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A Phase 1 trial of the PARP inhibitor olaparib (AZD2281) in combination with the anti-angiogenic cediranib (AZD2171) in recurrent epithelial ovarian or triple-negative breast cancer

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Abstract

Background—PARP-inhibitors and anti-angiogenics have activity in recurrent ovarian and breast cancer; however, the effect of combined therapy against PARP and angiogenesis in this population has not been reported. We investigated the toxicities and recommended phase 2 dosing (RP2D) of the combination of cediranib, a multitargeted inhibitor of VEGFR-1/2/3, and olaparib, a PARP-inhibitor (NCT01116648).

Methods—Cediranib tablets once daily and olaparib capsules twice daily were administered orally in a standard 3+3 dose escalation design. Patients with recurrent ovarian or metastatic triple-negative breast cancer were eligible. Patients had measurable disease by RECIST 1.1 or met GCIG CA125 criteria. No prior PARP-inhibitors or anti-angiogenics in the recurrent setting were allowed.

Results—28 patients (20 ovarian, 8 breast) enrolled to 4 dose levels. 2 DLTs (1 grade 4 neutropenia 4 days; 1 grade 4 thrombocytopenia) occurred at the highest dose level (cediranib 30mg daily; olaparib 400mg BID). The RP2D was cediranib 30mg daily and olaparib 200mg BID. Grade 3 or higher toxicities occurred in 75% of patients, and included grade 3 hypertension (25%) and grade 3 fatigue (18%). One grade 3 bowel obstruction occurred. The overall response rate

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Conflicts of Interest

The authors declare they have no conflicts of interest.

(ORR) in the 18 RECIST-evaluable ovarian cancer patients was 44%, with a clinical benefit rate (ORR plus SD >24 weeks) of 61%. None of the 7 evaluable breast cancer patients achieved clinical response; 2 patients had stable disease for >24 weeks.

Interpretation—The combination of cediranib and olaparib has hematologic DLTs and anticipated class toxicities, with promising evidence of activity in ovarian cancer patients.

Poly(ADP-ribose) polymerase (PARP) inhibitors are an emerging class of drugs that inhibit PARP-1 and PARP-2, proteins that play a critical role in base excision repair (BER) ¹. When PARP function is impaired, double-stranded DNA breaks accumulate in the absence of effective BER; in cells deficient in homologous recombination (HR), these breaks cannot be accurately repaired, resulting in synthetic lethality ². Preclinical work has supported the synthetic lethality of PARP-inhibition with impaired HR³, including in the setting of BRCA-deficiency ^{4,5}, which is associated with high grade serous ovarian cancer and triple negative breast cancer (TNBC). PARP-inhibitors are well-tolerated and have single-agent activity in breast and ovarian cancers in the setting of underlying BRCA germline mutation ^{6,7} as well as in BRCA wild-type ovarian cancers ⁸. However, combination studies of PARP-inhibitors with various chemotherapies have demonstrated increased myelosuppression ^{9,10}.

Anti-angiogenic therapies have proposed activity in both breast and ovarian cancer and have limited overlapping toxicities with PARP-inhibitors. A Phase 1 trial combining the PARP-inhibitor olaparib with bevacizumab, an anti-VEGF antibody, reported the combination to be well-tolerated ¹¹. Single agent bevacizumab has a response rate of ~18% in recurrent ovarian cancer ^{12,13}, while cediranib, a small-molecule inhibitor of VEGFR-1/2/3, has a 19% response rate in this setting ¹⁴. Similarly, anti-angiogenics in breast cancer have demonstrated increased response rates in combination with chemotherapy and more limited activity as single agents, although not associated with an overall survival benefit ^{15,16}. Major toxicities observed with anti-angiogenics include hypertension, fatigue, and, in patients with recurrent ovarian cancer, risk of bowel perforation ^{13,14}.

