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A Randomized Phase Ib/II Study of Niraparib plus Nivolumab or Ipilimumab in Patients with Platinum-Sensitive Advanced Pancreatic Cancer

Kim A. Reiss, MD,

Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; Department of Medicine

Rosemarie Mick, MS,

Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; Department of Biostatistics, Epidemiology and Informatics

Ursina Teitelbaum, MD,

Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; Department of Medicine

Corresponding Author Information Kim A. Reiss, MD, Perelman Center for Advanced Medicine, South Tower, 10th Floor, 3400 Civic Center Boulevard, Philadelphia, PA 19106, (215) 360-0735, Kim.reissbinder@pennmedicine.upenn.edu.

Contribution Statement

KAR: Conceptualization, formal analysis, funding acquisition, investigation, project administration, supervision, visualization, writing (original draft), writing (review and editing)
RM: Conceptualization, formal analysis, validation, visualization, writing (review and editing)
UT: Investigation, writing (review and editing)
MO: Investigation, writing (review and editing)
CS: Investigation, writing (review and editing)
RM: Investigation, writing (review and editing)
TK: Investigation, writing (review and editing)
RT: Investigation, writing (review and editing)
CO: Data curation, project administration, writing (review and editing)
MG: Investigation, project administration, writing (review and editing)
AD: Investigation, project administration, writing (review and editing)
SMD: Conceptualization, supervision, writing (review and editing)
RHV: Conceptualization, supervision, writing (review and editing)
CO and KAR independently accessed and verified the underlying data reported in this manuscript.

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The other authors declared no conflicts of interest.

Mark O'Hara, MD,
Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; Department of Medicine

Charles Schneider, MD,
Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; Department of Medicine

Ryan Massa, MD,
Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; Department of Medicine

Thomas Karasic, MD,
Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; Department of Medicine

Rashmi Tondon, MD,
Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; Department of Pathology

Chioma Onyiah, BA,
Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; Department of Medicine

Mary Kate Gosselin, RN,
Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; Department of Medicine

Alyssa Donze, RN,
Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; Department of Medicine

Susan M. Domchek, MD,
Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; Department of Medicine

Robert H. Vonderheide, MD, DPhil
Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, PA, USA; Department of Medicine

Abstract

Background—Establishing alternatives to perpetual chemotherapy for patients with advanced pancreatic cancer (PC) has been proposed to address chemotherapy resistance and cumulative toxicity. Poly (ADP ribose) polymerase (PARP) inhibitors have shown efficacy in this setting, and the addition of immune checkpoint blockade (ICB) may offer synergistic tumor control. The primary objective of this study was to test maintenance PARP inhibition plus ICB in patients with advanced PC who had achieved stability on platinum-based chemotherapy.

Methods—We conducted a randomized, phase Ib/II study of niraparib plus anti-PD-1 (nivolumab) or anti-CTLA-4 (ipilimumab) for patients with advanced PC whose cancer had not

progressed after ≥16 weeks of platinum-based therapy. Patients were randomly assigned 1:1 to niraparib 200 mg PO daily plus either nivolumab 240 mg IV q2 weeks or ipilimumab 3 mg/kg IV q3 weeks for four doses. The primary endpoints were safety and progression free survival rate at 6 months (PFS6) per arm. The null hypothesis of PFS6 = 44% vs a 2-sided alternative hypothesis of PFS Φ 44% was tested. Forty-two patients per arm provided 81% power for testing at a 2-sided 5% significance level to detect superior PFS6 = 60% (or inferior PFS6 = 27%). Per protocol analysis was performed. NCT 03404960; enrollment completed.

Findings—Ninety-one patients enrolled between February 7th, 2018 and October 5th, 2021. Eighty-four patients were evaluable for the PFS endpoint (44 niraparib/nivolumab; 40 niraparib/ipilimumab). Median follow-up was 23 months (IQR: 15-31.5mo). Niraparib/nivolumab, PFS6 was 20.6% (95% CI, 8.3-32.9, p = 0.0002); niraparib/ipilimumab, PFS6 was 59.6% (95% CI, 44.3-74.9, p = 0.045). Ten (22.2%) patients on nira/nivo and 23 (50%) patients on nira/ipi experienced a grade 3-4 treatment-related AE.

Interpretation—Niraparib/ipilimumab maintenance met the primary endpoint of superior PFS6; niraparib/nivolumab yielded inferior PFS6. These findings highlight the potential for non-cytotoxic maintenance therapies in patients with advanced PC.

Keywords

Pancreatic Cancer; Nivolumab; Ipilimumab; Niraparib; Maintenance; DNA Damage Repair; *BRCA* ; *PALB2*

Introduction

As increasingly effective multi-agent chemotherapy regimens for pancreatic cancer (PC) have been developed,[1-3] subsets of patients with advanced disease who respond durably to treatment have emerged. Establishing non-cytotoxic alternatives to perpetual chemotherapy for this patient population is a potential way to thwart chemotherapy resistance and to prevent cumulative toxicity.

For patients with metastatic PC and pathogenic germline *BRCA* variants who have responded favorably to platinum-based treatment, the PARP inhibitor (PARPi) olaparib is tolerable and effectively delays progression,[4] an approach that is likely also applicable to patients with locally advanced cancer and those with additional pathogenic DNA damage repair (DDR) variants (PVs).[5] These advancements pave the way to attempt maintenance strategies in a broader population of patients who might be identified by clinical features, biological signatures or a combination of both.

Selecting patients for treatment based on platinum-sensitivity regardless of known DDR variant is a strategy that has been effectively adopted in advanced ovarian cancer, leading to the FDA approval of maintenance niraparib in this setting.[6] Patients with PC and DDR deficiencies are highly sensitive to platinum-based chemotherapies[7,8] and recent data shows that not all PC patients with a DDR signature can be identified by clinical sequencing.[9] This latter finding provides rationale to select patients based on a clinical phenotype, such as sustained platinum sensitivity, for DDR-targeted therapeutic strategies. In preclinical models, PARP inhibition combined with immune checkpoint blockade (ICB)

has been shown to demonstrate activity in tumors characterized by DDR deficiencies.[10-13] Furthermore, some preclinical studies suggest that anti-CTLA-4 therapy may be more effective than anti-PD-1 in combination with PARPi.[10] The available preclinical data demonstrating that anti-PD-1 or anti-CTLA4 might synergize with PARP inhibition provided the rationale for our two-arm, randomized design.

Here, we report the results from an investigator-initiated, phase Ib/II trial designed to test the hypothesis that maintenance treatment with the PARPi niraparib (nira) plus either nivolumab (nivo) or ipiliumab (ipi) in patients with platinum-sensitive advanced PC can produce a progression-free survival (PFS) rate at 6 months (PFS6) of at least 60%.

Methods

Study Design

This trial was an open-label, randomized, phase Ib/II trial performed at the Abramson Cancer Center at the University of Pennsylvania (ClinicalTrials.gov identifier: NCT03404960). The IND Sponsor was the University of Pennsylvania. (**Study Protocol can be found on page 22 of the** Appendix).

