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Clinical Trial Results

Clinical Activity and Safety of Cediranib and Olaparib Combination in Patients with Metastatic Pancreatic Ductal Adenocarcinoma without *BRCA* Mutation

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Pancreatic ductal adenocarcinoma • Cediranib • Olaparib • *BRCA*

Trial Information

- **ClinicalTrials.gov Identifier**: NCT02498613
- **Sponsor**: NCI
- **Principal Investigator**: Joseph Kim
- **IRB Approved**: Yes

Lessons Learned

- Cediranib and olaparib combination did not result in clinically meaningful activity in patients with metastatic pancreatic ductal adenocarcinoma without known *BRCA* mutation.

Abstract

Background. Cediranib, a vascular endothelial growth factor receptor inhibitor, suppresses expression of BRCA1/2 and RAD51 inducing homologous recombination DNA repair deficiency (HRD) in several cancer cell lines and xenograft models [1]. Olaparib provides a clinical benefit in patients with metastatic pancreatic adenocarcinoma (mPDAC) with germline BRCA mutation (gBRCAmt) [2]. We hypothesized that cediranib induces HRD in the absence of gBRCAmt and synergizes with olaparib, resulting in an objective response in patients with mPDAC.

Methods. Patients with mPDAC with at least one prior systemic chemotherapy were enrolled. Patients with known gBRCAmt were excluded. Patients took cediranib 30 mg daily and olaparib 200 mg twice daily, orally. The primary endpoint was objective response (OR) rate.

Results. Nineteen patients received the study drugs. Seven patients came off treatment before the first restaging scan: six because of clinical progression and one because of an adverse event. No OR was observed. Six patients had stable disease (SD) as a best overall response. The median duration of SD was 3.1 months. The median overall survival was 3.4 months. Common treatment-related adverse events were fatigue, hypertension, and diarrhea.

Conclusion. Cediranib and olaparib combination did not result in clinically meaningful activity in patients with mPDAC without gBRCAmt. ***The Oncologist*** 2021;26:e1104–e1109

Discussion

Clinical efficacy of a poly-(ADP-ribose) polymerase (PARP) inhibitor in patients with HRD has been well-documented in pancreatic cancer and other solid tumors [2–4]. Hypoxia induces downregulation of homologous recombination DNA repair (HR) genes in several cancer cell lines and xenograft models including breast, lung, colon, and prostate cancers [5–7]. Cediranib, a vascular endothelial growth factor receptor (VEGFR) inhibitor, suppresses expression of *BRCA1/2* and *RAD51*, inducing HR deficiency (HRD) in breast and ovarian cancer cell lines and their xenograft models [1]. The

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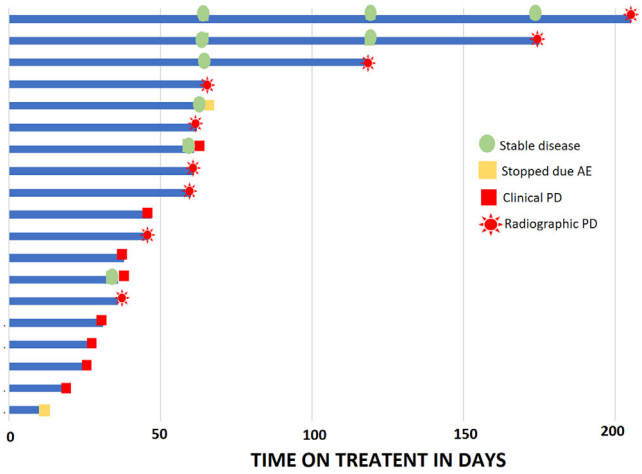

Figure 1. Duration of treatment.
Abbreviations: AE, adverse event; PD, progressive disease

central hypothesis of this study is that cediranib induces tumor hypoxia leading to a HRD phenotype and sensitizes the tumors to a PARP inhibitor, resulting in objective responses and disease control in the absence of a deleterious mutation in *BRCA* or other HR related genes. To that end, we accrued patients with metastatic solid tumors in four cohorts: pancreatic ductal adenocarcinoma (mPDAC), triple-negative breast cancer, small cell lung cancer, and non-small cell lung cancer. Patients with known germline *BRCA* mutation were excluded. Patients were treated with cediranib 30 mg orally once daily and olaparib 200 mg orally twice daily. The primary objective was to determine the objective response rate in each of the disease cohorts.

We found that the combination of cediranib plus olaparib did not result in any objective response in patients with mPDAC (Fig. 1). Six patients achieved stable disease as best overall response. The median duration of stable disease was only 3.1 months, with the range of 1.2 to 6.8 months. This did not translate into durable disease control. Given the lack of clinically meaningful activity of cediranib and olaparib combination in patients with mPDAC, the accrual to the PDAC cohort was terminated early because of futility.

A potential explanation for the lack of activity is that cediranib did not induce HRD phenotype deleterious enough to result in synthetic lethality with olaparib as hypothesized. It should be noted that although the preclinical studies supporting our hypothesis testing were done in several tumor cell lines and xenograft models including lung, colon, breast, prostate and cervical cancers [5–7], no preclinical studies were performed in pancreatic cancer models.

