

Development of Olaparib for BRCA-Deficient Recurrent Epithelial Ovarian Cancer

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Abstract

The FDA approval of the PARP inhibitor olaparib for fourth-line therapy of germline BRCA1/2-mutated ovarian cancer represents the first registered indication for this class of drugs in any disease. PARP is a family of proteins involved in the repair of single-strand DNA breaks. High-grade serous ovarian carcinomas with BRCA deficiencies may be particularly vulnerable to both direct and indirect effects of PARP inhibition. This phenotype frequently arises as a consequence of defects in the repair of damaged DNA, rendering cancer cells susceptible to DNA-damaging platinum compounds and targeted therapies affecting homologous recombination repair

(HRR). When cells already deficient in HRR are exposed to PARP inhibitors, apoptosis occurs by way of synthetic lethality. In this review, we trace the clinical development of olaparib for women with recurrent epithelial ovarian carcinoma harboring germline BRCA mutations, a biomarker for HRR deficiency present in 15% to 20% of cases. Clinical trials highlighted include not only those pivotal studies that have led to regulatory approval in the United States and in Europe, but also those in which olaparib was studied in novel combinations, including chemotherapy and antiangiogenesis agents. *Clin Cancer Res*; 21(17): 3829–35. ©2015 AACR.

Introduction

Ovarian cancer is the most lethal gynecologic cancer with 21,290 new cases and 14,180 deaths anticipated for 2015 in the United States (1). The lack of validated screening tools in the general population together with an absence of specific symptoms indicative of early disease accounts for the poor 5-year survival (1). The most common histologic subtype of epithelial ovarian (and fallopian tube) cancer is high-grade serous, which is characterized by genetic instability and almost universal p53 dysfunction (1).

Synthetic lethality occurs when a genetic defect or defective protein is compatible with cell viability, but is lethal when combined (i.e., synthesized) with another genetic/protein defect (1, 2). The most robust demonstration of the principle of harnessing synthetic lethality comes from the treatment of cancers resulting from loss of BRCA gene function. The discovery of BRCA1 and BRCA2 (BRCA1/2) is among the most important discoveries in human cancer genetics. The BRCA genes encode proteins involved in error-free repair of DNA double-strand breaks.

PARP1 is necessary for repair of DNA single-strand breaks (Fig. 1). PARP1 binds DNA and synthesizes PARP chains through PARYlation (1,2). Posttranslational modification of substrate proteins leads to recruitment of DNA repair effectors such as XRCC1 to the site of the single-strand break. PARP1

is released from the damaged DNA through auto-PARYlation (1,2).

Early Phase I and Phase II Monotherapy Trials

Clinical trials of interest appear in Tables 1 (refs. 3–15) and 2 (phase II and randomized phase II; refs. 16–24). In the initial accelerated dose-escalation phase I study, Fong and colleagues (3) reported that the MTD of the oral PARP inhibitor olaparib was 400 mg two times a day (Table 1). Toxicities (myelosuppression and central nervous system effects) were mild and self-limited. Included in the 60-patient study were 19 BRCA1/2-deficient patients with breast, ovarian, or prostate cancer, for whom the observed objective response rate (ORR) was 47% and the disease control rate was 63% (3). A secondary analysis involving a planned expansion of this study enriched with BRCA-mutated cases only suggested that the most favorable responses to olaparib were among platinum-sensitive patients (ORR 69%) as compared with those who were platinum resistant (ORR 23%; ref. 4). The relationship between prior platinum response and sensitivity to PARP inhibition is explored further below and may result from the ability of both PARP inhibitors and platinum salts to stall replication forks and cause DNA damage that otherwise would be repaired through BRCA-mediated homologous recombination in the wild-type setting (2).

