

Emerging treatment options for recurrent ovarian cancer: the potential role of olaparib

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Abstract: Olaparib has shown promising anticancer activity as a single agent in the treatment and maintenance of recurrent ovarian cancer in early clinical trials, but it is far from standard therapy. This article outlines the problem of relapsed ovarian cancer and the mechanisms of poly(ADP-ribose) polymerase inhibitors and reviews the recent literature pertaining to olaparib in ovarian cancer.

Keywords: anticancer, polymerase inhibitor

Introduction

Ovarian cancer is the most common cause of death from gynecologic cancer and is fourth on the list of cancer-related deaths in women.¹ A significant proportion of women present at an advanced stage of disease, and 60% present at stage 3 to 4 disease. Five-year survival for all stages of ovarian cancer is 43%, and 10-year survival is 28%, but the 5-year survival for patients presenting with stage 3 disease is only 21.9%, and for stage 4 disease it is a dismal 5.6%.² The vast majority (70%) of these cancers will be epithelial ovarian cancer, predominantly of serous type, but endometrioid, clear cell, and mucinous variants also exist.³ The lifetime incidence of a woman spontaneously developing ovarian cancer is 1.4%,⁴ but this incidence is significantly increased in carriers of germline mutations, mainly in either *breast cancer gene 1 (BRCA1)* (~40% lifetime risk) or 2 (*BRCA2*) (~10% lifetime risk) genes,⁵ which are implicated in 10%–15% of all epithelial ovarian cancer cases, including those women who have no family history of breast or ovarian cancer.⁶ Other gene candidates have also been demonstrated, but with increased rarity.⁷

Standard therapeutic approaches include optimal surgical debulking followed by adjuvant platinum doublet chemotherapy, usually in combination with a taxane. If immediate surgical resection is not possible, then neoadjuvant use of combination chemotherapy can be employed, with interval debulking as appropriate.^{8,9} These methods have high initial response rates, but only moderate progression-free survival (PFS) times, and three-quarters of patients with stage 3 and 4 disease will relapse. Recent developments include the use of bevacizumab (a monoclonal antibody against vascular endothelial growth factor receptor) to prolong the PFS and overall survival (OS) when used alongside standard chemotherapy and as maintenance treatment in a first-line setting. The success of this drug was particularly striking in those patients at high risk for relapse, in whom PFS increased from 14.5 months with standard therapy to 18.1 months with the addition of bevacizumab within the Gynecologic

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Cancer Intergroup International Collaboration on Ovarian Neoplasms 7 (ICON7) trial.^{10,11} OS was also affected (going from 28.8 to 36.6 months, respectively).¹²

In recurrent disease, the selection of subsequent therapy is influenced by the progression-free interval, number of lines and drugs used previously, performance status of the patient, and extent of relapse. In general, a PFS interval of greater than 6 months since platinum therapy would be considered to be platinum-sensitive disease and have a higher likelihood of a second response to a platinum-containing regimen. The International Collaborative Ovarian Neoplasm/Arbeitsgemeinschaft Gynäkologische Onkologie Studiengruppe Ovarialkarzinom (ICON 4/AGO-OVAR) 2.2 and other studies showed that a second challenge with a platinum/paclitaxel combination was effective, improving both PFS and OS.¹³ In those patients with significant adverse effects from their taxane exposure, gemcitabine can be used alongside platinum therapy.¹⁴ Recently published evidence also supports the use of bevacizumab in relapsed patients as part of the Study of Carboplatin and Gemcitabine Plus Bevacizumab in Patients With Ovary, Peritoneal, or Fallopian Tube Carcinoma (OCEANS) trial, and extended PFS (12.4 versus 8.4 months) and improved response rates (78.5% versus 57.4%) were seen when bevacizumab was added to carboplatin/gemcitabine chemotherapy.¹⁵ OS was unchanged, which was attributed to multiple further lines of therapy after participation in the OCEANS trial, including widespread use of bevacizumab in patients from the placebo group.

Patients considered to be platinum-resistant (<6 months since last platinum treatment) or refractory (disease progressed despite continuing platinum treatment) have a low rate of response to subsequent therapy, but liposomal doxorubicin, topotecan, or single-agent weekly paclitaxel are potential choices.¹⁶ Clinical trials of targeted therapy should also be considered, when available, in platinum-sensitive and platinum-resistant disease. In the past, therapies exploring the weaknesses of targets such as epidermal growth factor receptor, insulin-like growth factor 1, *BRAF*, mammalian target of rapamycin, and human epidermal growth factor receptor 2, as well as poly(ADP-ribose) polymerase (PARP), have been investigated.^{17–21}

BRCA1, BRCA2, and “BRCAness”

