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ORIGINAL REPORT

Olaparib Monotherapy in Patients With Advanced Cancer and a Germline *BRCA1/2* Mutation

Bella Kaufman, Ronnie Shapira-Frommer, Rita K. Schmutzler, M. William Audeh, Michael Friedlander, Judith Balmaña, Gillian Mitchell, Georgeta Fried, Salomon M. Stemmer, Ayala Hubert, Ora Rosengarten, Mariana Steiner, Niklas Loman, Karin Bowen, Anitra Fielding, and Susan M. Domchek

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A B S T R A C T

Purpose
Olaparib is an oral poly (ADP-ribose) polymerase inhibitor with activity in germline *BRCA1* and *BRCA2* (*BRCA1/2*) –associated breast and ovarian cancers. We evaluated the efficacy and safety of olaparib in a spectrum of *BRCA1/2*-associated cancers.

Patients and Methods
This multicenter phase II study enrolled individuals with a germline *BRCA1/2* mutation and recurrent cancer. Eligibility included ovarian cancer resistant to prior platinum; breast cancer with ≥ three chemotherapy regimens for metastatic disease; pancreatic cancer with prior gemcitabine treatment; or prostate cancer with progression on hormonal and one systemic therapy. Olaparib was administered at 400 mg twice per day. The primary efficacy end point was tumor response rate.

Results
A total of 298 patients received treatment and were evaluable. The tumor response rate was 26.2% (78 of 298; 95% CI, 21.3 to 31.6) overall and 31.1% (60 of 193; 95% CI, 24.6 to 38.1), 12.9% (eight of 62; 95% CI, 5.7 to 23.9), 21.7% (five of 23; 95% CI, 7.5 to 43.7), and 50.0% (four of eight; 95% CI, 15.7 to 84.3) in ovarian, breast, pancreatic, and prostate cancers, respectively. Stable disease ≥ 8 weeks was observed in 42% of patients (95% CI, 36.0 to 47.4), including 40% (95% CI, 33.4 to 47.7), 47% (95% CI, 34.0 to 59.9), 35% (95% CI, 16.4 to 57.3), and 25% (95% CI, 3.2 to 65.1) of those with ovarian, breast, pancreatic, or prostate cancer, respectively. The most common adverse events (AEs) were fatigue, nausea, and vomiting. Grade ≥ 3 AEs were reported for 54% of patients; anemia was the most common (17%).

Conclusion
Responses to olaparib were observed across different tumor types associated with germline *BRCA1*/2 mutations. Olaparib warrants further investigation in confirmatory studies.

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Bella Kaufman and Ronnie Shapira-Frommer, Sheba Medical Center, Tel Hashomer; Georgeta Fried, Institute of Oncology, Rambam Health Care Campus; Mariana Steiner, Linn Medical Centre, Haifa; Salomon M. Stemmer, Rabin Medical Center, Petah Tikva; Ayala Hubert, Hadassah-Hebrew University Hospital, Sharett Institute of Oncology; Ora Rosengarten, Shaare Zedek Medical Centre, Jerusalem, Israel; Rita K. Schmutzler, Center for Familial Breast and Ovarian Cancer and Center of Integrated Oncology, Cologne, Germany; M. William Audeh, Samuel Oschin Cancer Institute, Los Angeles, CA; Michael Friedlander, Prince of Wales Clinical School, University of New South Wales, Sydney, New South Wales; Gillian Mitchell, Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Victoria, Australia; Judith Balmaña, Vall d'Hebron Institute of Oncology, Barcelona, Spain; Niklas Loman, Skånes Universitetssjuk Lund, Lund, Sweden; Karin Bowen and Anitra Fielding, AstraZeneca, Macclesfield, United Kingdom; and Susan M. Domchek, Basser Research Center and Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA.

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Corresponding author: Susan M. Domchek, MD, Abramson Cancer Center, University of Pennsylvania, 3400 Civic Center Blvd, 3 West Pavilion, Philadelphia, PA 19104; e-mail: susan.domchek@uphs.upenn.edu.

