Published in final edited form as:

Eur J Cancer. 2018 January ; 89: 19–26. doi:10.1016/j.ejca.2017.11.004.

Phase II Trial of Veliparib in Patients with Previously-Treated BRCA-Mutated Pancreas Ductal Adenocarcinoma

Maeve A. Lowery^{1,2}, David P. Kelsen^{1,2}, Marinela Capanu¹, Sloane C. Smith¹, Jonathan W. Lee¹, Zsafia K Stadler^{1,2}, Malcolm J Moore³, Hedy L. Kindler⁴, Talia Golan^{5,7}, Amiel Segal⁶, Hannah Maynard¹, Ellen Hollywood¹, MaryEllen Moynahan^{1,2}, Erin E. Salo-Mullen¹, Richard Kinh Gian Do¹, Alice P. Chen⁸, Kenneth H. Yu^{1,2}, Laura H. Tang¹, Eileen M. O'Reilly^{1,2}

¹Memorial Sloan Kettering Cancer Center, New York, NY,

²Weill Cornell Medical College, New York, NY,

³Princess Margaret Cancer Center- University Health Network, Toronto,

⁴University of Chicago Medical Center, Chicago, IL,

⁵Sheba Medical Center, Tel Hashomer, Israel,

⁶Share Zedek Medical Center, Jerusalem, Israel,

⁷Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel,

⁸National Cancer Institute, Bethesda, MD.

Abstract

Purpose—BRCA-associated cancers have increased sensitivity to PARP inhibitors (PARPi). This single arm, non-randomized, multicenter phase II trial evaluated the response rate of veliparib in patients with previously-treated BRCA1/2 or PALB2 mutant pancreatic adenocarcinoma (PDAC).

Methods—Patients with stage III/IV PDAC and known germline BRCA 1/2 or PALB2 mutation, 1–2 lines of treatment, ECOG 0–2, were enrolled. Veliparib was dosed 300mg twice-daily (N=3), then 400mg BD (N=15) days 1–28. The primary endpoint was to determine the response rate of veliparib; secondary endpoints included progression-free survival (PFS), duration of response, overall survival (OS) and safety.

Results—Sixteen patients were enrolled; male N=8 (50%). Median age was 52 years (range 43–77). Five (31%) had a BRCA1 and 11 (69%) had a BRCA2 mutation. Fourteen (88%) patients had received prior platinum-based therapy. No confirmed partial responses were seen: 1 (6%)

Corresponding author: Eileen M. O'Reilly, M.D. Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, NY 10065, Tel: 646 888-4182, Fax: 646 888-4254, oreillye@mskcc.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclaimers: None

Conflict of Interest

No authors have declared a conflict of interest.

unconfirmed PR was observed at 4 months with disease progression (PD) at 6 months; 4 (25%) had stable disease, while 11 (69%) had PD as best response including 1 with clinical PD. Median PFS was 1.7 months (95% CI 1.57– 1.83) and median OS was 3.1 months (95% CI 1.9– 4.1). Six (38%) patients had grade 3 toxicity including fatigue (N=3), hematologic (N=2) and nausea (N=1).

Conclusions—Veliparib was well-tolerated but no confirmed response was observed although 4 (25%) patients remained on study with SD for 4 months. Additional strategies in this population are needed and ongoing trials are evaluating PARP inhibitors combined with chemotherapy (NCT01585805) and as a maintenance strategy (NCT02184195).

Keywords

Pancreatic cancer; veliparib; BRCA; germline; PARP inhibitor; platinum Data from this trial has been presented at the Gastrointestinal Cancers Symposium 2015