BRCA1 and *BRCA2* code for large proteins that participate in the repair of double-strand breaks in cellular DNA, via the homologous repair (HR) pathway.^{22,23} Cells from patients with the defect carry heterozygous mutations in either gene that are either germline or acquired. A further mutation in the remaining functional allele results in complete loss of either *BRCA1* or *BRCA2* function, resulting in aberrant double-strand deoxyribonucleic acid (DNA) repair and in chromosomal breaks, rearrangements, and other abnormalities, as well as associated genetic instability, causing cell death (Figure 1). Subsequent to the discovery of these two genes came an understanding that some sporadic epithelial ovarian cancers behaved in a very similar way to those

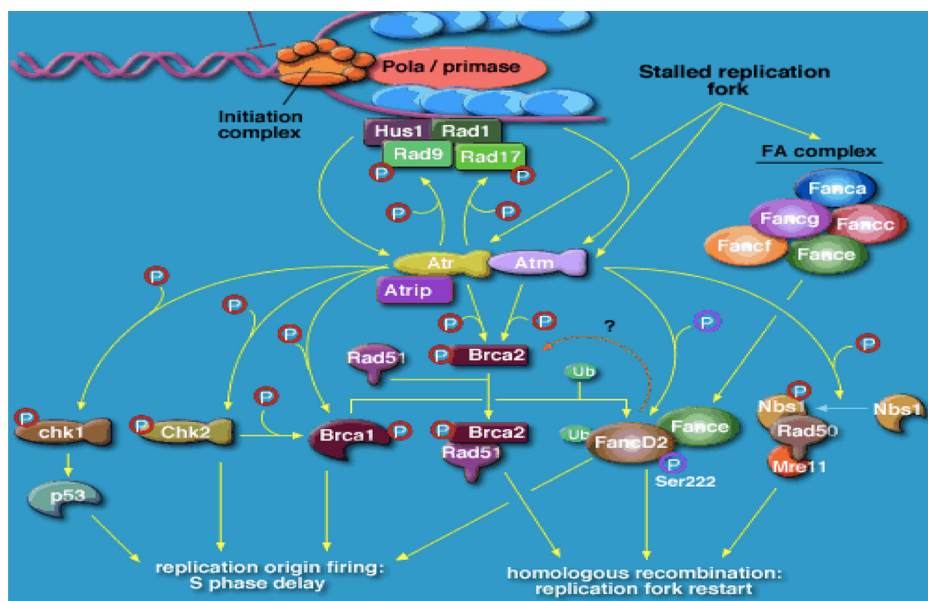


Figure 1 Role of *BRCA1* and *BRCA2* and ATR in cancer susceptibility.

Notes: Cartoon showing factors required for double-stranded DNA repair; malfunction of any of the involved factors can potentially cause a *BRCA*-like effect (“*BRCAness*”). For example, germline mutations, such as *CHEK2*, *PLAB*, *Rad50/51*, *FANC A/B/C* (etc), *BRIP1*, and *BRCA1/2*, and somatic mutations, such as somatic *BRCA* mutations, non-*BRCA* double-stranded DNA repair gene mutation, transcription factor binding site, polymorphisms/mutations, and epigenetic factors (eg, *BRCA* promoter methylation).

Abbreviations: DNA, deoxyribonucleic acid; *BRCA*, breast cancer genes 1 and 2.

known to bear either a *BRCA1* or *BRCA2* mutation, perhaps through expression of such genes as *TP53* and *FANCD2*^{24–27} (Figure 1). Recent work has also suggested a role for *BRCA1* and *BRCA2* and defective HR in sporadic ovarian cancer, with somatic mutation and epigenetic mechanisms eg (promoter methylation) implicated in as many as from 19% to 24% of unselected patients dependent on series, and potentially more (up to 50%) in high-grade serous cancer of the ovary.^{28,29} Overall, these patients tend to have a more favorable prognosis (Figure 2).

Olaparib: rationale and preclinical development

DNA repair is a vital function for all cells to be able to proceed through the cell cycle and replicate without errors.³⁰ DNA damage generally causes double-strand breaks, and HR is the main mechanism by which the double-strand breaks are repaired. However, HR is not the only method of double-strand DNA repair available to the cellular machinery: nonhomologous end joining and single-strand annealing can also be used, although these mechanisms are error-prone, resulting in loss of DNA and rearrangements, and, when repeatedly used, eventually result in overwhelming DNA damage, activation of cellular checkpoint mechanisms, cell-cycle exit, and cell death.³¹

Different mechanisms exist for repairing single-strand breaks. These include base excision repair, nucleotide excision repair, and mismatch repair. These processes are

modulated by PARP,³² which binds to the break sites and recruits other elements of the DNA repair complex (Figure 3). If cells are unable to repair single-strand breaks before attempting to replicate, then double-strand breaks form.

