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Rucaparib Monotherapy in Patients With Pancreatic Cancer and a Known Deleterious BRCA Mutation.

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Rucaparib Monotherapy in Patients With Pancreatic Cancer and a Known Deleterious *BRCA* Mutation

abstract

Purpose Pancreatic cancer has a poor prognosis and limited treatment options. Approximately 9% of pancreatic cancers harbor a germline or somatic *BRCA1* or *BRCA2* (*BRCA1/2*) mutation. Because poly (ADP-ribose) polymerase inhibitors have significant activity in *BRCA1/2*-mutant ovarian and breast cancers, RUCAPANC investigated the efficacy and safety of rucaparib in *BRCA1/2*-mutant pancreatic cancer.

Patients and Methods RUCAPANC enrolled patients with measurable locally advanced/metastatic pancreatic cancer who had received one to two prior chemotherapy regimens. Patients received oral rucaparib (600 mg twice daily) until disease progression. The primary end point was objective response rate.

Results Nineteen patients were enrolled. Sixteen of 19 *BRCA1/2* mutations were germline; three were somatic. Patients had received a median of two prior chemotherapy regimens. Four patients achieved a response; two partial responses and one complete response (CR) were confirmed (objective response rate, 15.8%; 3 of 19), with an additional CR unconfirmed. The disease control rate (CR, partial response, or stable disease for ≥ 12 weeks) was 31.6% (6 of 19) in all patients and 44.4% (4 of 9) in those who had received one prior chemotherapy regimen. As prespecified in the protocol, enrollment was stopped because of an insufficient response rate among the first 15 patients. Treatment-emergent adverse events included nausea (63.2%) and anemia (47.4%). Grade ≥ 3 adverse events included anemia (31.6%), fatigue (15.8%), and ascites (15.8%). Secondary resistance mutations were detected in circulating free tumor DNA in two patients with a germline *BRCA2* mutation. These mutations are predicted to lead to the reversion of a somatic—not germline—mutation.

Conclusion Rucaparib provided clinical benefit to patients with advanced pancreatic cancer and a *BRCA1/2* mutation, and demonstrated an acceptable safety profile. Additional trials of rucaparib in this population are warranted.

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INTRODUCTION

Pancreatic cancer (PC) is projected to become the second leading cause of cancer death by 2020.[1] The majority of PCs are diagnosed at an advanced stage, precluding a surgical, curative approach. In the setting of advanced disease, FOLFIRINOX treatment (folinic acid [leucovorin], fluorouracil, irinotecan, and oxaliplatin) and gemcitabine in combination with nab-paclitaxel are the standards of care, with both demonstrating an improvement in overall survival compared with gemcitabine alone.[2,3] In the second-line setting, prospective data have shown modest results, with response rates to chemotherapy generally less than 20%,[4] including second-line FOLFIRINOX or fluorouracil with nanoliposomal irinotecan.[4-8] Additional therapeutic options are needed.

Approximately 9% of unselected PCs are associated with a germline or somatic mutation in *BRCA1* or *BRCA2* (*BRCA1/2*).[9,10] Cells with a deleterious *BRCA1/2* mutation and resultant homologous recombination deficiency are unable to repair DNA double-strand breaks reliably[11,12] and are thus sensitive to poly (ADP-ribose) polymerase (PARP) inhibition.[13-16] Studies have demonstrated clinical benefit with PARP inhibitors in clinical trials of germline *BRCA1/2*-mutant breast and ovarian cancer. Responses to

PARP inhibitors have also been seen in PC with germline *BRCA1/2* mutations; however, the number of patients treated in these series is low.

Rucaparib is an orally available and potent PARP inhibitor (Ki, < 1.4 nM) that has received US Food and Drug Administration approval for treatment of patients with relapsed, high-grade epithelial ovarian cancer associated with a germline or somatic *BRCA1/2* mutation after two prior lines of chemotherapy on the basis of data from two open-label studies.[17,18] In this study, we assessed the efficacy and safety of rucaparib monotherapy in patients with locally advanced or metastatic PC with a known deleterious *BRCA1/2* mutation.

PATIENTS AND METHODS

Patients

RUCAPANC, a global, phase II study, was conducted at seven centers in the United States and Israel between April 2014 and April 2016 and was sponsored by Clovis Oncology. The study design was approved by the independent review board at each participating site and was conducted according to the provisions of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. All patients provided written informed consent before participating in the trial.