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INTRODUCTION

Poly (ADP-ribose) polymerase (PARP) inhibitors have been studied as potential cancer therapeutics in breast and ovarian cancers. PARP inhibitors have several documented mechanisms of action, including the inhibition of base excision repair (via blockade of enzymatic function) as well as trapping of PARP.[1-3] These mechanisms lead to the induction of double-stranded breaks after stalling and collapse of the DNA replication forks. Tumors in which there is an apparent defect in homologous DNA repair (and thus defect in repair of double-stranded breaks) seem to be susceptible to PARP inhibitor therapy. These include tumors associated with germline or somatic mutations in *BRCA1* and *BRCA2* (*BRCA1/2*).

Clinical trials to date have demonstrated tumor responses and/or progression-free survival (PFS) benefit with the orally active PARP inhibitor olaparib as well as other PARP inhibitors in breast and ovarian cancers associated with germline *BRCA1/2* mutations.[4-8] The underlying biology suggests that PARP inhibitors may also prove effective in other cancers, such as prostate and pancreatic, for which subpopulations of patients with a *BRCA1/2* mutation exist. There have been isolated reports of responses of germline *BRCA1/2*-associated prostate and pancreatic cancers to PARP inhibitors,[9,10] and thus, this is a population of interest. In addition, data are limited in germline *BRCA1/2* mutation carriers with platinum-resistant ovarian cancer and chemotherapy-refractory breast cancer.[11] Here, we

report results from an open-label noncomparative study examining olaparib monotherapy in germline *BRCA1/2*-associated cancers, regardless of tumor type.

PATIENTS AND METHODS

Study Design

This prospective, multicenter, nonrandomized phase II study included individuals with a known deleterious germline mutation in *BRCA1/2* and advanced solid tumor. Patients were treated continuously with oral olaparib 400 mg twice per day (capsule formulation) until disease progression. In the event of toxicity, dose reductions (to 200 mg twice per day or 100 mg twice per day, if necessary) and interruptions were permitted. Patients were enrolled and treated at 13 centers in Israel, Australia, Germany, Spain, Sweden, and the United States between February 21, 2010, and July 31, 2012.

Patients

Individuals (age ≥ 18 years) with a confirmed germline loss-of-function *BRCA1* or *BRCA2* mutation deemed deleterious or suspected deleterious by local practice before consent and advanced solid tumor were enrolled. Eligibility criteria included ≥ one measurable or evaluable lesion according to RECIST (version 1.1), Eastern Cooperative Oncology Group performance status of 0 to 2, and life expectancy ≥ 16 weeks. Further eligibility included one of the following: platinum-resistant (relapse within 6 months of platinum therapy) epithelial ovarian, primary peritoneal, or fallopian tube cancer (or unsuitable for further platinum therapy); breast cancer with progression despite ≥ three previous lines of chemotherapy (hormone receptor–positive and human epidermal growth factor receptor 2–positive patients also had to have not responded to hormonal and trastuzumab therapy, respectively, in advanced setting); pancreatic cancer with progression during gemcitabine treatment in the advanced setting (or felt to be unsuitable for gemcitabine); hormone-refractory prostate cancer with ≥ two consecutive rising prostate-specific antigen (PSA) values above their nadir, progression despite ≥ one systemic therapy course, and no anti–androgen therapy for 6 weeks before study entry; and other tumor types with progression despite ≥ one therapy course in the metastatic setting.

Patients were excluded for the following: receipt of prior PARP inhibitors; prior malignancy, active or treated within 5 years, with the exception of a second suspected *BRCA*-related malignancy, treated in situ cervical carcinoma, stage I endometrial cancer, or nonmelanoma skin cancer; receipt of systemic chemotherapy or radiotherapy within 2 weeks of study (stable doses of bisphosphonates for bone metastases and luteinizing hormone-releasing hormone in patients with prostate cancer were permitted); use of potent inhibitors of CYP4503A4 (CYP3A4); persistent therapy-related toxicities (grade > 2 according to Common Terminology Criteria for Adverse Events); major surgery < 2 weeks before study; symptomatic uncontrolled brain metastases; and other medical conditions suggesting poor medical risk. Patients provided written informed consent. The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by the independent ethics committee or institutional review board at every trial center.

Study End Points

The primary end point was tumor response rate (in all patients) according to RECIST, with confirmation of response at least 28 days apart. Tumor assessments according to RECIST were performed at baseline and at the end of every two cycles (28 days per cycle), up to and including the withdrawal visit. Secondary end points included: objective response rate (in those with measurable disease at baseline), PFS, and duration of response. Safety and tolerability were assessed by adverse events (AEs) and changes in laboratory parameters according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3).