Preclinically, PARP-inhibition has reported anti-angiogenic effects, where GPI 15427 (a potent PARP-1/2 inhibitor) inhibits *in vivo* angiogenesis in a matrigel plug assay ¹⁷. PARP-1 knockout mice also demonstrate decreased *in vivo* angiogenesis compared to control mice with wild-type PARP-1¹⁷, supporting the notion that the observed anti-angiogenic effects are specific to anti-PARP activity. More recent work has demonstrated that HR can be suppressed by hypoxia through downregulation of HR repair proteins such as *BRCA1* and *RAD51* and that PARP inhibitor sensitivity is enhanced in hypoxic states ^{18–21}. This information raises the hypothesis that PARP-inhibitors and anti-angiogenics may have synergistic effects.

In this study, we therefore explored the safety, dosing, and preliminary efficacy of the PARP-inhibitor olaparib in combination with the anti-angiogenic cediranib in patients with recurrent ovarian, fallopian tube, or primary peritoneal cancers, or in patients with metastatic TNBC.

PATIENTS AND METHODS

Trial design and procedures

This was an open-label, phase 1, dose-escalation trial performed at two participating institutions evaluating increasing doses of once daily cediranib and twice daily olaparib administered continuously in 28-day cycles. Cediranib was administered as 10mg and 15mg tablets and olaparib as 50mg capsules. The primary objectives were to determine the dose limiting toxicities (DLT) and maximum tolerated dose (MTD) of this combination. Secondary objectives included assessment of treatment-related toxicities and preliminary

assessment of clinical activity as measured by response rate, clinical benefit rate (CBR), and progression-free survival (PFS), defined as time from initiation of therapy to disease progression or death from any cause.

The starting dose level was cediranib 20mg daily and olaparib 100mg twice daily (BID). Dose escalation occurred in a standard phase 1 3+3 design. Additional dose levels were selected to escalate to the tolerated single-agent dosing of each drug (cediranib 30mg daily and olaparib 400mg BID^{6, 14}), and included: 1) cediranib 20mg daily, olaparib 200mg BID; 2) cediranib 30mg daily, olaparib 200mg BID; 3) cediranib 30mg daily, olaparib 400mg BID. Treatment continued until disease progression, unacceptable toxicity, or patient withdrawal. Patients were provided with blood pressure cuffs and were asked to assess their blood pressure at home twice daily. Patients were to contact their physician for blood pressures exceeding 140 mmHg systolic or 90 mmHg diastolic to optimize blood pressure control.

The MTD was defined as the highest dose level with at least 6 patients where 1 or fewer patients experienced a DLT. Following establishment of the MTD, an expansion cohort was enrolled to further assess toxicities at the MTD.

Patient Eligibility

Eligibility criteria included age ≥ 18 years, ECOG performance status 0 or 1, life expectancy >6 months, and either recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, or metastatic TNBC. Ovarian cancer patients were required to have measurable disease by RECIST 1.1 or an elevated CA125 level twice the upper limit of normal on two occasions at least 1 day but not more than 3 months apart; they also needed to have received a first-line platinum-based regimen. Breast cancer patients needed to have measurable disease by RECIST 1.1 and had to have recurred after both an adriamycin- and taxane-containing regimen. Prior PARP-inhibitors or anti-angiogenics were allowed in the adjuvant but not recurrent or metastatic settings. Exclusion criteria included pre-existing inadequately controlled hypertension (defined as a blood pressure >140/90 mmHg); a need for greater than three anti-hypertensive medications; history of hypertensive crisis; history of abdominal fistula or gastrointestinal perforation; signs or symptoms of bowel obstruction within the prior 3 months; and major surgical procedure within the prior 28 days. The trial was approved per the relevant institutional review boards, and written informed consent was obtained from all patients.

Toxicity criteria and dose modifications

DLTs were defined as non-hematologic toxicities of Grade 3 or 4 (excepting Grade 3 fatigue, hypophosphatemia, or hyponatremia, or controlled Grade 3 hypertension); Grade 4 neutropenia ≥ 4 days or with fever or infection; all other Grade 4 hematologic toxicities; and inability to take 75% or more of the planned dose in Cycle 1 due to treatment-related toxicities. Only DLTs that occurred during Cycle 1 were considered in determining the MTD. Toxicities were graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.

