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PARP inhibitors: the race is on

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Since the seminal publications in 2005 that demonstrated the exquisite sensitivity of *BRCA1* and *BRCA2* (*BRCA1/2*) mutant cell lines and xenografts to poly(ADP-ribose) polymerase (PARP) inhibition (Bryant *et al*, 2005; Farmer *et al*, 2005), the race has been on to exploit single-agent PARP inhibitors for clinical use through the concept of tumour-specific synthetic lethality (Yap *et al*, 2011; O'Connor, 2015). In 2014, olaparib (Lynparza; AstraZeneca, London, UK) was the first PARP inhibitor to be approved by the European Medicines Agency as maintenance therapy for responding patients with *BRCA1/2* mutant ovarian cancer following platinum-based chemotherapy, and the first to obtain accelerated approval by the US Food and Drug Administration (FDA) for advanced *BRCA1/2* mutant ovarian cancer while confirmatory trials are completed. There are, however, several other potent and bona fide PARP inhibitors, including rucaparib (AGO14699; Clovis, Boulder, CO, USA), niraparib (MK4827; Tesaro, Waltham, MA, USA), talazoparib (BMN-673; Medivation, San Francisco, CA,

USA) and veliparib (ABT-888; Abbvie, North Chicago, IL, USA), which are all currently in late phase clinical trial development (Table 1). Rucaparib was granted breakthrough therapy designation by the FDA in April 2015, following the results of the ARIEL2 trial (Krishteleit *et al*, 2015) for use as monotherapy in patients with *BRCA1/2* mutant (germline or somatic) advanced ovarian cancer after at least two prior lines of platinum-containing therapy.

This publication by Drew *et al*. is the first study to report the tolerability and efficacy of rucaparib administered either through intravenous or oral routes, in patients with germline *BRCA1/2* mutant advanced breast or ovarian cancers. The study investigated different schedules and dose levels of rucaparib and included detailed pharmacodynamic (PD) and pharmacokinetic (PK) studies to assess relationships between PARP enzyme inhibition, drug PK and anti-tumour response. This study provides interesting insights and important lessons on the use of PARP inhibitors in this patient population, including

Table 1. Table showing the response rates and predominant toxicities for different PARP inhibitors in patients with advanced ovarian cancer

Drug	<i>BRCA1/2</i> mutant		<i>BRCA1/2</i> wild type and unknown		Predominant toxicity (in order of frequency)	References
	No.	Response	No.	Response		
Olaparib (AZD2281)	> 100 (mostly platinum resistant)	30–60%	46	Platinum sensitive 50% Platinum resistant 4%	GI symptoms, fatigue, anaemia	(Fong <i>et al</i> , 2010; Gelmon <i>et al</i> , 2011; Kaye <i>et al</i> , 2012)
Rucaparib (AGO14699)	39 (all platinum sensitive)	69%	132	LOH ^{high} 29% LOH ^{low} 13%	GI symptoms, fatigue, anaemia, transient ALT/AST elevations	(Krishteleit <i>et al</i> , 2015)
Niraparib (MK4827)	20 (9 platinum sensitive)	40%	3 19	Platinum sensitive 67% Platinum resistant 16%	Anaemia, thrombocytopenia, neutropenia, GI symptoms, fatigue	(Sandhu <i>et al</i> , 2013)
Talazoparib (BMN-673)	26 ^a	46%	–	–	Fatigue, alopecia, GI symptoms, anaemia, neutropenia, thrombocytopenia	(Wainberg <i>et al</i> , 2014)
Veliparib (ABT-888)	28 ^{a,b}	40%	24 ^{a,b}	4%	Nausea, fatigue, lymphopenia	(Puhalla <i>et al</i> , 2014)

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; GI = gastrointestinal; LOH = loss of heterozygosity.
^aPlatinum responsiveness not known.
^bIncludes triple negative breast cancer.

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the importance of continuous drug dosing, the challenges of PD biomarkers and the need for predictive biomarkers of response.

By quantifying the loss of poly(ADP-ribose) (PAR) chain formation in peripheral blood lymphocytes, Drew and colleagues demonstrate that PARP inhibition following rucaparib dosing is transient, recovering within 7 days. Coupled with the low response rate observed with the intermittent IV dosing of rucaparib, the authors provide strong rationale for continuous drug dosing. Interestingly, even in the continuous oral dosing cohort, response rates remained relatively low in this study at 18%. This is likely to be because rucaparib dosing was still well below the recommended phase II dose of 600 mg twice daily that was subsequently established. In addition, there was a high proportion of platinum-resistant patients included in this trial.