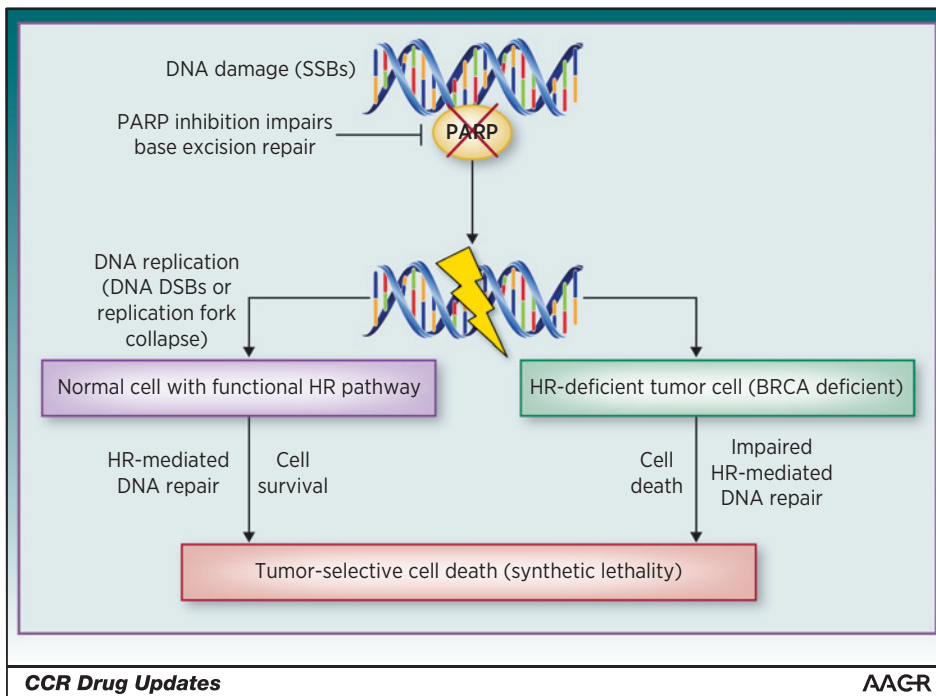
Phase II trials in both refractory breast and ovarian cancer studied olaparib at both the previously identified MTD dose of 400 mg two times a day, and a lower dose of 100 mg two times a day (Table 2; refs. 16, 17). Audeh and colleagues (17) reported the phase II study in women with BRCA-deficient ovarian cancer, for whom the median number of prior regimens was three. Two sequential cohorts were enrolled comprising 33 patients treated with the MTD, followed by 24 who received the lower dose. The higher dose was associated with a higher ORR (33% vs. 13%) and two cases (6%) of grade 3 and 4 nausea, one case (3%) of grade 3

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**Figure 1.**

Mechanism of synthetic lethality between BRCA deficiency and PARP inhibition. Reprinted by permission from Macmillan Publishers Ltd.: *Nature Reviews Clinical Oncology* (ref. 27), copyright 2010. DSB, double-strand break; HR, homologous recombination; SSB, single-strand break.

and 4 fatigue, and one case (3%) of grade 3 and 4 anemia (17). These early studies served as a proof of concept for the clinical application of synthetic lethality.

Later Phase II and Randomized Phase II Trials of Monotherapy and Maintenance Therapy

Because of the molecular, histopathologic, and clinical similarities (i.e., BRCAness) shared between both high-grade serous ovarian cancer and triple-negative breast and germline *BRCA*-deficient cancers, these two subtypes were selected for further study with PARP inhibition (Table 2). Gelmon and colleagues (18) performed a phase II, nonrandomized study of olaparib (400 mg two times a day) in *BRCA*-positive and -negative patients with advanced high-grade serous and/or undifferentiated ovarian cancer ($n = 65$) and triple-negative breast cancer ($n = 26$). Among those with ovarian cancer, confirmed objective responses were seen in 7 [41%; 95% confidence interval (CI), 22–64] of 17 patients with *BRCA1/2* mutations and 11 (24%; 95% CI, 14–38) of 46 without mutations (18). Responses correlated with prior platinum sensitivity. No confirmed objective responses were observed in the breast cancer cohort, although tumor-reduction effects and disease stabilization was higher in the mutants. Fatigue and nausea occurred in 50% or greater in both subpopulations (18).

