REVIEW

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PARP inhibitors for *BRCA1/2*-mutated and sporadic ovarian cancer: current practice and future directions

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Poly(ADP-ribose) polymerase (PARP) inhibitors cause targeted tumour cell death in homologous recombination (HR)-deficient cancers, including *BRCA*-mutated tumours, by exploiting synthetic lethality. PARP inhibitors are being evaluated in late-stage clinical trials of ovarian cancer (OC). Recently, olaparib was the first PARP inhibitor approved in the European Union and United States for the treatment of advanced *BRCA*-mutated OC. This paper reviews the role of *BRCA* mutations for tumorigenesis and PARP inhibitor sensitivity, and summarises the clinical development of PARP inhibitors for the treatment of patients diagnosed with OC. Among the five key PARP inhibitors currently in clinical development, olaparib has undergone the most extensive clinical investigation. PARP inhibitors have demonstrated durable antitumour activity in *BRCA*-mutated advanced OC as a single agent in the treatment and maintenance setting, particularly in platinum-sensitive disease. PARP inhibitors are well tolerated; however, further careful assessment of moderate and late-onset toxicity is mandatory in the maintenance and adjuvant setting, respectively. PARP inhibitors are also being evaluated in combination with chemotherapeutic and novel targeted agents to potentiate antitumour activities. Current research is extending the use of PARP inhibitors beyond *BRCA* mutations to other sensitising molecular defects that result in HR-deficient cancer, and is defining an HR-deficiency signature. Trials are underway to determine whether such a signature will predict sensitivity to PARP inhibitors in women with sporadic OC.

INTRODUCTION

Current efforts to treat *BRCA*-associated ovarian cancer (OC) with poly(ADP-ribose) polymerase (PARP) inhibitors result from >25 years of basic and translational cancer research. Recently, olaparib, the first PARP inhibitor to treat *BRCA* mutation-positive patients, has been approved in the European Union and United States (US). Clinical studies have shown that BRCA1/2-deficient tumours are sensitive to PARP inhibitors and platinum agents (Fong *et al*, 2009; Byrski *et al*, 2010). PARP inhibitors are molecules that inhibit the activity of PARP proteins, which are involved in a variety of DNA damage repair pathways. The European Commission granted marketing authorisation for the PARP inhibitor olaparib as monotherapy in the maintenance treatment of adult patients with platinum-sensitive, relapsed *BRCA*-mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete response (CR) or partial response (PR) following platinum-based chemotherapy (Lynparza prescribing information, 2014). In the United States, olaparib received accelerated approval by the Food and Drug Administration (FDA) as monotherapy in patients with deleterious or suspected deleterious germline *BRCA*-mutated (*gBRCAm*) advanced OC and who have been treated with three or more prior lines of chemotherapy (Lynparza prescribing information, 2014). Confirmatory phase III trials are underway. This article will review the current role of BRCA proteins and PARP inhibitors in OC, summarise completed and ongoing clinical studies with PARP inhibitors, and outline future directions for this new drug class.

***BRCA1/2* and cancer risk.** A major development in the treatment of breast cancer and OC was the cloning of the suppressor genes

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BRCA1 and *BRCA2* (Friedman *et al*, 1994; Miki *et al*, 1994; Wooster *et al*, 1995). *BRCA1/2* encode proteins that are involved in homologous recombination (HR) (Farmer *et al*, 2005). Epidemiologic studies have revealed an association between germline BRCA1/2 (g*BRCA1/2*) mutations and the development of OC and breast cancer, and mutation frequencies are estimated to be 5–15% for patients diagnosed with OC (Ramus and Gayther, 2009) and 10% for those diagnosed with breast cancer (Neuhausen *et al*, 2009). However, mutation frequency can be much higher among certain high-risk populations; for example, the mutations are present in 41% of women of Ashkenazi Jewish decent (Moslehi *et al*, 2000). Among a general female population, the lifetime risk for development of OC and breast cancer ranges between 1% and 12%, respectively (National Cancer Institute, 2015a, b). However, for patients harboring a deleterious g*BRCA1/2* mutation, the estimated lifetime risk by age 70 for developing OC is 40% for g*BRCA1* mutation carriers and 11–18% for *gBRCA2* mutation carriers, and the risk for developing breast cancer is 57–65% for g*BRCA1* and 45–49% for g*BRCA2* mutation carriers (Antoniou *et al*, 2003; Chen and Parmigiani, 2007).

Patients with a g*BRCA1/2* mutation have inherited a loss-of-function mutation in a single copy of either *BRCA1* or *BRCA2* in every cell. Although it is understandable that the risk for developing cancer is increased as the remaining second wild-type copy of the gene can be inactivated by a somatic mutation or epigenetic inactivation (Venkitaraman, 2014), it remains unclear why mutations in *BRACA1/2* specifically lead to OC or breast cancer; and to a lesser degree, to pancreatic or prostate cancer. Recent evidence indicates that oestrogen controls the survival of *BRCA1*-deficient cells via a PI3K/NRF2-regulated pathway, which may partially explain the reported occurrence of hormonally driven tumours in patients who carry a *BRCA1/2* mutation (Gorrini *et al*, 2014). Preclinical mouse studies have found that BRCA1 protein interacts with NRF2 and that cells lacking BRCA1 activity accumulate reactive oxygen species resulting in attenuated cell viability (Gorrini *et al*, 2013). NRF2 is a transcription factor that regulates the antioxidant response (Li *et al*, 2004) and reactivation of NRF2 by oestrogen results in cell survival (Gorrini *et al*, 2013). NRF2 activity is governed by the activation of PI3K pathway, which promotes oestrogen stimulation of NRF2 activity to compensate for the lack of antioxidant response in the absence of BRCA1 activity (Gorrini *et al*, 2014).

DNA repair and role of *BRCA*. Currently, six primary pathways have been identified for DNA repair, and they are engaged variably to repair single- (SSB) and double-strand (DSB) DNA breaks resulting from DNA damage (Lee *et al*, 2014). These repair mechanisms include homologous recombination (HR), non-homologous end joining (NHEJ), base excision repair, nucleotide excision repair, mismatch repair, and trans-lesional synthesis (Lee *et al*, 2014). DNA damage can occur in a number of ways including generation of reactive oxygen species, ultraviolet light, ambient and therapeutic irradiation, day-to-day replication errors, and chemical exposures (Lee *et al*, 2014).

In response to DNA damage, proteins that comprise repair complexes are recruited to the site of damage (Gudmundsdottir and Ashworth, 2006). Loss or reduction of function in proteins involved in these complexes can result in impairment or loss of proper DNA repair. Double-stranded breaks trigger HR, which demonstrates high fidelity, and NHEJ, which is error prone (Lee *et al*, 2014; Scott *et al*, 2015). BRCA1/2 proteins mediate what might be the rate limiting step in HR (Farmer *et al*, 2005) and play a critical step in HR by facilitating the recruitment of RAD51 to single-stranded DNA generated during the HR process (Ciccia and Elledge, 2010; Polo and Jackson, 2011). RAD51 is a component of a complex of factors, which also includes MRE11 and NBS1, that is essential for HR (Stracker and Petrini, 2011). Therefore, cells that lack BRCA1/2 are deficient in HR and demonstrate a high degree of chromosomal instability as well as increased sensitivity to ionising radiation and chemotherapeutic agents that lead to DSBs (Ashworth, 2008). Whether HR or NHEJ occurs to correct DSBs depends upon a number of factors, one of which is the cell-cycle status; HR is used if DSBs arise during the S or G2 stages of mitosis, and NHEJ is utilised if DSBs occur during G1 (Symington and Gautier, 2011; Chapman *et al*, 2012, 2013; Karanam *et al*, 2012; Di Virgilio *et al*, 2013; Escribano-Diaz *et al*, 2013; Zimmermann *et al*, 2013). Other factors that influence which mechanism is used to repair DSBs are the complexity of the breaks and the presence of co-factors (Karanam *et al*, 2012).

PARP function. Poly(ADP-ribose) polymerase 1 is the first identified among a family of enzymes that transfer ADP-ribose moieties from the dinucleotide NAD+ to certain polypeptides resulting in mono- or poly(ADP-ribosylation) (pADPr) of these substrates (Burkle, 2001; Kim *et al*, 2005; Schreiber *et al*, 2006). PARP inhibitors are designed to compete with NAD+ for the substrate binding to PARP, inhibiting PARP activity (Kim *et al*, 2005). Poly(ADP-ribose) polymerase 1, PARP2, and PARP3 have all been implicated in DNA repair, with PARP1 being the most abundant (Sousa *et al*, 2012). Certain types of DNA damage, particularly DNA nicks and DSBs, result in an about a 500-fold increase in PARP1 catalytic activity (Mendoza-Alvarez and Alvarez-Gonzalez, 1993; Mendoza-Alvarez and Alvarez-Gonzalez, 2004; Hassler and Ladurner, 2012). Active PARP1 covalently adds pADPr chains to a number of chromatin proteins, including itself (Althaus and Richter, 1987; Hassler and Ladurner, 2012), which alters the function of the respective proteins (Althaus and Richter, 1987; Realini and Althaus, 1992; Malanga and Althaus, 2004).