A specific inhibitor of PARP1 and PARP2 was developed by testing a series of substituted 4-benzyl-2H-phthalazin-1-ones. 4-[3-(4-cyclopropanecarbonylpiperazine-1-carbonyl)-4-fluorobenzyl]-2H-phthalazin-1-one 47 (KU-0059436, AZD2281), now known as olaparib, was taken forward for further development as a nanomolar inhibitor of PARP with single-agent activity against BRCA-1-deficient cells.³³ Inhibition of PARP-1 by olaparib prevents repair of single-strand breaks, which is of no consequence to normal cells that efficiently repair double-strand DNA via HR. In cells with deficiencies of HR where nonhomologous end joining and single-strand annealing are the only mechanisms of DNA repair, PARP inhibition produces stalled replication forks, increasing the number of double-strand breaks, which cannot be repaired in these cells homologous for *BRCA* mutations, leading to genetic chaos and cell death via apoptosis or senescence (Figure 4). Taking advantage of an abnormality within the cancer cells (homozygous loss of *BRCA* function) that is not present in the normal somatic cells of the body (they are heterozygous for the mutation and therefore produce sufficient functional *BRCA* protein) is a concept described as synthetic lethality.^{34,35}

Synthetic lethality means there is much higher sensitivity to treatment with PARP inhibitors among cancer

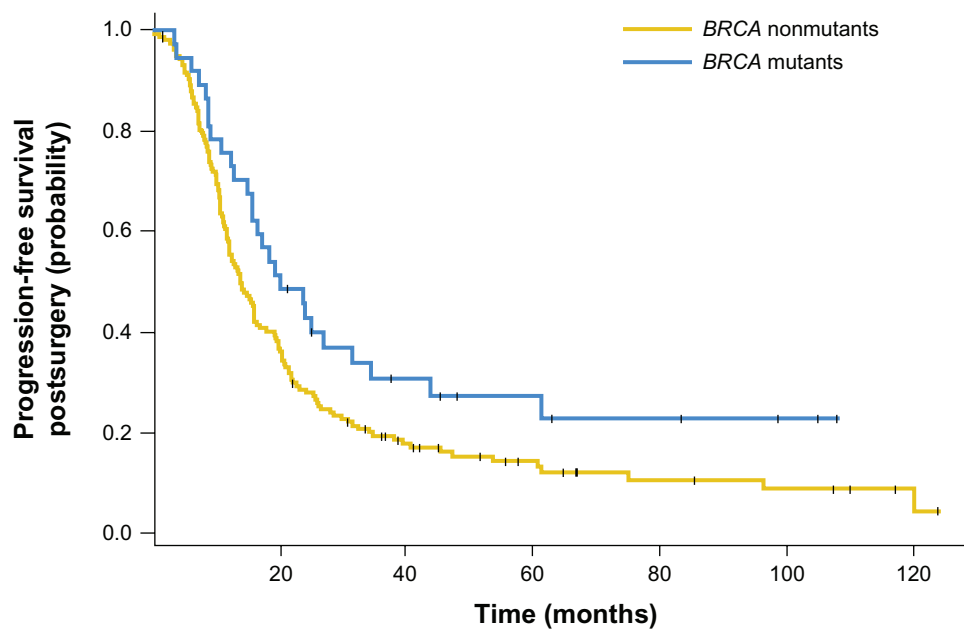


Figure 2 Kaplan–Meier curves showing that *BRCA1/2* mutations were associated with significantly improved progression-free survival time after surgery when compared with a *BRCA* wild-type ovarian cancer population.

Notes: 235 patients in total, 19% with mutant *BRCA1/2*. Median progression-free survival for *BRCA* mutants and nonmutants was 20.1 (CI, 15.6–43.8) and 13.8 (CI, 11.9–16.3) months, respectively. Reprinted with permission. © 2010 American Society of Clinical Oncology. All rights reserved. Hennessy B, et al. *J Clin Oncol.* 2010;28(22):3570–3576.²⁹

Abbreviations: *BRCA*, breast cancer genes 1 and 2; CI, confidence interval.