Patients

Eligible patients were at least 18 years old and had histologically or cytologically confirmed diagnosis of locally advanced or metastatic pancreatic cancer (neuroendocrine excluded). Evidence of a DDR pathway variant was not required for enrollment; patients with a known variant were permitted to enroll. Patients were required to have received ≥16 weeks of palliative platinum-based chemotherapy without evidence of platinum resistance, which was defined as growing tumors, new lesions, or a steadily rising tumor marker during or within eight weeks of platinum therapy. Duration of platinum chemotherapy was unlimited. If disease was at least stable during prior platinum-based therapy but there was active progression on a non-platinum based regimen (for example, progression while on maintenance FOLFIRI or 5FU/Leucovorin), this was acceptable for enrollment. Patients were required to have adequate organ function, an Eastern Cooperative Group performance status of 0-1 and a life expectancy of at least 12 weeks. Prior treatment with PARPi or ICB were not permitted. Measurable disease was not required for enrollment. Written informed consent was obtained from all patients. The study was approved by the institutional review board of the University of Pennsylvania.

Randomization and Masking

Randomization was computer-based and utilized a permuted block technique. No stratification factors were used. Randomization was performed on R using the blockrand function. Randomization was performed by R.M.

Procedures

There was an initial phase Ib safety assessment of up to six patients per arm. Patients were randomized in a 1:1 fashion to receive either niraparib (nira; 200 mg daily) plus nivolumab (nivo; 240 mg IV every two weeks) or nira (200 mg daily) plus ipilimumab (ipi; 3mg/kg).

The protocol was later amended to allow nivolumab 480 mg IV every four weeks (resulting in the same monthly dosage) as recommended by the manufacturer. The original protocol allowed nira to be increased to 300 mg PO daily if patients tolerated the first cycle of therapy at the 200 mg dose level. In September of 2018, based on emerging phase I data of nira plus pembrolizumab, the manufacturer recommended that patients remain on the 200 mg dosing.[14]

Laboratory parameters and clinical assessments occurred on the first day of every treatment cycle. Additionally, a complete blood count was performed weekly during the first cycle. Patients were treated until unacceptable toxicity or progression as determined by central radiology review. If ICB was discontinued for toxicity, patients were permitted to remain on study and receive niraparib monotherapy until progression. Patients who continued to derive clinical benefit after documented disease progression by RECIST v1.1 were permitted to stay on trial at the discretion of the treating physician.

In order to align with infusion schedules, computed tomography or magnetic resonance imaging of the chest, abdomen and pelvis were performed at baseline and then every eight weeks in the nira/nivo arm and every nine weeks in the nira/ipi arm. The protocol was later amended to allow patients who had been on study for at least 12 cycles to be clinically and radiographically evaluated every 12 weeks, but with laboratory assessment every four (nira/nivo) or three (nira/ipi) weeks.

Outcomes

The primary endpoints were safety and PFS, defined as time from initiation of study therapy until progression or death from any cause. Patients alive and progression-free at last follow-up were censored at the date of their most recent progression-free clinical assessment. The efficacy population consisted of all patients who received at least one dose of study treatment and had a least one post-treatment assessment of response by RECIST. At the time of original protocol development, investigator assessment of the primary endpoint was planned. However, it was later felt that this may introduce unnecessary bias. Therefore, blinded, central radiology review was substituted and was used for assessment of all patients on study.

The dose limiting toxicity (DLT) period was defined as the first three weeks of study therapy. DLTs were defined as non-hematologic AEs of grade 3 or higher that were at least possibly related to treatment (exceptions: grade 3 or higher nausea and vomiting that has not been optimally treated and grade 3 or higher hypertension that has not been optimally treated) and/or grade 4 neutropenia lasting >7 days, febrile neutropenia or platelet count of $<10{,}000/mm^3$. Adverse events (AEs) were classified and graded according to the NCI Common Terminology Criteria of Adverse Events, version 5.0. The safety population consisted of all patients who received at least one dose of study treatment.

Secondary endpoints objective response rate (ORR) (i.e., percentage of patients with confirmed complete or partial response according to RECIST v1.1), overall survival (OS) (i.e., time from initiation of study therapy until death or last follow-up) and correlation of

DDR deficiency with response to treatment. RECIST v1.1, and not iRECIST, was selected given that niraparib was felt to be the driving mechanism of response to therapy.

Statistical Analysis

For this non-comparative phase Ib/II trial which randomized patients to one of two experimental arms, safety and PFS were the primary endpoints. At the time of study design, the solely available study of maintenance treatment after best response to chemotherapy[15] demonstrated a PFS rate at 6 months (PFS6) of 22%. It was felt that a doubling of this result would be clinically meaningful. Therefore, the study was designed with a null hypothesis that the PFS6 in each arm was equal to 44%. The two-sided alternative hypothesis was that the PFS6 in each arm was not equal to 44%. Forty-two patients per arm provided 81% power for testing at a two-sided 5% significance level to detect superior PFS6 = 60% (or inferior PFS6 = 27%), assuming an exponential hazard distribution, enrollment would continue for 36 months and an additional 6 months of follow-up prior to final statistical analysis. The data cutoff was January 25th, 2022.

Baseline patient and tumor features were summarized by descriptive statistics. Median PFS and OS were estimated by the Kaplan-Meier method along with 95% confidence intervals (CIs) constructed using the Brookmeyer-Crowley formula. Milestone rate, such as PFS6, was estimated along the 95% confidence interval by Greenwood's formula. To test the primary hypothesis on each arm, it was determined whether the lower or upper bound of the two-sided 95% confidence interval for PFS6 excluded 44%. The associated two-sided Z test was employed on each arm to determine statistical significance. Planned exploratory analyses determined clinical outcomes within defined subgroups of interest (i.e., DDR, no DDR, family history of *BRCA*-related cancers) for each arm.

The per-protocol (PP) approach in our study required at least one post-treatment response assessment, which guaranteed that the primary endpoint would be measured by an objective and reproducible determination of progressive disease or lack thereof. Such an approach may lead to an overestimation of the treatment effect. Thus an unplanned intent to treat (ITT) analysis of the niraparib plus ipilimumab arm was also performed. Statistical analyses were performed using IBM SPSS v.26. $P < 0.05$ was considered statistically significant. There were no missing data.

This study is registered as NCT03404960 at ClinicalTrials.gov.

Role of the Funding Source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patients

Between February 7th, 2018 through October 5th, 2021, 91 patients who underwent randomization and received at least a single dose of a study intervention comprised the safety population (Figure 1): 46 patients, nira/nivo; 45, nira/ipi. Seven patients

were excluded from efficacy analysis for the following reasons: rapid clinical decline without repeat imaging assessment (two), non-malignant small bowel obstruction (one), niraparib-related AEs (two), internal pathology assessment identifying the primary cancer as neuroendocrine (two) (Supplemental Table 1**, Page 1 of** Appendix). Ultimately, 84 patients were evaluable for the primary endpoint: 44 nira/nivo and 40 nira/ipi. The baseline characteristics of evaluable patients are listed in Table 1.