Kaufman and colleagues (19) studied olaparib (400 mg two times a day) in a spectrum of *BRCA1/2*-mutated cancers in Study 42. Enrollment was restricted to germline *BRCA1/2*-positive patients with (i) platinum-resistant recurrent ovarian cancer, (ii) metastatic breast cancer following three or more chemotherapy regimens, (iii) pancreatic cancer with prior gemcitabine treatment, or (iv) prostate cancer with progression on hormonal therapy and one systemic therapy. In the entire cohort of 298 evaluable patients, the ORR was 26.2% overall (19). The highest responses were reported in patients with prostate (50.0%, $n = 4$

8) and ovarian cancer (31.1%, $n = 60$ of 193; 95% CI, 24.6–38.1; ref. 19). Only 8 (12.9%; 95% CI, 5.7–23.9) of the 62 women with breast cancer experienced objective tumor response by RECIST criteria. Grade 3 or higher adverse events (AE) were reported for 54% of patients with anemia (17%) being most common (19).

The first randomized phase II study of olaparib was reported by Kaye and colleagues (20), and included nearly 100 women with *BRCA1/2*-positive, recurrent ovarian cancer who were randomized to two different dosages of olaparib or to two different dosages of pegylated liposomal doxorubicin (PLD; Table 2). Equivalence of all three arms for progression-free survival (PFS) and ORR was reported, with the activity and tolerability of olaparib consistent with previous studies.

Ledermann and colleagues (21) performed a randomized, double-blind, placebo-controlled, phase II study using olaparib as maintenance therapy (400 mg two times a day) among patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who had received two or more platinum-based regimens and had a partial or complete response to their most recent platinum-based regimen. This trial is known as Study 19 and its primary endpoint, PFS, was significantly longer with olaparib than with placebo (median 8.4 vs. 4.8 months; HR for progression or death, 0.35; 95% CI, 0.25–0.49; $P < 0.001$; Table 2; ref. 21). The majority of AEs were grade 1 and 2 and those occurring by more than 10% in the olaparib group compared with placebo included, nausea, fatigue, vomiting, and anemia.

Of those patients in the trial with known *BRCA* status, 74 (56%) in the olaparib group and 62 (50%) in the placebo group had a deleterious or suspected germline *BRCA* mutation (22). In a protocol-specified retrospective analysis stratified by mutational status, Ledermann and colleagues (22) reported that among patients with *BRCA*-deficient cancers, those treated with olaparib had a significantly longer median PFS as compared with the placebo group (11.2 vs. 4.3 months; HR, 0.18; $P < 0.0001$). Thus far, two interim analyses suggest that overall survival (OS) is not