Statistical Analysis

The safety and intention-to-treat populations (full analysis set) comprised all patients who received ≥ one dose of olaparib. Efficacy data are reported for the full analysis set unless otherwise specified. The first patient was enrolled on February 21, 2010, and the study database was locked on July 31, 2012. Statistical analyses were performed by the sponsor with SAS software (version 9.1.3; SAS Institute, Cary, NC). 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. Binomial distribution was used to calculate 95% CIs. Kaplan-Meier plots of PFS are presented by cancer type.

Role of Funding Source

The sponsor designed the study in collaboration with the study investigators but did not participate in data collection. The sponsor performed the statistical analysis. B.K. and S.M.D. had full access to all of the data in the study, wrote the initial draft of the manuscript, and had final responsibility for the decision to submit for publication.

RESULTS

A total of 317 patients with advanced cancer and a confirmed germline *BRCA1/2* mutation were screened for eligibility, of whom 298 (94%) were enrolled and received ≥ one dose of olaparib. Table 1 lists the baseline characteristics of patients.

Of the 193 patients in the ovarian cancer cohort, 178 had ovarian cancer, four had fallopian tube cancer, and 11 had primary peritoneal cancer; 148 (77%) of those in the ovarian cancer cohort had a germline mutation in *BRCA1*, 44 (23%) had a *BRCA2* mutation, and one had a germline mutation in both *BRCA1* and *BCRA2*. These patients were heavily pretreated, with a mean number of prior regimens of 4.3 (standard deviation [SD], 2.2; range one to 14). All patients had received prior platinum and were considered to be platinum resistant or not suitable for further platinum therapy. The most common chemotherapeutic agents received included carboplatin (99.5%), paclitaxel (95%), liposomal doxorubicin (64%), and gemcitabine (44%). In addition, 28% of these patients received cisplatin.

Of the 62 patients with breast cancer, 37 (60%) had a *BRCA1* mutation (Table 1). The mean number of prior chemotherapy courses for metastatic disease was 4.6 (SD, two; range, three to 11); 67.8% of patients (42 of 62) had received prior platinum (cisplatin, 26%; carboplatin, 48%); > 75% of patients had received prior cyclophosphamide, doxorubicin, or paclitaxel, and > 45% had received flurouracil, capecitabine, docetaxel, or gemcitabine.

Of the 23 individuals with advanced pancreatic cancer, 17 (74%) had a *BRCA2* mutation, and one had a mutation in both *BRCA1* and *BRCA2*. The mean number of prior therapies was two (SD, 1.6; range, one to eight); all but one had received gemcitabine, and 65% had received prior platinum. Prior chemotherapy included cisplatin (35%), carboplatin (9%), and oxaliplatin (30%).

Eight patients had metastatic prostate cancer, of whom seven had a *BRCA2* mutation. The median number of prior therapies was two. All patients had experienced disease progression despite hormonal therapy; 75% had received prior docetaxel, and 50% had received prior platinum (carboplatin or cisplatin). The remaining 12 patients had a range of cancers, including cancers of the biliary tract (n = 4), bladder (n = 2), colorectum (n = 1), lung (n = 3), esophagus (n = 1), and uterus (n = 1; Table 1).

Table 1. Baseline Patient Demographic and Clinical Characteristics by Tumor Type

Characteristic	Ovarian (n = 193)*		Breast (n = 62)		Pancreas (n = 23)		Prostate (n = 8)		Other (n = 12)†		Total (N = 298)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years												
Median	57		48		58		71		56		56	
Range	29-79		29-73		43-73		51-77		36-74		29-79	
Sex												
Female	193	100.0	61	98.4	10	43.5	0	0.0	8	66.7	272	91.3
ECOG PS												
0	113	58.5	32	51.6	11	47.8	1	12.5	6	50.0	163	54.7
1	69	35.8	27	43.5	9	39.1	4	50.0	6	50.0	115	38.6
2	10	5.2	3	4.8	3	13.0	3	37.5	0	0.0	19	6.4
BRCA status												
BRCA1 mutation	148	76.7	37	59.7	5	21.7	1	12.5	7	58.3	198	66.4
BRCA2 mutation	44	22.8	25	40.3	17	73.9	7	87.5	5	41.7	98	32.9
BRCA1 and *BRCA2* mutation	1	0.5	0	0.0	1	4.3	0	0.0	0	0.0	2	0.7
No. of prior regimens for advanced disease												
Mean	4.3		4.6		2.0		2.0		2.2		4.0	
SD	2.2		2.0		1.6		1.0		1.3		2.2	
Measurable disease at baseline	167	86.5	58	93.5	23	100.0	7	87.5	11	91.7	266	89.3