In both nira/nivo and nira/ipi arms, the majority of patients had metastatic disease at the time of study enrollment (36 [82%] and 32 [80%], respectively) and most had measurable disease (40 [91%] and 39 [97%]). The most common sites of metastatic disease were liver (26 [59%] and 24 [60%]), lung (9 [20%] and 6 [15%]) and the peritoneum (5 [11%] and 7 [17%]). Most patients had stable or responding disease at study entry (38 [86%] and 34 [85%]) though several patients were progressing or were experiencing mixed response to their current non-platinum based treatment (6 [14%] and 6 [15%]). There was no significant difference in percentage of males and females between arms (29 [66%] vs 20 [50%], p = 0.14 by chi-square test).

All but three patients (81 [96%]) had available germline testing results and 43 patients (52%) had undergone clinical somatic next generation sequencing (Supplemental Table 2**, Page 2 of** Appendix). The following genes, when identified in clinical sequencing, were considered to be DDR variants: *BRCA1, BRCA2, PALB2, ATM, FANCA, FANCC, RAD50, RAD51, RAD51C, RAD51D, ATR, CHEK1, CHEK2, BARD1, BRIP1, NBN, BAP1, BLM, FAM175A, RTEL1, MRE-11* and *ARID1A*. Of the 44 evaluable patients in the nira/nivo arm, eight (16%) had a pathogenic variant in either *gBRCA1* (1), *gBRCA2* (5) or *sPALB2* (1). Of the 40 evaluable patients in the nira/ipi arm, seven (17%) had a pathogenic variant in either *gBRCA1* (4) *gBRCA2* (1), *gPALB2* (1) or *sBRCA1* (1). Five additional patients in the nira/nivo arm and three additional patients in the nira/ipi arm had mutations in non-core DDR genes. These are listed in Table 1. Of all patients who had somatic sequencing, the majority had a pathogenic *KRAS* variant (81% and 82%).

Among patients without a known DDR variant, 18 (49%) in the nira/nivo arm and 20 (50%) in the nira/ipi arm had a personal or family history of at least one BRCA-related cancer.

At the time of data cutoff for this analysis, (January 25, 2022), three patients were still receiving nira/nivo and eight were still receiving nira/ipi. Analysis of the primary endpoint was performed after 73 of 84 patients had had disease progression (assessed by blinded independent central review) or had died. With a median follow-up of 23 months (IQR: 15-31.5mo) for all 84 patients and 15 months for 32 living patients, the median PFS (mPFS) in the nira/nivo arm was 1.9 months (95% CI, 1.4-2.3) and the PFS6 rate was 20.6% (95% CI, 8.3-32.9, vs 44% p = 0.0002) (Figure 2). In the nira/ipi arm, the mPFS was 8.1 months (95% CI, 5.5-10.6) and the PFS6 rate was 59.6% (95% CI, 44.3-74.9; vs 44% p = 0.045). Since the lower bound of the 95% CI exceeded the null hypothesis rate of 44% on the nira/ipi arm, it was deemed superior and this arm met its primary objective. Since the upper bound of the 95% CI did not include the null hypothesis rate of 44% on the nira/nivo arm, it was deemed inferior.

The median OS (mOS) in the nira/nivo arm was 13.2 months (95% CI, 8.1-16.7) and the mOS in the nira/ipi arm was 17.3 months (95% CI, 12.8-21.9). The ORR (patients with measurable disease only) in the nira/nivo arm was 7.1% (3/42 95% CI 1.5-19.5) and the ORR in the nira/ipi arm was 15.4% (6/39 95% CI 5.9-30.5).

In a planned secondary analysis, patient outcomes were evaluated by presence or absence of a DDR variant and/or family history of *BRCA*-related cancers (Supplemental Figure 1**, Page 6 of** Appendix and Table 2). When patients with pathogenic *BRCA* or *PALB2* variants were removed from the analysis, the mPFS in the 37 patients on the nira/nivo arm was 1.9 mo (95% CI, 1.8-1.9) and mOS 13.2 mo (95% CI, 8.1-16.7); the mPFS in the 33 patients on the nira/ipi arm was 7.6 mo (95% 4.0-11.1) and mOS 17.3 mo (95% CI, 12.5–22.2) (Supplemental Figure 1A). When all patients with known DDR variants were removed from the analysis, the mPFS in the 32 patients on the nira/nivo arm was 1.8 mo (95% CI, 1.8-1.9) and mOS 13.2 mo (95% CI, 6.1-20.3); the mPFS in the 30 patients on the nira/ipi arm was 7.6 mo (95% CI, 2.8-12.3) and mOS 15.0 mo (95% CI, 4.3-25.7) (Supplemental Figure 1B).

Patients without DDR mutations but with a known family history of *BRCA*-related cancers had a mPFS of 1.8 mo (95% CI, 1.7-2.0) and mOS 15.4 mo (95% CI, 11.8-18.9) in the 18 patients on the nira/nivo arm and a mPFS of 6.2 mo (95% CI, 1.5-10.8) and mOS 18.7 mo (95% CI, 0.0-38.3) in the 15 patients on the nira/ipi arm (Supplemental Figure 1C).

In patients with *BRCA* or *PALB2* variants, the mPFS in the seven patients on the nira/nivo arm was 3.7 mo (95% CI, 1.1-6.3) and mOS 12.2 mo (95% CI not estimable). In the seven patients on the nira/ipi arm, the mPFS was 10.4 mo (95% CI 1.5 – 19.2) and mOS 38.0 mo (95% CI not estimable).

The overall response rate (ORR) of patients with response-evaluable (measurable) disease at study start was 7% (six patients) in the nira/nivo arm and 15% (three patients) in the nira/ipi arm (Figure 3).

Following study discontinuation, 15 patients in the nira/nivo arm and 14 patients in the nira/ipi arm were rechallenged with platinum-based therapy. Of these, six (40%) and eight (57%), respectively, had at least stable disease in response to this treatment (Supplemental Table 3**, Page 12 of** Appendix).

Ninety-one patients were evaluable for toxicity (Table 3). No dose-limiting toxicities occurred in either treatment arm during the phase Ib portion of the trial and therefore only three patients per arm were enrolled during this phase. The median number of cycles of nira/nivo was three (IQR: 2-8); the median number of cycles of nira/ipi was eight (IQR: 3-17.5). Ten (22%) patients in the nira/nivo arm experienced a grade 3-4 treatment-related AE and 23 (50%) patients in the nira/ipi arm experienced a grade 3-4 treatment-related AE. Five patients (11%) discontinued nivolumab due to AEs but continued on niraparib; 11 patients (24%) discontinued ipilimumab prematurely (prior to C4) due to AEs but continued niraparib. The AEs resulting in premature ICB discontinuation are described in Supplemental Table 4 **(Page 16 of** Appendix). Five patients discontinued niraparib due to AEs: thrombocytopenia (two), anemia (two) and fatigue (one). No patient required discontinuation of both investigational agents due to AEs.