Table 1. Selected phase I studies of olaparib

Study	Population	Dose and schedule	DLT	MTD
Olaparib monotherapy				
Fong et al. (3)	Advanced solid tumors, selection aimed to enrich BRCA1/2 mutation carriers	Olaparib 10 mg qd PO × 2 wk q21d up to 600 mg BID PO qd	G3 mood alteration and fatigue (<i>n</i> = 1; 400 mg BID); G4 thrombocytopenia (<i>n</i> = 1; 600 mg BID); G3 somnolence (<i>n</i> = 1; 600 mg BID)	Olaparib 400 mg BID
Fong et al. (4)	BRCA1/2-mutated ovarian cancer; single-stage expansion of a phase I trial (3)	Dose-escalation cohort: Olaparib 40 mg PO qd × 2 wk q21d up to 600 mg BID PO qd Dose-expansion cohort: Olaparib 200 mg BID PO qd (28-day cycle)	No new DLTs	As per (3)
Yamamoto et al. (5)	Advanced solid tumors in Japanese patients	Olaparib 100, 200, or 400 mg BID PO	None	Olaparib 400 mg BID PO
Olaparib plus chemotherapy				
Khan et al. (6)	Advanced solid tumors	Olaparib 20–200 mg PO days 1–7 plus dacarbazine 600–800 mg/m ² i.v. d1 (cycle 2, day 2) q21d	Neutropenia, thrombocytopenia	Olaparib 100 mg BID plus dacarbazine 600 mg/m ²
Samol et al. (7)	Advanced solid tumors	Olaparib 50, 100, or 200 mg BID PO plus topotecan 0.5 or 1 mg/m ² /d i.v. × 3d	Neutropenia, thrombocytopenia	Olaparib 100 mg BID PO plus topotecan 1.0 mg/m ² /d × 3d
Rajan et al. (8)	Advanced solid tumors	Olaparib 100 mg BID PO d1–4 plus gemcitabine 500 mg/m ² i.v. d3 and d10 with CDDP 60 mg/m ² i.v. d3	DLI: Thrombocytopenia and febrile neutropenia; GI bleed, syncope, hypoxia	Not determined
Dent et al. (9)	≤1 prior cytotoxic regimen for metastatic TNBC	Olaparib 200 mg BID PO daily plus paclitaxel 90 mg/m ² weekly × 3 wk q4wk	G3 ⁺ neutropenia (<i>n</i> = 6), including 1 case of febrile neutropenia	Not determined
Del Conte et al. (10)	Advanced solid tumors	Olaparib 50–400 mg BID PO d1–28 or d1–7 plus PLD 40 mg/m ² i.v. d1	G3 stomatitis and fatal pneumonia/pneumonitis; G4 thrombocytopenia	Continuous/intermittent olaparib (up to 400 mg BID) plus PLD 40 mg/m ² tolerable; MTD using continuous olaparib not reached
Balmana et al. (11)	Advanced solid tumors	Olaparib 50–200 mg BID PO continuously or intermittently (d1–5 or d1–10) plus CDDP 60–75 mg/m ² i.v. d1 q21 days	G3 neutropenia and G3 lipase elevation with continuous olaparib	Olaparib 50 mg BID d1–5 plus CDDP 60 mg/m ² (no DLTs)
Bendell et al. (12)	Advanced solid tumors	Olaparib 50–200 mg BID PO d1–14 q28 days plus gemcitabine 600–800 mg/m ² d1, 8, 15, and 22 (cycle 1), days 1, 8, 15 (cycle 2+)	Increased alanine aminotransferase <i>n</i> = 2, neutropenia <i>n</i> = 1, febrile neutropenia <i>n</i> = 1	Olaparib 100 mg BID d1–14 plus gemcitabine 600 mg/m ²
Chiou et al. (13)	Platinum-sensitive and platinum-resistant ovarian cancer	Olaparib 400 mg BID PO d1–7 q21d with escalating dosages of carboplatin (AUC 3, 4, 5)	G3/4 neutropenia (<i>n</i> = 7, 23%) G3/4 thrombocytopenia (<i>n</i> = 6, 20%)	Olaparib 400 mg BID PO d1–7 plus carboplatin AUC 4 q21d

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Table 1. Selected phase I studies of olaparib (Cont'd)

Study	Population	Dose and schedule	DLT	MTD
Olaparib plus antiangiogenesis therapy				
Dean et al. (14)	Advanced solid tumors	Olaparib 100, 200, and 400 mg BID PO plus bevacizumab 10 mg/kg i.v. q2wk	None	Olaparib 400 mg BID PO plus bevacizumab 10 mg/kg i.v. q2wk
Liu et al. (15)	Recurrent ovarian (<i>n</i> = 20) and metastatic TNBC (<i>n</i> = 8)	Olaparib up to 400 mg BID PO and cediranib 30 mg PO daily	G4 neutropenia (<i>n</i> = 1) G4 thrombocytopenia (<i>n</i> = 1)	Olaparib 200 mg BID plus cediranib 30 mg daily

Abbreviations: BID, two times a day; CDDP, cisplatin; d, day; DLT, dose-limiting toxicity; G, grade; GI, gastrointestinal; PO, orally; qd, every day; TNBC, triple-negative breast cancer; wk, week.

significantly different between the olaparib and placebo cohorts, whether stratified by mutation status or not.