PARP1 functions in a number of DNA repair pathways (Rouleau *et al*, 2010; Curtin, 2012). It has been most extensively studied in base excision repair (de Murcia *et al*, 1997; Masson *et al*, 1998; Trucco *et al*, 1998) in which it facilitates the recruitment and formation of DNA repair complexes, including XRCC1, which in turn promotes SSB repair (Caldecott, 2008; Odell *et al*, 2013; O'Sullivan *et al*, 2014). In addition, PARP1 acts in HR by sensing stalled replication forks and recruitment of MRE11 and NBS1 to initiate HR (Schultz *et al*, 2003; Helleday *et al*, 2005; Haince *et al*, 2008; Bryant *et al*, 2009). PARP1 also adds pADPr to BRCA1 to influence DSB repair during HR (Hu *et al*, 2014), and inhibits NHEJ repair by preventing the binding of the Ku proteins to free DNA ends (Wang *et al*, 2006; Scott *et al*, 2015). In addition, PARP1 is necessary for the alternative microhomology-mediated end joining repair (Robert *et al*, 2009; Soni *et al*, 2014). PARP2 and PARP3 also contribute to DNA repair; PARP2 cooperates with PARP1 to synthesise pADPr and PARP3 inhibits error prone NHEJ (Ame *et al*, 1999; Schreiber *et al*, 2002; Rulten *et al*, 2011).

PARP inhibitor activity

Synthetic lethality. Genetically, synthetic lethality occurs when two genetic lesions, which are individually not lethal, become lethal when combined in a single organism (or cell). Similarly, cells that are deficient in HR (which is not lethal in itself) are hypersensitive to reduction in PARP activity by PARP inhibitors (Bryant *et al*, 2005; Farmer *et al*, 2005; Patel *et al*, 2011; Scott *et al*, 2015). Currently there are four models proposed for how PARP inhibitors may instigate synthetic lethality: inhibition of base excision repair, trapping PARP1 on damaged DNA, defective recruitment of BRCA1 to damaged DNA, and activation of error-prone NHEJ (Figure 1).

Base excision repair. Synthetic lethality, observed with BRCA1/2 mutations plus inhibition of PARP activity, may result both from removal of HR, and reduction in base excision repair (Scott *et al*, 2015) (Figure 1). Under pharmacologic PARP inhibition, SSBs, normally

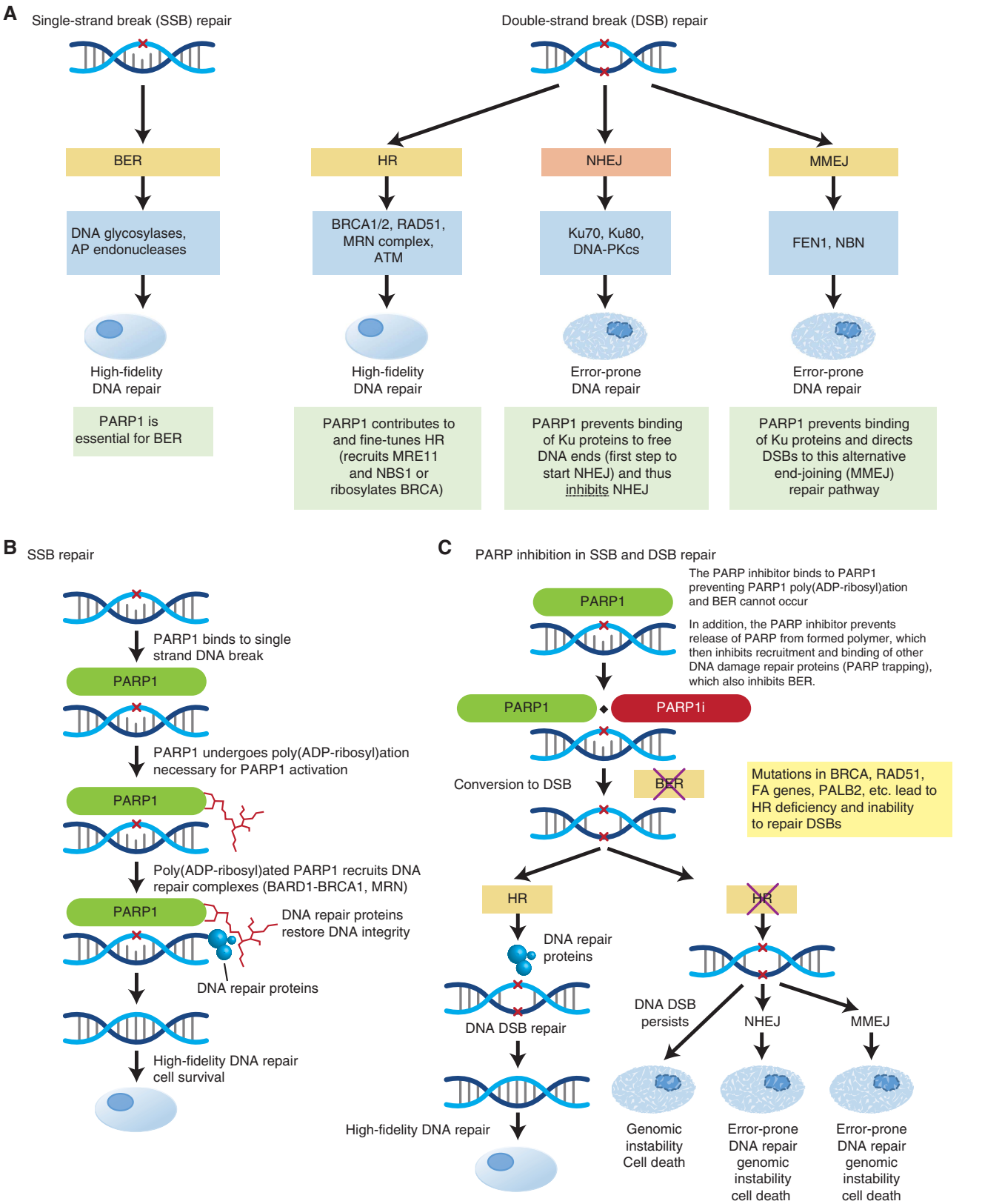

Figure 1. Role of PARP in DNA repair and main effects of PARP inhibitors. (**A**) Main DNA repair mechanisms, key pathway components and role of PARP1 for each pathway. (**B**) DNA single strand break repair by base excision repair. (**C**) Effect of PARP inhibition on DNA single and double strand break repair. AP, apurinic/apyrimidinic; ATM, ataxia telangiectasia; BER, base excision repair; DNA-PKcs, DNA-dependent protein kinase, catalytic subunit; DSB, double-strand break; FA, Fanconi anemia; FEN1, flap sructure-specific endonuclease 1; HR, homologous recombination; KU70 and KU80, make up the Ku heterodimer; MMEJ, microhomologymediated end joining; MRN, MRE11–RAD50–NBS1 protein complex; NBN, Nibrin; NHEJ, non-homologous end joining; PARP, poly (ADP-ribose) polymerase; PALB2, partner and localiser of BRC; PARPi, PARP inhibitor; RAD51, eukaryote gene of RAD51 protein family; SSB, single-strand break.

repaired by the base excision repair pathway, are left unresolved. Following duplication of the DNA strand this can lead to a DSB, which under normal circumstances can be repaired by the HR pathway, preserving cell viability. When HR repair is compromised as in BRCA-deficient cells, the DNA DSBs are not repaired (Ashworth, 2008). However, the validity of this premise has been debated, as removal of XRCC1 (a protein acting immediately downstream of PARP1 that is essential for base excision repair) in HR-deficient cells does not result in cell death suggesting that loss of PARP is critical for killing HR-deficient cells, but loss of base excision repair is not (Rouleau *et al*, 2010; Patel *et al*, 2011; Curtin, 2014; Scott *et al*, 2015).

