules and support with granulocyte colony stimulating factors (G-CSF) such as filgrastim. Phase I/II clinical trial NCT00707707 was amended to include an algorithm for filgrastim rescue and subsequent prophylaxis for women with metastatic TNBC being treated with olaparib, 200 mg *p.o. b.i.d.* continuously, in combination with paclitaxel, 90 mg/m^2 weekly × 3 weeks of a 28-day cycle, after 7/9 women in cohort 1 developed neutropenia (4/9 grade 3 or 4) with 8/9 requiring dose delay or reduction of paclitaxel.[73] After implementation of neutropenia management with G-CSF, cohort 2 (n=10) fared better, with 4/10 developing neutropenia (2/10 grade 3 or 4) and fewer paclitaxel dose reductions.

In the ongoing phase II neoadjuvant I-SPY 2 trial (NCT01042379), breast cancer patients with operable stage II–III or stage IV with solely supraclavicular lymph node involvement ('regional stage IV') and tumors ≥ 2.5 cm are randomized to one of many experimental arms with a standard-of-care control arm of paclitaxel, 80 mg/m^2 weekly × 12 weeks (*T*), followed by doxorubicin + cyclophosphamide (AC) ×4 cycles.[77] The primary outcome measure is probability of pathologic complete response (pCR) over standard neoadjuvant therapy. I-SPY 2 included an experimental arm with PARP inhibitor veliparib, which was dosed at 50 mg *p.o. b.i.d.* continuously in conjunction with paclitaxel + carboplatin AUC6 on day 1 of a 21-day cycle (TCV) and followed by AC ×4 cycles. The estimated pCR rate in TNBC of TCV ⇒ AC (n=72) was estimated to be 51% (95% Bayesian probability interval 36–66%) compared to 26% in the *T* ⇒ AC arm (n=44) (95% Bayesian probability interval 9–43%). The predicted probability of success of TCV ⇒ AC in TNBC patients in a phase III trial was estimated to be 88%.

Table 2. Results of phase I dose escalation studies combining chemotherapy with PARP inhibitors.

Trial	Patient characteristics	Dosing strategy	Doses studied	RP2D	Results	DLTs	Most frequent Gr 3–5 AEs
NCT00782574[54,118]	• Ovarian, pancreatic, or breast cancer • 52/54 female • 42/54 with breast cancer • 29/54 gBRCA1/2+, 11/54 unknown	Dose-escalation of olaparib Cisplatin decreased to 60 mg/m^2 only for cohort 6	• **Olaparib**, 50–200 mg po bid continuously or intermittently (days 1–5 or days 1–10) + cisplatin, 60–75 mg/m^2 IV on day 1 of a 21-day cycle ⇒ olaparib monotherapy	Olaparib, 50 mg po bid days 1–5 + cisplatin 60 mg/m^2	ORR 71% (12/17) in gBRCA1/2+ breast cancer. Authors note this falls within the range of ORR to single agent carboplatin or cisplatin in this population • 5/17 breast patients achieved objective durable treatment responses of >1 year	• Gr 3 neutropenia • Gr 3 lipase elevation	• Neutropenia[§] (16.7%) • Anemia (9.3%) • Leukopenia (9.3%)
NCT01445418[119]	• **gBRCA1/2+** TNBC or ovarian cancer • 8/45 breast cancer (four TNBC, four ER/PR+ HER2–)	Dose-escalation of olaparib followed by dose-escalation of carboplatin	• **Olaparib**, 100–400 mg po bid intermittently (days 1–7) or continuously (days 1–21) + carboplatin AUC 3–5 every 3 weeks	Olaparib, 400 mg po twice daily on days 1–7 + carboplatin AUC5	• CBR 8/8 breast cancer patients • CR of 23 months in 1/8 • 6/8 PR with mDOR 10 months • 1/8 SD of 14 months	• MTD not reached on intermittent schedule	• Neutropenia[§] (42.2%) • Anemia (15.6%) • Thrombocytopenia (20.0%)
NCT01237067[120]	• Breast and gynecological cancers (n=59) • 10/59 TNBC (four with BRCA1/2+)	• Arm A: C1 olaparib ×7 days prior to carbo, C2 carbo prior to olaparib, and C3+ concurrent • Arm B: C1 carbo prior to olaparib, C2 olaparib ×7 days prior to carbo, and C3+ concurrent	• **Olaparib**, 200 mg po bid ×7 days + carboplatin AUC4 day 1 of 21-day cycle ⇒ olaparib, 300 mg po bid maintenance	Olaparib, 200 mg bid ×7 days with carboplatin AUC4 q21 days	• 1 CR TNBC of 32 months • 3 PR TNBC	• Myelosuppression	• Neutropenia (22%) • Anemia (12%) • Thrombocytopenia (10%) • Carboplatin hypersensitivity (3%)
NCT02418624 (**REVIVAL**)[57]	• gBRCA1/2+ HER2– breast cancer	Dose-escalation of carboplatin followed by dose-escalation of olaparib	• **Olaparib**, 25–100 mg po bid + carboplatin AUC 3–4×2 cycles ⇒ olaparib, 300 mg po bid monotherapy	N/A	Protocol published; no results	N/A	N/A