Olaparib in Combination with Chemotherapy

Clinical development of olaparib has included multiple attempts to combine the PARP inhibitor with chemotherapy. In the phase I trial reported by Samol and colleagues (Table 1; ref. 7), the combination of olaparib plus topotecan was associated with significant dose-limiting hematologic AEs resulting in a subtherapeutic MTD, essentially halting further development of this combination. The combination of olaparib with cisplatin plus gemcitabine was piloted by Rajan and colleagues (8) who reported significant myelosuppression even at relatively low dosages (Table 1). Similarly, an MTD could not be determined for the combination of olaparib plus weekly paclitaxel, which was complicated by significant clinical interaction and greater than expected rates of neutropenia despite secondary prophylaxis (9). In phase I studies evaluating continuous and intermittent dosing of olaparib with cisplatin (11) or with gemcitabine (12), only chemotherapy combined with intermittent dosing of olaparib at 50 mg (days 1–5) or 100 mg (days 1–14) was tolerable.

At the recent 2015 Annual Meeting of the American Society of Clinical Oncology, Chiou and colleagues (13) reported results from their phase I/Ib trial of olaparib with escalating dosages of carboplatin in heavily pretreated patients with high-grade serous ovarian cancer with low genetic risk. The median number of prior therapies was six. Among evaluable subjects, platinum-sensitive patients (*n* = 11) experienced a higher ORR than those with platinum-resistant disease (*n* = 14; 36% vs. 7%).

In an open-label, phase II study (Study 41), Oza and colleagues (23) randomized 162 women with platinum-sensitive high-grade serous ovarian cancer who had remained progression free for a minimum of 6 months before study entry to carboplatin (AUC 4) plus paclitaxel (175 mg/m²) with and without olaparib, 200 mg two times a day d1–10, followed by 400 mg two times a day monotherapy continuously. The arm administering olaparib was associated with significantly improved PFS (Table 2), with the greatest benefit conferred to those with known *BRCA* mutations (*n* = 20; HR, 0.21; 95% CI, 0.08–0.55; *P* = 0.0015; ref. 23). Serious AEs were reported in 15% of patients in the olaparib-plus-chemotherapy arm as compared with 21% in the chemotherapy-alone group. Interestingly, when comparing the hazard of progression for the platinum-sensitive *BRCA*-mutated patients in this study (23) with that of the platinum-sensitive *BRCA* mutation–positive patients in Study 19 (HR, 0.21 vs. 0.18, respectively; ref. 21), it

would appear that there is no additional benefit to adding olaparib to chemotherapy.

Olaparib in Combination with Antiangiogenic Agents

Phase I studies of olaparib (400 mg two times a day) combined with drugs that target the VEGF axis have been informative, with no dose-limiting toxicities (DLT) reported in the olaparib plus bevacizumab trial (Table 1; ref. 14). Provocative data from the phase I combining olaparib with cediranib identified the MTD (Table 1; ref. 15) and led directly to a randomized phase II study of 46 women with either measurable platinum-sensitive, recurrent, high-grade serous, or endometrioid ovarian carcinoma or those with deleterious germline *BRCA1/2* mutations (Table 2; ref. 24). Compared with olaparib monotherapy, the combination was associated with significantly improved PFS (17.7 vs. 9.0 months; HR, 0.42; 95% CI, 0.23–0.76; *P* = 0.005; ref. 24). Grade 3 and 4 fatigue, diarrhea, and hypertension were more common with combination therapy (24). The olaparib-plus-cediranib combination may constitute a chemotherapy-free alternative for select patients with recurrent disease.