Enrolled patients were men and women at least 18 years of age with histologically confirmed locally advanced or metastatic pancreatic adenocarcinoma with measureable disease and a known deleterious germline or somatic *BRCA1/2* mutation by local testing. Patients could have received up to two prior lines of chemotherapy in the locally advanced/metastatic setting, but could not have received prior therapy with a PARP inhibitor. Adjuvant chemotherapy was considered a prior line of therapy if disease progression occurred within 6 months of completion of treatment. Patients with GI disorders that would interfere with rucaparib absorption were excluded. Study patients received continuous therapy with oral rucaparib 600 mg tablets twice daily until disease progression or other reasons for discontinuation. Dose reductions and interruptions were permitted on development of toxicity. Patients could continue to receive rucaparib treatment beyond disease progression if the treating oncologist felt the patient was deriving clinical benefit.

Tumor and Plasma Analyses

Available archival tumor tissue was submitted for somatic sequencing analysis by Foundation Medicine (Cambridge, MA). To infer loss of heterozygosity (LOH), the log-ratio profile of sequencing data was segmented, and the allele frequencies of sequenced genome-wide single nucleotide polymorphisms were used to estimate the copy and minor allele frequency for each segment. All but four patients had a local laboratory test result for germline *BRCA1/2* mutation status at the time of study entry. After completion of the study, germline DNA from all patients underwent sequencing at Color Genomics (Burlingame, CA). Fifteen of the 16 germline mutations identified locally were detected and interpreted as pathogenic by Color Genomics. One germline alteration, reported as 10095delT by Myriad Genetics Laboratories (Salt Lake City, UT) as deleterious, was identified by Color Genomics (c.9867delT, p.Phe3289Leufs*24) and interpreted as likely benign. Pretreatment plasma specimens were collected on day 1 of cycle 1 for circulating tumor DNA (ctDNA) analysis by Foundation Medicine, which is a hybrid capture-based next-generation sequencing assay that sequences the coding regions of 62 cancer-related genes, including *BRCA1/2*. The assay identifies all classes of genetic alterations, including base substitutions, insertions, and deletions.[19]

Statistical Methods

The primary end point was the Response Evaluation Criteria in Solid Tumors (version 1.1; (RECIST) tumor response rate. Tumor assessments according to RECIST were performed at baseline, within 7 days before the start of every third cycle of treatment, and at the treatment discontinuation visit. Secondary efficacy end points included duration of response, progression-free survival, and overall survival. Safety results were reported by analysis of adverse events (AEs) and graded according to the Common Terminology Criteria for Adverse Events (version 4).

The safety analysis included all patients who received at least one dose of rucaparib. Efficacy

data are reported for the full analysis set. The study was closed in April 2016, and the last patient visit was on April 11, 2016. Statistical analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC). For inclusion in the objective response rate (ORR), a complete response (CR) or partial response (PR) per RECIST had to have been confirmed at least 28 days after the initial response was observed. A response that did not meet these criteria was considered unconfirmed. The Clopper-Pearson exact method was used to determine 95% CIs.

The data monitoring committee examined trial results after the first 15 patients were enrolled. No responses were seen at that time, and per the interim monitoring plan in the study protocol, accrual to the trial was halted; however, patients already consented to the trial and actively in screening were allowed to enroll.

RESULTS

A total of 19 patients were enrolled and received at least one dose of rucaparib. Table 1 lists the baseline demographic and tumor characteristics. The median age was 57 (range, 41 to 75) years, 57.9% of patients (11 of 19) were male, the median number of prior chemotherapy regimens for locally advanced/metastatic disease (excludes adjuvant treatment where progression occurred > 6 months after completion of treatment) was two (range, 1 to 3), 78.9% of patients (15 of 19) had an Eastern Cooperative Oncology Group performance status of 1, and 78.9% (15 of 19) had a *BRCA2* mutation. Three patients had somatic *BRCA2* mutations, whereas all other mutations were germline.

Outcomes

The confirmed ORR was 15.8% (95% CI, 3.4% to 39.6%; Table 2). Responses were observed in three of 19 patients, with two confirmed PRs and one confirmed CR; Figs 1 and 2). An additional patient received rucaparib for 72 weeks before transitioning to continue to receive rucaparib under an individual patient investigational new drug (IND) application after study closure. One week before discontinuing the study, scans showed an unconfirmed CR. As of December 1, 2017, this patient has been receiving rucaparib for > 160 weeks. The duration of confirmed responses was 36 weeks (PR), 19 weeks (CR), and 5 weeks (PR). Three of the four patients with either a confirmed or unconfirmed response had received only one prior therapy; none had tumors that had progressed with prior platinum therapy. The disease control rate (CR, PR, or stable disease [SD] for ≥ 12 weeks) was 31.6% (6 of 19; 95% CI, 12.6% to 56.6%) in all patients and 44.4% (4/9; 95% CI, 13.7% to 78.8%) in patients who had received only one prior chemotherapy regimen for locally advanced or metastatic disease. As prespecified in the protocol, enrollment was stopped because of lack of responses in the first 15 patients evaluated; the three confirmed responses occurred in the last four patients enrolled.