PARP1 trapping. Recent evidence suggests that PARP inhibitors promote cell death by trapping PARP1 on the damaged DNA (Figure 1; Helleday, 2011; Strom *et al*, 2011; Murai *et al*, 2012; Horton *et al*, 2014). Normally, when DNA damage activates PARP1, the resulting pADPr recruits additional repair proteins, but once repair is initiated, it also diminishes the affinity of PARP1 for DNA, allowing PARP1's dissociation and the subsequent binding of other repair factors (Satoh and Lindahl, 1992; Scott *et al*, 2015). If PARP1 activity is inhibited such that it cannot synthesise pADPr polymers, it remains bound (trapped) to the damaged DNA, essentially blocking DNA repair (Satoh and Lindahl, 1992). Similarly, PARP inhibitor inactivation of PARP1 activity may consequently trap PARP1 on DNA repair intermediates, obstructing replication forks (Figure 1c; Horton *et al*, 2014). Therefore, PARP inhibitors may act, in part, as 'poisons' that trap the PARP1 enzyme on DNA. Importantly, PARP trapping may be more cytotoxic than loss of its catalytic activity (Murai *et al*, 2012). In support of this premise, the PARP catalytic inhibitory activities of the three PARP inhibitors, niraparib, olaparib, and veliparib, do not correlate strongly with respect to cytotoxic and trapping potency; niraparib and olaparib have greater cytotoxic and trapping activity than veliparib (Table 1; Murai *et al*, 2012). This may be the result of the differences in drug allosteric binding to the NAD^+ site, with the bulky inhibitors, niraparib and olaparib, possessing greater potency to produce PARP-DNA 'trapped' complexes compared with veliparib (Murai *et al*, 2012). Preclinical studies have also suggested that differences in the catalytic inhibitory and trapping activities of various PARP inhibitors may explain differences in synergism when combined with selected chemotherapeutic agents (Murai *et al*, 2012). For example, because temozolomide forms PARP–DNA complexes at SSBs, combining it with PARP inhibitors with higher PARP-trapping properties, such as niraparib or olaparib, may be a more efficacious option than a combination with an agent expressing less potent trapping activity, such as veliparib (Murai *et al*, 2012). Preclinical studies have also shown that stereospecific PARP trapping is more pronounced for talazoparib when compared to olaparib or rucaparib (Murai *et al*, 2014). These differences in catalytic and trapping activities may be important when combining PARP inhibitors with chemotherapeutic agents. One example is the observation that talazoparib demonstrates greater cytotoxicity than other PARP inhibitors in combination with the DNA alkylating agents methyl methane sulfonate or temozolomide (Murai *et al*, 2014; Hopkins *et al*, 2015).

Defective BRCA1 recruitment. BRCA1 is recruited to damaged DNA via several steps. BRCA1 is recruited through its binding to BARD1, which binds pADPr at the damage site. BRCA1 also binds with γ-H2AX a histone that is modified in response to damaged DNA (De Lorenzo *et al*, 2013) (Figure 1). If a specific mutation in BRCA1 disrupts the γ-H2AX interaction, the binding of the BRCA1–BARD1 complex becomes critical for HR. The ability of PARP inhibitors to reduce recruitment of the BARD1–BRCA1 complex to damaged DNA may result in cell death in the setting of a BRCA mutation where the interaction with γ-H2AX is diminished (Li and Yu, 2013). However, this model does not explain PARP inhibitor effects in cells that do not carry mutations in BRCA1, which disrupt BRCA1/ γ-H2AX complex formation (Scott *et al*, 2015).

Activation of non-homologous end joining. Another proposed mechanism for PARP inhibitor activity is based on the role of PARP1 in suppression of the microhomology-mediated end joining and error-prone NHEJ repair pathways (Figure 1). Several proteins including Ku70, Ku80, and DNA-PKcs are pADPr binding proteins (Scott *et al*, 2015). PARP inhibitors prevent the binding of Ku proteins to free DNA ends (the first step to initate NHEJ) and thus inhibit NHEJ (Lieber, 2010; Patel *et al*, 2011) resulting in mutations, chromosomal rearrangements, and cell death (Figure 1).

BRCAness: proposed PARP inhibitor efficacy. Certain sporadic OCs display a *BRCA*-like phenotype; therefore, it was proposed that PARP inhibitors may also demonstrate efficacy in such cancers. Data from The Cancer Genome Atlas suggest that approximately 50% of high-grade serous OC (HGSOC) cases display a *BRCA*-like phenotype (Cancer Genome Atlas Research Network, 2011). Such *BRCA*ness may occur as a result of epigenetic silencing of *BRCA* genes or inactivation of other HR-associated genes, including ATM, RAD51, or members of the FANC family of genes (Yap *et al*, 2011; O'Sullivan *et al*, 2014). Deficiencies in HR are associated with gene copy number changes that can be described as genomic instability. Recent studies suggest that it may be possible to capture this genomic instability by measuring allelic imbalance or loss of heterozygosity. The burden and pattern of allelic imbalance may distinguish subtypes of OC, and genomic signatures might predict response to treatment with PARP inhibitors (Haluska *et al*, 2014; Matulonis *et al*, 2014; Swisher *et al*, 2014).

CLINICAL APPLICATION

Multiple PARP inhibitors, including olaparib, veliparib, niraparib, rucaparib, and talazoparib, are currently being evaluated in clinical trials (Table 2). The most common PARP inhibitor chemistry is that of reversible NAD mimetics. The drugs differ in bioavailability, molar equivalence of PARP enzyme inhibition, and PARP trapping capability (Table 1). The loss of DNA repair in the presence of these molecules has led to the evaluation of these drugs as single agents and as potential enhancers of cytotoxic agents that provoke DNA damage, such as alkylating agents and radiation therapy (Lee *et al*, 2014). Several of these agents have been and are being investigated in patients with g*BRCA1/2*-associated and sporadic platinum-sensitive and/or platinum-resistant OC (Liu *et al*, 2014). In addition, PARP inhibitors are being investigated in combination with other targeted agents, such as in PI3-kinase or angiogenesis inhibitors. The VEGF monoclonal antibody (mAb) bevacizumab has been shown to induce hypoxia in the tumour microenvironment which may contribute to genomic instability and in doing so is thought to increase the sensitivity of cells to PARP inhibitors (Bindra *et al*, 2004, 2005; Chan *et al*, 2010; Sehouli *et al*, 2016).

Of note, iniparib, which was originally thought to be a PARP inhibitor, failed to demonstrate clinical activity in a randomised phase III study in patients with BRCA mutation-positive breast cancer. Following further preclinical studies iniparib is no longer classified as a PARP inhibitor as it failed to exhibit characteristic properties of PARP inhibitors. Therefore, results of iniparib studies should have no bearing on clinical decisions regarding PARP inhibitors (Patel *et al*, 2012).

Olaparib. Olaparib was the first PARP inhibitor to gain US FDA approval, based in-part on data from a single-arm trial that included 137 advanced OC patients with g*BRCA* mutations who were

Table 1. PARP inhibitors under development

PARP inhibitor	Route	PARP catalyitic inhibition (IC_{50}) (Murai *et al*, 2012, 2014)	*In vitro* Cytotoxicity (Murai *et al*, 2012, 2014)	*In vitro* PARP trapping (Murai *et al*, 2012, 2014)	Treatment	Cancer types
Olaparib (AZD-2281) (AstraZeneca)	Oral	1.2 nmol l^{-1}	+ +	+ +	•Monotherapy •Combination with cytotoxic chemotherapy •Combination with targeted agents •Combination with RTs	•BRCA1/2MUT + associated •BrCa/OvCa •BRCA-like tumours •Advanced hematologic malignancies and solid tumours •Maintenance study following remission in platinum sensitive OvCa
Veliparib (ABT-888) (Abbvie)	Oral	10.5 nmol l^{-1}	+	+	•Monotherapy •Combinations with cytotoxic chemotherapy •Combinations with targeted agents •Combinations with RT	•BRCA1/2MUT + associated BrCa/OvCa •BRCA-like tumours, •Advanced hematologic malignancies and solid tumours
Talazoparib (BMN 673) (Pfizer)	Oral	4 nmol l^{-1}	+ + + +	+ + + +	•Monotherapy	•Advanced hematologic malignancies and solid tumours
Rucaparib (Clovis)	Oral	21 nmol l^{-1}	+ +	+ +	•Monotherapy •Combinations (carboplatin)	•Advanced solid tumours •Recurrent OvCa, •BRCA1/2MUT + associated BrCa/OvCa
Niraparib (MK-4827) (TesaroBio)	Oral	50.5 nmol l^{-1}	+ + +	+ + +	•Monotherapy •Combinations (temozolomide)	•Advanced hematologic malignancies and solid tumours •BRCA1/2MUT + associated and HER2 negative BrCa, •Maintenance study following remission in platinum sensitive •OvCa

Abbreviations: BrCa = breast cancer; OvCa = ovarian cancer; RT = radiation therapy.

previously treated with three or more lines of chemotherapy. In this study, patients received olaparib 400 mg twice daily; the objective response rate (ORR) was 34% (46/137), of those, 32% (44/137) had partial response (PR) and 2% (2/137) demonstrated a complete response (CR). The median duration of response (DoR) was 7.9 months (Domchek *et al*, 2016). The approval was also based on supportive efficacy outcomes derived from other clinical trials in which olaparib had been previously assessed (Fong *et al*, 2009, 2010; Audeh *et al*, 2010; Gelmon *et al*, 2011; Kaye *et al*, 2012).