Regulatory Approval of Olaparib in the United States

During February 2014, AstraZeneca filed a U.S. regulatory submission for olaparib as a maintenance therapy in platinum-sensitive recurrent disease based on Study 19 (21). On June 25, 2014, the Oncology Drugs Advisory Committee (ODAC) panel members voted 11 to 2 against regulatory approval of olaparib and in response to a request by the FDA for additional data, AstraZeneca submitted a major amendment to their New Drug Application on July 24, 2014, highlighting Study 42 (19).

These data prompted the FDA to extend the original October 3, 2014, Prescription Drug User Fee Act action date to January 3, 2015. On December 19, 2014, the FDA granted accelerated approval to olaparib as fourth-line therapy for women with *BRCA*-deficient (germline only) ovarian carcinoma. Approval was based on the analysis of 137 patients from Study 42 with measurable *BRCA*-deficient recurrent disease treated with a median of 3.4 prior lines of chemotherapy. The ORR for patients in this cohort with measurable disease was 34% (95% CI, 26%–42%) and the median duration of response was 7.9 months (95% CI, 5.6–9.6 months).

The phase III randomized, placebo-controlled olaparib monotherapy study, SOLO 1 (NCT01844986), will attempt to validate

Table 2. Selected phase II and randomized phase II trials of olaparib alone and in combination

Study	Population	Intervention	Primary endpoint	Toxicology
Phase II olaparib monotherapy				
Tutt et al. (16)	<i>N</i> = 54; recurrent, BRCA1/2 breast cancer	Cohort 1: Olaparib 400 mg BID PO daily Cohort 2: Olaparib 100 mg BID PO daily	Cohort 1: ORR 41% Cohort 2: ORR 22%	Cohort 1: G3/4 fatigue (<i>n</i> = 4, 15%), G3/4 nausea (<i>n</i> = 4, 15%), G3/4 vomiting (<i>n</i> = 3, 11%), G3/4 anemia (<i>n</i> = 3, 11%)
Audeh et al. (17)	<i>N</i> = 57; recurrent, measurable, BRCA1/2 ovarian cancer	Cohort 1 (<i>n</i> = 33): Olaparib 400 mg BID PO daily Cohort 2 (<i>n</i> = 24): Olaparib 100 mg BID PO daily	Cohort 1: ORR 33% Cohort 2: ORR 13%	Cohort 1: G3/4 nausea (<i>n</i> = 2, 6%), G3/4 fatigue (<i>n</i> = 1, 3%), G3/4 anemia (<i>n</i> = 1, 3%)
Gelmon et al. (18)	<i>N</i> = 91; advanced high-grade serous and/or undifferentiated ovarian (<i>N</i> = 65) or triple-negative breast cancer (<i>N</i> = 26)	Olaparib 400 mg BID PO daily	Ovary: ORR 41% of 17 BRCA1/2 positive patients and 24% of 46 BRCA negative; Breast: ORR 0%	Ovary: fatigue (70%), nausea (66%), vomiting (39%), decreased appetite (36%)
Kaufman et al. (19; also known as Study 2)	<i>N</i> = 298; recurrent ovarian, breast, pancreatic, and prostate cancer with BRCA1/2 mutations	Olaparib 400 mg BID PO daily	Tumor response rate: 31.1% (<i>n</i> = 60 of 193: ovarian); 12.9% (breast); 21.7% (pancreatic); 50.0% (prostate)	Most common G3 ⁺ : anemia (17% entire study population)
Randomized phase II olaparib monotherapy and maintenance therapy				
Kaye et al. (20)	<i>N</i> = 97; BRCA1/2 positive ovarian cancer with recurrence <12 mo of prior platinum therapy	Randomization: Olaparib 200 mg BID PO daily vs. olaparib 400 mg BID PO daily vs. PLD 50 mg/m ² i.v. q28 days	PFS and RECIST-assessed ORR n.s. for combined olaparib doses vs. PLD	Tolerability as expected on the basis of prior trials
Ledermann et al. (21; also known as Study 19)	<i>N</i> = 265; platinum-sensitive, recurrent, high-grade serous ovarian cancer (2 or more prior platinum-based regimens with PR or CR)	Randomization: Olaparib 400 mg BID PO daily vs. placebo	Olaparib median PFS 8.4 vs. 4.8 mo (HR, 0.35; 95% CI, 0.25–0.49; <i>P</i> < 0.001); interim analysis for OS n.s.	Olaparib vs. placebo: nausea (68% vs. 35%), fatigue (49% vs. 38%), vomiting (32% vs. 14%), anemia (17% vs. 5%) — majority of AEs GI/2
Ledermann et al. (22)	<i>N</i> = 136 germline BRCA1/2-positive patients from the randomized phase II maintenance study (20); preplanned retrospective analysis	Olaparib 400 mg BID PO (<i>n</i> = 74) vs. placebo (<i>n</i> = 62)	Olaparib BRCA ⁺ median PFS 11.2 vs. 4.3 mo (HR, 0.18; 95% CI, 0.10–0.31; <i>P</i> < 0.0001); OS n.s.	Olaparib group: G3 ⁺ fatigue (7% vs. 3%); anemia (5% vs. <1%); tolerability similar in women with mutated BRCA and overall population
Randomized phase II olaparib plus chemotherapy				
Oza et al. (23; also known as Study 41)	<i>N</i> = 162; platinum-sensitive, high-grade serous ovarian cancer, up to 3 prior courses of platinum-based chemotherapy, progression free at least 6 mo	Randomization: Carboplatin AUC 4 mg/mL/min plus paclitaxel 175 mg/m ² i.v. day 1 with and without olaparib 200 mg BID PO d1–10 followed by monotherapy 400 mg BID daily	PFS significantly longer in the olaparib + ChemoRx arm: 12.2 mo vs. 9.6 mo; HR, 0.51; 95% CI, 0.34–0.77; <i>P</i> = 0.0012. Among BRCA mutation carriers (<i>n</i> = 41: 20 in the olaparib arm, 21 in the ChemoRx alone arm), HR, 0.21; 95% CI, 0.08–0.55; <i>P</i> = 0.0015	Most common G3 ⁺ in the olaparib + ChemoRx arm vs. ChemoRx alone: neutropenia (43% vs. 35%); anemia (9% vs. 7%)