After study closure, one patient continued therapy on an individual patient IND application. Thirteen patients discontinued the study because of radiologic or clinical progression, two discontinued therapy within a week of beginning (one because of investigator decision, the other for an unknown reason), one discontinued because of AEs with simultaneous radiologic progression confirmed at the end of treatment, one discontinued because of an AE with ongoing SD, and one withdrew consent with an ongoing PR. Patients received rucaparib for a median of 57 days in the study (range, 2 to 504 days).

BRCA1 and BRCA2 Mutation Status

Sixteen of 19 patients had a germline *BRCA1/2* mutation. Specific mutations are listed in Appendix Table A1. Five of the 12 germline *BRCA2* mutations were c.5946deIT (6174delT), the common Ashkenazi Jewish founder mutation. Of the 16 tumors associated with a germline mutation, paired somatic sequencing was available in eight; the allelic frequency of the known germline mutant allele was between 41% and 53%. Two of these tumors also had a somatic *BRCA2* mutation (with an allelic frequency of 12% and 6%), suggesting a possible mechanism of biallelic inactivation. Three patients had a somatic *BRCA2* mutation (confirmed negative germline result), with allele frequencies of 14%, 14%, and 36%. Two of three tumors with a somatic *BRCA2* mutation had a confirmed objective response. The somatic *BRCA2* mutations were detected at allele frequencies similar to the *KRAS* driver mutations, supporting the clonality of these somatic *BRCA2* mutations.

Table 1. Baseline Characteristics (N = 19)

Parameter	Value
Median age (range), years	57 (41–75)
Male, No. (%)	11 (57.9)
Median time from initial diagnosis (range), months	16.4 (4–44)
Time since diagnosis, No. (%)*	
> 3–6 months	1 (5.3)
> 6–12 months	2 (10.5)
> 12–24 months	11 (57.9)
> 24 months	4 (21.1)
ECOG PS, No. (%)	
0	4 (21.1)
1	15 (78.9)
Histologic classification, No. (%)	
Adenocarcinoma	19 (100.0)
BRCA mutation type, No. (%)	
Germline	16 (84.2)
Somatic	3 (15.8)
BRCA mutation, No. (%)	
BRCA1	4 (21.1)
BRCA2	15 (78.9)
Prior surgery, No. (%)	10 (52.6)
No. of prior lines of chemotherapy, No. (%)	
1	9 (47.4)
2	9 (47.4)
3	1 (5.3)†
Prior platinum, No. (%)	
Yes	15 (78.9)
Oxaliplatin containing	13
Cisplatin containing	2
No	4 (21.1)
Gemcitabine	1
Gemcitabine/nab-paclitaxel	3
Progressed on prior platinum, No. (%)	
Yes	8 (42.1)
No	7 (36.8)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.

*Time since diagnosis was not provided for one patient (5.3%).

†One patient received FOLFIRINOX (folinic acid (leucovorin), fluorouracil, irinotecan, oxaliplatin), gemcitabine plus paclitaxel, and then an additional two cycles of FOLFIRINOX as bridging therapy while waiting for tumor analysis results to determine study eligibility. This was counted as three separate chemotherapy treatment regimens per the protocol-specified criteria.

Circulating Tumor DNA

Samples for ctDNA analyses at cycle 1, day 1 (before treatment with rucaparib) were available for 16 patients, and somatic mutations were detected in 11 patients (10 of whom had *KRAS* mutations; Appendix Table A1). In the five patients with samples analyzed for ctDNA without somatic mutations detected, two had SD, two had progressive disease, and one had a PR. Two patients were of particular note: both patients had a germline *BRCA2* mutation and a separate somatic *BRCA2* mutation noted. Both also had ctDNA sequencing that revealed a

Table 2. Investigator-Assessed Responses (RECIST) in Patients with Pancreatic Cancer and a *BRCA* Mutation (N = 19)

Response	No. (%)
CR	1 (5.3)
Unconfirmed CR/confirmed SD	1 (5.3)
PR	2 (10.5)
SD	3 (15.8)
PD	9 (47.4)
Not evaluable	3 (15.8)
Confirmed response rate (CR or PR)	3 (15.8)
Confirmed response rate (CR or PR) in patients with only one prior chemotherapy for locally advanced/metastatic disease	3 (33.3)*
Disease control rate (CR, PR, or SD ≥ 12 weeks)	
All patients	6 (31.6)
Patients with only one prior chemotherapy regimen for locally advanced/metastatic disease	4 (44.4)*

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
*n = 9.