In an initial phase I trial, antitumour activity of olaparib was observed in patients with g*BRCA*-mutated advanced OC and the maximum tolerated dose (MTD) was determined to be 400 mg twice daily (Fong *et al*, 2009). A phase II trial confirmed durable antitumour responses with olaparib in advanced OC patients with *BRCA1/2* mutations. The ORR was 33% for 33 patients who received olaparib 400 mg twice daily and 13% for 24 patients who received 100 mg twice daily (Audeh *et al*, 2010). In an expanded cohort of the phase I trial, patients with ovarian, primary peritoneal, or fallopian tube cancer were treated with 200 mg olaparib twice daily and 20 of 50 patients(40%) had an objective and/or tumour marker response. Median DoR was 7 months. The clinical benefit rate correlated with platinum sensitivity (69% in platinum-sensitive, 46% in platinum-resistant, and 23% in platinum-refractory disease) (Fong *et al*, 2010).

A phase II open-label, randomised, controlled trial compared olaparib and pegylated liposomal doxorubicin (PLD) in patients with g*BRCA*-mutated advanced OC; olaparib demonstrated efficacy consistent with previous studies. No significant differences were observed between treatments in overall response rate (ORR) or progression-free survival (PFS). The ORR was 25%, 31%, and 18% for olaparib 200 mg twice daily, olaparib 400 mg twice daily, and PLD, respectively. Median PFS was 6.5 months for olaparib 200 mg twice daily, 8.8 months for olaparib 400 mg twice daily, and 7.1 months for PLD (Kaye *et al*, 2012).

In addition, a phase II open-label, nonrandomised, single-arm study was the first to demonstrate antitumour activity of a PARP inhibitor in sporadic HGSOC. Confirmed PRs were seen in 24% (11/46) of patients without g*BRCA* mutations and in 41% (7/17) of patients with g*BRCA* mutations (Gelmon *et al*, 2011).

A large, randomised phase II maintenance therapy trial of olaparib demonstrated efficacy among patients with platinum-sensitive (CR or PR), relapsed OC (Ledermann *et al*, 2012, 2014). Results of this randomised, double-blind, placebo-controlled study revealed a significant improvement in PFS in patients treated with olaparib maintenance therapy 400 mg twice daily ($n = 136$) compared with placebo ($n = 129$; 8.4 *vs* 4.8 months for placebo, hazard ratio = 0.35 (95% CI, 0.25–0.49); $P < 0.001$; Ledermann *et al*, 2012). Subset analyses showed that among patients with a germline or tumour *BRCA* mutation median PFS was significantly longer in the olaparib group ($n = 74$) than in the placebo group ($n = 62$; 11.2 *vs* 4.3 months, hazard ratio = 0.18 (95% CI, 0.10–0.31); $P < 0.0001$). Significant improvements in PFS were also noted for patients without a *BRCA* mutation ($n = 57$) compared with placebo ($n = 61$); however, the difference was less robust (7.4

Table 2. Most common AEs (any grade and grade ⩾3) with olaparib treatment based on data from 2 large olaparib clinical trials. Shown are any grade AEs reported in at least 15% of patients or grade ⩾3 AEs reported in at least 5% of patients

	Kaufman *et al* (2015)		Ledermann *et al* (2012)			
	Olaparib *N* = 193		Olaparib *N* = 136		Placebo *N* = 128	
	Any grade number (%)	Grade ⩾3 number (%)	Any grade number (%)	Grade ⩾3 number (%)	Any grade number (%)	Grade ⩾3 number (%)
Fatigue	116 (60.1)	12 (6.2)	66 (48.5)	9 (6.6)	48 (37.5)	4 (3.1)[a]
Nausea	119 (61.7)	1 (0.5)	93 (68.4)	3 (2.2)	45 (35.2)	0 (0)
Vomiting	75 (38.9)	5 (2.6)	43 (31.6)	3 (2.2)	18 (14.1)	1 (0.8)
Anemia	62 (32.1)	36 (18.7)	23 (16.9)	7 (5.1)	6 (4.7)	1 (0.8)
Diarrhea	56 (29.0)	3 (1.6)	31 (22.8)	3 (2.2)	29 (22.7)	3 (2.3)
Abdominal pain	58 (30.1)	14 (7.3)	24 (17.6)	2 (1.5)	33 (25.8)	4 (3.1)
Decreased appetite	36 (18.7)	1 (0.5)	25 (18.4)	0 (0)	17 (13.3)	0 (0)
Dyspepsia	38 (19.7)	0 (0)	22 (16.2)	0 (0)	11 (8.6)	0 (0)
Headache	32 (16.6)	0 (0)	25 (18.4)	0 (0)	15 (11.7)	1 (0.8)
Dysgeusia	39 (20.2)	0 (0)	19 (14.0)	0 (0)	8 (6.3)	0 (0)

[a]One patient in the placebo group inadvertently received olaparib at a dose of 400 mg twice daily for approximately 2 weeks. The exact dates and duration are unknown. It is not known whether the patient was receiving olaparib or placebo when the adverse event (AE) occurred. This AE was counted in the safety analysis for placebo, but the possibility that it was attributable to olaparib cannot be excluded.

vs 5.5 months, hazard ratio = 0.54 (95% CI, 0.34–0.85); $P = 0.0075$). At a second interim analysis of OS (58% maturity), OS for patients with germline or tumour *BRCA* mutations did not significantly differ between the groups (hazard ratio = 0.88 (95% CI, 0.64–1.21); $P = 0.44$; Ledermann *et al*, 2014). In an updated analysis olaparib significantly improved times to first and second subsequent therapy (Ledermann *et al*, 2016). Moreover, maintenance olaparib gave patients a survival advantage, however, analyses suggest that these results may have been driven by the BRCAm group (5-year survival was 29.2% and 20.4% in the olaparib and placebo arms, respectively, and 36.9% and 24.3% in BRCAm patients; Ledermann *et al*, 2016).

Although most studies have assessed olaparib in patients with platinum-sensitive OC, results of the recent single-arm, phase II study showed encouraging results in patients with platinum-resistant OC (Kaufman *et al*, 2015). The study included 298 patients with confirmed germline BRCA1 or BRCA2 mutation and advanced solid tumours. Among the cohort of 193 patients with platinum-resistant OC, 31% (60/193) achieved a response and 40% (78/193) had stable disease for ⩾8 weeks. Median PFS and OS were 7 months and 16.6 months, respectively.

Across trials, olaparib has shown a consistent adverse event (AE) profile. The most common treatment-related AEs were fatigue, gastrointestinal symptoms (nausea, vomiting, diarrhea), and anemia, most of which were grade 1/2. The reported major toxicities of the two largest clinical trials with olaparib are shown in Table 2 (Ledermann *et al*, 2012; Kaufman *et al*, 2015). Although most AEs were mild-to-moderate, consideration must be given to the development of serious, potentially fatal conditions, such as myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) and pneumonitis, which have occurred rarely with olaparib treatment. MDS/AML was confirmed in 2% (3/136) of treated patients in a randomised placebo-controlled trial and in 2% (6/298) of treated patients in a single-arm monotherapy trial (Lynparza prescribing information, 2014). Across all reported olaparib studies, MDS/AML was reported in <1% (22/2,618) of patients and pneumonitis, including fatal cases, occurred in <1% of patients. MDS/AML likely result from PARP inhibitor-related disruption in DNA repair, as altered DNA repair mechanisms can lead to the development of genomic instability that in itself may promote carcinogenesis (Bhatia, 2013).

Additional phase III maintenance trials for olaparib following chemotherapy are underway (Table 3). These trials use the new tablet formulation of olaparib developed to facilitate olaparib dosing. Current approval of olaparib is based on completed clinical studies where the dose of olaparib was 400 mg twice daily using a capsule formulation; each capsule was 50 mg, equaling a total pill count of 16 capsules per day. Clinical studies have now been completed which compare the bioavailability and match the efficacy and tolerability of the tablet to that of the capsule (Mateo *et al*, 2016). As a result, the 300-mg tablet formulation (2 × 150 mg tablets twice daily) was chosen as the most suitable dose for all phase III studies. The phase III SOLO1 study, conducted in collaboration with the Gynecologic Oncology Group, will provide information on the role of maintenance olaparib after frontline chemotherapy for OC patients with g*BRCA* mutations. SOLO2, in collaboration with the European Network of Gynaecological Oncological Trial Groups, will evaluate the role of maintenance olaparib after ⩾2 lines of chemotherapy for OC patients with g*BRCA* mutations. Both trials are randomised, double-blind, placebo-controlled studies that utilise the new tablet formulation of olaparib at a dose of 300 mg twice daily (Moore *et al*, 2014). In addition, SOLO3 is a randomised, phase III trial in patients with g*BRCA* mutated, recurrent OC in which single-agent olaparib will be compared with standard-of-care chemotherapy in patients who failed ⩾2 lines of prior chemotherapy for recurrent disease (Table 3).