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Table 2. Selected phase II and randomized phase II trials of olaparib alone and in combination (Cont'd)

Study	Population	Intervention	Primary endpoint	Toxicology
Randomized phase II olaparib plus antiangiogenesis therapy				
Liu et al. (24)	N = 90; platinum-sensitive, recurrent, high-grade serous or endometrioid ovarian, tubal, or peritoneal cancer and/or germline BRCA1/2 mutations	Randomization: Olaparib 400 mg BID PO twice daily or olaparib 200 mg BID PO twice daily plus cediranib 30 mg PO daily	Olaparib plus cediranib median PFS 17.7 vs. 9.0 mo (HR, 0.42; 95% CI, 0.23–0.76; P = 0.005)	G3/4 more common in combination group: fatigue, diarrhea, hypertension

Abbreviations: ChemoRx, chemotherapy; CI, confidence interval; CR, complete response; G, grade; HR, hazard ratio; mo, months; n.s., not statistically significant; PO, orally; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

the findings of Study 19, while SOLO 2 (NCT01874353), the phase III randomized, placebo-controlled olaparib-without-chemotherapy trial in platinum-sensitive disease was designed on the heels of Study 41. Both SOLO 2 and its successor, SOLO 3 (NCT02282929), are integral to the phase IV commitment following accelerated approval. FDA approval was done in conjunction with regulatory approval of a companion diagnostic genetic test (BRCAanalysis CDx) that will screen serum from ovarian cancer patients for mutations in the *BRCA* genes (gBRCAm). Interestingly, one day before regulatory approval in the United States, AstraZeneca announced on December 18, 2014, that the European Commission granted marketing authorization for olaparib as a first-line maintenance therapy for adult patients with platinum-sensitive, relapsed *BRCA*-mutated (germline and/or somatic) high-grade serous epithelial ovarian, tubal, or peritoneal carcinoma.