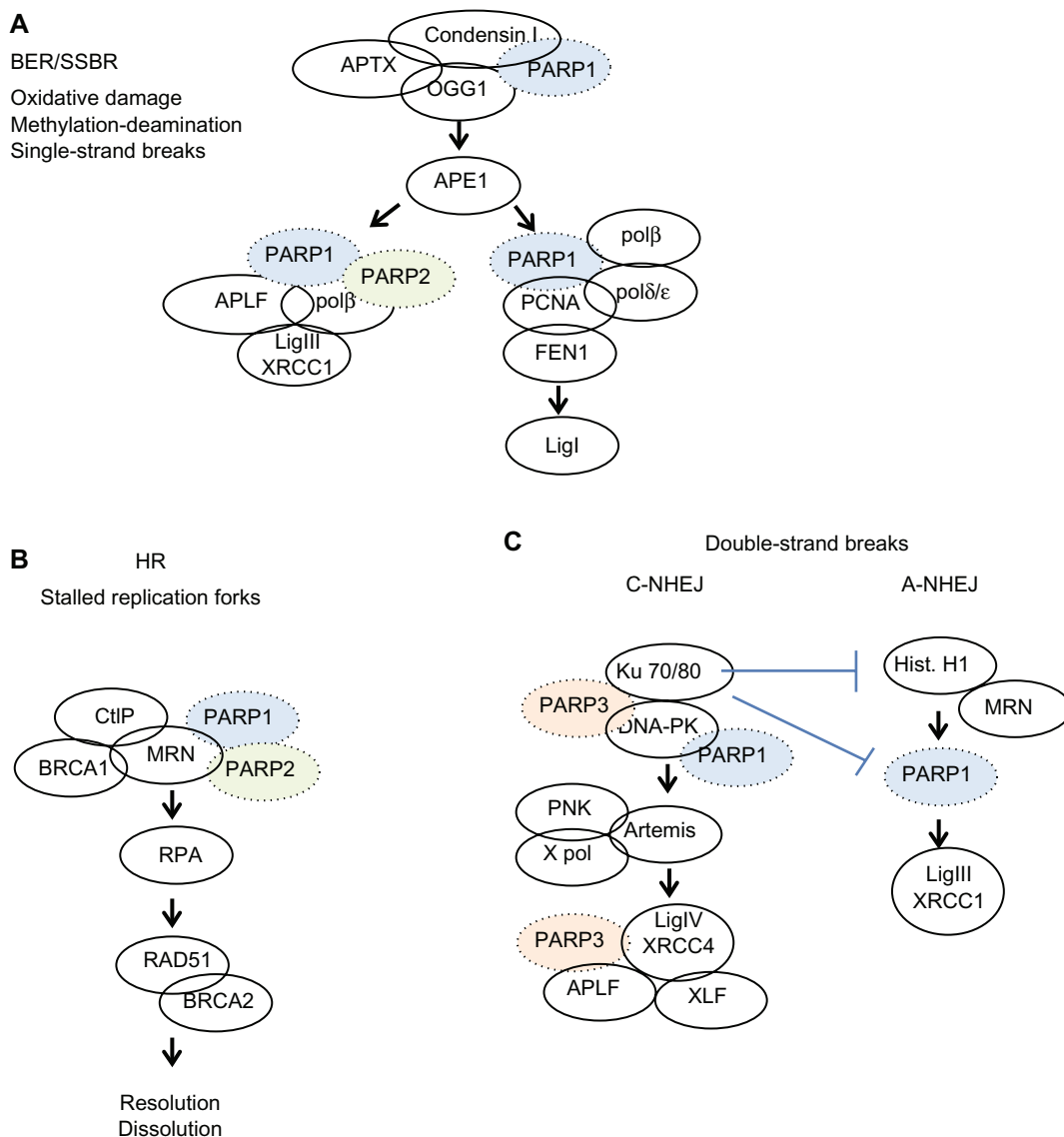


Figure 3 Simplified overview of the events involving PARP1, PARP2, or PARP3 in DNA repair pathways. **(A)** Base excision repair/single strand break repair, **(B)** homologous recombination, **(C)** double strand breaks.

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Abbreviations: ADP, adenosine diphosphate; PARP, poly (ADP-ribose) polymerase; BER, base excision repair; SSBR, single strand break repair; HR, homologous repair; *BRCA*, breast cancer genes 1 and 2; DNA, deoxyribonucleic acid.

cells carrying homozygous mutations in either *BRCA1* or *BRCA2*.³⁶ In contrast, cells that were either wild-type or heterozygous for *BRCA1* and *BRCA2* showed no increase in cell death when treated. These findings indicate there should be minimal toxicity in test participants and, indeed, humans, offering scope for dose increments to produce the desired pharmacodynamic effect.^{37,38}

Xenograft studies in NOD/SCID (nonobese diabetic/severe combined immunodeficiency) mice with patient-derived *BRCA2*-deficient ovarian tumor tissue showed significant reduction in the growth of tumors of those treated with either olaparib alone ($19.7 \pm 25.0 \text{ mm}^3$ versus $97.3 \pm 72.6 \text{ mm}^3$) or

carboplatin alone ($4.4 \pm 7.4 \text{ mm}^3$ versus $97.3 \pm 72.6 \text{ mm}^3$), but the most striking response was in those mice treated with a combination of olaparib and carboplatin ($1.2 \pm 1.4 \text{ mm}^3$ versus $97.3 \pm 72.6 \text{ mm}^3$) versus vehicle. Reimplantation of residual tumors after treatment did not result in any regeneration after 18 months for combination treatment, in comparison with just 6 weeks to develop palpable tumors after vehicle treatment. None of the treatment regimens caused the mice to lose significant weight or reduce oral intake, indicating the treatment was well tolerated.³⁹

Much work was also carried out in *BRCA1/2* carrier breast cancer cell lines but is beyond the scope of this review.^{40,41}