Introduction

Patients with germline BRCA1/2 mutations (BRCA+) are at increased lifetime risk for the development of pancreatic adenocarcinoma (PDAC), estimated at 2 –3.5 times that of the general population[1]. Up to 1 in 10 cases occur in the setting of a hereditary cancer predisposition syndrome, of which BRCA+ are the most common[2, 3]. In a series of patients of Ashkenazi ancestry unselected for family history with resected PDAC, 5.5% were found to be BRCA+, while in a subsequent series evaluating 211 Ashkenazi Jewish patients with a personal history of breast cancer and a family history of pancreatic adenocarcinoma, 30 (14.2%) were BRCA+[4, 5]. Among 159 patients with PDAC and a family history of malignancy who pursued genetic testing at Memorial Sloan Kettering Cancer Center (MSKCC), BRCA+ prevalence was 13.7% in Ashkenazi Jewish (AJ) patients (N=95) and 7.1% in non-AJ patients (N=56)[6, 7]. More recently, germline mutations in the gene *PALB2*, which encodes a protein critical for the initiation of homologous recombination (HR), have also been identified in patients with PDAC and a personal or family history of breast cancer[8].

Overall, BRCA+ population represents a small but significant number of patients with PDAC, in whom the identification of an inherited cancer predisposition syndrome may be potentially exploited for therapeutic benefit. Superior overall survival (OS) has been observed for BRCA+ patients with advanced PDAC treated with platinum versus those treated with non-platinum chemotherapies (22 vs 9 months; p=0.039), making platinum based therapy a preferred choice for these patients[9, 10]. Poly(ADP-ribose) polymerase inhibitors (PARPi) target defective DNA repair by blocking PARP-mediated repair of single strand breaks, leading to DSBs which are repaired by the error prone NHEJ pathway in BRCA1/2 mutant cells. These cells are thus unable to maintain genomic integrity, resulting in cell death via a synthetic lethal effect[11]. A prospective phase II study of the PARPi, olaparib, in patients with BRCA+ malignancies enrolled N= 23 patients with PDAC, of whom 22% had either a complete or partial response to treatment with single agent olaparib[12]. Additionally, 35% of PDAC patients demonstrated stable disease for 8 weeks. Overall survival at one year was 41% for patients with BRCA+ PDAC on this trial[13]. Olaparib has recently obtained FDA approval for treatment of recurrent BRCA+

ovarian cancer, following 3 lines of chemo and is FDA and EMEA approved for a maintenance indication in second remission in the same population.

Despite initial sensitivity to platinum agents however, resistance to platinum drugs emerges as a result of several potential mechanisms, including the development of secondary mutations in BRCA1/2 which restore the ability to repair DNA by HR[14]; the ability to exploit HR deficiency for therapeutic effect in BRCA+ patients who have progressed on prior chemotherapy therefore remains unclear.

Veliparib is an oral potent inhibitor of PARP 1/2, which has demonstrated single agent preclinical and clinical activity in several germline BRCA+ cancers including breast and prostate cancer[15]. This phase II study evaluated the safety and efficacy of the PARP inhibitor veliparib in patients with BRCA+ PDAC, with progressive disease on 1–2 prior chemotherapy regimens. This study was designed in conjunction with the Cancer Therapeutics and Evaluation Program (NCI CTEP) and the Lustgarten Foundation.

Patients and Methods

Study Design and Treatment

This was a prospective, multicenter, non-randomized phase II study. The primary endpoint of the study was to evaluate the response rate according to RECIST 1.1 of single agent veliparib in previously-treated BRCA+ PDAC. Secondary endpoints were to evaluate progression-free survival, disease control rate, overall survival and duration of response, and to describe the safety and tolerability of veliparib in this population of BRCA+ PDAC. The study was conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by the institutional review board at every center. All patients provided written informed consent.

Fifteen- 33 patients were planned for this study. Patients were treated continuously with oral veliparib 400 mg twice per day until disease progression. In the event of toxicity, dose reductions and interruptions were permitted.