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.
*Includes ovary (n = 178), fallopian tubes (n = 4), peritoneum (n = 9), and primary peritoneal (n = 2).
†Includes biliary tract (n = 4), bladder (n = 2), colorectal (n = 1), lung (n = 3), mediastinal (esophagus; n = 1), and uterus (n = 1).

Tumor Response, Overall Response Rate, and Duration of Response

The tumor response rate for all 298 patients was 26.2% (n = 78 of 298; 95% CI, 21.3 to 31.6; Table 2); 31.1% (95% CI, 24.6 to 38.1), 12.9% (95% CI, 5.7 to 23.9), 21.7% (95% CI, 7.5 to 43.7), and 50.0% (95% CI, 15.7 to 84.3) of patients with ovarian, breast, pancreatic, and prostate cancers, respectively, achieved a response. Stable disease that persisted ≥ 8 weeks was observed in 41.6% of patients (n = 124 of 298; 95% CI, 36.0 to 47.4; Table 2), including 40.4% of those with ovarian cancer (n = 78; 95% CI, 33.4 to 47.7), 46.8% of those with breast cancer (n = 29; 95% CI, 34.0 to 59.9), 34.8% of those with pancreatic cancer (n = 8; 95% CI, 16.4 to 57.3), 25% of those with prostate cancer (n = 2; 95% CI, 3.2 to 65.1), and 58.3% of other patients (n = 7; 95% CI, 27.7 to 84.8). Overall median duration of response was 208 days (ovarian cancer, 225 days; breast cancer, 204 days; pancreatic cancer, 134 days; prostate cancer, 327 days). Median time to onset of response

Table 2. Tumor Response Rates (full analysis set)

Response	Ovarian (n = 193)		Breast (n = 62)		Pancreas (n = 23)		Prostate (n = 8)		Other (n = 12)		Total (N = 298)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Tumor response rate	60	31.1	8	12.9	5	21.7	4	50.0	1	8.3	78	26.2
95% CI	24.6 to 38.1		5.7 to 23.9		7.5 to 43.7		15.7 to 84.3		0.02 to 38.5		21.3 to 31.6	
CR*	6	3	0	0	1	4	0	0	0	0	7	2
PR*	54	28	8	13	4	17	4	50	1	8	71	24
Stable disease ≥ 8 weeks	78	40	29	47	8	35	2	25	7	58	124	42
95% CI	33.4 to 47.7		34.0 to 59.9		16.4 to 57.3		3.2 to 65.1		27.7 to 84.8		36.0 to 47.4	
Stable disease	64	33	22	36	5	22	2	25	6	50	99	33
Unconfirmed PR	12	6	7	11	3	13	0	0	1	8	23	8
PD†	41	21	23	37	9	39	2	25	3	25	78	26
95% CI	15.7 to 27.7		25.2 to 50.3		19.7 to 61.5		3.2 to 65.1		5.5 to 57.2		21.3 to 31.6	
RECIST progression	33	17	16	26	6	26	1	13	3	25	59	20
Early death‡	8	4	7	11	3	13	1	13	0	0	19	6
Not evaluable	14	7	2	3	1	4	0	0	1	8	18	6
No follow-up assessments	12	6	2	3	1	4	0	0	0	0	15	5
Stable disease < 8 weeks	2	1	0	0	0	0	0	0	1	8	3	1

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response.
*Response confirmed ≥ 4 weeks after initial observation of response.
†Progression events that occurred within 118 days of last evaluable assessment during first 182 days of treatment period or that occurred within 174 days of last evaluable assessment after first 182 days of treatment period.
‡Death in absence of evaluable RECIST assessment.