Two patients on the nira/nivo arm and three patients on the nira/ipi arm had the nira dose increased from 200 mg to 300 mg after Cycle 1. After this time period and after discussion with the manufacturer, it was determined that 200 mg was the recommended phase II dose in combination with ICB.[14] Therefore, no additional patients underwent this dose increase.

Treatment-related serious adverse events (SAEs) were observed in six (14%) patients in the nira/nivo arm and in 11 (27%) patients in the nira/ipi arm. In the nira/nivo arm, the most common treatment-related toxicities were thrombocytopenia (13 patients; 28%), arthralgia (12 patients; 25%), nausea (11 patients; 23%), and fatigue (11 patients; 23%). Most toxicities (88%) were grade 1 or 2. In the nira/ipi arm, the most common treatment-related toxicities were thrombocytopenia (20 patients; 45%), anemia (19 patients; 43%), fatigue (19 patients; 43%), nausea, (18 patients; 41%), AST increase (16 patients; 36%), rash (15 patients; 34%) and ALT increase (13 patients; 29%). Grade 3 fatigue was observed in the nira/ipi arm at a rate of 14% (six patients); no patients in the nira/nivo arm had grade 3 fatigue. There were was an overall higher number of grade 3 immune-mediate adverse events observed in the nira/ipi arm, including rash (3), pneumonitis (2) and colitis (1). The only grade 3 adverse event considered immune-mediated in the nira/nivo arm was colitis (1). There were no grade 4 or 5 immune-mediated adverse events.

At the time of data analysis, 32 (73%) patients in the nira/nivo arm and 24 (60%) patients in the nira/ipi arm had died. None of the deaths were treatment-related.

All AEs, regardless of relationship to treatment, can be found in Supplemental Table 5 **(Page 17 of** Appendix).

An unplanned ITT analysis was performed. Of the five patients previously scored as unevaluable, two with symptomatic deterioration without imaging confirmation of progression were scored as PFS events. Three patients were censored for PFS. Incidental imaging showed no progression in one patient and in two patients adverse events caused withdrawal without progression (Supplemental Table 1**, Page 1 of the** Appendix). The ITT estimate of PFS6 was 56.8% as compared to 59.6% in the PP analysis. In the ITT analysis, the 95% CI for PFS6 was 41.7 – 71.9% which included the null hypothesis PFS6 rate of 44%.

Discussion

This phase Ib/II study demonstrated efficacy of the PARP niraparib plus ipilimumab as maintenance therapy for patients with advanced PC in whom chemotherapy was stopped after non-progression to platinum-containing regimens. With a PFS6 of 59.6% in the niraparib plus ipilimumab arm, the study met its primary objective in this arm. The study demonstrated a lack of efficacy of niraparib plus nivolumab in the same clinical setting, with a PFS6 of 20.6%.

The concept of maintenance treatment for advanced PC is a relatively new consideration. Indeed, the original Conroy study of FOLFIRINOX for patients with metastatic PC had no maintenance component at all; chemotherapy ended after six months of treatment [1]. At the time our study concept was designed, the only published trial of maintenance

following response to platinum therapy was that of sunitinib versus observation. This trial demonstrated a PFS6 of 22% in the experimental arm.[15] A doubling of this historical PFS6 rate was felt to be clinically relevant, and this strategy continues to be used in other ongoing PC maintenance studies (NCT03331562). Therefore, our primary endpoint was a PFS6 of 44%.

Our study surpassed the target PFS6 in the niraparib plus ipilimumab arm, with a PFS6 59.6%. Moreover, mPFS was higher in the niraparib plus ipilimumab arm compared to the niraparib plus nivolumab arm across the entire population and across subgroups, without overlapping CIs. mOS, ORR and PFS12 were numerically higher in the group that received niraparib plus ipilumab compared to those who received niraparib plus nivolumab. The non-overlapping 95% CIs provided evidence that a difference between treatment arms may exist, but this observation must be interpreted with caution as estimation, and not comparison, was the intent of the study.

Two recent trials exploring the role of maintenance therapy in all-comer populations of patients with metastatic PC have been reported and provide additional context for our results. Dahan et al reported a mPFS of 5.1 months in patients receiving maintenance 5FU/Leucovorin following four months of FOLFIRINOX[16] and Wu et al reported a mPFS of 5.5 months in patients receiving maintenance FOLFIRINOX derivatives following 4-6 months of FOLFIRINOX[17]. The latter trial reported a mOS of 14.7 months during the maintenance period. Nivolumab plus ipilimumab maintenance demonstrated mPFS 8.1 months and mOS 17.3 months during the maintenance period, suggesting that non-cytotoxic maintenance therapy may be superior to modern cytotoxic agents in this setting. However, it should be noted that direct cross-trial comparison cannot be made, in particular because approximately 20% of our patients had locally advanced PC and those progressing on non-platinum regimens were permitted to enroll.

Despite increasing clinical applications of PD-1 or PD-L1 antibodies in cancer, these agents have had minimal utility in pancreatic cancer and our findings from this randomized clinical study highlight a novel opportunity for CTLA-4 antibody as a more important checkpoint molecule than PD-1/PD-L1. Our results are consistent with preclinical observation suggesting that anti-CTLA-4 therapy may be more effective than anti-PD-1 in combination with PARPi, a rationale for our two-arm, randomized design. In a BRCA-1 deficient ovarian cancer animal model, PARPi plus anti-CTLA4, but not of PARPi plus anti-PD-1,[10] appeared effective, associated by an increase in intra-tumoral effector T-cells after PARPi plus anti-CTLA-4. An increase in effector T-cells with the use of ipilimumab was also identified in a trial of maintenance allogeneic GM-CSF-Transfected Pancreatic Tumor Vaccine (GVAX) plus ipilimumab for patients with advanced, platinum-sensitive PC.[17] Although no clinical activity was observed in this trial, T-cell differentiation into effector memory phenotypes was identified. These observations highlight the central and unique role of CTLA-4 in certain therapeutic settings and potential for combination with PARPi to induce clinical efficacy.

Analyzing results for only patients without DDR variants showed sustained therapeutic efficacy of niraparib plus ipilimumab, thus reflecting an effect independent of a clinically

identified DDR deficiency. There was no imbalance between arms with regard to clinical or other features, including no differences in rates of metastatic disease, hepatic or peritoneal metastases, *KRAS* variants, baseline CA 19-9 levels, baseline albumin levels, pathogenic DDR variants, or a family history of *BRCA*-related cancers. Blood for germline whole exome sequencing, serial peripheral blood mononuclear cells and serial circulating DNA samples have been collected on all patients; tissue samples were collected whenever feasible. Correlative immunologic and genomic assays are underway, with the goal of identifying signatures beyond clinical panel sequencing that may predict for response to therapy.