Patient Population

Individuals (age >18 years) with a confirmed germline loss-of-function *BRCA1* or *BRCA2* mutation deemed deleterious by central review and locally advanced or metastatic pancreatic adenocarcinoma were enrolled. Eligibility criteria also included the presence of measurable disease according to RECIST (version 1.1), Eastern Cooperative Oncology Group (ECOG) performance status of 0– 2. Patients were permitted to have had up to two prior treatment regimens for PDAC, one of which may have been given in the adjuvant setting. Patients with a prior malignancy were eligible if it was successfully treated and the patient required no ongoing active treatment. Patients were required to have normal organ and marrow function as defined by: absolute neutrophil count (ANC) > 1,500/mcL, hemoglobin > 9.0 mg/dL, platelets > 100,000/mcL, total bilirubin < 2 X institutional upper limit of normal (ULN), AST/ALT < 2.5 X institutional ULN, unless evidence of liver metastases, in which case AST/ALT must be < 5 X institutional ULN, and creatinine < 1.5 X ULN. Females of child-bearing potential required a negative blood or urine pregnancy test. Patients with a known

active infection, e.g. hepatitis B, hepatitis C, or HIV positive patients who did not have evidence of significant immune compromise, were eligible.

Patients were excluded for the following: receipt of prior PARP inhibitor; receipt of systemic therapy or radiotherapy within 3 weeks of study, persistent therapy-related toxicities, life expectancy < 3 months, and symptomatic uncontrolled brain metastases. Patients with a history of or active seizures or allergic reactions attributed to compounds of similar composition to veliparib or other agents were also excluded. Additionally, patients with uncontrolled infection, cardiovascular disease, or psychiatric illness were ineligible.

Biostatistical Design

The primary endpoint of the study was to evaluate the response rate of single agent veliparib in previously-treated BRCA+ PDAC. Tumor assessments according to RECIST were performed at baseline and every two cycles (28 days per cycle). A Simon two stage design was employed, assuming an unacceptable response rate of 10% and a promising rate of 28% with type I and II errors of 10% each. Fifteen patients were planned for enrolment in the first stage, and if 2 or more responses observed, a further 18 patients would be enrolled for a total of N=33 patients.

Secondary endpoints included progression-free survival (PFS), disease control rate, OS and duration of response, and to describe the safety and tolerability of veliparib in this population of BRCA+ PDAC.

Statistical analyses were performed with SPSS software. Patients with a best RECIST response of complete or partial response had to have a confirmed response > 28 days later. A complete or partial response that was not maintained at 28 days was considered unconfirmed. Response was assessed by central review of imaging. PFS and OS were estimated using the Kaplan-Meier method.

Results

Patient Characteristics

A total of 16 (8 male, 8 female) patients with BRCA+ PDAC were enrolled and treated between May 2012 and September 2015 were enrolled and treated at 5 centers in Israel, Canada, and the United States between May 2012 and September 2014. Collaborating sites included University of Chicago Medical Center, Princess Margaret Cancer Center, Toronto, Share Zedek Medical Center and Sheba Medical Center, Israel. Five (31%) patients were BRCA1+ and 11 (69%) were BRCA2+. Fifteen patients had AJCC stage IV disease and 1 patient had locally advanced AJCC stage 3. ECOG performance status was 0 in N= 6 (38%) and ECOG 1 in N= 8 (50%). Baseline demographic information is summarized in Table 1.

All except 2 patients (12.5%) had previously been treated with platinum therapy and one of these two patients had been treated with irinotecan/mitomycin (both DNA-damaging agents). Nine patients (56%) had received 2 prior lines of treatment. Of 14 who had had prior platinum therapy, 9 (64.3%) had discontinued for disease progression, while reason for discontinuation was unclear in 1 (7.1%) patient who had received just one month of

platinum therapy. The best response to prior platinum therapy was a partial response lasting 6 months. Four (28.6%) patients had discontinued platinum therapy for toxicity. Median duration of chemotherapy before entering study treatment was 11 months (range 5 – 21).