reversion mutation for the somatic (but not the germline) variant. In the first patient (patient 5), ctDNA analysis detected the germline *BRCA2* mutation c.7060C>T (allele frequency, 48%), the somatic alteration c.1499_1499delG (allele frequency, 22%), and the secondary somatic mutation c.1416_1420delGCATC (allele frequency, 19%) that restored the open reading frame of the *BRCA2* gene. This patient's tumor progressed on rucaparib at the time of the first assessment after two 28-day cycles. Prior treatment included FOLFIRINOX. In the second patient (patient 14), ctDNA analysis detected the germline *BRCA2* mutation c.5946deIT (allele frequency, 46%), the somatic alteration c.1387delA (allele frequency, 13%), and the secondary somatic mutation c.1355_1380delTACCAAAATCAGAGAAGCCATTAAAT, which also restored the open reading frame, but seemed to be subclonal (with an allelic frequency of only 1%). This patient, who had also previously received FOLFIRINOX, developed significant clinical progression at day 18, although target lesions were stable.

Assessment of Allele-Specific LOH

Tumor was available for analysis in 10 patients. In only two tumor specimens was there sufficient tumor content to infer allele-specific LOH. In

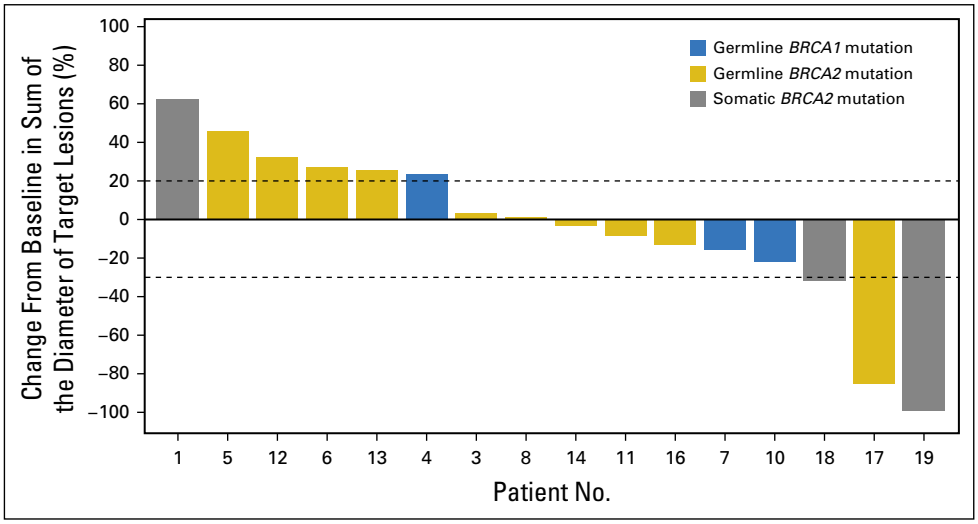

Fig 1. Best response in target lesions. Only patients with baseline and at least one postbaseline tumor assessment were included (n = 16). Each bar represents a single patient. Patients with zero percent change from baseline are shown as 0.5 for visual clarity.