The previously published results of the POLO trial and our own rucaparib study have demonstrated that maintenance PARP inhibition is effective in a population of patients with pathogenic *BRCA* or *PALB2* variants.[4,5] The role of adding ICB to maintenance PARP inhibition in this population remains undefined, with several studies exploring PARP inhibition plus anti-PD-1 in this population (NCT04666740, NCT04493060 and NCT04548752). We enrolled 14 patients with known germline (n = 12) or somatic (n = 2) pathogenic *BRCA* or *PALB2* variants on this study. Despite a very limited sample size, it is notable that the mPFS in niraparib plus nivolumab was akin to the placebo arm of the POLO study (3.8 months), while the mPFS of 10.4 months in the niraparib plus ipilimumab arm was closer to that demonstrated in the experimental arm of the POLO study (7.4 months) and in the rucaparib study (13.1 months). Inter-trial differences such as rates of specific mutations (germline vs somatic; *BRCA1* vs *BRCA2*), variance in baseline tumor characteristics (ie tumor burden at study start; location of metastases) and possible differences between specific PARP inhibitors may account for the differences in mPFS between the rucaparib study and the *BRCA/PALB2* patients on niraparib/ipilimumab, despite these studies having been conducted at the same institution. Regardless, the differences in outcomes between *BRCA/PALB2* patients who received niraparib/nivolumab compared to those who received niraparib/ipilimumab raise several important questions that will require exploration in future studies: first, is the addition of ICB to PARP inhibitor maintenance beneficial in this patient population? Second: is there an enhanced benefit of anti-CTLA-4 therapy compared to anti-PD-1 treatment with PARPi in patients with *BRCA* or *PALB2* variants?

AEs associated with niraparib, ipilimumab and nivolumab were similar to what has been observed in prior studies, with no suggestion that combining these treatments increases toxicity risks. As expected based on prior experience,[18] more irAEs in the ipilimumab arm were observed. Rates of toxicities associated with niraparib including myelosuppression and hypertension were consistent with previously published observations.[6,19]

Our study had several key limitations including that it was conducted at a single institution, and that the population of enrollees was somewhat heterogeneous in regards to disease stage (locally advanced or metastatic) and disease responsivity at enrollment (stable or progressing on non-platinum therapy). As such, the results need to be interpreted with some caution.

In conclusion, niraparib plus ipilimumab as maintenance therapy met the primary endpoint of superior PFS6 while niraparib plus nivolumab yielded inferior PFS6 for patients

with advanced pancreatic cancer who had not progressed on first-line platinum-based chemotherapy. The benefit of niraparib plus ipilimumab maintenance extended to patients without known DDR variants, suggesting that the effect may be independent of DDR deficiency or, equally likely, that such deficiencies were not detected using clinical grade testing. The effect of PARPi monotherapy in an all-comer, platinum-sensitive population is unknown. Future studies to explore maintenance niraparib plus ipilimumab compared to PARP inhibitor monotherapy and to maintenance cytotoxic chemotherapy should be pursued.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing Statement

Data collected for the study will be made available upon specific request.

Available data will include deidentified participant data and the data dictionary.

The study protocol, including statistical analysis plan will be available with publication.

Any requests for data should be sent to kim.reissbinder@pennmedicine.upenn.edu

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Research in Context Panel

Evidence Before This Study:

Two previously published clinical trials showed efficacy of maintenance PARP inhibitors in patients with *BRCA* or *PALB2* alterations and platinum-sensitive disease. Sensitivity to platinum therapy is a phenotypic hallmark of DNA damage repair deficiencies, however, the majority of patients with advanced pancreatic cancer who respond to platinum-based therapy do not have a clinically identifiable genomic variant to suggest such a deficit. Preclinical data has shown potential synergy between PARP inhibitors and immune checkpoint blockade, with a suggestion that anti-CTLA-4 may be superior to anti-PD-1 in this context.

Added Value of This Study:

Previous clinical trials have shown the efficacy of maintenance PARP inhibition in patients with advanced pancreatic cancer and specific genomic alterations, namely those with *BRCA* or *PALB2* variants. This current study highlights the potential of non-cytotoxic maintenance treatments for a broader population of pancreatic cancer patients.

Implications of the Available Evidence:

Niraparib/ipilimumab should be further explored as a maintenance therapy for patients with advanced pancreatic cancer. Genomic and immunological signatures of responding patients may further refine the selection of patients who may benefit from this strategy.