Inpatient dose escalation was allowed if the patient had not experienced any DLTs on their assigned dose level and if assessment at the next higher dose level had completed with a DLT frequency of <33%. Patients experiencing DLTs or prolonged non-hematologic grade 2 toxicities could interrupt drug dosing for up to 14 days until the toxicity resolved to grade 1 or less. Subsequent reduction to the next lower dosing level was allowed. Patients could have multiple dose reductions, but could not be dosed lower than cediranib 15mg daily and olaparib 100mg BID.

Clinical Activity

Clinical response in patients with measurable disease was assessed by RECIST 1.1. Imaging assessments were performed by CT or MRI at baseline and every 8 weeks. Any partial or complete response required confirmatory imaging 4 weeks after the initial imaging demonstrating response. Ovarian cancer patients without measurable disease were followed by GCIG CA125 response criteria²². CA125 response was defined as 50% decrease in the CA125 level, confirmed by repeat testing 4 weeks after the initial sample. CA125 progression was defined as doubling of the CA125 from baseline. Clinical benefit was defined as response or stable disease 24 weeks.

RESULTS

Patient Characteristics

In total, 28 patients were enrolled and all received at least 1 dose of olaparib and cediranib. Baseline characteristics are presented in Table 1. Twenty patients had ovarian, fallopian tube, or primary peritoneal cancer, and 8 patients had TNBC. Of the ovarian cancer patients, 12 (60%) had a known deleterious germline BRCA mutation, 3 (15%) were BRCA wild-type, and BRCA status was unknown in the remaining. Of the TNBC patients, 3 (38%) had a BRCA mutation, 1 (13%) was BRCA wild-type, and the remainder were unknown. All ovarian cancer patients had received prior platinum/taxane therapy. One ovarian and one breast cancer patient had received an anti-angiogenic in the adjuvant setting.

Dose Escalation

Dose escalation proceeded per protocol. Three patients were treated at dose level (DL) 0 (cediranib 20mg; olaparib 100mg), 3 at DL1 (cediranib 20mg; olaparib 200mg), 7 at DL2 (cediranib 30mg; olaparib 200mg), and 6 at DL3 (cediranib 30mg; olaparib 400mg). Two intra-patient dose escalations occurred at DL0, with an increase in olaparib to 200mg. Two of the six patients in the highest planned dosing cohort, DL3, experienced DLTs (1 grade 4 neutropenia >4 days; 1 grade 4 thrombocytopenia). No additional DLTs were observed on any dosing cohort. Therefore, the previous dose level of cediranib 30mg daily and olaparib 200mg twice daily was determined to be the MTD. An expansion cohort of 9 patients was subsequently enrolled at the MTD.

Safety Profile

All 28 patients experienced at least one treatment-related adverse-event (AE; Table 2), with the most frequently occurring treatment-related AEs being fatigue (93%), diarrhea (86%), nausea (57%), and hypertension (46%). Grade 3/4 treatment-related AEs occurred in 21 (75%) patients. Grade 3/4 AEs occurring in greater than 10% of patients included hypertension (25%), fatigue (18%), and decreased neutrophil count (11%). In general, although Grade 3 or higher events occurred in 75% of patients, the AEs experienced were anticipated and manageable; two patients withdrew consent for drug-related toxicity, one after 47 days and the other after 196 days on study. A third patient with ovarian cancer was removed from study due to grade 3 small bowel obstruction in the setting of increasing size of her pelvic masses.

Clinical Activity

Twenty-five patients (18 ovarian, 7 breast) were evaluable for response by RECIST 1.1. The two ovarian cancer patients not evaluable by RECIST 1.1 were followed by GCIG CA125 criteria. The non-evaluable breast cancer patient experienced clinical progression within the first cycle of treatment and therefore did not undergo comparative imaging. Overall response data are shown in Table 3. There was 1 confirmed complete response (CR) and 7 confirmed

partial responses (PR) among the 18 evaluable ovarian patients, for an overall response rate of 44%. An additional 3 patients had stable disease (SD) for at least 24 weeks, for an overall CBR of 61%. Both ovarian patients followed by CA125 had SD, with one patient having SD for 24 weeks. In the 11 evaluable ovarian patients with known BRCA mutation, there was 1 CR and 4 PRs, for an overall response rate of 45%. None of the breast cancer patients met RECIST 1.1 criteria for clinical response. Two patients had SD for 24 weeks. The median PFS was 8.7 months for ovarian cancer patients and 3.7 months for breast cancer patients. Waterfall plots of the best response to therapy in the 25 ovarian and breast patients with RECIST-evaluable disease are shown in Figure 1.