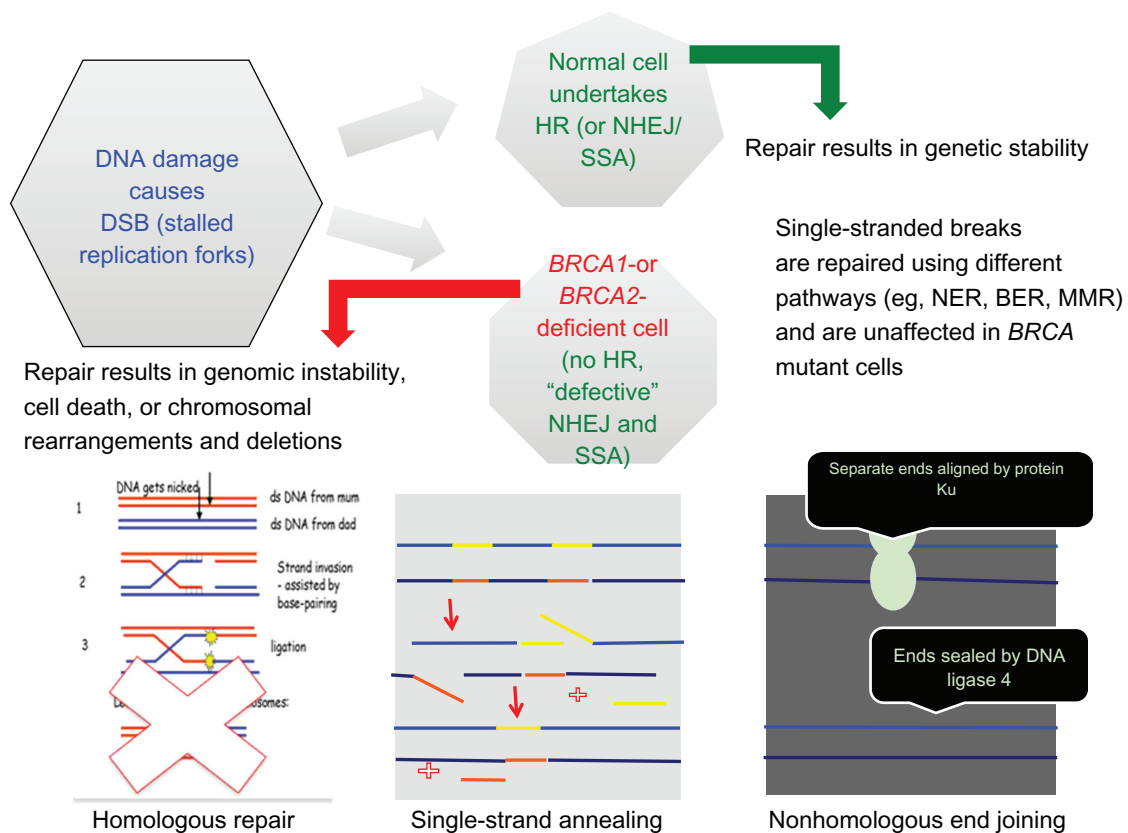


Figure 4 Cartoon detailing DNA repair mechanisms in the absence of functional BRCA proteins.

Abbreviations: ds, double stranded; DNA, deoxyribonucleic acid; DSB, double-strand breaks; HR, homologous repair; NHEJ, nonhomologous end joining; SSA, single-strand annealing; BER, base excision repair; NER, nucleotide excision repair; MMR, mismatch repair; BRCA, breast cancer genes 1 and 2.

Clinical trials

The first published trial in humans using olaparib was a Phase I study with an unselected dose-escalation (from 10 mg to 600 mg twice daily [bd]) and an expansion cohort in which only patients carrying *BRCA1* or *BRCA2* mutations were permitted and treated at 200 mg bd (Table 1).⁴⁴ The maximum tolerated dose was set as 400 mg bd. PARP inhibition of greater than 90% was seen at doses of 60 mg bd and over.

Objective antitumor responses were seen only in those carrying *BRCA1* or *BRCA2* mutations and at doses of olaparib of 100 mg or greater bd. Eight (of 16) patients with ovarian cancer had a partial response by either Response Evaluation Criteria In Solid Tumors (RECIST)⁴² or Gynecologic Cancer InterGroup (GCIg) criteria,⁴³ and a further patient had stabilization of disease for more than 4 months. The main toxicities were nausea, vomiting, fatigue, taste alteration, and anorexia. Only a 3%–5% incidence of myelosuppression was seen. The toxicity in the *BRCA* mutated population was not significantly different than in the noncarrier population.⁴⁴ This trial provided proof-of-concept of synthetic lethality in a clinical setting, as well as

proof that PARP inhibition could provide tumor responses as a single agent.