(*Continued*)

Table 2. (*Continued*)

Trial	Patient characteristics	Dosing strategy	Doses studied	RP2D	Results	DLTs	Most frequent Gr 3–5 AEs
NCT00819221[121]	• Solid tumors (n=44) • Breast cancer n=13/44	Dose-escalation of olaparib	• **Olaparib, 50–400 mg po bid** days 1–7 or continuously + liposomal doxorubicin 40 mg/m^2 on day 1 of a 28-day cycle	• MTD not reached. RP2D olaparib, 400 mg po bid continuously	• 1/13 breast cancer pts achieved PR (gBRCA1/2+)	• Gr 3 stomatitis • Gr 5 (fatal) pneumonia/ pneumonitis • Gr 4 thrombocytopenia	• Stomatitis (16%) • Nausea (11%) • Neutropenia (20%) • Thrombocytopenia (7%)
NCT01009190[122]	• Advanced solid tumors (n=85) • Breast cancer n=22/85 • 10/85 known to harbor gBRCA1/2+	• A: Four cohorts with dose-escalation of carbo, then rucaparib • B: Three cohorts with dose-escalation of paclitaxel, then carbo, then rucaparib • C: Four cohorts with dose-escalation of pem and cis concurrently, then rucaparib • D: One cohort • E: Eight cohorts with dose-escalation of rucaparib, then carboplatin	• A: **Rucaparib** IV + carboplatin (n=7/18) • B: **Rucaparib** IV + carboplatin + paclitaxel (n=1/13) • C: **Rucaparib** IV + premetrexed + cisplatin (n=4/16) • D: **Rucaparib** IV + epirubicin + cyclophosphamide (n=4/5) • E: **Rucaparib** po + carboplatin (n=6/33)	Arm E: MTD 240 mg po daily rucaparib + carbo AUC 5 mg/mL*min; rucaparib doses of 12, 18, and 24 mg IV are ~ equivalent to 33, 50, and 57 mg po, respectively	• Overall, >2/3 of patients had clinical benefit • One breast patient achieved CR on rucaparib IV + premetrexed + cisplatin • One BRCA1+ breast patient achieved PR ×3 months on rucaparib po + IV carboplatin	Arm E: • Neutropenia • Thrombocytopenia	Arm E: • Neutropenia[§] (21.2%) • Thrombocytopenia (27.3%)
NCT01251874[123]	• gBRCA1/2+ or FANC-associated HER2-breast cancers (n=44) • TNBC=39/44	De-escalation of carboplatin followed by dose-escalation of veliparib	• **Veliparib**, 50–200 mg po bid intermittent or continuous + carboplatin AUC 5–6 on day 1 of a 21-day cycle	RP2D V, 250 mg po bid, days 1–21 + carbo AUC 5 on day 1 of a 21-day cycle	• 43 evaluated: 18.6% PR, 48.8% SD • gBRCA1/2+ or gFANC+: 25% PR, 62.5% SD	• Gr 3–4 thrombocytopenia • Gr 4 neutropenia • Gr 3 akathisia	• Thrombocytopenia
NCT01281150[124]	• Advanced solid tumors (n=30) • 2/30 HR+HER2– breast • 22/30 TNBC	Dose-escalation of veliparib	• **Veliparib**, 50–200 mg po bid + carboplatin AUC 2 weekly + paclitaxel, 80 mg weekly	RP2D 150 mg po bid + carbo AUC 2 + paclitaxel 80 mg/m^2	• ORR TNBC 52%, BRCA1/2+ 60% (3/5 PR), 67% BRCA1/2-wt (1/9 CR, 5/9 PR), 29% in BRCA-unknown (2/7 PR)	• Prolonged Gr 2 thrombocytopenia • Gr 4 neutropenia	• Neutropenia (60%) • Anemia (17%) • Thrombocytopenia (10%)