Table 3. Tumor Response Rates by Prior Platinum Chemotherapy and Tumor Type

Prior Platinum Use	No. of Patients	No. of Responses	Response Rate (%)	95% CI (%)
Breast				
Yes	42	4	9.5	2.7 to 22.6
No	20	4	20.0	5.7 to 43.7
Pancreas				
Yes	15	3	20.0	4.3 to 48.1
No	8	2	25.0	3.2 to 65.1
Prostate				
Yes	4	1	25.0	0.6 to 80.6
No	4	3	75.0	19.4 to 99.4
Other				
Yes	9	1	11.1	0.3 to 48.3
No	3	0	0.0	0.0 to 70.8

was 56.0 days (ovarian cancer, 56.5 days; breast cancer, 54.5 days; pancreatic cancer, 113.0 days; prostate cancer, 54.5 days). The objective response rate (restricted to those with measurable disease at baseline) was 29.3% (95% CI, 23.9 to 35.2).

Response Rate by BRCA1 *Versus* BRCA2 *Status*

Response rates were similar for patients with a *BRCA1* mutation (26.3%; 95% CI, 20.3 to 33.0) and those with a *BRCA2* mutation (26.5%; 95% CI, 18.1 to 36.4) and seemed similar across tumor types (Appendix Table A1, online only).

Response by Prior Platinum

Tumor response rates in patients within each tumor type are listed according to prior platinum chemotherapy use (yes *v* no) in Table 3. Patients with ovarian cancer are excluded, because all had prior platinum chemotherapy. There was no apparent difference in response rates in those with (20%; 95% CI, 4.3 to 48.1) or without (25%; 95% CI, 3.2 to 65.1) prior platinum for pancreatic cancer. Patients with breast cancer with prior platinum exposure had a response rate of 9.5% (95% CI, 2.7 to 22.6) compared with 20% (95% CI, 5.7 to 43.7) in those without prior platinum; however, the CIs associated with these responses overlap.

Response by Estrogen Receptor Status in Breast Cancer Cohort

Of the 32 patients with estrogen receptor (ER) –positive breast cancer, four (12.5%; 95% CI, 3.5 to 29.0) had a tumor response to olaparib, compared with four of 30 (13.3%; 95% CI, 3.8 to 30.7) of those with ER-negative breast cancer.

PFS and Overall Survival

PFS and overall survival (OS) are shown in Figures 1 and 2, respectively. Median PFS was 7, 3.7, 4.6, and 7.2 months in the ovarian, breast, pancreatic, and prostate cancer groups, respectively. The proportion of patients who were progression free at 6 months was 54.6%, 29.0%, 36.4%, and 62.5% in the ovarian, breast, pancreatic, and prostate cancer groups, respectively. Median OS was 16.6, 11, 9.8, and 18.4 months in the ovarian, breast, pancreatic, and prostate groups, respectively. The proportion of patients alive at 12 months was 64.4%, 44.7%, 40.9%, and 50.0% in the ovarian, breast, pancreatic, and prostate cancer groups, respectively.

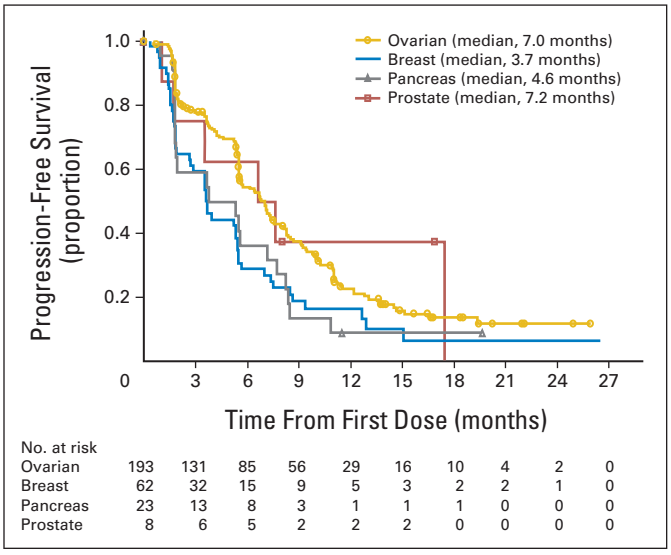

Fig 1. Progression-free survival.

Treatment Exposure

Median total duration of olaparib treatment was 166.5 days, ranging from 112.5 to 223.5 days for patients with breast and prostate cancers, respectively. Thirty-three patients remained on study treatment at data cutoff. Overall, 119 patients (40%) required a dose interruption, ranging from 30% of patients with pancreatic cancer to 50% of those with prostate cancer.