Treatment

The study was closed after the first stage as insufficient activity was observed per Simon two-stage design. The starting dose of veliparib was 300 mg BID for the first 3 patients and 400mg BID for the remainder of the patients related to emerging single agent data from other studies. Of specific note of the 16 patients enrolled, one patient received only 12 days of veliparib and withdrew early. This patient was deemed inevaluable for the primary endpoint per pre-specified protocol criteria and was replaced. This patient was evaluable for toxicity. The best observed response was stable disease in 5 patients (31%) and progressive disease (PD) in 11 patients (69%); clinical PD 1 patient, radiographic PD 10 patients. One patient who had received prior single agent gemcitabine only had an unconfirmed PR at cycle 2 week 4 and progression of disease at the end of month 6. No confirmed partial response was observed among 16 patients; 4 patients (25%) had stable disease 8 weeks, all of whom had been exposed to a prior platinum agent. Tumor response information is summarized in Table 2 and Figure 3.

The median PFS was 1.7 months (95% CI 1.57– 1.83). This information is depicted in Figure 1. One patient (6%) was progression-free at 6 months and progressed after 9.5 months of study treatment. This particular patient had had 1 line of prior therapy with FOLFIRINOX and had experienced a PR for 6 months to this prior therapy.

Patient Survival

Median overall survival from start of study treatment was 3.1 months (95% CI 1.9– 4.1 months), 2 patients (12%) were alive 12 months from start of study treatment. Figure 2 depicts the Kaplan-Meier curve for overall survival. No difference in median PFS or OS was observed between patients who had progressed on prior platinum based chemotherapy compared to those who had not. Five patients (31%) went on to receive a subsequent line of systemic therapy.

Toxicities

Grade 3–4 adverse events (AE's) occurred in 11 (69%) patients: 6 (54.5%) patients experienced grade 3–4 toxicity considered causally related to veliparib; fatigue (N=4) , thrombocytopenia (N=1), lymphopenia (N=1) , nausea, vomiting, hyponatremia (N1). Table 3 summarizes grade 3–4 AE's.

Discussion

This single arm phase II study evaluated the use of the PARPi veliparib in patients with confirmed germline BRCA+ previously treated PDAC. No confirmed radiographic responses were observed, although stable disease 8 weeks was seen in 25% of patients. Although veliparib was well tolerated, we do not feel this was a sufficient signal of activity to warrant further investigation of single agent veliparib in this population. This is in contrast to

previously reported findings by Kaufman et al, who observed a response rate of 22% in N=23 patients with BRCA+ PDAC treated on a phase II single arm study with olaparib at similar schedule as utilized in this study[13]. In addition, median overall survival from start of study treatment was just 2.9 months in our study, compared to 9.8 months in that study. Patients enrolled in the study by Kaufman et al had received an average of 2 prior lines of chemotherapy, and 15 patients (65%) had received prior platinum therapy. In this latter subset a 20% response rate was evident although unclear whether resistance on prior platinum therapy had been observed. Our results also contrast with findings by Domchek et al[16], who observed a response rate of 11% in 19 patients with BRCA+ PDAC (included both somatic and germline BRCA mutations) in a phase II single arm study with single agent rucaparib. Of additional note, best results in this latter study were evident in less pre-treated patients.

Taking the collective data thus far, the presence of a BRCA+ mutation in isolation is not sufficient to predict response to PARP inhibition in patients with advanced pre-treated PDAC. Further, there may be intrinsic differences between PARP inhibitors that account for the differing observations between studies. Notably, in our data set the one patient with an unconfirmed PR had not received prior platinum chemotherapy, and had been treated with only 3 months of single agent gemcitabine before entering the study. This implies that the evolution of molecular changes that occur in a tumor during chemotherapy with DNA damaging agents including platinum likely has a significant impact on the response to subsequent attempts at targeting a defective DNA damage response pathway using PARPi or other strategies. In our study, 9/14 (64%) patients who received platinum based therapy had documented disease progression during platinum treatment; it is not known what proportion of patients treated by Kaufman et al had discontinued prior platinum chemotherapy for toxicity rather than for disease progression. An alternative explanation is that olaparib is a more potent drug and some data infers this possibility with respect to PARP trapping as a putated mechanism of action of PARP inhibitors [17, 18]. Several mechanisms of acquired resistance to platinum agents have been described, including secondary mutations in BRCA 1/2 which restore the wild-type reading frame and result in restored expression of the BRCA1 or BRCA2 protein. Genetic reversion events have been identified in BRCA1 and BRCA2 mutated ovarian cancer samples with acquired resistance to cisplatin, and in cisplatin resistant clones of the BRCA2 mutant CAPAN1 pancreatic cell line[19, 20].