(*Continued*)

Table 2. (*Continued*)

NCT01104259[125]	• TNBC or gBRCA1/2+-associated breast cancer (n=38) • Nine gBRCA1+ and three gBRCA2+ • 21 BRCA1/2-wt • Six BRCA1/2-unknown	Dose-escalation of veliparib	• **Veliparib**, 20–300 mg po bid + cisplatin 75 mg/m^2 day 1 + vinorelbine tartrate 25 mg/m^2 days 1 and 8 of a 21-day cycle ×6–10 cycles ⇒ velaparib, 300 mg po bid maintenance	MTD not reached	• Overall ORR 55% (2 CR + 19 PR) • Overall CBR 89% 34% (13) with SD • BRCA1/2+ ORR 73% (6/11 PR, 2/11 CR) • BRCA-wt ORR 53% (11/21 PR) • BRCA-unknown ORR 33% (2/6 PR)	• Gr 4 thrombocytopenia • Gr 3–4 neutropenic fever	• Neutropenia (13/38) • Anemia (11/38) • Thrombocytopenia (6/38)
NCT01063816[69]	• Advanced solid tumors, primarily ovarian (n=75) • Breast n=12/75, at least 1 gBRCA1/2+	Dose-escalation of veliparib	• **Veliparib**, 30–310 po bid continuously + carboplatin AUC4 day 1 + gemcitabine, 800 mg/m^2 days 1 and 8 of a 21-day cycle ⇒ optional veliparib maintenance after max ten cycles; veliparib started with cycle 2	MTD veliparib, 250 mg po bid + carboplatin AUC4 + gemcitabine, 800 mg/m^2 on days 1 and 8 of a 21-day cycle	• Not reported for breast cancer patients	• Thrombocytopenia • Neutropenia	• Neutropenia[§] (56%) • Anemia (20%) • Thrombocytopenia (53%)

Combination trials of PARP inhibitors plus chemotherapy have primarily been designed to maximize cytotoxic chemotherapy doses while dose-escalating the PARP inhibitor to MTD. DLTs and grade 3–4 adverse events are most often myelosuppressive in nature.

[§]G-CSF allowed.

AEs, adverse events as defined by the Common Terminology Criteria for Adverse Events (CTCAE); AUC, area under the curve; bid, *bis in die* (twice a day); carbo, carboplatin; CBR, clinical benefit rate = CR + PR + SD; cis, cisplatin; CR, complete response rate = proportion of patients with no measurable disease; DLT, dose-limiting toxicity = drug-related grade 3–5 adverse events using CTCAE; DOR, duration of response = time from initial response to first documented tumor progression; g*BRCA1/2*+, germline-mutated *BRCA1* or *BRCA2*; Gr, grade as defined by CTCAE; HER2–, HER2 negative; HR+, hormone receptor positive; IV, intravenous; MTD, maximum tolerated dose = one dose level below the highest dose at which 1/3 of the patients at that dose level experience a dose-limiting toxicity as defined by CTCAE; n, number of patients; N/A, not applicable/available; ORR, objective response rate = CR + PR; OS, overall survival = time from study enrollment until death from all causes; pem, pemetrexed; PFS, progression-free survival = time from study enrollment to determination of tumor progression or death due to any cause; po, per os (by mouth); PR, partial response rate = proportion of patients with favorable but incomplete response of a predefined amount for a predefined minimum time period; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose = highest oncology drug dose with acceptable toxicity, usually defined in reference to DLT and MTD established in phase I clinical trials; SD, stable disease rate = proportion of patients without disease shrinkage or progression by RECIST criteria; TNBC, triple-negative breast cancer; wt, wild-type gene.