Tolerability

The most common AEs are listed in Table 4. Grade ≥ 3 AEs were experienced by 162 (54.4%) of 298 patients; 92 patients (30.9%) experienced grade ≥ 3 AEs considered causally related to olaparib; the most frequently reported were anemia and fatigue.

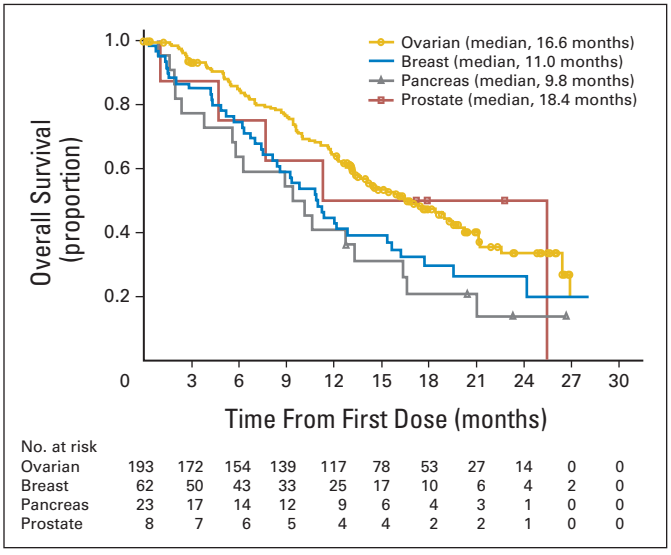

Fig 2. Overall survival.

Table 4. Any-Grade AEs Reported in > 15% of Patients Overall or Grade ≥ 3 AEs Reported in > 5% of Patients Overall

	Ovarian (n = 193)				Breast (n = 62)				Pancreas (n = 23)				Prostate (n = 8)				Other (n = 12)				Total (N = 298)			
	Any Grade		Grade ≥ 3		Any Grade		Grade ≥ 3		Any Grade		Grade ≥ 3		Any Grade		Grade ≥ 3		Any Grade		Grade ≥ 3		Any Grade		Grade ≥ 3	
AE	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Fatigue	116	60.1	12	6.2	30	48.4	3	4.8	17	73.9	3	13.0	1	12.5	0	0.0	12	100.0	1	8.3	176	59.1	19	6.4
Nausea	119	61.7	1	0.5	33	53.2	0	0.0	11	47.8	0	0.0	3	37.5	0	0.0	10	83.3	0	0.0	176	59.1	1	0.3
Vomiting	75	38.9	5	2.6	21	33.9	1	1.6	9	39.1	1	4.3	0	0.0	0	0.0	6	50.0	0	0.0	111	37.2	7	2.3
Anemia	62	32.1	36	18.7	16	25.8	9	14.5	9	39.1	4	17.4	5	62.5	1	12.5	6	50.0	2	16.7	98	32.9	52	17.4
Diarrhea	56	29.0	3	1.6	11	17.7	1	1.6	7	30.4	0	0.0	3	37.5	0	0.0	4	33.3	0	0.0	81	27.2	4	1.3
Abdominal pain	58	30.1	14	7.3	5	8.1	1	1.6	7	30.4	1	4.3	0	0.0	0	0.0	7	58.3	1	8.3	77	25.8	17	5.7
Decreased appetite	36	18.7	1	0.5	17	27.4	0	0.0	4	17.4	0	0.0	2	25.0	0	0.0	3	25.0	0	0.0	62	20.8	1	0.3
Dyspepsia	38	19.7	0	0.0	9	14.5	0	0.0	2	8.7	0	0.0	0	0.0	0	0.0	3	25.0	0	0.0	52	17.4	0	0.0
Headache	32	16.6	0	0.0	14	22.6	1	1.6	1	4.3	0	0.0	0	0.0	0	0.0	1	8.3	0	0.0	48	16.1	1	0.3
Dysgeusia	39	20.2	0	0.0	4	6.5	0	0.0	1	4.3	0	0.0	0	0.0	0	0.0	3	25.0	0	0.0	47	15.8	0	0.0

Abbreviation: AE, adverse event.