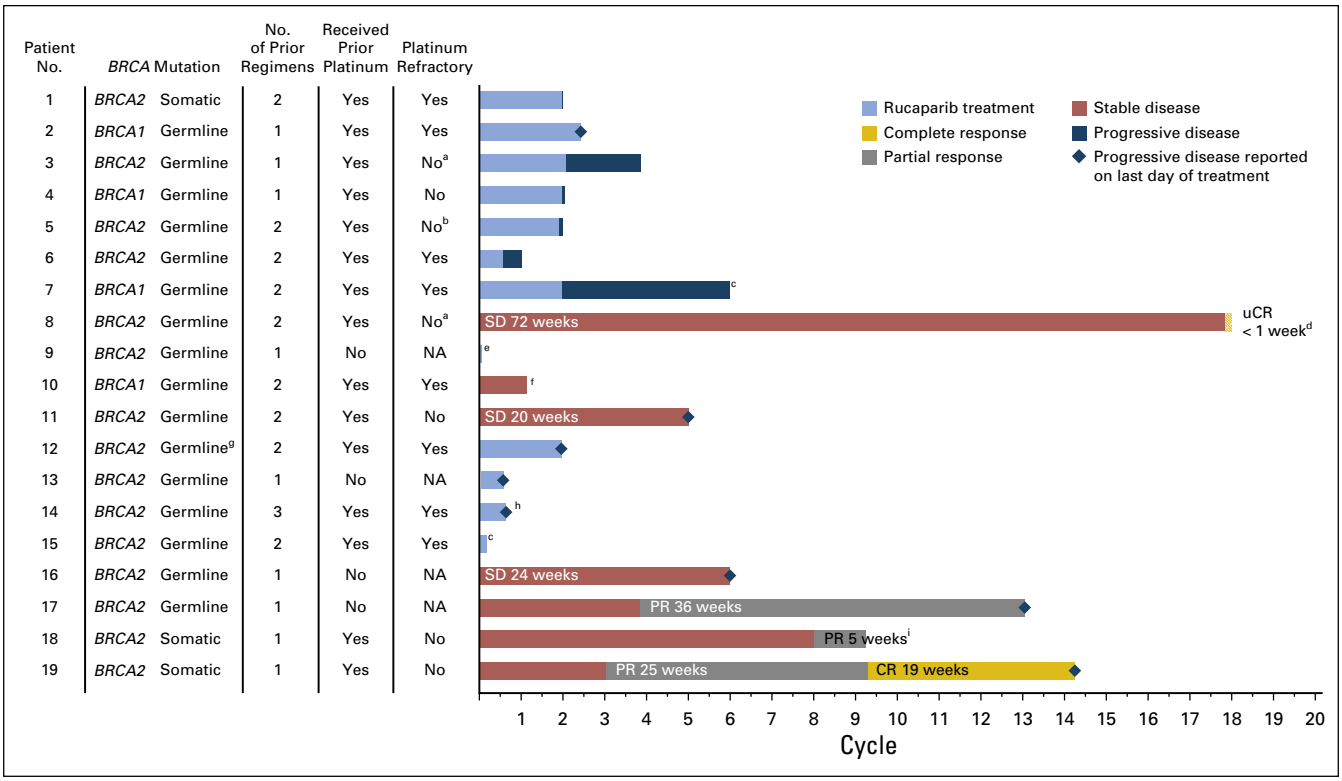

Fig 2. Treatment duration for patients with pancreatic cancer and a *BRCA* mutation (N = 19). (a) Patient discontinued treatment because of intolerability. (b) Patient progressed after more than 3 months of platinum-based therapy. (c) Patient discontinued treatment for other reason. (d) Study was terminated, patient was rolled over to an individual patient investigational new drug application. (e) Patient discontinued because of investigator decision. (f) Patient discontinued because of adverse events (AEs; grade 3 fatigue and grade 4 thrombocytopenia); best response of stable disease (SD) was ongoing after the last day of treatment. (g) Reported as 10095delT by Myriad Genetics Laboratories (Salt Lake City, UT) and as deleterious, identified by Color Genomics (c.9867delT, p.Phe3289Leufs*24; Burlingame, CA), and interpreted as likely benign. (h) Patient discontinued because of AEs; progressive disease was noted after discontinuation of treatment. (i) Patient withdrew consent; partial response (PR) was confirmed with a scan after last treatment day. Bars represent duration of rucaparib treatment of individual patients; plot is sorted by treatment start date. CR, confirmed response; uCR, unconfirmed complete response.

each of these, LOH was observed at *BRCA1* and *BRCA2* loci, respectively, with *BRCA* mutations inferred as homozygous. The first patient (patient 2) had a germline *BRCA1* mutation and was nonevaluable because there was no post-baseline tumor assessment available. However, the patient was noted to have clinical progression on day 67. The second patient had a somatic BRCA2 mutation (c.1748T>A) and had a CR as best response (patient 19).

Safety

All patients had at least one treatment-emergent AE (Table 3). Common treatment-emergent AEs included nausea (63.2% [12 of 19]) and anemia (47.4% [9 of 19]). Common treatment-emergent grade ≥ 3 AEs included anemia (31.6% [6 of 19]), fatigue (15.8% [3 of 19]), and ascites (15.8% [3 of 19]). Four patients (21.1%) required a dose reduction. AEs leading to dose reduction included an increase in ALT or AST, fatigue, neutropenia, and thrombocytopenia (5.3% [1 of 19] each). One patient discontinued treatment because of fatigue and thrombocytopenia, both assessed as related to rucaparib by the investigator. Another patient discontinued treatment because of upper gastrointestinal hemorrhage and acute kidney injury, both of which were deemed to be unrelated to rucaparib by the investigator. This patient also had progressive disease noted at the same time as the AEs that led to discontinuation and subsequent death. Two other patients died as a result of disease progression.

DISCUSSION

This study tested the efficacy of a single-agent PARP inhibitor, rucaparib, in patients with advanced PC with a known deleterious *BRCA1/2* mutation. A total of 19 patients were enrolled,

Table 3. Treatment-Emergent Adverse Events (N = 19)

Event	Incidence, No. (%)	
	Any Grade	Grade 3-4
Nausea	12 (63.2)	2 (10.5)
Anemia	9 (47.4)	6 (31.6)
Abdominal pain	7 (36.8)	2 (10.5)
Fatigue	7 (36.8)	3 (15.8)
Increased ALT/AST	6 (31.6)	2 (10.5)
Decreased appetite	6 (31.6)	0
Vomiting	6 (31.6)	2 (10.5)
Diarrhea	5 (26.3)	0
Thrombocytopenia*	5 (26.3)	2 (10.5)
Ascites	4 (21.1)	3 (15.8)
Constipation	4 (21.1)	0
Dysgeusia	4 (21.1)	0
Peripheral neuropathy	4 (21.1)	0

NOTE. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4).