Olaparib is also under investigation in combination with chemotherapeutic agents. In a randomised, open-label, phase II study, patients with platinum-sensitive, recurrent OC received either olaparib (200 mg twice daily, days 1–10 of each 21-day treatment cycle) plus paclitaxel (175 mg m^{-2}, intravenously, day 1 of each cycle) and carboplatin (area under the curve (AUC) 4, according to the Calvert formula, intravenously, day 1 of each cycle) followed by olaparib monotherapy (400 mg twice daily, continuously), or paclitaxel (175 mg m^{-2}, day 1 of each cycle) and carboplatin (AUC 6, day 1 of each cycle) followed by no further treatment in the maintenance phase. PFS was significantly improved for the olaparib plus paclitaxel/carboplatin group *versus* chemotherapy alone (12.2 *vs* 9.6 months, respectively (hazard ratio = 0.51, 95% CI, 0.34–0.77; $P = 0.0012$)); the toxicity profile for the olaparib group was manageable (Oza *et al*, 2015). In a phase

Table 3. Clinical Trials of PARP inhibitors in ovarian cancer

Agent	NCT no./trial name	Phase	Population	Study design	Interventions	Primary outcome measure	Selected additional outcome measures	Start date- estimated completion
Monotherapy trials								
Niraparib	NCT01847274 NOVA	III	Platinum-sensitive, recurrent g*BRCA*m OC or HGSOC	Randomised double-blind, placebo-controlled, parallel-group	Oral niraparib, placebo	PFS	PRO, chemotherapy-free interval, OS	Jun 2013-Oct 2016 Jun 2016 (primary data)
Niraparib	NCT02354586 QUADRA	II	Advanced, relapsed HGSOC following completion of at least 3 prior chemotherapy regimens	Single-arm, open-label	Oral niraparib	Antitumour activity	PFS, disease control rate, safety	Mar 2015- Jan 2016 Jan 2016 (primary data)
Niraparib	NCT02655016 PRIMA	III	HRD-positive tumours OC, as identified with a centralised HRD test, at high risk for PD, as identified by the stage of cancer and previous response to surgery	Randomised, double-blind, placebo-controlled, parallel group	Oral niraparib, placebo	PFS	OS, safety and tolerablilty, PRO, TTP	Apr 2016-Mar 2018 Mar 2018 (primary data)
Olaparib	NCT02282020 SOLO3	III	Platinum-sensitive relapsed, g*BRCA*m OC	Randomised open-label controlled, parallel group	Oral olaparib (300 mg tablets) vs physicians choice single-agent chemo-therapy	PFS	OS, TTP, PFS, QoL	Feb 2015-Dec 2019 Dec 2017 (primary data)
Olaparib	NCT02477644	III	Advanced FIGO stage IIIB - IV HGSOC or endometrioid ovarian, fallopian tube, or peritoneal cancer treated with standard first-line platinum-taxane chemotherapy plus bevacizumab	Randomised double blind	Oral olaparib 300 mg tablets, placebo	PFS	-	Apr 2015–Apr 2022 Apr 2022 (primary data)
Olaparib	NCT02489006	II	Platinum sensitive recurrent HGSOC, primary peritoneal, and fallopian tube cancer	Randomised, open label	Oral olaparib, platinum-based chemotherapy	Difference in PAR or PARP1 levels before and after treatment, mutations in BRCA1/2, RAD51B, RAD51C, RAD51D, PPM1D, FANCM, BRIP1, PALB2 and BARD1 in germline tissue compared to tumour tissue	Safety, response rate, duration of PFS,	Jun 2015–Jun 2019 Dec 2018 (primary data)
Olaparib	NCT00628251	II	Measurable BRCA1- or BRCA2-positive advanced ovarian cancer which has failed previous platinum therapy.	Randomised open-label, parallel study	Oral olabarib 200 mg BID; or 400 mg BID, liposomal doxorubicin	PFS, ORR, DoR, CA-125 levels	Safety	Jul 2008–Dec 2015 Sep 2009 (primary data)
Olaparib	NCT00753545	II	Platinum sensitive relapsed serous ovarian cancer following treatment with two or more platinum containing regimens	Randomised double blind, parallel group	Oral olabarib 400 mg BID, placebo	PFS	OS, ORR, disease control rate, DoR	Aug 2008–Nov 2012 Jun 2010 (primary data)
Olaparib	NCT01844986 SOLO-1	III	Newly diagnosed, high-risk advanced, g*BRCA*m OC in complete or partial response following first line platinum therapy	Randomised double-blind, placebo-controlled, parallel-group	Oral olaparib (300 mg tablets), placebo	PFS	OS, TTP, QoL, safety	Aug 2013-Jan 2023 Feb 2017 (primary data)
Olaparib	NCT01874353 SOLO2	III	Platinum-sensitive, relapsed g*BRCA*m high-grade OC or high grade endometrial cancer with CR or PR following platinum-based chemotherapy	Randomised double-blind, placebo-controlled, parallel-group	Oral olaparib (300 mg tablets), placebo	PFS	OS, TTP, QOL, safety	Sep 2013-Apr 2021 Sep 2016 (primary data)

Table 3. (Continued)

Agent	NCT no./trial name	Phase	Population	Study design	Interventions	Primary outcome measure	Selected additional outcome measures	Start date- estimated completion
Olaparib	NCT02392676	III	Platinum sensitive relapsed *gBRCAm*, ovarian cancer in CR or PR following platinum-based chemotherapy	Randomised double-blind, parallel group	Oral olaparib, placebo	PFS using modified RECIST in cohort of patients with sBRCA ovarian cancer	PFS, OS, TTP	July 2016 -June 2019 June 2019 (primary data)
Rucaparib	NCT00664781	II	Advanced or metastatic g*BRCA*m breast cancer or advanced ovarian cancer.	Dose-escalation study followed by an open label multicenter study	Oral rucaparib	Antitumour activity, safety	TTP, OS	Dec 2007–Jan 2015 Jan 2015 (primary data)
Rucaparib	NCT01891344 ARIEL2	II	Platinum-sensitive, relapsed high grade epithelial ovarian, fallopian, primary peritoneal cancer. Part 1: received ⩾1 prior platinum-based regimen. Part 2: received ⩾3 prior chemotherapy regimens	Single-arm, open-label two part study	Oral rucaparib	Disease progression (part 1), ORR (part 2)	ORR (part 1), disease progression (part 2), DoR, OS, safety, PK	Sep 2013-Mar 2017 Mar 2017 (primary data)
Rucaparib	NCT01482715	I/II	High grade, measurable disease relapsed g*BRCA*m OC following ⩾3 prior chemotherapy regimens, or have advanced solid tumour	Single-arm, open-label dose finding study	Oral rucaparib	Safety, PK, ORR	DoR, OS, safety	Nov 2011- Apr 2017 Apr 2017 (primary data)
Rucaparib	NCT01968213 ARIEL3	III	Platinum-sensitive relapsed g*BRCA*m HGSOC or endometrial, primeary peritoneal, or fallopian tube cancer	Randomised double-blind, placebo-controlled, parallel-group	Oral rucaparib, placebo	PFS	OS, PRO, safety, PK	Jan 2014-Mar 2017 2016 Mar 2017 (primary data)
Talazoparib	NCT02326844	II	Recurrent, g*BRCA*m OC following progression on prior PARP inhibitor therapy	Single-arm, open-label	Oral talazoparib	ORR	Safety	Dec 2014-Dec 2016 Sept 2016 (primary data)
Talazoparib	NCT01989546	I/II	g*BRCA*m OC, primary peritoneal, breast, or other solid tumours following progression on standard therapy or who have no acceptable standard treatment options	Single-arm open-label	Oral talazoparib	PD effect		Nov 2013-Mar 2017 Mar 2017 (primary data)
Veliparib	NCT01472783	I/II	g*BRCA*m platinum-resistant or partially platinum-sensitive relapsed epithelial OC	Single-arm, open-label	Oral veliparib	MTD, response rate	PFS, OS	Nov 2011-Aug 2016 Jan 2016 (primary data)
Veliparib	NCT01540565	II	g*BRCA*m recurrent or persistent epithelial ovarian, fallopian tube, or primary pertioneal cancer	Single-arm open-label	Oral veliparib	Safety, objective tumour response, safety	PFS, OS	Apr 2012-Apr 2017 April 2017 (primary data)
Veliparib	NCT02470585	III	Newly diagnoses Stage III or IV HGSOC, fallopian tube, or primary peritoneal carcinoma	Randomised, double-blind, three-arm, parallel group	Oral veliparib, carboplatin, paclitaxel, placebo	PFS	OS, tdisease related symptom score	July 2015 Jan 2019 Jan 2019 (primary data)
Combination therapy trials								
Niraparib + bevacizumab	NCT02354131 AVANOVA1	I/II	Recurrent, HRD platinum sensitive HGSOC, fallopian tube, or peritoneal cancer	Randomised open-label, parallel group	Oral niraparib and/or oral niraparib + bevacizumab IV vs bevacizumab IV alone	PFS	Disease control rate	Feb 2015-Dec 2019 Nov 2017 (primary data)
Olaparib + cediranib	NCT01116648	I/II	Recurrent papillary serous OC, fallopian tube, or peritoneal cancer of for recurrent TNBC	Randomised open-label, parallel group	Oral olaparib + oral cediranib or oral olaparib	MTD, DLT, PFS	OS, tumour response rate, CBR, safety	Mar 2010-Feb 2016 Feb 2016 (primary data)