Serious AEs were seen in 30.1%, 25.8%, 30.4%, and 50.0% of the ovarian, breast, pancreatic, and prostate cancer groups, respectively. In these groups, 10.4%, 9.7%, 17.4%, and 12.5% of patients, respectively, experienced serious AEs considered causally related to olaparib. Nine patients died as a result of AEs, including sepsis (n = 2), leukemia (n = 2), chronic obstructive pulmonary disease (n = 1), pulmonary embolism (n = 1), myelodysplastic syndrome (MDS; n = 1; reported during post–follow-up period), wound dehiscence (n = 1), and cerebrovascular accident (n = 1). Two events (sepsis and MDS) were considered causally related to olaparib.

The two patients with leukemia and the one patient with MDS were treated with 188, 155, and 296 days of olaparib, respectively, for recurrent primary peritoneal cancer (n = 1) and ovarian cancer (n = 2). One patient also had prior breast cancer, and all three patients were heavily pretreated with prior chemotherapy, having received a total of 34, 25, and 26 cycles of chemotherapy, respectively, before olaparib exposure.

Eleven patients (3.7%) experienced ≥ one AE that led to discontinuation of study treatment. These events were hyperbilirubinemia, anemia, gastroesophageal reflux, nausea, abdominal pain, transaminitis, cerebrovascular accident, intestinal obstruction, thrombocytopenia, leukopenia, vomiting, and hyponatremia. One hundred twenty (40.3%) of 298 patients experienced AEs that led to olaparib dose modification (interruption and/or reduction), including 29 patients (9.7%) with anemia, 21 (7%) with vomiting, and 15 (5%) with fatigue.

DISCUSSION

In this study of germline *BRCA1/2* mutation carriers, prolonged tumor responses were seen across a spectrum of malignancies, including ovarian, breast, pancreatic, and prostate cancers, supporting the hypothesis that therapy directed against a genetically defined target has activity regardless of anatomic organ of origin. Germline status of *BRCA1/2* in individuals with cancer defines a target population for whom PARP inhibitors seem beneficial.

By design, this was a single-arm phase II study, and therefore, it is not possible to directly compare responses with those expected with other agents. However, the response rate of 22% (95% CI, 7.5 to 43.7) in patients with metastatic pancreatic cancer who had received an average of two prior lines of chemotherapy for metastatic disease is a significant finding. Therapeutic options for those patients with pancreatic cancer with progression during first-line therapy are limited. In the first-line setting, disease response rates of 23% with gemcitabine plus nab-paclitaxel[12] and 31.6% with FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin)[13] have been seen. In the second-line setting, prospective data have shown modest results, with response rates to chemotherapy generally < 20%,[14] including with second-line FOLFIRINOX.[15] For the majority of patients in our study, olaparib was ≥ third-line therapy; thus, the findings are compelling and support further evaluation in this disease.

BRCA2-associated prostate cancer is more aggressive, with poorer survival.[16] For this reason, it is difficult to compare the response rate seen here with that of unselected prostate cancer, particularly given the small numbers. However, the 50% response rate (95% CI, 15.7 to 84.3) and 25% stable disease rate (95% CI, 3.2 to 65.1) are encouraging in a patient population with a mean of two prior cytotoxic regimens.

The response rate in patients with heavily pretreated refractory breast cancer was 12.9% (95% CI, 5.7 to 23.9), and an additional 47% of patients (95% CI, 34.0 to 59.9) had stable disease (including 11% with unconfirmed partial response). Neither ER status nor *BRCA* status seemed predictive of response. Tutt et al[4] reported a response rate of 41% (11 of 27) in patients with *BRCA1/2*-associated metastatic breast cancer with olaparib 400 mg twice per day. However, the participants included in our study were more heavily pretreated, with a mean of 4.6 prior chemotherapy regimens in the metastatic setting. To place this in context, eribulin was approved after a randomized trial demonstrating superiority to standard of care. The tumor response rate to eribulin was 13%, and patients had received a median of four prior chemotherapy regimens.[17]

Limited data are available on the activity of olaparib in platinum-resistant or -refractory ovarian cancer. Fong et [11] reported RECIST responses in eight (33.5%) of 24 platinum-resistant and zero (0%) of 13 platinum-refractory patients. In a randomized study comparing liposomal doxorubicin with olaparib 200 or 400 mg twice per day,