*Includes adverse events of thrombocytopenia and decreased platelet count.

with a confirmed ORR of 16% and an observed disease control rate of 32%. Although the study was stopped at the interim analysis, the responses seen in *BRCA*-mutant PCs were durable and clinically significant. Our findings suggest that there may be a role for PARP inhibition in patients with a *BRCA1/2* mutation, particularly in those whose disease has not progressed while taking prior platinum therapy.

Although this was a single-arm study, making comparisons to other agents difficult, the clinical relevance of our results merits comparison with other current standards of care for this patient population. Even in the front-line setting, both chemotherapy combinations of FOLFIRINOX and gemcitabine with nab-paclitaxel demonstrate response rates of 32% and 23%, respectively. Importantly, the only approved chemotherapy combination in the second-line setting, fluorouracil with nanoliposomal irinotecan, had an overall response rate of 7.7% in the pivotal registration study.[8] Other small single-center studies investigating FOLFIRINOX or other chemotherapy combinations in a refractory population show similarly low response rates, reflecting the known chemoresistance of this disease. Furthermore, as treatment options improve for PC, patients are even able to move beyond second-line therapy, for which there are no standard of care options. This underscores the importance of looking outside of chemotherapy options, particularly in patients with potentially targetable mutations.

Previous small studies investigating PARP inhibition in *BRCA*-mutated PC have shown similar efficacy. The response rate of single-agent olaparib in patients with metastatic PC harboring a germline *BRCA1/2* mutation who had received prior chemotherapy was 22%.[20]

A phase II study of veliparib alone in 16 previously treated patients with *BRCA*-mutated PC demonstrated single-agent activity, with 25% of patients having SD for at least 4 months. Analysis is ongoing to understand the role platinum sensitivity played in these four patients.[21] When considered with the prior studies, these trials should provide insight into the clinical utility of single-agent PARP inhibition in patients with PC and a known *BRCA1/2* mutation.

In this study, responses to rucaparib were seen in individuals harboring a germline or somatic *BRCA1/2* mutation. The allelic frequencies of *BRCA2* for the two tumors with a somatic mutation and a confirmed response were 36% and 14%. Although the results were based on only two patients, these data suggest that caution should be exercised regarding the use of allele frequency as a predictor of response. Because of significant stromal infiltration in PC, assessing allele frequency of somatic tumor alterations may be challenging.

None of the four patients with a confirmed or unconfirmed response had experienced disease progression on prior platinum therapy (one had never received platinum), and three of the four patients had only received one prior chemotherapy regimen for locally advanced or metastatic disease. This finding highlights the important question of the role of platinum sensitivity in the setting of advanced/metastatic PC and underscores a potential role for rucaparib as a treatment for patients whose tumors are not platinum refractory. Similar findings were noted in patients with advanced ovarian cancer treated with olaparib, because the highest response rates were noted in patients who were deemed platinum sensitive rather than resistant or refractory.[22] This will need to be investigated in a larger clinical study. The majority of patients in this study had received oxaliplatin. Additional study is also needed on whether the type of prior platinum (oxaliplatin *v* cisplatin) contributes to PARP inhibitor resistance.

Secondary mutations that likely confer resistance have been observed in patients with ovarian or prostate cancer who harbor a *BRCA1/2* mutation and whose disease has progressed while receiving platinum chemotherapy or PARP inhibitors; however, these reports have demonstrated reversion mutations that have restored the open reading frame in the vicinity of the germline mutation. The majority (but not all) of *BRCA1/2*-mutant breast and ovarian cancers have allele-specific LOH[23]; however, the loss of the second allele is most commonly due to copy neutral LOH and rarely due to a somatic mutation. That the two reversion mutations noted in this study occurred with the somatic mutation and not the germline mutation is interesting and bears additional study. Both of these patients had previously been treated with oxaliplatin. Several studies have demonstrated the presence of reversion mutations in patients previously treated with chemotherapy, particularly platinum based.[24-27] Our study has several limitations, including a small sample size and lack of corresponding somatic sequencing and ctDNA analysis for some patients.

Rucaparib is a well-tolerated PARP inhibitor that could be considered in patients with advanced PC with known *BRCA1/2* mutations who have received prior chemotherapy. Consideration should be given to use of this therapy for treatment of patients whose tumors have not progressed while receiving prior platinum therapy. Future studies should focus on better understanding of the sequencing of PARP inhibitor treatment and potential maintenance therapy, as well as potential predictors of resistance to therapy.