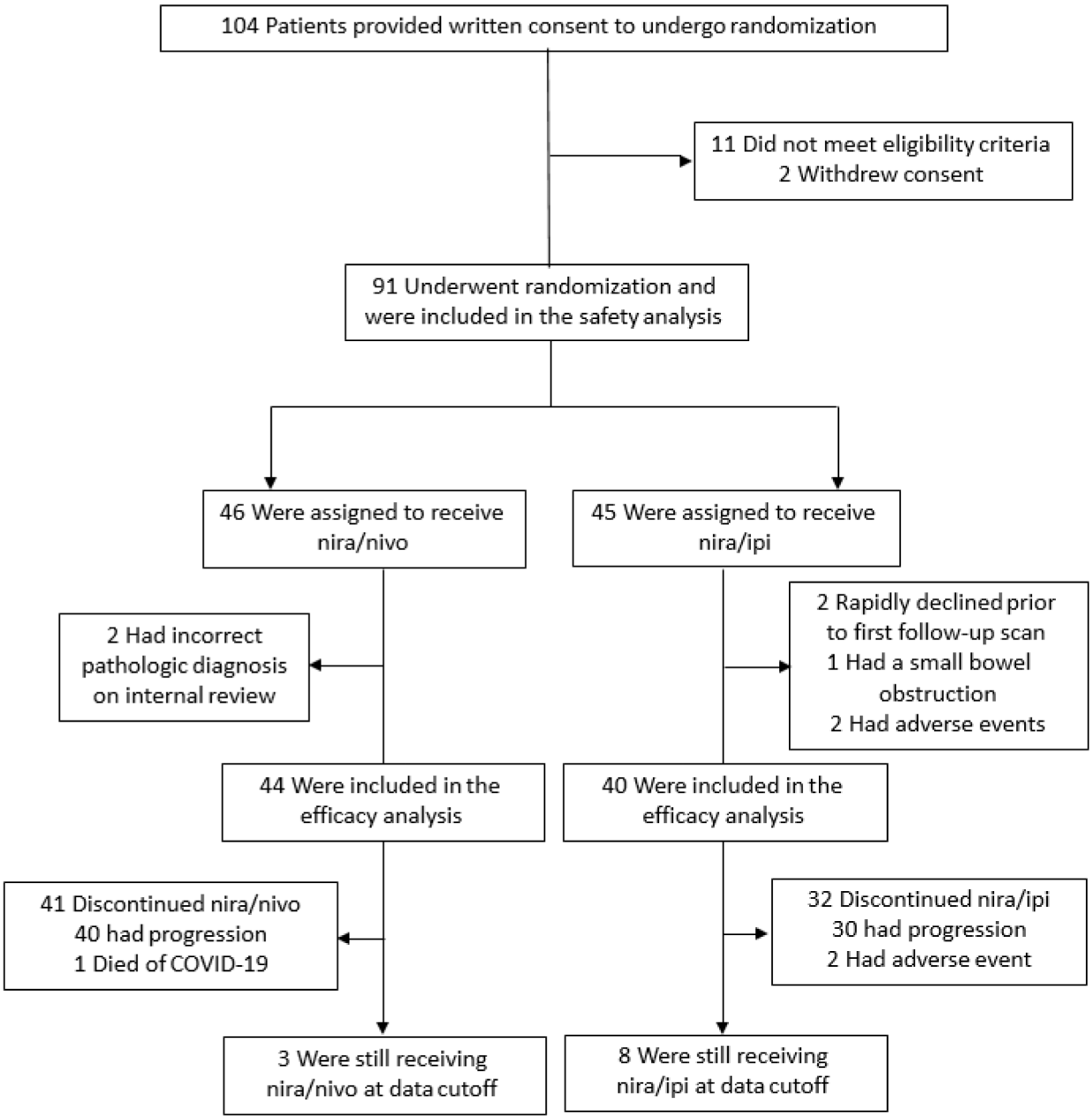
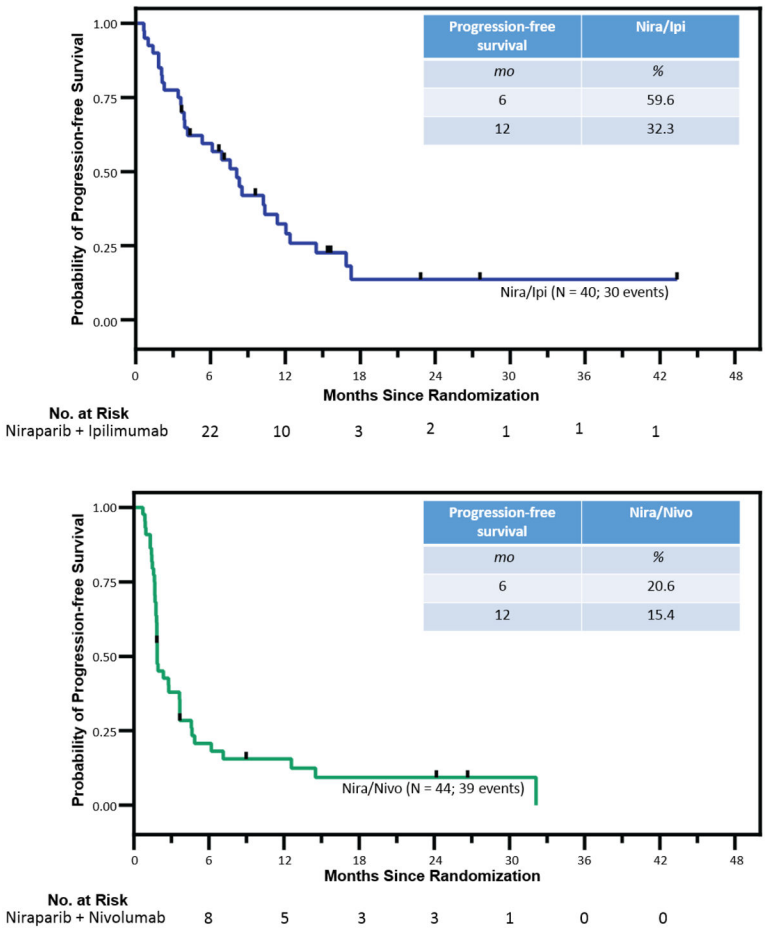


Figure 1. CONSORT Diagram.

A



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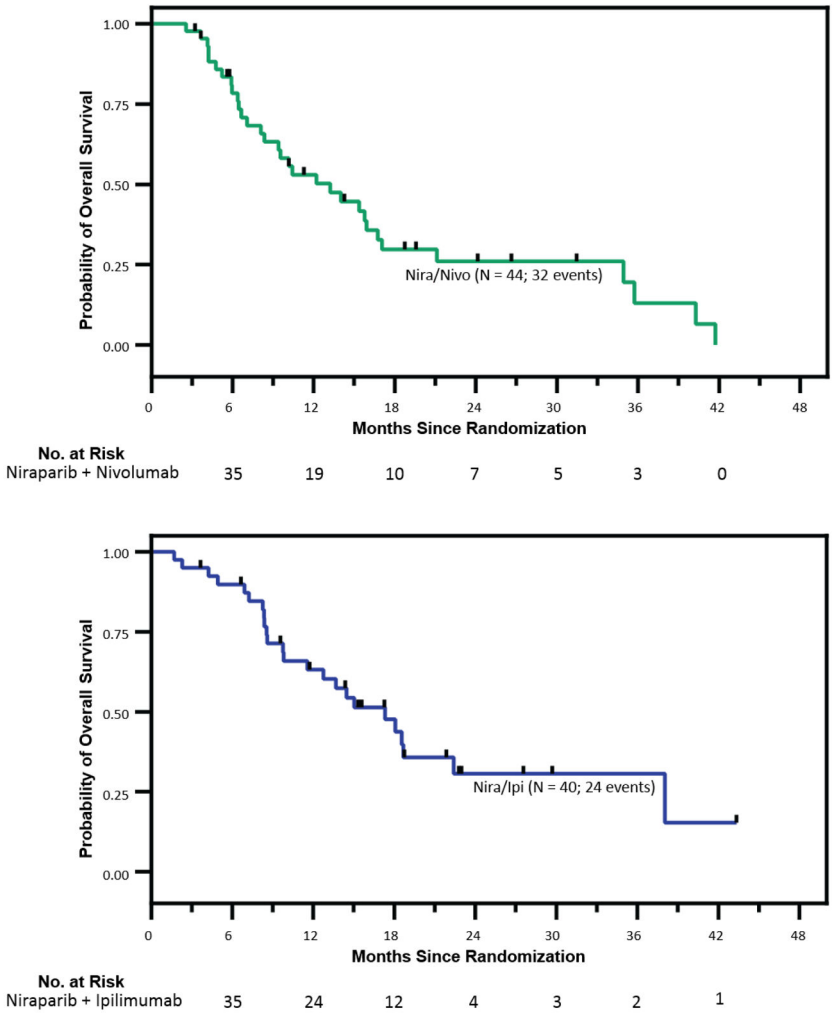

Figure 2. Kaplan-Meier estimates of progression-free survival and overall survival.