The trial data were further analyzed with regard to *BRCA1/2* carriers and their platinum sensitivity. Fifty patients carrying germline *BRCA1* and *BRCA2* mutations were enrolled to the study (*BRCA1*, 41; *BRCA2*, 8; family history only, 1); 13 patients had platinum-sensitive disease, 24 patients had platinum-resistant disease, and 13 patients had platinum-refractory disease. Most patients (39/50) were treated in the expansion cohort, whereas the remainder (11/50) was treated within the dose-escalation cohort. No significant differences were seen between responses in either the *BRCA1* or *BRCA2* carrier groups. However, when the responses were examined with regard to platinum status, a statistically significant correlation with the platinum-free interval was demonstrated (Spearman rank [Rs], 0.33; 95% confidence interval [CI], 0.04–0.57). The overall clinical benefit rate (defined as those patients with an objective response by either RECIST or GCIg criteria or with stable disease for 4 or more months) was 69.2% in the platinum-sensitive, 45.8% in platinum-resistant, and 23.1% in the platinum-refractory groups. This did not translate to a difference in the duration of response between

Table 1 Trials using olaparib, reported and currently underway

Author	Trial Phase	Single-agent (bd) versus combination	Maintenance plt sens/res	PFS	OS/CBR	BRCA popn only?
Fong et al ⁴⁴	I	Single agent Dose esc from 10 to 600 mg	Plt res and sens	MTD: 400 mg PFS 7 months	CBR at 4 months: 69% plt sens, 46% plt res, and 23% plt ref	Yes (1 and 2)
Khan et al ⁵³	I	Dacarbazine	Any solid tumor 20/36 pts melanoma	MTD: 100 mg bd with 600 mg/m ² dacarb 20 mg bd with 800 mg/m ² dacarb	PR 1/36 pts; CBR 7/36	All comers
Samol et al ⁵⁴	I	Topotecan	Any solid tumor	MTD: 100 mg bd × 3 d plus topo 1 mg/m ² × 3 d	Not progressed as subtherapeutic MTD (hem tox)	All comers
Dean et al ⁵⁵	I	Bevacizumab	Any solid tumor (2 gyne)	MTD: 400 mg bd with 10 mg/kg/14 d bevacizumab	No response documented	All comers
Rajan et al ⁵⁶	I	Cisplatin/gemcitabine	Any solid tumor	MTD: 100 mg bd d 1 only	PR in 2/21	All comers
Audeh et al ⁴⁶	II	400 mg versus 100 mg	No maintenance Plt res and sens	33% CR/PR for 9.6 months	69%	Yes (1 and 2)
Kaye et al ⁴⁸	II	200 mg versus 400 mg versus PLD	No maintenance	6.5 versus 8.8 versus 7.1 months	N/A	Yes (1 and 2)
Ledermann et al ⁵¹	II	Carbo/taxol then olaparib versus placebo maintenance	Maintenance Plat sens only	Olaparib: 8.4 months versus placebo: 4.8 months	29.7 versus 29.9 months	All comers
National Cancer Institute ⁵⁷	I	Carboplatin	No maintenance Plt res and sens	Recruiting	Recruiting	Yes (1 and 2)
ClinicalTrials.gov ⁵⁸	I	Carboplatin	No maintenance Any gyne malig	Recruiting	Recruiting	All comers
ClinicalTrials.gov ⁵⁹	I	Carboplatin/paclitaxel	No maintenance Any solid tumor	Closed in FU	Closed in FU	All comers
ClinicalTrials.gov ⁶⁰	II	Carboplatin/paclitaxel	Maintenance Plat sens	Closed PFS 12.2 versus 9.6 months (control)	Close OS 12 versus 11 months (control)	All comers
ClinicalTrials.gov ⁶¹	Ib	Weekly carboplatin/weekly paclitaxel	Any gyne malig	Recruiting	Recruiting	All comers
ClinicalTrials.gov ⁶²	I	BKM120 (PI3 kinase inhibitor)	Plt res and sens	In setup	In setup	All comers
ClinicalTrials.gov ⁶³	I	Cediranib	Plt sens	Recruiting	Recruiting	All comers

Abbreviations: BRCA1/BRCA2, breast cancer genes 1 and 2; bd, twice a day; plt, platinum; sens, sensitive; res, resistant; ref, refractory; CBR, clinical benefit rate; popn, population; esc, escalation; MTD, maximum tolerated dose; dacarb, dacarbazine; PR, partial response; topo, topotecan; hem tox, hematological toxicity; CR, complete response; carbo, carboplatin; taxol, paclitaxel; gyne, gynecological; malig, malignancy; FU, follow up; PI3, PI3 kinase; N/A, not applicable.

the groups, which was reported as approximately 7 months. The results of the study inferred that some mechanisms of sensitivity to platinum and PARP inhibition may be shared, but to confound this some patients with platinum-refractory disease had responses. Platinum sensitivity is therefore not the only factor involved in guiding the use of PARP inhibition with olaparib in a clinical setting.⁴⁵