The clinical implications of approving a drug for fourth-line therapy need to be framed in the context of toxicity assessment. This is particularly important in the setting of recurrent disease, where quality of life/disease control is the goal and not cure. Contemporary regimens for recurrent platinum-sensitive disease include carboplatin (or cisplatin) plus either paclitaxel or gemcitabine, and carboplatin plus PLD. Women with partially platinum-sensitive and platinum-resistant disease may receive bevacizumab plus either PLD, topotecan, or weekly paclitaxel or monotherapy using PLD, topotecan, weekly albumin-stabilized nanoparticle-formulation paclitaxel, trabectedin, or pemetrexed (the latter two not having a label in the United States). Olaparib as monotherapy may have a much more favorable safety profile compared with conventional chemotherapy used in the recurrent setting.

Discussion

All patients with recurrent ovarian cancer will ultimately progress on olaparib. On the basis of the preclinical data, early essayists were concerned that treatment with PARP inhibitors would result in acquisition of secondary *BRCA1/2* mutations that would limit the efficacy of subsequent chemotherapy, specifically, platinum-based agents. Ang and colleagues (25) collected data from 89 patients with *BRCA*-deficient ovarian cancer who had been previously treated with olaparib at daily dosages of 200 mg and higher. The ORR by RECIST to post-olaparib chemotherapy was 36% ($n = 24$ of 67 patients). For patients treated post-olaparib with platinum-based chemotherapy, the ORR was 40% ($n = 19$ of 48 patients; ref. 25). The corresponding ORRs when incorporating CA-125 were 45% and 49%, respectively (25). The length of the

platinum-to-platinum interval with intervening olaparib was associated with an increased likelihood of response (25). Tumor was available from 6 cases and subjected to massively parallel sequencing, which demonstrated no evidence of secondary *BRCA* mutations (25). These data suggest that not only does PARP inhibitor-resistant ovarian cancer retain the potential to respond to chemotherapy, but that treatment with PARP inhibitors may enhance the response to subsequent platinum.

Using targeted capture and massively parallel genomic sequencing, Pennington and colleagues (26) recently reported that germline (24%) and somatic (9%) mutations were detected in one or more of 13 homologous recombination genes, including *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIPI1*, *CHEK1*, *CHEK2*, *FAM175A*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*, and *RAD 51D*. Homologous recombination deficiency was found in both serous and nonserous ovarian carcinomas, including clear cell, endometrioid, and ovarian carcinosarcoma. Both germline and somatic homologous recombination mutations were highly predictive of platinum sensitivity and improved OS, with OS durations of 66 months (germline), 59 months (somatic), and 41 months (no homologous recombination deficiency) noted (26). These data support interrogating ovarian tumors for genomic scars indicative of homologous recombination deficiency to assess candidacy for treatment with olaparib and other PARP inhibitors.

Conclusions

Moving forward, the prevalence of homologous recombination deficiency in tumors other than ovarian and breast requires assessment and predictive biomarkers need to be discovered. In addition, indications for combining olaparib with chemotherapy and additional chemotherapy-free olaparib-based regimens should be explored.

Regulatory approval of the first-in-class PARP inhibitor, olaparib, as a monotherapy for patients with *BRCA*-deficient or suspected *BRCA*-deficient recurrent ovarian cancer is accompanied by discrete consequences for drug development in the fourth-line space. At the very minimum, newer agents will need to deliver ORR in excess of 30% with the lower limit of a 95% CI settling in at 26% to 28%.

Disclosure of Potential Conflicts of Interest

R.N. Eskander reports receiving speakers bureau honoraria from AstraZeneca. B.J. Monk reports receiving speakers bureau honoraria from AstraZeneca, and is a consultant/advisory board member for AstraZeneca and TESARO. No potential conflicts of interest were disclosed by the other author.

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Conception and design: K.S. Tewari, R.N. Eskander, B.J. Monk
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B.J. Monk
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B.J. Monk

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