Table 3. (Continued)

Agent	NCT no./trial name	Phase	Population	Study design	Interventions	Primary outcome measure	Selected additional outcome measures	Start date- estimated completion
Olaparib + AZD2014 or AZD5363	NCT02208375	I/II	Recurrent endometrial, OC, or TNBC	Non-randomised, open-label, parallel group	Oral olaparib + oral AZD2014 or oral olaparib + oral AZD5363	MTD	Disease response and biomarker response	Nov 2014-Nov 2020 Nov 2020 (primary data)
Olaparib + BKM120 or BYL719	NCT01623349	I	Recurrent HGSOC or TNBC	Non-randomised, open-label	Oral olaparib + oral BKM120 or oral olaparib + BYL719	MTD, RP2D	Safety, PK	Sept 2012-Dec 2016 Aug 2016 (primary data)
Olaparib + cisplatin, paclitaxel, bevacizumab	NCT02121990	I	Newly diagnosed optimally debulked OC, primaryperitoneal, and fallopian tube cancer	Single arm, open-label	Oral olaparib + IP cisplatin, IV/IP paclitaxel, IV bevacizumab	MTD	Toxicity	Apr 2014- Apr 2017 Apr 2017 (primary data)
Olaparib + carboplatin + paciltaxel	NCT01650376	I/II	Relapsed OC or uterine cancer	Single arm, open label, safety study	Oral olaparib + IV carboplatin + IV paciltaxel	DLT	Safety, OS, response to therapy, TTP	Aug 2012–Dec 2017 Dec 2016 (primary data)
Olaparib + cediranib maleate	NCT02446600	III	Recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer	Randomised, comparative, open label, parallel group	Carboplatin + paclitaxel or carboplatin + gemcitabine hydrochloride or carboplatin + liposomal hyrdocholride or olaparib or olaparib + cediranib maleate	PFS	OS, safety, PRO	Feb 2016–Dec 2019 Dec 2019 (primary data)
Olaparib + cediranib maleate	NCT02502266	II/III	Recurrent platinum-resistant or -refractory ovarian, fallopian tube, or primary peritoneal cancer	Randomised, comparative, open label, parallel group	Physician choice standard of care with eith paclitaxel or toptecan hydrocholoride or olaparib + cediranib maleate or cediranib maleat or olaparib	OS (phase III); PFS (phase II)	Safety, ORR, PRO	Feb 2016–Jun 2023 Jun 2023 (primary data)
Olaparib + carboplatin + paclitaxel	NCT01081951	II	Platinum-sensitive advanced serious ovarian cancer	Randomised open-label, parallel group	Oral olaparib + IV carboplatin + IV paclitaxel or IV paclitaxel + IV carboplatin	PFS	OS. Percentage change in tumour size	Feb 2010–Dec 2016 Oct 2011 (primary data)
Talazoparib	NCT02627430	I	Metastatic advanced solid tumour or recurrent ovarian, fallopian tube, primary peritoneal, or TNBC	Open label, single arm	Talazoparib and AT13387 (HSP90 inhibitor)	MTD	Adverse events, PK	Mar 2016-Mar 2019 Mar 2019 (primary data)
Veliparib + topotecan	NCT01690598	I/II	Platinum-sensitive relapsed epithelial OC, primary fallopian or primary peritoneal cancer	Single-arm, open-label	Oral veliparib + topotecan IV	MTD, ORR	PFS, OS	Nov 2012-Feb 2015 Jan 2015 (primary data)
Veliparib + paclitaxel + carboplatin + bevacizumab	NCT00989651	I	Newly diagnosed, stage II-IV epithelial OC, fallopian tube or primary peritoneal cancer	Single-arm, open-label	Oral veliparib + paclitaxel IV, carboplatin IV, bevacizumab IV	DLT	Objective tumour response, PFS, safety	Oct 2009-Sep 2020 Sep 2020 (primary data)
Veliparib + PLD + carboplatin + bevacizumab	NCT01459380	I	Recurrent, platinum- sensitive OC, primary peritoneal or fallopian tube cancer	Randomised open-label, parallel group	Oral veliparib + PLD IV + carboplatin IV + bevacizumab IV	DLT, safety	ORRl	Oct 2011- Aug 2016 Aug 2016 (primary data)
Veliparib + carboplatin + paclitaxel	NCT02470585	III	Newly diagnosed stage III or IV HGSOC, fallopian tube, or primary peritoneal cancer	Randomiseddouble blind, parallel group	Oral veliparib, IV carboplatin, and IV paclitaxel or IV carboplatin + IV paclitaxel + placebo	PFS,	OS, disease related symptom score	July 2015- Jan 2019 Jan 2019 (primary data)
Veliparib + temozolomide	NCT01113957	II	Recurrent high grade serous ovarian cancer	Randomised open label, parallel group	Oral veliparib + temoxolomide or PLD	ORR	PFS, TTP, OS, safety, QoL	Mar 2010-June 2013 Jun 2013 (primary data)

Table 3. (Continued)

Agent	NCT no./trial name	Phase	Population	Study design	Interventions	Primary outcome measure	Selected additional outcome measures	Start date- estimated completion
Veliparib + cyclophosphamide	NCT01306032	II	Refractory BRCA-positive ovarian, primary peritoneal, or HGSOC, fallopian tube cancer, TNBC, and low-gread non-Hodgkin's lymphoma	Randomised, open label, cross-over	Oral veliparib and oral cyclophosphamide or cyclophosphamide	ORR, PFS	Safety	Jan 2011-Dec 2014 Dec 2014 (primary data)

Abbreviations: CBR = clinical benefit rate; DDFS = distant disease-free survival; DLT = dose-limiting toxicities; DoR = duration of response; *gBRCAm* = germline *BRCA* mutation; HER2 = human epidermal growth factor receptor 2; HGSOC = high-grade serous OC; HRD = homologous recombination deficiency; IDFS = invasive disease-free survival; IP = intraperitoneal; IV = intravenous; MTD = maximum tolerated dose; ORR = overall response rate; OS = overall survival; PARP = poly(ADP-ribose) polymerase; PD = pharmacodynamic; PFS = progression-free survival; PK = pharmacokinetic; PLD = pegylated liposomal doxorubicin; PRO = patient-reported outcomes; QoL = quality of life; RP2D = recommended phase II dose; TNBC = triple-negative breast cancer; TTP = time to progression. Source: clinicaltrials.gov.

I, open-label, dose-finding study, olaparib (100, 200, or 400 mg twice daily) was administered intermittently (7 days) or continuously (28-day treatment cycle) in combination with liposomal doxorubicin ($40\,mg\,m^{-2}$ every 28 days). The MTD was not reached with olaparib 400 mg twice daily. The combination was active and generally well-tolerated (Del Conte *et al*, 2014).

Pooled data from the previously mentioned six olaparib trials (two Phase I trials and four Phase II studies; Fong *et al*, 2009, 2010; Audeh *et al*, 2010; Gelmon *et al*, 2011; Kaye *et al*, 2012; Mateo *et al*, 2013; Kaufman *et al*, 2015) that recruited women with relapsed ovarian, fallopian tube, or peritoneal cancer were used to explore the activity of olaparib in relation to the number of prior treatment lines in patients with *gBRCAm* ovarian cancer (Matulonis *et al*, 2016). All patients received 400 mg of olaparib twice per day. In the pooled population with measurable disease at baseline ($n = 273$), the ORR was 36% with a 7.4 month median DoR. For patients who had received $\geqslant 3$ lines of prior chemotherapy ($n = 205$), the ORR was 31% and median DoR was 7.8 months. The ORR declined as the number of lines increased from 50% for patients who had received one prior regimen to 24% for patients who had received $\geqslant 6$ prior regimens. Grade $\geqslant 3$ adverse events were reported in 50% of the pooled population and 54% of the population who had $\geqslant 3$ lines of prior chemotherapy. The findings of the study indicated that olaparib was associated with durable response in patients with relapsed g*BRCA*-mutated ovarian cancer and who had been administered $\geqslant 3$ lines of prior chemotherapy.