A Phase II study enrolled two cohorts of BRCA1- and BRCA2-positive women with recurrent advanced ovarian cancer who had previously received one or more lines of chemotherapy.⁴⁶ This study was designed to look at whether equivalent responses would be seen at the maximum tolerated dose of 400 mg bd or at a lower, but still pharmacodynamically active, dose of 100 mg bd. An objective response was seen in 33% of patients in the

400 mg bd and 13% of the 100 mg bd group, with a median PFS of 5.8 months (95% CI 2.8–10.6) and 1.9 months (1.8–3.6), respectively. The toxicity profile was similar to that seen in the Phase I study but with more reported hematological toxicity, particularly anemia (15%–17%), although the majority of cases were grade 1 or 2 by Common Terminology Criteria for Adverse Events. The dose of 400 mg bd appeared to be more effective than 100 mg bd, but the prognostic characteristics of the latter group were described as less desirable. The study data supported the use of olaparib for recurrent pretreated ovarian cancer in both BRCA1 and BRCA2 germline mutation carriers. Responses were seen in both platinum-sensitive and resistant subgroups, although the study was not powered to look at this directly.⁴⁶

Because pegylated liposomal doxorubicin (PLD) is a currently approved second-line therapeutic option for relapsed ovarian cancer, a Phase II trial to compare response to PLD versus olaparib was carried out.⁴⁸ The data before this comparison study showed an overall response rate (ORR) to PLD therapy of 20% (with a PFS of 16 weeks) from a Phase III trial versus topotecan,⁴⁷ in which the ORR to olaparib at 400 mg bd was 33% (response duration, 9.5 months) from the Phase I study of olaparib.⁴⁴ The hypothesis therefore was that olaparib would be superior to PLD in *BRCA1/2* mutated patients. The trial design consisted of three groups: PLD infusion at 50 mg/m² every 28 days or olaparib 400 mg bd or olaparib 200 mg bd (as per the expansion cohort within the Phase I study) in a 1:1:1 ratio. Patients were stratified according to *BRCA1* or 2 status and platinum sensitivity. Crossover to olaparib from PLD was permitted if a central assessment of response defined progressive disease. Median PFS times were 6.5 months (95% CI, 5.5–10.1 months), 8.8 months (95% CI, 5.4–9.2 months), and 7.1 months (95% CI, 3.7–10.7 months) for the olaparib 200 mg, olaparib 400 mg, and PLD groups, respectively. In the same group order, the ORRs were 25%, 31%, and 18%. Neither of these outcomes demonstrated statistically significant differences between olaparib at either dose versus PLD. Both treatments were generally well tolerated, although there was a tendency for more grade 3–4 adverse events with PLD use. The authors suggest that the better-than-expected PFS for PLD of 7.1 months confounded the ability of the study to detect a statistical benefit in favor of olaparib in *BRCA1/2*-mutated patients but is in agreement with recent work suggesting that this patient population derives greater benefit from anthracycline-based chemotherapy than unselected patients.^{48–50}

One of the most significant occurrences in ovarian cancer is the potential for multiple relapses over time. To

investigate the role of olaparib in the maintenance and potential extension of PFS, a randomized, double-blind, placebo-controlled Phase II study was carried out in patients with platinum-sensitive recurrent serous ovarian cancer.⁵¹ Patients were required to have received two or more courses of platinum chemotherapy, with the most recent course inducing a RECIST- or GCIg-defined response. At entry to trial, the CA125 level had to be below the upper limit of normal. *BRCA1/2* status was not required for inclusion. Patients were stratified by interval from last platinum regimen to progression, response to last regimen, and ancestry before randomization in a blinded 1:1 ratio to either olaparib 400 mg bd continuously or placebo within 8 weeks of completion of last chemotherapy regimen, until defined progression of disease. No crossover was permitted. Two hundred and sixty five patients were treated within the trial, with approximately half receiving olaparib. The median PFS was 8.4 months in the olaparib group versus 4.8 months in the placebo group (hazard ratio for progression or death, 0.35; 95% CI, 0.25–0.49; $P < 0.001$). Subgroup analysis demonstrated olaparib to be superior to placebo in all categories with regard to PFS. Complete response to the last chemotherapy regimen before trial entry significantly improved PFS (hazard ratio, 0.46; $P < 0.001$). OS was not affected (29.7 months in the olaparib group and 29.9 months in the placebo group). The olaparib group had slightly more nausea, vomiting, fatigue, and anemia, but generally did not require stoppage of trial therapy. Subanalysis of *BRCA1/2* or, “*BRCAness*,” could not be done in the limited study data, which might have been valuable in selecting a group of patients for whom this maintenance therapy may result in an improved OS as well as PFS.⁵¹ Figure 5 shows the disappointing OS data in comparison to the promising PFS results obtained earlier. More recently, the formulation of olaparib has been changed from capsules to tablets, and this has required further initial