These events restore function of the BRCA protein, thereby restoring function. In addition, correlation between platinum sensitivity and response to PARPi has been observed in high grade serous ovarian cancer although responses have been seen in patients with platinum resistant disease, albeit at lower frequency[21].

Limitations of this study include the lack of a treatment arm specifically for patients who had not progressed on platinum based therapy. Archival tissue was collected on all patients and results will be reported in a separate manuscript and may provide insight into the clinical observations.

Current ongoing clinical trials are evaluating the use of PARP inhibitors in patients with BRCA+ PDAC in combination with platinum based chemotherapy as first line treatment,

and as a maintenance strategy in patients who have not progressed on platinum based chemotherapy[22]. For both these studies a randomized controlled design including extensive tissue and blood correlative studies will provide key information on the mechanisms of resistance to platinum and parp inhibitors in PDAC.

Optimally, patients could be selected for therapy targeting the DNA damage response pathway based on identification of a molecular signature indicating a defective HR pathway, potentially expanding significantly the population of patients who may benefit from such an approach. In fact, it is possible that presence of a germline BRCA+ mutation may be neither required nor sufficient for predicting benefit from PARPi in PDAC, and other acquired genetic alterations may play a significant role in the development of a HR deficient cancer. Other inherited cancer predisposition syndromes which are predicted to lead to a HR deficient phenotype include ATM mutations, Fanconi anemia pathway mutations and PALB2 mutations, while somatic alterations in BRCA 1/2 have been estimated to occur in up to 5–7% of cases; the development of a reliable assay to identify tumors with a defective HR pathway which may benefit from a synthetically lethal approach is crucial to success of this strategy[23].

In summary, we did not identify objective responses to single agent veliparib in patients with predominantly platinum-resistant BRCA+ PDAC. Prospective randomized placebo controlled trials evaluating PARPi as 1st line treatment in combination with platinum based chemotherapy and as a maintenance strategy in patients with platinum sensitive disease are underway in this population. Functional assays to identify HR deficiency in patients with PDAC are needed and may serve as predictive biomarker of response.

Acknowledgements:

Erica Kaufmann, Michal Segal

Funding Support

Lustgarten Foundation

National Cancer Institute Cancer Therapeutics Evaluation Program (CTEP) David M. Rubenstein Center for Pancreatic Cancer Research

Cancer Center Support Grant P30 CA008748

National Cancer Institute of the National Institutes of Health: R25CA020449

Presented in part: Gastrointestinal Cancers Symposium, 2015

References

1. Iqbal J, Ragone A, Lubinski J et al. The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers. *Br J Cancer* 2012; 107: 2005–2009. [PubMed: 23099806]
2. Lucas AL, Shakya R, Lipsyc MD et al. High Prevalence of BRCA1 and BRCA2 Germline Mutations with Loss of Heterozygosity in a Series of Resected Pancreatic Adenocarcinoma and Other Neoplastic Lesions. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2013; 19: 3396–3403. [PubMed: 23658460]