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Appendix

Table A1. *BRCA* Mutation, Investigator-Assessed Responses (RECIST), and Baseline ctDNA Sequencing Results (N = 19)

Patient No.	BRCA Mutation	BRCA Mutation Type	BRCA Alteration	Best Response Target Lesions	Primary Alterations Detected by ctDNA Sequencing (percent-reads, coverage)	Alterations Detected By Tumor Tissue Sequencing (percent-reads, coverage)
1	*BRCA2*	Somatic	c.7805+2T>C	PD	None detected	ARID1A_c.3826C>T_p.R1276* (0.09,524)
						KRAS_c.35G>A_p.G12D (0.12,518)
						TP53_c.796G>T_p.G266* (0.1,534)
						BRCA2_c.7805+2T>C (0.14,304)
						STK11_c.1062C>G_p.F354L (0.58,370)
2	*BRCA1*	Germline	c.807_808insCATGTGGAGC (943ins10)	NE	KRAS_c.35G>A_p.G12D (0.34,2729)	KRAS_c.35G>A_p.G12D (0.23,596)
					TP53_c.844C>T_p.R282W (0.39,4186)	TP53_c.844C>T_p.R282W (0.27,561)
					BRCA1_c.807_808insCATGTGGAGC_ p.T276fs*14 (0.59,8535)	BRCA1_c.807_808insCATGTGGAGC_p. T276fs*14 (0.47,593)
					CDKN2A_ c.19_34delAGCAGCATGGAGCCTT_ p.S7fs*14 (0.16,2901)	CDKN2A_c.19_ 34delAGCAGCATGGAGCCTT_p.S7fs*14 (0.06,131)
						PIK3C2B_c.2150C>T_p.P717L (0.53,541)
						SPTA1_c.5431C>T_p.R1811* (0.07,609)
3	*BRCA2*	Germline	c.5946deIT (6174delT)	SD	BRCA2_c.5946_5946delT_p.S1982fs*22(0.47,4238)	CDKN2A_c.130_131insA_p.Y44fs*1 (0.16,287)
						BRCA2_c.5946_5946delT_p.S1982fs*22 (0.47,729)
						KRAS_c.34G>C_p.G12R (0.1,652)
						TP53_c.993+1G>A (0.11,567)
4	*BRCA1*	Germline	c.4964_ 4982delCTGGCCTGACCCCAGAAGA (5083del19)	PD	NA	NA

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Table A1. *BRCA* Mutation, Investigator-Assessed Responses (RECIST), and Baseline ctDNA Sequencing Results (N = 19) (Continued)

Patient No.	BRCA Mutation	BRCA Mutation Type	BRCA Alteration	Best Response Target Lesions	Primary Alterations Detected by ctDNA Sequencing (percent-reads, coverage)	Alterations Detected By Tumor Tissue Sequencing (percent-reads, coverage)
5	*BRCA2*	Germline	c.7060C>T	PD	KRAS_c.35G>A_p.G12D (0.37,3974) BRCA2_c.7060C>T_p.Q2354* (0.48,4520) BRCA2_c.1416_1420delGCATC_p.Q472fs*2 (0.19,7416)* BRCA2_c.1499_1499delG_p.G500fs*9 (0.22,7179)†	NA
6	*BRCA2*	Germline	c.6541dupC	PD	KRAS_c.35G>T_p.G12V (0.07,3953) BRCA2_c.6641_6642insC_p.Y2215fs*10 (0.52,8344)	NA
7	*BRCA1*	Germline	c.213-11T>G	SD	KRAS_c.35G>A_p.G12D (0.01,3630) TP53_c.659A>G_p.Y220C (0.01,4513)	NA
8	*BRCA2*	Germline	c.5946deIT (6174delT)	SD	NA	NA
9	*BRCA2*	Germline	c.2287delC (2515delC)	NE	KRAS_c.35G>T_p.G12V (0.3,2598) KRAS_c.34G>C_p.G12R (0.3,2526) TP53_c.493C>T_p.Q165* (0.48,2545) BRCA2_c.2287_2287delC_p.H763fs*9(0.73,4933) CDKN2A_c.1_158del161_p.M1fs*25 (0.06,3045)	NA
10	*BRCA1*	Germline	c.66_67delAG (185delAG)	SD	KRAS_c.35G>A_p.G12D (0.01,3445) TP53_c.524G>A_p.R175H (0.01,4668) BRCA1_c.66_67delAG_p.E23fs*17 (0.44,5204)	BRCA1_c.66_67delAG_p.E23fs*17 (0.48,489)