Panel A shows Kaplan-Meier estimates of progression-free survival (based on blinded independent central review) with a median PFS of 1.9 mo in nira/nivo and PFS 8.1 mo in nira/ipi. Panel B shows Kaplan Meier estimates of overall survival with a median OS of 14.0 mo in nira/nivo and 17.3 mo in nira/ipi.

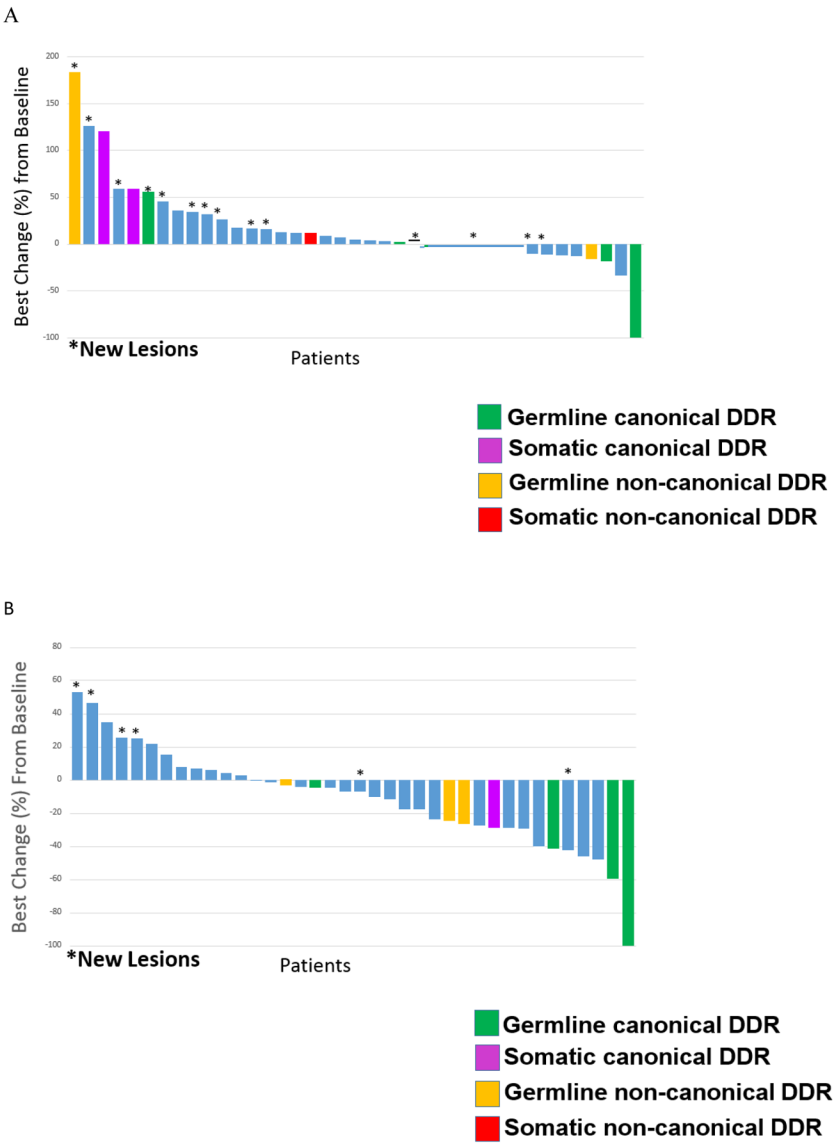

Figure 3. Waterfall plot of best responses of the 77 patients with measurable disease at study start.

Panel A shows best responses of the 39 patients with baseline measurable disease in the nira/nivo arm. Panel B shows best responses of the 38 patients with baseline measurable disease in the nira/ipi arm.

Table 1.

Baseline Characteristics of the Efficacy Population

Baseline Characteristics		**Arm A: PARP+NIVO, N=44**	**ARM B: PARP+IPI, N=40**
		No (%)	**No (%)**
Sex	Male	29 (66)	20 (50)
	Female	15 (34)	20 (50)
Age	Mean	65	63
	IQR	54-73	58-69
Race	White	38 (86)	37 (92)
	Black	3 (7)	3 (7)
	Asian	2 (4)	0 (0)
	Other	1 (2)	0 (0)
Ethnicity	Hispanic	0 (0)	0 (0)
	Non-Hispanic	44 (100)	40 (100)
ECOG Performance	0	29 (66)	22 (55)
	1	15 (34)	18 (45)
Measurable Disease	No	4 (9)	1 (2)
	Yes	40 (91)	39 (97)
Stage at Enrollment	Metastatic	36 (82)	32 (80)
	Locally Advanced	8 (18)	8 (20)
Time on Palliative Platinum Treatment	= 16 weeks	18 (41)	18 (45)
	> 16 weeks	26 (59)	22 (55)
Platinum Regimen	FOLFIRINOX	36 (82)	32 (80)
	Cis/Gem	2 (4)	1 (2)
	FOLFOX or CAPOX	6 (14)	6 (15)
	Other	0 (0)	1 (2)
Platinum Line of Treatment	First Line	39 (89)	33 (82)
	Second Line	5 (11)	6 (15)
	Third Line	0 (0)	1 (2)
Any DDR Variant	No	32 (73)	30 (75)
	Yes	12 (27)	10 (25)
	gATM	3 (7)	1 (2)
	gBRIP1	1 (2)	0 (0)
	sFANCA	1 (2)	0 (0)
	gRAD50	0 (0)	1 (2)
	gCHEK2	0 (0)	1 (2)
	BRCA or *PALB2*	7 (16)	7 (17)
Core DDR Variant (*BRCA* or *PALB2*)	No	37 (84)	33 (82)
	Yes	7 (16)	7 (17)
	gBRCA1	1 (2)	4 (10)

Baseline Characteristics		**Arm A: PARP+NIVO, N=44**	**ARM B: PARP+IPI, N=40**
		No (%)	**No (%)**
	gBRCA2	5 (11)	1 (2)
	gPALB2	0 (0)	1 (2)
	sBRCA1	0 (0)	1 (2)
	sPALB2	1 (2)	0 (0)
Family/Personal Hx of *BRCA*-Related Cancer *	No	14 (44)	15 (50)
	Yes	18 (49)	15 (50)
Sites of Disease at Enrollment	Pancreas only	6 (14)	6 (15)
	Liver	26 (59)	24 (60)
	Lung	9 (20)	6 (15)
	Peritoneum	5 (11)	7 (17)
	Bone	2 (4)	1 (2)
	Nodal	7 (16)	5 (12)
Underwent Germline Testing	Yes	42 (95)	39 (97)
	No	2 (4)	1 (2)
Underwent Somatic Testing	Yes, Liquid	6 (14)	1 (2)
	Yes, Tumor	19 (43)	15 (37)
	Yes, Unknown	0 (0)	2 (5)
	No	19 (43)	22 (55)
KRAS Mutation	Yes (% of known)	21 (81)	14 (82)
	No (% of known)	5 (19)	3 (18)
	Unknown	18 (41)	23 (57)
Stable, Progressing [1] or Mixed Response at Enrollment	Stable/Responding	38 (86)	34 (85)
	Progressing	4 (9)	4 (10)
	Mixed Response	2 (4)	2 (5)
CA 19-9 (U/mL)	Mean	1,831	1,710
	Range	1-37,501	1-35,960
Albumin (g/dL)	Mean	3.99	3.91
	Range	3-4.6	3.1-4.6
Total WBC (THO/uL)	Mean	6.55	5.98
	Range	3.4-36.8	2.5-11.2
Neutrophil to Lymphocyte Ratio (THO/uL)	Mean	3.51	3.50
	Range	0.87-12.48	0.91-13.8

[1] Patients who were progressing radiographically on non-platinum based treatment (such as FOLFIRI or 5FU/LV) were permitted to enroll.