DISCUSSION

We investigated the safety and dosing of the combination of an oral anti-angiogenic, cediranib, and an oral PARP-inhibitor, olaparib, in patients with epithelial ovarian cancer or TNBC. This Phase 1 trial demonstrated that AEs observed with this combination are generally anticipated and manageable, with an MTD of cediranib 30mg daily and olaparib 200mg BID on a continuous dosing schedule. At the highest dosing level of cediranib 30mg daily and olaparib 400mg BID, 2 DLTs were observed. Only one additional grade 4 toxicity, a grade 4 neutropenia, was observed, suggesting that this combination has an acceptable toxicity profile for further clinical exploration.

Fatigue, diarrhea, and hypertension were the most commonly observed AEs in this study, consistent with previously reported toxicities of cediranib and olaparib. Fatigue, which has been observed with both cediranib and olaparib in single-agent studies^{14, 23}, may have been more prominent due to overlapping toxicity. Diarrhea was generally controllable with loperamide, although several patients required dose-reduction. Hypertension, a well-documented toxicity of anti-angiogenics, was manageable with aggressive anti-hypertensive therapy; of note, only one patient required dose reduction for hypertension. Although all three grade 4 AEs observed were hematologic, in general, the combination was well-tolerated with primarily Grade 1/2 hematologic toxicities.

Significant clinical activity was observed in the 20 ovarian cancer patients, with activity present at all dose levels. The response rate of 44% is comparable to results from a phase I study by Fong et al., where the response rate was 28%. Higher response rates have been seen in subsequent Phase 2 trials of single agent olaparib^{6, 8}, although the activity we observed remains comparable to these studies as well. As these are differing patient populations, it is unclear whether the addition of an anti-angiogenic to olaparib is adding significant benefit, and this should be further investigated in a future study. We noted evidence of activity in both platinum-sensitive and -resistant populations, as well as in BRCA mutation carriers and BRCA wild-type patients.

Limited clinical activity was observed in the 8 patients with TNBC, although evidence of clinical activity was seen in two BRCA mutation carriers, with one having SD for 4 months with a 26.6% decrease in tumor size, and the other having SD for 7 months with a 28.9% decrease in tumor size. Given the limited sample size and the dose-escalation nature of this trial, it is difficult to draw conclusions regarding the activity of this drug combination in patients with TNBC, although Tutt et al. have reported single-agent olaparib activity in BRCA-mutation carriers with metastatic breast cancer⁷.

This is one of the first clinical trials to assess the combination of an anti-angiogenic with a PARP-inhibitor. The results of another Phase 1 clinical trial combining olaparib with bevacizumab were recently published¹¹. This trial enrolled 12 patients over 3 dose levels and observed no DLTs, with a maximum dosing of olaparib 400mg BID and bevacizumab

10mg/kg every 14 days. Fatigue, headache, and gastrointestinal AEs were the most frequently reported AEs; 1 patient developed a small bowel obstruction/perforation attributed to bevacizumab. Patients had a variety of solid tumor types, and there was no estimate of preliminary efficacy in this very mixed population. In our trial, one patient was removed from study due to a bowel obstruction in the setting of an increase in size of her pelvic masses. The occurrence of bowel obstruction in both of these studies emphasizes the potential for this rare but significant AE with anti-angiogenic agents, especially in patient populations where bowel obstructions are a frequent complication. The rate of grade 3/4 toxicities was higher in our study; this may be related to differences between bevacizumab and cediranib, which has additional activity against c-kit and PDGFR-beta. Overall, however, these results support the conclusion that anti-angiogenics and PARP-inhibitors can be combined with minimal overlapping toxicities.