Combination studies with a number of other agents are also being assessed. Olaparib was studied in combination with the antiangiogenic multikinase inhibitor, cediranib. The rationale behind this combination is based on the observation that vascular endothelial growth factor receptor (VEGFR) inhibition may lead to increased DNA damage through downregulation of DNA repair proteins, including ERCC1 and XRCC1 (Yadav *et al*, 2011). Stemming from supportive preclinical data (Pyriochou *et al*, 2008), a phase II trial of olaparib in combination with the VEGF multikinase inhibitor, cediranib, was recently completed (Liu *et al*, 2014). Patients received 30-mg cediranib daily and olaparib 200 mg twice daily. Median PFS was 17.7 months for women treated with cediranib plus olaparib ($n = 44$) compared with 9.0 months for those treated with olaparib monotherapy ($n = 46$; hazard ratio = 0.42; $P = 0.005$). OS data were not mature; OS at 24 months was 81% (95% CI, 60–91) in the combination group compared with 65% (95% CI, 42–81) in the olaparib-monotherapy group. Treatment-related AEs were more common in patients treated with cediranib plus olaparib than with monotherapy. These included grade 1/2 AEs of hypertension (17 *vs* 0 patients, respectively), diarrhea (31 *vs* 1), fatigue (26 *vs* 21), headache (17 *vs* 4), hypothyroidism (7 *vs* 1), and decrease in white blood cell (5 *vs* 4) and platelet counts (6 *vs* 3), as well as grade 3/4 AEs including fatigue (12 *vs* 5 patients), diarrhea (10 *vs* 0), and hypertension (18 *vs* 0; Liu *et al*, 2014).

Most recently, results of phase I studies of olaparib in combination with the PI3K inhibitor BKM120 and the AKT inhibitor AZD5363 have been reported with evidence of activity in OC (Matulonis *et al*, 2015; Michalarea *et al*, 2015). The rationale for these studies was based on preclinical data in breast cancer models showing that inhibition of the PI3/AKT pathway can result in *BRCA1/2* downregulation, HR impairment, and sensitivity to PARP inhibition (Ibrahim *et al*, 2012; Juvekar *et al*, 2012).

Veliparib. Veliparib has been evaluated in phase I studies as single agent and in combination with chemotherapeutic agents. Advanced-phase trials are currently ongoing. A phase II study is investigating veliparib monotherapy in patients with g*BRCA* mutations and recurrent OC (Table 3). Preliminary results

reported an ORR of 26% (13/50 patients). Responses were observed in both platinum-sensitive and platinum-resistant patients and median PFS was 8.1 months. Gastrointestinal symptoms, fatigue, and anemia were the most common AEs (Coleman *et al*, 2015).

A phase I trial of veliparib with cyclophosphamide observed antitumour responses in patients ($N=35$) with OC, breast cancer, urothelial or lymphoid malignancies. The MTD was found to be veliparib 60 mg once daily plus cyclophosphamide 50 mg once daily (Kummar *et al*, 2012). Seven patients had PR; an additional 6 patients had disease stabilisation for at least six cycles. Based on preclinical data supporting the interaction between inihibition of PARP and the VEGF signalling pathway (Pyriochou *et al*, 2008; Yadav *et al*, 2011), a phase I study was conducted to evaluate veliparib in combination with a platinum/taxane regimen plus bevacizumab in epithelial ovarian fallopian or primary peritoneal cancer ($N=189$) (Bell-McGuinn *et al*, 2015). An ongoing GOG phase III study is currently evaluating carboplatin/paclitaxel with or without concurrent and continuation maintenance veliparib in patients with previously untreated stages III or IV high-grade serous epithelial ovarian, fallopian, or primary peritoneal cancer (NCT02470585).

Niraparib. Niraparib is under investigation in patients with and without *BRCA*-mutated cancer (Sandhu *et al*, 2013). In a phase I/Ib study, 100 patients with advanced solid tumours were enrolled and 300 mg daily was established as the MTD. A PR was confirmed in 8 of 20 (40%) *BRCA*-mutation carriers with OC or primary peritoneal cancer, with more responses in platinum-sensitive (50%) than platinum-resistant (33%) disease. Durable PRs were also observed in sporadic HGSOC in 2 of 3 patients with platinum-sensitive disease and 3 of 19 (16%) patients with platinum-resistant disease. Fatigue, GI symptoms, and hematologic toxicity (anemia, thrombocytopenia, and neutropenia) were the most commonly reported drug-related toxicities. Niraparib was also evaluated in the recently completed phase III maintenance study, NOVA (NCT01847274), in patients with recurrent platinum sensitive HGSOC (Table 3). The NOVA trial successfully achieved its primary endpoint of PFS in patients with germline BRCA mutations (21.0 *vs* 5.5 months HR 0.27, $P<0.0001$) and in patients who were not germline BRCA mutation carriers but whose tumours were determined to be HR-deficiency positive (12.9 *vs* 3.8 months HR 0.38, $P<0.0001$). http://www.globenewswire.com/NewsRoom/AttachmentNg/6ea284b2-a663-4aeb-96c1-22ac847b460f. A phase I/II study is exploring the efficacy of niraparib and/or the combination of niraparib plus bevacizumab compared with bevacizumab alone (Table 3). In addition, the QUADRA (NCT02354586) phase II study is evaluating the safety and efficacy of niraparib in patients who have received at least three previous chemotherapy regimens (Table 3). Finally, the PRIMA study (NCT02655016) is assessing the efficacy of niraparib maintenance treatment following first-line platinum-based chemotherapy in patients with advanced primary ovarian cancer that demonstrates HR DNA repair deficiency.

Rucaparib. Rucaparib has demonstrated favorable preclinical and clinical activity in patients with gBRCA-mutated OC and sporadic, platinum-sensitive OC. A phase I study of rucaparib in patients with advanced solid tumours including gBRCA-mutated ovarian, breast, and pancreatic cancer determined the recommended dose to be 600 mg twice daily based on maximum exposure, manageable toxicity and promising clinical activity (Kristeleit *et al*, 2014; Shapiro *et al*, 2013). Durable antitumour responses were observed in a subgroup of platinum-sensitive and platinum-resistant ovarian and primary peritoneal cancer patients. Of 14 patients with a gBRCA mutation, 13 had CR, PR, or stable disease at 12 weeks (Kristeleit *et al*, 2014). Part 2b of the original dose-finding study (Study 10, NCT01482715) is investigating the efficacy of rucaparib 600 mg twice daily in heavily pre-treated high-grade serous, BRCAm OC (Drew *et al*, 2016).

Next to g*BRCA1/2* mutations, there are other possible causes of deficient DSB repair that may likewise be associated with responsiveness to PARP inhibitor. Both Foundation Medicine and Myriad Genetics are aiming to identify a genomic signature for *BRCA*-like OCs. Myriad Genetics has selected a combination of three slightly variable algorithms that are indicative of defective DNA DSB repair in cancer cells and will soon be incorporating the MyChoice HR deficiency assay into ovarian cancer clinical trials (Timms *et al*, 2014, 2015). Foundation Medicine has partnered with Clovis, who is conducting the phase II and phase III rucaparib trials, ARIEL2 and ARIEL3, in platinum-sensitive, recurrent OC, to prospectively validate an HR deficiency score in the tumours of patients using a next generation DNA sequencing test which determines the degree of loss of heterozygosity (LOH) as a marker of genomic instability for predicting response to rucaparib (Swisher *et al*, 2014). Preliminary data from 135 patients using a prespecified genomic LOH cut-off have shown response to rucaparib in patients with *BRCA* mutations (ORR 69%) and in patients with a *BRCA*-like LOH high signature (ORR 39%), which is in contrast to patients without a *BRCA* mutation or without a *BRCA*-like signature (ORR 11%) (McNeish *et al*, 2015). Refinement of the genomic LOH cutoff improves selection of patients with a BRCA-like LOH high signature more likely to benefit from rucaparib. Updated data from 204 patients using the refined cut off have shown response to rucaparib in patients with BRCA mutations (ORR 80%) and in patients with a BRCA-like LOH high signature (ORR 39%), which is in contrast to patients without a BRCA mutation or without a BRCA-like signature (ORR 14%) (Coleman *et al*, 2016).

The main treatment-related AEs for rucaparib, most of which were of grade 1/2 severity, have been nausea, vomiting, fatigue, elevated aspartate aminotransferase/alanine aminotransferase, dysgeusia, decreased appetite, anemia, and constipation. Full results of the ARIEL2 trial will inform the pivotal phase III maintenance trial, ARIEL3. ARIEL3 has enrolled subjects and will evaluate rucaparib in patients with platinum-sensitive relapsed ovarian cancer. ARIEL3, will also prospectively validate the predictive power of an HR deficiency assay/score in patients with platinum sensitive ovarian cancer (Table 3) (Swisher *et al*, 2013).