The phase III randomized, placebo-controlled neoadjuvant trial BrighTNess (NCT02032277) was developed based on the carboplatin + veliparib results of I-SPY 2, and results were recently published.[128] Women with operable stage II–III TNBC were enrolled with stratification by g*BRCA1/2* status and randomization to one of the three arms: paclitaxel, 80 mg/m^2 weekly + carboplatin AUC6 on day 1 of a 21-day cycle + veliparib, 50 mg *p.o. b.i.d.* continuously (n=316), paclitaxel + carboplatin + placebo *p.o. b.i.d.*, or paclitaxel + IV placebo + placebo *p.o. b.i.d.* All patients received AC ×4 cycles in the adjuvant setting. The primary outcome was pCR. The pCR for the triple combination therapy was 53% (168/316), paclitaxel + carboplatin yielded a pCR of 58% (92/160), and paclitaxel alone had a pCR of 31% (49/158). The triplet combination was superior to paclitaxel alone (p<0.0001) but equivalent to paclitaxel + carboplatin (p=0.36). It should be noted that paclitaxel, 80 mg/m^2, and carboplatin AUC6 are standard full doses, but the veliparib dose is 1/8 of the monotherapy dose of veliparib, 400 mg *p.o. b.i.d.* The addition of veliparib, 50 mg *p.o. b.i.d.*, to paclitaxel and carboplatin did not improve therapeutic benefit, though the addition of carboplatin to paclitaxel clearly did.

The phase II BROCADE trial (NCT01506609) evaluated veliparib in g*BRCA1/2*+ patients with inoperable locally recurrent or metastatic HER2-negative breast cancer.[129,130] Patients were randomized to one of the three arms: (1) paclitaxel, 175 mg/m^2 on day 1 + carboplatin AUC6 on day 1 + veliparib, 120 mg *p.o. b.i.d.* on days 1–7 of a 21-day cycle (VCP; n=97), (2) paclitaxel, 175 mg/m^2 on day 1 + carboplatin AUC6 on day 1 + placebo *p.o. b.i.d.* on days 1–7 of a 21-day cycle (PCP; n=99), or (3) temozolomide, 150–200 mg/m^2 on days 1–5 + veliparib, 40 mg *p.o. b.i.d.* on days 1–7 of a 28-day cycle (VT; n=94). Forty percent of the breast cancer patients had TNBC. mPFS was 14.1 months (95% CI: 11.5–16.2 months) in the veliparib + carboplatin + paclitaxel (VCP) arm compared to 12.3 months (95% CI: 9.3–14.5 months) in the placebo + carboplatin + paclitaxel (PCP) arm (HR 0.789, 95% CI: 0.536–1.162, p=0.227). mPFS in the veliparib + temozolomide (VT) arm was 7.4 months (95% CI: 5.9–8.5 months) with a HR 1.858 (95% CI: 1.278–2.702, p=0.001) compared to VCP. Although they were unable to detect improvements in the primary endpoint of PFS at p<0.05, secondary endpoints of ORR and CBR were improved by the addition of veliparib to paclitaxel and carboplatin. ORR was 77.8% (95% CI: 66.4–86.7) with VCP compared to 61.3% (95% CI: 49.7–71.9) with PCP (p=0.027). Only 28.6% of patients receiving VT achieved a partial or CR (PCP versus VT p<0.001). The CBR at 18 weeks was 87.0% (95% CI: 78.3–92.4) for PCP, 90.7% (95% CI: 82.2–95.2) for VCP, and 73.0% (95% CI: 62.2–81.2) for VT. The phase III randomized, placebo-controlled BROCADE 3 trial for g*BRCA1/2*+ breast cancer patients in the advanced setting includes paclitaxel, 80 mg/m^2 weekly + carboplatin AUC6 on day 1 of a 21-day cycle in each of two arms, but the veliparib dose is 120 mg *p.o. b.i.d.* and is only given on days 1–7 of a 28-day cycle.[131] We eagerly await results from this trial.

Olaparib in combination with chemotherapy is being evaluated in the neoadjuvant setting in TNBC or g*BRCA1/2*+ HER2-negative tumors in the phase III randomized, placebo-controlled PARTNER study (NCT03150576) in combination with weekly paclitaxel, 80 mg/m^2 weekly + carboplatin AUC5 on day 1 of a 21-day cycle.[81] At 150 mg *p.o. b.i.d.*, the olaparib dose is half of the 300 mg *p.o. b.i.d.* monotherapy dose and is given for 12 days of a 21-day cycle starting either 2 days prior to chemotherapy administration or 2 days after chemotherapy administration.