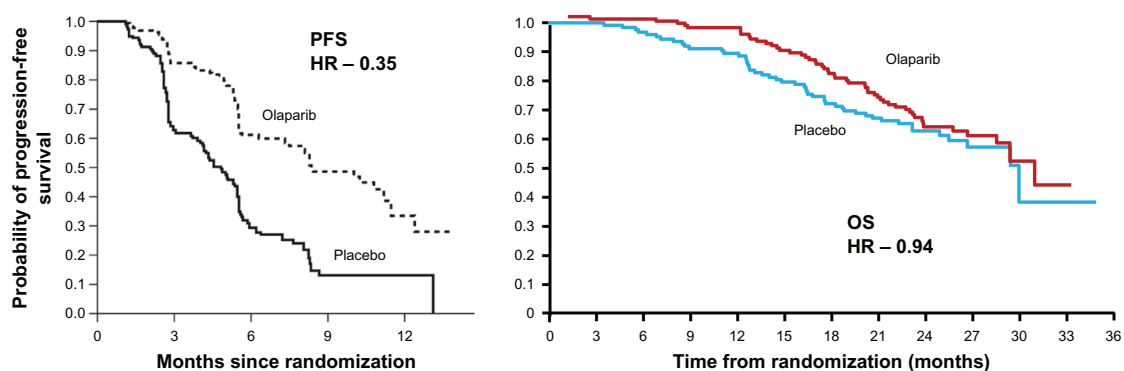


Figure 5 Progression-free survival (PFS) and overall survival (OS) following maintenance treatment with the PARP inhibitor, olaparib, in patients with relapsed ovarian cancer. **Abbreviations:** HR, hazard ratio; PARP, poly(ADP-ribose) polymerase.

studies of dose and efficacy. These trials have now completed recruitment and are currently being evaluated. Both the lack of OS benefit and the uncertainty around the optimal dosing of olaparib have led to a proposed Phase III maintenance trial being stopped from further development at this stage.⁵²

Multiple other Phase I combination studies with a variety of other agents have recently been reported, including dacarbazine,⁵³ topotecan,⁵⁴ bevacizumab,⁵⁵ and cisplatin with gemcitabine.⁵⁶ The topotecan and cisplatin combinations were particularly myelosuppressive and would require further dosing schedule modification before further work was undertaken.

Currently underway either Phase I, or Phase II in ovarian cancer, are studies of olaparib with carboplatin (Clinical Trials.gov identifiers NCT01445418, NCT01237067),^{57,58} carboplatin and paclitaxel (NCT00516724, NCT01081951, and NCT01650376),^{59–61} BKM120 (a PI3-kinase inhibitor, NCT01623349),⁶² and cediranib (a small molecule inhibitor of VEGF (vascular endothelial growth factor), NCT01116648).⁶³ In addition to olaparib, many other PARP inhibitors are also under scrutiny (eg, rucaparib, veliparib) and are in development. It is clear that much interest surrounds the use of PARP inhibition in ovarian cancer, and the results of these trials will guide future direction with olaparib and other related compounds.

Resistance

Not all patients with *BRCA1* or *2* somatic or germline mutations respond to PARP inhibition, and indeed, even patients carrying what appears to be the same mutation can demonstrate differences in responses. This is likely to be multifactorial in origin, but recent work has shown that secondary mutations within *BRCA2* can restore function of the protein in patients who are clinically resistant to PARP inhibition;⁶⁴ partial restoration of HR resulting from a loss of 53BP1,^{65,66} and functional Rad51 can provide escape mechanisms from growth inhibition by PARP inhibitors.⁶⁷ As more work is carried out on these cellular pathways, a greater understanding of secondary resistance, and indeed potential biomarkers of initial response to PARP inhibition, will be delineated. There is already ongoing research in the role of predictive markers in PARP inhibition sensitivity: in vitro work has shown an increase in double-strand breaks with the addition of PARP inhibitors to radiation, using γ -H2AX foci, a well established marker of DNA double-strand breaks.⁶⁸ Reduction of poly(ADP-ribose) levels has also been used as a surrogate to indicate PARP inhibitor activity.⁶⁹

Conclusion

Olaparib has shown promising anticancer activity as a single agent in the treatment and maintenance of recurrent ovarian cancer in early clinical trials, but it is far from standard therapy, and much more work will be required to secure its optimal use. This patient group is particularly enriched in the *BRCA1/2* germline mutation carriers but somatic mutations of *BRCA* and other defects of DNA repair mechanisms are also found in sporadic epithelial ovarian cancer, with an emphasis on high-grade serous type. Further work in combination studies with various chemotherapeutic agents and other targeted molecules is required to elucidate the best treatment strategies for this complex and deadly disease. As more is known regarding the molecular subgroups of ovarian carcinoma, the implications for platinum-sensitivity mechanisms, as well as acquired and inherent resistance to PARP inhibition, treatment can be increasingly tailored to the individual patient to maximize potential for response and increases in PFS and, ultimately, OS.

Disclosure

The authors report no conflicts of interest in this work.

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