* Only patients without a known DDR variant were assessed for personal or family history of *BRCA*-related cancers.

Table 2.

Efficacy Data by Arm

Arm	PFS6	ORR (measurable only)	mPFS	mOS	mPFS (non-*BRCA* or *PALB2*)	mOS (non-*BRCA* or *PALB2*)	mPFS (no DDR variant)	mOS (no DDR variant)
	% (95% CI)		Mo (95% CI)					
Nira/Nivo	N = 44	N = 42	N = 44	N = 44	N = 37	N = 37	N = 32	N = 32
Nira/Ipi	N = 40	N = 39	N = 40	N = 40	N = 33	N = 33	N = 30	N = 30
Nira/Nivo	*20.6 (8.3-32.9) p=0.0002 vs 44%*	7.1 (1.5-19.5)	*1.9 (1.4-2.3)*	13.2 (8.1-16.7)	*1.9 (1.8-1.9)*	13.2 (8.1-16.7)	*1.8 (1.8-1.9)*	13.2 (6.1-20.3)
Nira/Ipi	*59.6 (44.3-74.9) p=0.045 vs 44%*	15.4 (5.9-30.5)	*8.1 (5.5-10.6)*	17.3 (12.8-21.9)	*7.6 (4.0-11.1)*	17.3 (12.5-22.2)	*7.6 (2.8-12.3)*	15.0 (4.3-25.7)

Italics indicate lack of overlap between CIs

Table 3.

Adverse Events Deemed at Least Possibly Related to Therapy in the Safety Population

	Arm A (Niraparib + Nivolumab); N = 46			Arm B (Niraparib + Ipilimumab); N = 45		
	Number (Percentage)					
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
GASTROINTESTINAL						
Abdominal Pain	6 (13)	0	0	1(2)	1(2)	0
ALT Increased	7 (15)	0	0	11 (25)	2(4)	0
AST Increased	8 (17)	0	0	16 (36)	0	0
Alkaline Phosphatase Increased	7 (15)	0	0	5 (11)	0	0
Anorexia	3(6)	0	0	2 (4)	0	0
Bilirubin Increased	1(2)	1(2)	1(2)	2(4)	0	0
Colitis	1(2)	1(2)	0	0	1(2)	0
Diarrhea	3(6)	0	0	7 (16)	0	0
Constipation	1(2)	1(2)	0	3 (7)	0	0
Dysgeusia	3(6)	0	0	1(2)	0	0
Dyspepsia	0	0	0	2(4)	0	0
Gastritis	1(2)	0	0	2(4)	0	0
Nausea	11 (23)	0	0	17 (39)	1(2)	0
Vomiting	5 (11)	0	0	4 (9)	1(2)	0
Mucositis	1(2)	0	0	1(2)	0	0
Flatulence	2(4)	0	0	0	0	0
Clinical Pancreatitis	1(2)	0	0	0	0	0
HEMATOLOGIC						
Anemia	6 (13)	2(4)	0	14 (32)	5 (11)	0
Neutropenia	5 (11)	0	1(2)	4 (9)	2(4)	0
Thrombocytopenia	12 (25)	1(2)	1(2)	18 (41)	0	2(4)
Leukopenia	1(2)	1(2)	0	3 (7)	0	0
Eosinophilia	0	0	0	1(2)	0	0
PULMONARY						

	Arm A (Niraparib + Nivolumab); N = 46			Arm B (Niraparib + Ipilimumab); N = 45		
	Number (Percentage)					
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Cough	2(4)	0	0	2(4)	0	0
Dyspnea	4 (8)	0	0	2(4)	0	0
Pneumonitis	1(2)	0	0	2(4)	2(4)	0
Pulmonary Edema	0	0	0	0	1(2)	0
ENDOCRINE						
Adrenal Insufficiency	0	0	0	1(2)	0	0
Hypophysitis	0	0	0	1(2)	0	0
Hypothyroidism	0	0	0	1(2)	0	0
Hyperthyroidism	2(4)	0	0	3 (7)	0	0
RENAL						
Acute Kidney Injury	5 (11)	0	0	5 (11)	1(2)	0
Hyperkalemia	0	0	0	1(2)	1(2)	0
Hypomagnesemia	3(6)	0	0	3 (7)	0	0
Hyponatremia	3(6)	0	0	2(4)	0	0
Hyperphosphatemia	1(2)	0	0	0	0	0
Hypocalcemia	1(2)	0	0	0	0	0
INTEGUMENTARY						
Arthralgias	12 (25)	0	0	7 (16)	2(4)	0
Dry Eyes	0	0	0	1(2)	0	0
Dry Mouth	1(2)	0	0	3 (7)	0	0
Dry Skin	0	0	0	1(2)	0	0
Limb Edema	0	0	0	1(2)	0	0
Photosensitivity	2(4)	0	0	0	0	0
Rash	5 (11)	0	0	12 (27)	3 (7)	
CONSTITUTIONAL						
Fatigue	11 (23)	0	0	13 (29)	6 (14)	0
Fever	4 (8)	0	0	6 (14)	1(2)	0

	Arm A (Niraparib + Nivolumab); N = 46			Arm B (Niraparib + Ipilimumab); N = 45		
	Number (Percentage)					
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Hot Flashes	2(4)	0	0	2(4)	0	0
Night Sweats	1(2)	0	0	2(4)	0	0
Insomnia	6 (13)	1(2)	0	1(2)	0	0
Pruritus	3(6)	0	0	4 (9)	1(2)	0
Generalized Weakness	1(2)	0	0	0	1(2)	0
Weight Loss	2(4)	0	0	2(4)	0	0
VASCULAR						
Hypertension	0	4 (8)	0	2(4)	4 (9)	0
Headache	5 (11)	0	0	6 (14)	0	0
Hyperlipidemia	0	0	0	1(2)	0	0
NEUROLOGICAL						
Insomnia	6 (13)	1(2)	0	0	0	0
Blurred Vision	1(2)	0	0	0	0	0
Dizziness	2(4)	0	0	2(4)	0	0
Neuropathy	1(2)	0	0	1(2)	0	0

No treatment-related grade 5 events occurred during the course of the study.