This regimen is currently under clinical investigation in other solid tumors with tissue and blood-based correlative studies and will be reported separately.

Trial Information	
Disease	Pancreatic cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	No designated number of regimens
Type of Study	Phase II, single arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Toxicity
Additional Details of Endpoints or Study Design	
The primary objective was to assess the objective response rate (ORR) of the combination of cediranib and olaparib in patients with metastatic pancreatic ductal adenocarcinoma. Simon's two-stage design was used. The null hypothesis that the true ORR is 5% was tested against a one-sided alternative. In the first stage, 18 response-evaluable patients were accrued. At least one confirmed objective response was required to proceed to the second stage accrual for a total of 32 patients. The null hypothesis would be rejected if four or more responses are observed in 32 patients. This design yields a type I error rate of 10% and power of 90% when the true ORR is 20%.	
Investigator's Analysis	Inactive because results did not meet primary endpoint

Drug Information	
Generic/Working Name	cediranib
Company Name	AstraZeneca
Drug Type	Small molecule
Drug Class	VEGFR
Dose	30 mgs per flat dose
Route	oral (po)
Schedule of Administration	once daily
Generic/Working Name	olaparib
Trade Name	Lynparza
Company Name	AstraZeneca

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Drug Type	Small molecule
Drug Class	PARP
Dose	200 mg per flat dose
Route	oral (po)
Schedule of Administration	twice daily

Patient Characteristics	
Number of patients, male	11
Number of patients, female	8
Stage	IV
Age	Median (range): 68 (45–85) years
Number of Prior Systemic Therapies	Median (range): 3 (1–5)
Performance Status: ECOG	0 — 7 1 — 12 2 — 0 3 — 0 Unknown — 0
Total Number of Patients	*n* = 19
Race	White: 16 (84%) Black or African American: 1 (5%) Asian: 2 (11%)
Prior Lines of Therapy	Median: 3 1: 3 (16%) 2: 6 (32%) ≥3: 10 (53%)
Prior Therapies	FOLFIRINOX: 14 (74%) Gemcitabine-based regimen: 18 (95%)
BRCA 1/2 Mutation Status	Known or suspected germline BRCA mutation: 0 Unknown: 19

Primary Assessment Method	
Title	Clinical activity summary
Number of Patients Screened	24
Number of Patients Enrolled	24
Number of Patients Evaluable for Toxicity	19
Number of Patients Evaluated for Efficacy	18
Evaluation Method	RECIST 1.1
Response Assessment CR	0 (0%)
Response Assessment PR	0 (0%)
Response Assessment SD	6 (33%)
Response Assessment PD	12 (67%)
(Median) Duration Assessments OS	3.4 months
(Median) Duration Assessments Duration of Treatment	47 days

Adverse Events (all cycles)

Name	NC/NA	1	2	3	4	5	All grades
Fatigue	26%	37%	37%	0%	0%	0%	74%
Hypertension	53%	0%	32%	16%	0%	0%	47%
Diarrhea	68%	26%	5%	0%	0%	0%	32%
Platelet count decreased	68%	26%	5%	0%	0%	0%	32%

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Nausea	79%	11%	11%	0%	0%	0%	21%
Anorexia	79%	21%	0%	0%	0%	0%	21%
Aspartate aminotransferase increased	79%	11%	11%	0%	0%	0%	21%
Alkaline phosphatase increased	79%	11%	11%	0%	0%	0%	21%
Vomiting	84%	11%	5%	0%	0%	0%	16%
White blood cell decreased	84%	11%	5%	0%	0%	0%	16%
Lymphocyte count decreased	84%	0%	11%	5%	0%	0%	16%
Dizziness	84%	16%	0%	0%	0%	0%	16%
Alanine aminotransferase increased	84%	5%	11%	0%	0%	0%	16%
Voice alteration	89%	0%	11%	0%	0%	0%	11%
Anemia	89%	0%	11%	0%	0%	0%	11%
Constipation	89%	5%	5%	0%	0%	0%	11%
Hyponatremia	89%	5%	0%	5%	0%	0%	11%
Peripheral sensory neuropathy	89%	11%	0%	0%	0%	0%	11%

Commonly reported treatment-related adverse events.
Abbreviation: NC/NA, no change from baseline/no adverse events.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Inactive because results did not meet primary endpoint

Maintenance olaparib prolongs progression-free survival (PFS) in patients with a germline *BRCA* mutation (gBRCAmt) and metastatic pancreatic ductal adenocarcinoma (mPDAC) [2] and has become a standard of care. Although there is no question that the approval of olaparib has provided a hope for patients with mPDAC, the scope of the benefit is limited to the 4% to 7% of the pancreatic cancer patients who carry gBRCAmt [8,9]. Preclinical studies showed that hypoxia and cediranib downregulate the expression of *BRCA1*, *BRCA2*, and *RAD51*, the key factors of homologous recombination DNA repair (HR), resulting in HR deficiency (HRD) and sensitivity to a PARP inhibitor in several tumor cell lines [1,5–7,10]. Consistent with these preclinical data, cediranib and olaparib has demonstrated superior progression-free survival and overall survival in women with platinum-sensitive ovarian cancer compared with olaparib monotherapy regardless of germline *BRCA* mutation status [11,12]. The question we asked in this study was if HRD phenotype could be induced in patients without germline *BRCA* mutation with an hypoxia-inducing, vascular endothelial growth factor receptor inhibitor, cediranib [13], resulting in a synthetic lethality with a poly-(ADP-ribose) polymerase inhibitor, olaparib.