Radiation therapy

Radiation therapy induces DNA double-strand breaks, which are lethal if not repaired. By interfering with DNA repair, PARPi could be expected to act as radiosensitizers. Although radiosensitization is a common therapeutic approach in the definitive management of some cancers, such as squamous cell carcinomas of the head and neck, it is an uncommon strategy in the treatment of metastatic breast cancers. Nonetheless, the combination of PARPi with radiation therapy is intriguing. There are three clinical trials in the clinicaltrials.gov database involving PARPi and radiation therapy for the treatment of breast cancer. RadioPARP (NCT03109080) is recruiting women with (1) inoperable advanced disease, (2) residual disease after neoadjuvant therapy and surgery, and (3) metastatic TNBC for a dose-escalation trial with olaparib.[100] NCT02227082 is an olaparib dose-escalation trial in women with inoperable locally recurrent and/or metastatic breast cancer.[101] Phase I NCT01477489 with veliparib + radiation therapy also includes patients in the adjuvant setting; this trial has been completed, but results have not been published.[102]

Angiogenesis, heat-shock protein inhibitors, and immune checkpoint inhibitors

Angiogenesis inhibitors and immune checkpoint inhibitors have thus far not reliably been shown to be of benefit in the treatment of breast cancer, and so there are no current FDA-approved indications for their use in breast cancer.[132] The combination of angiogenesis inhibitors and/or immune checkpoint inhibitors with PARP inhibitors will likely be safe due to nonoverlapping toxicities, and it might be expected that PARP inhibitors could be used at full monotherapy dosages.

Biologically, it has been hypothesized that hypoxia induces down-regulation of HRR proteins BRCA1 and RAD51 and induces a *BRCA*-like state that could sensitize cells to PARP inhibitors.[133,134] NCT01116648 is a completed phase I/II clinical trial involving women with recurrent ovarian carcinoma (n=20) or metastatic TNBC (n=8; 3 g*BRCA1/2*+, 1 *BRCA1/2*-wt, 4 unknown *BRCA1/2* status).[85] The MTD was olaparib, 400 mg *p.o. b.i.d.*, in combination with small-molecule VEGFR tyrosine kinase inhibitor (TKI) cediranib, 30 mg *p.o.* daily; the RP2D was olaparib, 200 mg *p.o. b.i.d.*, with cediranib, 30 mg *p.o.* daily. None of the breast cancer patients achieved complete or partial responses by RECIST criteria, but it should also be noted that only two breast cancer patients were in the highest dose arm with a therapeutic dose of olaparib, 400 mg *p.o. b.i.d.* Three breast patients had SD on olaparib, 200 mg *p.o. b.i.d.*, including two g*BRCA1/2*+ patients with progression at 4 and 7 months.[135] Three phase I or II clinical

trials combining PARP inhibitors with VEGFR TKIs are currently recruiting patients with advanced or metastatic TNBC in the second-line-or-beyond setting: NCT03075462 (PARP inhibitor fluzoparib + VEGFR inhibitor apatinib), NCT02484404 (olaparib + VEGFR inhibitor cediranib), and NCT02498613 (olaparib + cediranib).[84,86,87] NCT02484404 also includes an arm with olaparib + cediranib + PDL1 inhibitor durvalumab.

Induction of a BRCA-like phenotype is also the rationale behind the phase I dose-escalation clinical trial NCT02898207, which combines olaparib with heat-shock protein 90 (HSP90) inhibitor onalespib for patients with metastatic TNBC.[88] HSP90 is a chaperone protein that facilitates folding and stabilization of BRCA1 (among many other proteins).[136] Preclinical data suggest that stabilization of deleteriously mutated BRCA1 could be a mechanism of resistance to platinum agents and PARP inhibitors.[137]

There are several studies combining PARP inhibitors with immune checkpoint inhibitors, including phase I/II KEYNOTE-162 (NCT02657889) in TNBC with niraparib, 200 mg *p.o. b.i.d.* + PD1 inhibitor pembrolizumab and phase I/II MEDIOLA (NCT02734004) in g*BRCA1/2*+ HER2-negative metastatic breast cancer patients with olaparib, 300 mg *p.o. b.i.d.* + PD-L1 inhibitor durvalumab.[89–91,138] Phase II NCT02849496 has enrolled g*BRCA1/2*+ TNBC patients for veliparib in combination with PD-L1 inhibitor atezolizumab, phase Ib/II JAVELIN PARP MEDLEY (NCT03330405) is recruiting patients with g*BRCA1/2*+ or ATM-deficient breast cancer for evaluation of talazoparib + PD-L1 inhibitor avelumab, and phase II DORA (NCT03167619) is soon to start recruiting women with platinum-sensitive metastatic TNBC with olaparib, 300 mg *p.o. b.i.d.* + durvalumab.[92–94]