In conclusion, the MTD and recommended Phase 2 dosing of cediranib and olaparib is cediranib 30mg daily and olaparib 200mg twice daily. Clinical responses were reported in 44% of ovarian cancer patients in this dose-escalation trial, with an overall CBR of 61%. More limited activity was observed in TNBC patients. Overall, the combination of these drugs was a tolerable regimen, with some patients remaining on study for over a year. Further determination of the degree of clinical activity of this combination as compared to olaparib alone in high-grade serous ovarian cancer is ongoing in a randomized Phase 2 trial (NCT01116648).

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Figure 1. Waterfall plots of best response in patients with RECIST-evaluable disease

Figure 1 represents the best responses observed in the 25 patients on the trial who had RECIST-evaluable disease. Breast patients are represented in yellow and ovarian patients in blue. The diamond pattern denotes patients with a known germline BRCA-mutation. Asterisks represent ovarian cancer patients with platinum-resistant disease.

Table 1

Patient characteristics

Age (years)	
Median	57
Range	36–70
ECOG performance status	
0	17 (61%)
1	11 (39%)
Diagnosis	
Ovarian	20 (71%)
Breast	8 (29%)
BRCA status	
Mutation carrier	15 (54%)
Wild-type	4 (14%)
Unknown	9 (32%)
Number of prior regimens (median)	
Ovarian	2 (range 1–12)
Breast	3 (range 2–6)
Platinum-sensitivity (ovarian pts)	
Sensitive	14 (70%)
Resistant	6 (30%)
Histology (ovarian pts)	
Papillary-serous	16 (80%)
Endometrioid	1 (5%)
Mixed	2 (10%)
Other	1 (5%)

Table 2

All study-related AEs observed in >10% of patients

Toxicity	Grade 1/2	Grade 3	Grade 4	Overall
Fatigue	21 (75%)	5 (18%)		26 (93%)
Diarrhea	22 (79%)	2 (7%)		24 (86%)
Nausea	15 (54%)	1 (4%)		16 (57%)
Hypertension	6 (21%)	7 (25%)		13 (45%)
Hypothyroidism	7 (25%)			7 (25%)
WBC decreased	5 (18%)	2 (7%)		7 (25%)
Anorexia	6 (21%)	1 (4%)		7 (25%)
Vomiting	6 (21%)			6 (21%)
Headache	6 (21%)			6 (21%)
Hoarseness	6 (21%)			6 (21%)
AST increased	5 (18%)			5 (18%)
ANC decreased	2 (7%)	1 (4%)	2 (7%)	5 (18%)
Oral mucositis	4 (14%)			4 (14%)
Oral pain	4 (14%)			4 (14%)
ALT increased	4 (14%)			4 (14%)
Hypomagnesemia	4 (14%)			4 (14%)
Hyponatremia	3 (11%)	1 (4%)		4 (14%)
Hypophosphatemia	3 (11%)	1 (4%)		4 (14%)
Dysgeusia	4 (14%)			4 (14%)
Alopecia	3 (11%)			3 (11%)
PPE syndrome	1 (4%)	2 (7%)		3 (11%)
Abdominal pain	3 (11%)			3 (11%)
Alk phos increased	3 (11%)			3 (11%)
Lymphocyte decreased	3 (11%)			3 (11%)
Platelet decreased	1 (4%)	1 (4%)	1 (4%)	3 (11%)
Hypocalcemia	3 (11%)			3 (11%)
Myalgia	3 (11%)			3 (11%)
Dyspnea	2 (7%)	1 (4%)		3 (11%)

Table 3

RECIST Responses by Dose Level

Dose Level	20mg cediranib 100mg BID olaparib	20mg cediranib 200mg BID olaparib	30mg cediranib 200mg BID olaparib	30mg cediranib 400mg BID olaparib
All Patients *	3	3	15	5
Ovarian pts	2	2	11	3
CR	0	1	0	0
PR	2	0	4	1
SD	0	1	1	2
Breast pts	1	1	4	2
CR	0	0	0	0
PR	0	0	0	0
SD	0	1	2	0

* includes only patients with measurable disease