We accrued patients without known mutations in *BRCA* genes in four disease-specific cohorts: pancreatic ductal adenocarcinoma (PDAC), non-small cell lung cancer, small cell lung cancer, and triple-negative breast cancer. Herein, we report the results from the safety and clinical activity analyses of PDAC cohort.

We found that the combination of cediranib 30 mg once daily plus olaparib 200 mg twice daily did not result in any objective response in patients with metastatic PDAC. Although six (32%) patients achieved stable disease as best overall response, including four patients with regression in the tumor burden, the median duration of disease control was only 3.1 months. This did not translate into durable disease control. Given the lack of clinically meaningful activity of cediranib and olaparib combination in patients with mPDAC without gBRCAmt, the accrual to the PDAC cohort was terminated early because of futility.

There are a few things to comment about the study populations. First, during enrollment of the PDAC cohort, the study intentionally excluded those with known germline *BRCA* mutation to test our hypothesis of cediranib-induced HRD phenotype. Although the testing was not required to prove, none of the study patients had known deleterious mutations in *BRCA* genes prior to enrollment. Second, the study population was heavily pretreated. Eighty-five percent of the patients had two or more lines of prior systemic therapies. Five (32%) patients had clinical progression prior to the first restaging scan in 2 months. The median overall survival of 3.4 months suggested that the patients were indeed in terminal stage of their disease. Plus, the median duration of drug exposure was less than 2 months, which undermines our confidence in sufficiency of treatment exposure to test the clinical activity of the regimen. Although the adverse event profile was consistent with prior reports, [11,12,14] adverse events such as fatigue, anorexia, and diarrhea requiring dose-interruption, and hypertension requiring close blood pressure monitoring and adjustment of antihypertensives made this regimen less easily tolerated and challenging for some patients (Table 1).

A potential explanation for lack of activity is that cediranib does not induce HRD phenotype in heavily pretreated patients with pancreatic cancer or does not sensitize the tumors to a PARP inhibitor. It should be noted that although the preclinical studies supporting our hypothesis testing were done in several tumor cell lines and

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xenograft models including lung, colon, breast, prostate, and cervical cancers [5–7,10], it was not tested in pancreatic cancer models.

Olaparib remains a treatment option for metastatic patients with PDAC with gBRCAmt as a maintenance therapy after a course of platinum-based chemotherapy without disease progression. We did not find any sign of clinically meaningful activity with the cediranib and olaparib combination in patients with heavily pretreated mPDAC and without gBRCAmt.

Future studies should focus on the patient population with a limit on prior lines of therapy in which patients can receive sufficient treatment exposure. The hypothesis of cediranib-induced HRD phenotype remains to be tested in other tumors. The analyses of clinical activities in other tumor cohorts are ongoing. Biomarkers analyses including circulating tumor DNA and angiogenesis markers in mPDAC patients are underway.

Cediranib and olaparib did not result in any clinically meaningful activity in patients with heavily pretreated metastatic pancreatic ductal adenocarcinoma without *BRCA* mutation.

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/ inventor/patent holder; (SAB) Scientific advisory board

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Table

Table 1. Common (>10%) treatment-related adverse events

AE terms	Grade 1 (*n* = 15), *n* (%)	Grade 2 (*n* = 13), *n* (%)	Grade 3 (*n* = 8), *n* (%)	Grade 4 (*n* = 0), *n* (%)	Total (*n* = 19), *n* (%)
Fatigue	7 (37)	7 (37)			14 (74)
Hypertension		6 (32)	3 (16)		9 (47)
Diarrhea	5 (26)	1 (5)			6 (32)
Thrombocytopenia	5 (26)	1 (5)			6 (32)
Nausea	2 (11)	2 (11)			4 (21)
Anorexia	4 (21)				4 (21)
AST increased	2 (11)	2 (11)			4 (21)
Alkaline phosphatase increased	2 (11)	2 (11)			4 (21)
Vomiting	2 (11)	1 (5)			3 (16)
Leukopenia	2 (11)	1 (5)			3 (16)
Lymphopenia		2 (11)	1 (5)		3 (16)
Dizziness	3 (16)				3 (16)
ALT increased	1 (5)	2 (11)			3 (16)
Hoarseness		2 (11)			2 (11)
Anemia		2 (11)			2 (11)
Constipation	1 (5)	1 (5)			2 (11)
Hyponatremia	1 (5)		1 (5)		2 (11)
Peripheral sensory neuropathy	2 (11)				2 (11)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase.

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