Intracellular signaling

The intracellular phosphorylation cascades of the Rat sarcoma, rapidly accelerated fibrosarcoma, extracellular signal-regulated kinases (RAS–RAF–MEK–ERK) and PI3K–AKT–mTOR pathways have been implicated in the proliferation, survival, and metastatic potential of numerous types of cancer, thus driving development of small-molecule inhibitors targeting these pathways.[139,140] PI3K, AKT, and mTOR inhibitors are of special interest in clinical trials for breast cancer in particular, as enhanced signaling through the PI3K–AKT–mTOR pathway is thought to represent a major mechanism of resistance to therapies targeting the estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2).[141] There are dozens of inhibitors of the PI3K–AKT–mTOR pathway in development and a wide array of combination clinical trials in early and late stages, though FDA-approved-indications for treatment of breast cancer with PI3K–AKT–mTOR inhibitors has been thus far limited to mTOR inhibitor everolimus in combination with exemestane after failure of letrozole or anastrozole for advanced hormone-receptor-positive (HR+), HER2-negative breast cancer based on BOLERO-2.[142,143]

Preclinical data suggest that upregulation of the PI3K–AKT–mTOR pathway may contribute to PARP inhibitor resistance as well.[144] If this is clinically relevant, perhaps combinations of PARP inhibitors with inhibitors of PI3K, AKT, or mTOR are meant to enhance clinical benefit and prolong duration of response to PARPi. Phase I clinical trial NCT01623349 is evaluating olaparib in combination with PI3K inhibitors BKM120 or BYL719 in patients with metastatic TNBC after failure of one or more cytotoxic regimens.[95,145] Olaparib, 300 mg *p.o. b.i.d.*, in combination with mTOR inhibitor AZD2014 or AKT inhibitor AZD5363 is being evaluated in the phase I/II study NCT02208375.[98,99]

Conclusions

The recent FDA approval of olaparib has been a much-welcomed expansion of therapeutic options for metastatic gBRCA1/2+ breast cancer patients. If PARPi approvals for breast cancer are to follow the same path as those for ovarian cancer, we are likely to see the approval of additional PARP inhibitors in the near future. To date, there is no data demonstrating an OS benefit for PARP inhibitors in breast cancer patients, though to be fair, none of the studies discussed in this manuscript has been powered to detect OS. In the metastatic setting, OS data are difficult to interpret, as treatment options are numerous and patients are likely to be treated with a series of therapies for disease control. The phase III trial OlympiA is powered to assess OS in patients with HER2-negative breast cancer with *gBRCA1/2* mutations treated with olaparib in the adjuvant setting; data are expected in 2020.

Active PARPi monotherapy phase I and II trials hint at a willingness to explore their use beyond patients with deleterious germline *BRCA1/2* mutations to cancers with defects in homologous recombination repair, either germline or acquired, as well as in TNBC. Several academic and commercial institutions are developing assays to test tumor tissue for a BRCA-like phenotype, loosely defined as homologous recombination repair deficiency, and thus to expand the number of patients who could be offered PARP inhibitors.[26,27]

Combination strategies could also potentially expand the role of PARP inhibitors beyond cancers with homologous recombination repair defects, though it will take time to understand how best to use them to full effect while minimizing toxicities. The diversity of currently active early phase combination clinical trials is a fascinating reflection of a rapidly growing understanding of DNA repair, PARP inhibitor resistance mechanisms, and cancer biology. In the details and designs of the clinical trials discussed herein, there are clues that platinum sensitivity predicts response to PARP inhibitors, PARP inhibitors may be useful radiosensitizers and chemosensitizers, induction of 'BRCAness' is being explored for therapeutic exploitation, and that intermittent dosing and G-CSF support are feasible tactics to mitigate myelosuppressive toxicities of PARP inhibitors in the same way as for cytotoxic chemotherapies. PARP inhibitors remain a very active area of research, to the benefit of our future patients.

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Correspondence: Kelly E. McCann, UCLA Dept of Medicine, Division of Hematology/Oncology, 2336 Santa Monica Suite 304, Santa Monica, CA 90404, USA. kmccann@mednet.ucla.edu

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