Talazoparib. Talazoparib, formerly known as BMN673, is an oral PARP inhibitor that is under investigation in patients with advanced or recurrent solid tumours (Shen *et al*, 2013). In preclinical experiments, talazoparib exhibited selective antitumour cytotoxicity at much lower concentrations than olaparib, rucaparib, and veliparib (Table 1; Shen *et al*, 2013). Preclinical studies have shown that talazoparib, olaparib, rucaparib, and veliparib inhibit PARP catalytic activity similarly; however, talazoparib is more potent at trapping PARP-DNA complexes (Table 1; Shen *et al*, 2013). Whether the observed increased preclinical potency translates into improved clinical efficacy will need to be shown in clinical studies. A phase I dose-escalation trial determined the MTD of talazoparib to be 1000 μg once daily and revealed promising clinical activity. Eleven of 17 patients with g*BRCA*-associated OC or primary peritoneal cancer had an objective response to talazoparib (De Bono *et al*, 2013). In a phase I dose escalation study, patients with advanced malignancies, including OC, were treated with talazoparib plus temozolomide chemotherapy. The results demonstrated efficacy and established an MTD using the standard dose of the PARP inhibitor in combination with a reduced dose of the sensitising chemotherapeutic agent (Wainberg *et al*, 2015, 2016). Although nearly all of the previously mentioned PARP inhibitors (olaparib, velaparib, niraparib) have been combined with chemotherapeutic agents in early phase I clinical trials, the majority of these early combination studies had

to be closed prematurely due to increased toxicities or the PARP inhibitor doses needed to be reduced to subtherapeutic dose levels. Of note, in all of these earlier studies the chemotherapy doses were given at or near standard dosing levels and the PARP inhibitor concentrations were gradually increased. In contrast, in the present phase I trial that combined talazoparib with temozolomide, the PARP inhibitor dose was kept high from the onset at a dose with proven single agent activity, and the temozolomide dose was started at a low dose and carefully escalated until an MTD was reached. Based on promising clinical activity seen in the ovarian cancer patients, talazoparib will now be further studied either alone or in combination with temozolomide in patients with recurrent HR-deficient ovarian cancer that has progressed after/or failed prior PARP inhibitor treatment or have not yet been exposed to a PARP inhibitor. This trial will provide us with valuable insights as to whether talazoparib, which has unique PARP trapping capability, will have activity as a second line PARP-inhibitor treatment either as single agent or in combination with low dose chemotherapy.

CLINICAL CHALLENGES

The presence of a g*BRCA* mutations appears to be positively correlated with increased survival and responsiveness to chemotherapy (Chetrit *et al*, 2008; Alsop *et al*, 2012; Bolton *et al*, 2012). Because of this, it is expected that patients with g*BRCA*-associated OC will be exposed to multiple lines of various chemotherapeutic agents during their treatment. Therefore, treatment-free intervals may be of particular importance to this patient population, as they allow adequate recovery from cumulative adverse reactions in preparation for additional treatment regimens. Future studies to assess survival and quality of life are needed to clarify whether the optimal treatment strategy will be treatment at disease recurrence or use of PARP inhibitors as maintenance therapy following response to a platinum-based chemotherapy.

Despite durable antitumour activity reported in patients with g*BRCA* mutations to date, the lack of validated biomarkers to predict patients with sporadic OC who may respond to PARP inhibitors remains an important clinical challenge. The attempt to capture genomic instability by identification of 'genomic scarring' or BRCAness (identifying tumours that share molecular features of BRCA mutant tumours) may be accomplished by determining the overall degree of allelic imbalance (loss of heterozygosity; Abkevich *et al*, 2012), telomeric specific allelic imbalance (Birkbak *et al*, 2012), and/or large-scale transitions in tumour DNA (Popova *et al*, 2012). As mentioned above, the approach being pursued by Foundation Medicine and Myriad Genetics is to assess patterns of increased genomic instability as biomarkers for defective HR DNA repair. The resulting genomic signature may indicate an HR deficiency sufficient to predict patients whose cancers are more likely to respond to PARP-inhibitor therapy. However, further studies, both preclinical and clinical, will be needed to define and validate algorithms and cut-offs that are currently being developed to predict response to a PARP inhibitor in ovarian cancer.

Inherent or acquired resistance to PARP-inhibitor therapy also confers a significant clinical challenge. A potential mechanism of acquired resistance to PARP inhibition is the restoration of normal BRCA1/2 protein function by secondary intragenic mutations (Konstantinopoulos *et al*, 2015). This can occur by mutations that cancel the frameshift of the original mutation and restore an open reading frame or by a genetic reversion of the original mutation resulting in the expression of a functional protein (Edwards *et al*, 2008; Konstantinopoulos *et al*, 2015). The actual clinical relevance of secondary mutations that restore BRCA function is, however, currently a matter of debate and requires further study. A retrospective study was conducted in a cohort of 89 patients with relapsed epithelial ovarian cancer and gBRCA 1/2 mutations who demonstrated disease progression on olaparib 200 mg twice-daily and subsequently retreated with platinum-based chemotherapy. Secondary BRCA1/2 mutations were not detected in 6 of the patients with evidence of disease progression, suggesting that other mechanisms may play a role in PARP inhibitor resistance. (Ang *et al*, 2013). Somatic mutations of *TP53BP1*, which encodes p53BP1, might also result in partial restoration of HR and DNA repair (Jaspers *et al*, 2013). In addition, increased drug efflux, mediated by MDR1, might limit exposure of the cancer cells to the effects of a PARP inhibitor (Rottenberg *et al*, 2008). Importantly, evidence suggests a lack of significant clinical cross-resistance between PARP inhibition and platinum-based chemotherapy, which has important implications for sequencing therapy (Ang *et al*, 2013).

Long term safety issues are a significant concern, especially if PARP inhibitors are adopted in the frontline treatment of OC. PARP inhibitors, as single-agent therapy, are associated with predominantly mild-to-moderate (grade 1/2) toxicities; however, rarer, more severe toxicities demand special consideration in an adjuvant setting. A small number of cases of MDS/AML or severe pneumonitis have been reported after olaparib therapy, with an overall incidence of $<1\%$ for each toxicity across all reported studies (Lynparza prescribing information, 2014). However, most of these patients had previously received multiple lines of DNA-damaging, platinum-containing chemotherapies, which may have contributed to these AEs. Future studies will need to capture these AEs, especially in the adjuvant setting.

Although the importance of g*BRCA1/2* mutations in managing women with ovarian cancer is well understood, the number of patients who are currently being tested for germline mutations is still limited (Schmid and Oehler, 2014). More widespread genetic testing of patients diagnosed with ovarian cancer including the adoption of multi-gene panels (that capture rare germline mutations in high risk genes next to *BRCA1/2* mutations) will provide clinicians valuable additional stratification tools to help integrate PARP inhibitors into the treatment of all patients diagnosed with familial ovarian cancer. Moreover, the development of assays that capture deficiencies in HR will extend these advances to a larger group of patients diagnosed with sporadic ovarian cancer.

Finally, cost considerations are a further challenge relevant to PARP inhibitors. Cost-effectiveness studies are needed that take quality of life assessments into consideration to allow a comprehensive value-based assessment of PARP inhibitors in ovarian cancer care. (Sfakianos and Havrilesky, 2011).

FUTURE DIRECTIONS

Future development of PARP inhibitors will need further clinical studies to better understand: (a) when and how to sequence therapy, (b) which combination treatment strategies potentiate PARP inhibitor antitumour activity, and (c) long-term toxicities (Liu and Matulonis, 2014). High clinical research priorities should be aimed to better understand whether PARP inhibitors are best used (a) as actual treatment of recurrent disease or as maintenance therapy, (b) before or after platinum-based therapy, (c) as single agents or in combination with chemotherapeutic or novel targeted agents. Furthermore, accurate definition of molecular features that reliably identify BRCAness will allow clinicians to extend the use of PARP inhibitors to non-*BRCA*–mutated OC. Novel combinations that warrant further clinical exploration include, but are not limited to, PI3-kinase inhibitors, angiogenesis inhibitors or ATM

and cell cycle inhibitors (Wee1 inhibitor). A recent preclinical study showed that talazoparib exhibited immunoregulatory effects in a murine model providing a rational to evaluate a combination with an immune check point inhibitor (Huang *et al*, 2015). This rationale is further supported by the fact that HR deficiency is associated with genomic instability, and may therefore, also be associated with an increase in the expression of neoantigens and immunogenicity warranting the use of an immune check point inhibitor. Finally, comparative studies are needed to examine whether the preclinical differences in potency or mechanism of action among PARP inhibitor will have clinical implications. With completion of these ongoing efforts, PARP inhibitors are poised to help improve clinical outcomes for patients with *BRCA*-associated and sporadic OC.

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CONFLICT OF INTEREST

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