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Table A1. *BRCA* Mutation, Investigator-Assessed Responses (RECIST), and Baseline ctDNA Sequencing Results (N = 19) (Continued)

Patient No.	BRCA Mutation	BRCA Mutation Type	BRCA Alteration	Best Response Target Lesions	Primary Alterations Detected by ctDNA Sequencing (percent-reads, coverage)	Alterations Detected By Tumor Tissue Sequencing (percent-reads, coverage)
11	*BRCA2*	Germline	c.3847 _3848delGT	SD	BRCA2_c.3847_3848delGT_p.V1283fs*2 (0.47,5414)	NA
12	*BRCA2*	Germline	c.9867delT (10095deIT)‡	PD	BRCA2_c.9867_9867delT_p.F3289fs*24 (0.47,5002)	NA
13	*BRCA2*	Germline	c.5645C>A	PD	BRCA2_c.5645C>A_p.S1882* (0.57,4306) CDKN2A_c.130_131insA_p.Y44fs*1 (0.07,8295) KRAS_c.35G>A_p.G12D (0.07,2768) TP53_c.673-2A>G_ (0.1,2358)	NA
14	*BRCA2*	Germline	c.5946deIT (6174delT)	SD	KRAS_c.34G>C_p.G12R (0.24,2333) BRCA2_c.5946_5946delT_p.S1982fs*22 (0.46,6604) BRCA2_c.1355_1380delTACCAAAATCAGAGAAGCCATTAAAT_p.L452fs*7 (0.01,6928)* BRCA2_c.1387_1387delA_p.T463fs*3 (0.13,6757)†	KRAS_c.34G>C_p.G12R (0.13,390) SF3B1_c.2098A>G_p.K700E (0.14,297) SMAD4_c.257G>T_p.G86V (0.19,279) BRCA2_c.5946_5946delT_p.S1982fs*22 (0.41,379) BRCA2_c.1387_1387delA_p.T463fs*3 (0.12,364) CHEK2_c.444+2T>C (0.1,341) RNF43_c.849+1G>A (0.25,253)
15	*BRCA2*	Germline	c.2426T>G_p.Leu809Stop	NE	KRAS_c.35G>A_p.G12D (0.4,3719) TP53_c.844C>T_p.R282W (0.42,4132) BRCA2_c.2426T>G_p.L809* (0.64,2289)	KRAS_c.35G>A_p.G12D (0.11,818) TP53_c.844C>T_p.R282W (0.18,774) PTPN11_c.214G>A_p.A72T (0.02,693) BRCA2_c.2426T>G_p.L809* (0.53,475)

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Table A1. *BRCA* Mutation, Investigator-Assessed Responses (RECIST), and Baseline ctDNA Sequencing Results (N = 19) (Continued)

Patient No.	BRCA Mutation	BRCA Mutation Type	BRCA Alteration	Best Response Target Lesions	Primary Alterations Detected by ctDNA Sequencing (percent-reads, coverage)	Alterations Detected By Tumor Tissue Sequencing (percent-reads, coverage)
16	*BRCA2*	Germline	c.5946deIT (6174delT)	SD	BRCA2_c.5946_5946delT_p.S1982fs*22 (0.48,8316)	NA
					JAK2_c.1849G>T_p.V617F (0.03,3046)	
17	*BRCA2*	Germline	c.5946deIT (6174delT)	PR	BRCA2_c.5946_5946delT_p.S1982fs*22 (0.47,8836)	BRCA2_c.5946_5946delT_p.S1982fs*22 (0.51,386)
						KRAS_c.34G>C_p.G12R (0.1,501)
						SMAD4_c.1558G>T_p.E520* (0.13,595)
18	*BRCA2*	Somatic	c.976_977insA	PR	NA	NA
19	*BRCA2*	Somatic	c.1748T>A	CR	KRAS_c.35G>A_p.G12D (0.0,1829)	KRAS_c.35G>A_p.G12D (0.28,529)
						TP53_c.490A>G_p.K164E (0.35,475)
						BRCA2_c.1748T>A_p.L583* (0.36,356)
						CDKN2A_c.151-2A>C (0.39,325)
						CUL3_c.1486_1487del138_p.V496fs*6 (0.2,455)
						NF2_c.805A>T_p.K269* (0.11,338)

NOTE. Sequencing analysis of ctDNA and tumor tissue was performed by Foundation Medicine.

Abbreviations: CR, complete response; ctDNA, circulating tumor DNA; NA, not available; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

*Reversion mutation.

†Primary somatic mutation.

‡Originally reported as 10095delT and deleterious by Myriad Genetics Laboratories. The same alteration, but known as c.9867delT, p.Phe3289Leufs*24 was interpreted as likely benign by Color Genomics.