In general, reduction in PAR chain formation has been a useful PD biomarker to confirm target engagement for PARP inhibitors. Unsurprisingly, there is no correlation between this PD read-out and clinical anti-tumour activity for rucaparib (Drew *et al.*, 2016), as previously observed with olaparib (Fong *et al.*, 2009); near complete inhibition of PARP enzymatic activity was demonstrated even at subtherapeutic doses where there is no appreciable relationship between PK and PD studies. This discordance highlights an important point with regards to the mechanism of action of PARP inhibitors. PARP detects and localises to DNA single-strand breaks (SSBs) to facilitate SSB repair. Its activity then potentiates the recruitment of DNA SSB repair proteins to the chromatin and also promotes the dissociation of PARP itself from the DNA. PARP inhibition therefore traps PARP on the DNA at the sites of unrepaired SSBs, resulting in the generation of DNA double-strand breaks in S-phase that require homologous recombination for successful repair (Helleday, 2011; Murai *et al.*, 2012). In keeping with this, at least in preclinical models, the most potent PARP inhibitors appear to be those that bind DNA most strongly; for example, talazoparib is ~100-fold more potent at trapping PARP-DNA complexes than rucaparib and olaparib (Shen *et al.*, 2015). However, preclinical potency may not necessarily translate into clinical efficacy, as other factors such as drug-related toxicities limiting dose escalation and patient selection come into play. As discussed by Drew and co-workers, inter-assay variability makes the quantification and subsequent comparison of PARP activity between samples difficult. However, if PARP trapping is of clinical importance, it is possible that PARP expression or baseline PARP activity may be alternative or additional PD biomarkers for PARP inhibitors. Other biomarkers such as RAD51 and γ H2AX should also be incorporated into early phase clinical trials to build confidence that robust PD activity was achieved.

A number of other critical questions remain in terms of optimising and widening the clinical efficacy and utility of PARP inhibitors, respectively. Although benefits are observed following PARP inhibitor treatment in patients with a range of tumour types with germline *BRCA1/2* mutations (Kaufman *et al.*, 2015), it is now clear that clinical efficacy is not restricted to this niche population of patients. A number of strategies have been explored to select patients who may benefit from PARP inhibitors, with the focus on the identification of predictive biomarkers for homologous recombination-deficient (HRD) tumours (Lord and Ashworth, 2016). Genomic approaches have included attempts to identify a molecular signature that predicts PARP inhibitor sensitivity (Konstantinopoulos *et al.*, 2010), as well as the molecular characterisation of patients with castration-resistant prostate cancer for aberrations in multiple DNA repair genes (Mateo *et al.*, 2015). Other approaches use one or a number of different genomic aberrations to determine HRD or an HRD score (Telli *et al.*, 2015). More functional approaches have looked at *ex vivo* RAD51 foci formation in tumour cells before and after DNA-

damaging treatment. The clinical development of rucaparib in high-grade serous ovarian cancer has included a loss of heterozygosity scoring system as a way of predicting response in patients with *BRCA* wild-type high-grade serous ovarian cancer. Preliminary data presented to date suggest that this may be a promising approach. In the ARIEL2 phase 2 study, a correlation between HRD score (high/low) and efficacy was noted, although interestingly the efficacy in HRD high patients still did not equate to patients with germline *BRCA1/2* mutations (Table 1; Kristeleit *et al.*, 2015). Thus, a robust predictive biomarker of PARP inhibitor sensitivity beyond *BRCA1/2* mutations has yet to be established prospectively in large clinical trials. Currently, prior sensitivity to cross-linking agents remains a useful clinical predictor of HRD and thus potential anti-tumour response to a PARP inhibitor (Fong *et al.*, 2010). There are also preliminary data to suggest that the length of the time from the patient's last platinum chemotherapy will affect the sensitivity to PARP inhibitor treatment (Rafii *et al.*, 2015).

To date, at least in an ovarian cancer population where PARP inhibitors have been most extensively studied, there appears to be little difference in the clinical effectiveness and toxicity profiles across the most advanced PARP inhibitors (Table 1), and the results of further large randomised trials with olaparib, rucaparib and niraparib are awaited with interest. It is interesting that relative to most other approved molecularly targeted agents, the clinical activity of single-agent PARP inhibitors in *BRCA1/2* mutant tumours appears to be less context specific, although undoubtedly to date, high-grade serous ovarian cancers demonstrate the most impressive response rates, perhaps because of additional genomic aberrations that contribute to HRD. In order to become established in the clinic, it is likely that each of the PARP inhibitors will need to find their niche and area of unmet need. Being the first to demonstrate anti-tumour activity in a particular cancer type is one-way forward; other strategies may include successfully characterising a molecular subtype or a biomarker beyond germline *BRCA1/2* mutant patients or defining a unique PARP inhibitor combination regimen. These include combinations of PARP inhibitors with inhibition of angiogenic, immune checkpoint, PI3K/AKT, WEE-1 and ATR pathways—all of which have the objective of tackling the key problem of PARP inhibitor resistance. In any event, the race is certainly now on with the availability of multiple potent PARP inhibitors, and such a wide and diverse range of new drug applications still open for exploration.

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