3. Zhen DB, Rabe KG, Gallinger S et al. BRCA1, BRCA2, PALB2, and CDKN2A Mutations in Familial Pancreatic Cancer (FPC): A PACGENE Study. *Genetics in medicine : official journal of the American College of Medical Genetics* 2015; 17: 569–577. [PubMed: 25356972]
4. Ferrone CR, Levine DA, Tang LH et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. *J Clin Oncol* 2009; 27: 433–438. [PubMed: 19064968]
5. Stadler ZK, Salo-Mullen E, Patil SM et al. Prevalence of BRCA1 and BRCA2 mutations in Ashkenazi Jewish families with breast and pancreatic cancer. *Cancer* 2012; 118: 493–499. [PubMed: 21598239]
6. Salo-Mullen EE, O'Reilly E, Kelsen D et al. Identification of Germline Genetic Mutations in Pancreatic Cancer Patients. *Cancer* 2015; 121: 4382–4388. [PubMed: 26440929]
7. Holter S, Borgida A, Dodd A et al. Germline BRCA Mutations in a Large Clinic-Based Cohort of Patients With Pancreatic Adenocarcinoma. *Journal of Clinical Oncology* 2015; 33: 3124–3129. [PubMed: 25940717]
8. Jones S, Hruban RH, Kamiyama M et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. *Science* 2009; 324: 217. [PubMed: 19264984]
9. Golan T, Kanji ZS, Epelbaum R et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. *British Journal of Cancer* 2014; 111: 1132–1138. [PubMed: 25072261]
10. Lowery MA, Kelsen DP, Stadler ZK et al. An Emerging Entity: Pancreatic Adenocarcinoma Associated with a Known BRCA Mutation: Clinical Descriptors, Treatment Implications, and Future Directions. *The Oncologist* 2011; 16: 1397–1402. [PubMed: 21934105]
11. Bryant HE, Schultz N, Thomas HD et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* 2005; 434: 913–917. [PubMed: 15829966]
12. Kaufman B, Shapira-Frommer R, Schmutzler RK et al. Olaparib Monotherapy in Patients With Advanced Cancer and a Germline BRCA1/2 Mutation. *Journal of Clinical Oncology* 2015; 33: 244–250. [PubMed: 25366685]
13. Bella Kaufman RS-F, Rita K. Schmutzler. Olaparib monotherapy in patients with advanced cancer and a germ-line BRCA1/2 mutation: An open-label phase II study. *J Clin Oncol* 31, 2013 (suppl; abstr 11024.
14. Norquist B, Wurz KA, Pennil CC et al. Secondary Somatic Mutations Restoring BRCA1/2 Predict Chemotherapy Resistance in Hereditary Ovarian Carcinomas. *Journal of Clinical Oncology* 2011; 29: 3008–3015. [PubMed: 21709188]
15. Pahuja S, Appleman LJ, Belani CP et al. Preliminary activity of veliparib (V) in BRCA2-mutated metastatic castration-resistant prostate cancer (mCRPC). *Journal of Clinical Oncology* 2015; 33: 170–170.
16. Domchek SM, Hendifar AE, McWilliams RR et al. RUCAPANC: An open-label, phase 2 trial of the PARP inhibitor rucaparib in patients (pts) with pancreatic cancer (PC) and a known deleterious germline or somatic BRCA mutation. *Journal of Clinical Oncology* 2016; 34.
17. Murai J, Huang SY, Das BB et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. *Cancer Res* 2012; 72: 5588–5599. [PubMed: 23118055]
18. Pommier Y, O'Connor MJ, de Bono J. Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. *Sci Transl Med* 2016; 8: 362ps317.
19. Sakai W, Swisher EM, Karlan BY et al. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. *Nature* 2008; 451: 1116–1120. [PubMed: 18264087]
20. Swisher EM, Sakai W, Karlan BY et al. Secondary BRCA1 Mutations in BRCA1-Mutated Ovarian Carcinomas with Platinum Resistance. *Cancer Research* 2008; 68: 2581–2586. [PubMed: 18413725]
21. Fong PC, Yap TA, Boss DS et al. Poly(ADP)-Ribose Polymerase Inhibition: Frequent Durable Responses in BRCA Carrier Ovarian Cancer Correlating With Platinum-Free Interval. *Journal of Clinical Oncology* 2010; 28: 2512–2519. [PubMed: 20406929]
22. Schwartz GK, Ilson D, Saltz L et al. Phase II study of the cyclin-dependent kinase inhibitor flavopiridol administered to patients with advanced gastric carcinoma. *J Clin Oncol* 2001; 19: 1985–1992. [PubMed: 11283131]

23. Waddell N, Pajic M, Patch A-M et al. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature* 2015; 518: 495–501. [PubMed: 25719666]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Highlights

- Veliparib has modest activity in previously treated germline BRCA-related pancreas ductal adenocarcinoma exposed to prior platinum therapy.
- PARP inhibition in pancreas ductal adenocarcinoma may be best evaluated in a platinum sensitive disease setting and ongoing trials are evaluating these approaches.
- There may be intrinsic differences between PARP inhibitors that explain therapeutic outcomes.

Figure 1:
Median Progression-Free Survival from Start of Therapy

Figure 2:
Median Overall Survival from Start of Therapy

Figure 3:
Waterfall Plot of Radiographic Response

Table 1:

Patient Demographics and Baseline Characteristics Fifteen (93.8%) patients had stage IV disease and 1 (6.3%) patient had stage III. Eleven (68.8%) patients had a BRCA2 mutation and 5 (31.3%) patients had a BRCA1 mutation. Seven (43.8%) patients had one line of treatment prior to this study and 9 (56.3%) patients had two.

<u>Age</u>	
Median (range)	59 (43–79) years
<u>Sex</u>	
Male	8 (50%)
Female	8 (50%)
<u>ECOG PS</u>	
0	6 (38%)
1	8 (50%)
2	2 (12%)
<u>BRCA status</u>	
BRCA1 germline mutation	5 (31%)
BRCA2 germline mutation	11 (69%)
<u>AJCC Stage</u>	
Locally advanced (III)	1 (6%)
Metastatic (IV)	15 (94%)
<u>No of Sites of Metastases</u>	
<u>Median</u>	2 range 1–4
<u>Primary only</u>	1 (6%)
<u>1 site</u>	2 (13%)
<u>2 sites</u>	7 (44%)
<u>3 sites</u>	4 (24%)
<u>4 sites</u>	2 (13%)
<u>No of Prior Treatments</u>	
One line	
Gemcitabine single agent	7 (44%)
FOLFIRINOX	1 (6%)
Gemcitabine/cisplatin	5 (31%)
Two lines	9 (56%)
Gemcitabine/nab-paclitaxel + Oxaliplatin based	7 (44%)
Gemcitabine + Mitomycin, irinotecan, capecitabine	1 (6%)
Gemcitabine/oxaliplatin + Gemcitabine	1 (6%)
<u>Prior Platinum Therapy</u>	
Yes	14 (88%)
Oxaliplatin-based	13 (81%)
Cisplatin-based	2 (12%)
Carboplatin-based	1 (6%)

Both Cisplatin or carboplatin + Oxaliplatin	1 (6%)
No*	2 (12%)
Median (range) duration of therapy prior to study treatment	11 (5-21) months

**1 patient had received only prior single agent gemcitabine; 1 patient had received gemcitabine and then irinotecan, mitomycin, capecitabine

Table 2:

Tumor Response Rates No patients had measurable responses. There was 1 (6.3%) patient with an unconfirmed partial response at 4 months with disease progression at 6 months.

Response	N (%)
<u>Tumor Response Rate</u>	
Complete response	-
Partial response	-
<u>Stable disease 8 Weeks</u>	
Stable disease	4 (25%)
Unconfirmed partial response	1 (6%)
<u>Progressive Disease</u>	
RECIST progression	10 (63%)
Clinical progression/early death*	1 (6%)

Table 3:

Grade 3 Adverse Events Grade 3–4 adverse events occurred in 11 (69%) patients, 6 (54.5) of these patients experienced grade 3–4 toxicities were casually related to their therapy.

Adverse Event	N (%)
Fatigue	4 (25%)
Elevated bilirubin	3 (19%)
Thrombocytopenia	2 (13%)
Alkaline phosphatase increase	2 (13%)
Dehydration	2 (13%)
Hyponatremia	2 (13%)
Anemia	1 (6%)
HTN	1 (6%)
AST increase	1 (6%)
Nausea	1 (6%)
Vomiting	1 (6%)
Lymphopenia	1 (6%)
Constipation	1 (6%)
Thromboembolic event	1 (6%)
Edema	1 (6%)