50% of the participants had platinum resistant disease. The response rate to olaparib 400 mg twice per day was 31%, but this was not reported by prior platinum status.[18] In our study, which included 193 patients with platinum-resistant ovarian cancer, the tumor response rate was 31% (95% CI, 24.6 to 38.1), and stable disease (at > 8 weeks) was seen in 40% of patients (95% CI, 33.4 to 47.7), confirming significant activity. Of note, patients were eligible for the study if they were deemed (by their primary oncologist) not suitable for further platinum therapy. This criterion was written with the intent to include those with significant toxicity or hypersensitivity to platinum. However, specific information on the percentage of patients fitting this criterion (as opposed to platinum-resistant disease) was not prospectively collected.

Mechanisms of PARP resistance in *BRCA1/2*-associated tumors have been proposed, including genetic reversion of truncating mutations in *BRCA1* or *BRCA2*, stabilization of mutant protein, loss of *53BP1*, and presence of hypomorphic *BRCA1* or *BRCA2* function (such as that postulated with *BRCA1* C61G mutation).[19-21] Many of these proposed mechanisms may be important to platinum resistance as well, and therefore, there has been concern that platinum-resistant tumors would not respond to PARP inhibition. In our study, responses to olaparib were seen in > 30% of patients with ovarian cancer with platinum-resistant disease, suggesting that there is not always cross resistance. Mechanisms of resistance were not assessed. Additional studies are needed to better understand the interplay between prior platinum exposure and response to PARP inhibition.

There are several limitations to this study. There was no central laboratory or central review of mutational status before enrollment. However, the vast majority of patients (265 [89%] of 298) carried truncating mutations, including 158 (53%) who carried one of the Ashkenazi Jewish founder mutations (and one patient carried two). Of the remaining patients, 17 carried missense mutations. Although it can be more difficult to establish the deleterious nature of missense mutations (and there is no universal standard for classification at this time), six missense mutations were *BRCA1* C61G (clearly established pathogenic founder mutation). Thus, we feel that the chance of misclassification of mutation status is low.

Olaparib was reasonably well tolerated, even in this heavily pretreated population. The increased incidence of anemia compared with other studies may have been the result of the longer history of cancer, lower Eastern Cooperative Oncology Group status, and higher number of prior chemotherapy regimens in the study population. Most toxicity was managed by dose interruption and dose reduction. There were two cases of AML and one case of MDS, all in patients with ovarian cancer who were heavily treated; therefore, the role of olaparib in the development of these diseases is unknown.

In summary, we report encouraging data on olaparib monotherapy in patients with a *BRCA1/2* mutation and broad range of tumor types. Olaparib warrants further investigation in phase III trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Bella Kaufman, M. William Audeh, Judith Balmaña, Susan M. Domchek
Financial support: Karin Bowen
Administrative support: Bella Kaufman, Judith Balmaña, Karin Bowen, Susan M. Domchek
Provision of study materials or patients: Bella Kaufman, Ronnie Shapira-Fommer, Rita K. Schmutzler, M. William Audeh, Michael Friedlander, Gillian Mitchell, Georgeta Fried, Salomon M. Stemmer, Ayala Hubert, Ora Rosengarten, Mariana Steiner, Niklas Loman, Karin Bowen, Susan M. Domchek
Collection and assembly of data: Bella Kaufman, Ronnie Shapira-Fommer, Rita K. Schmutzler, M. William Audeh, Michael Friedlander, Judith Balmaña, Gillian Mitchell, Georgeta Fried, Salomon M. Stemmer, Ayala Hubert, Ora Rosengarten, Mariana Steiner, Karin Bowen, Anitra Fielding, Susan M. Domchek
Data analysis and interpretation: Bella Kaufman, Ronnie Shapira-Fommer, Rita K. Schmutzler, M. William Audeh, Judith Balmaña, Gillian Mitchell, Salomon M. Stemmer, Ayala Hubert, Ora Rosengarten, Mariana Steiner, Niklas Loman, Karin Bowen, Anitra Fielding, Susan M. Domchek
Manuscript writing: All authors
Final approval of manuscript: All authors

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GLOSSARY TERMS

***BRCA1*:** a tumor suppressor gene known to play a role in repairing DNA breaks. Mutations in this gene are associated with increased risks of developing breast or ovarian cancer.

***BRCA2*:** a tumor suppressor gene whose protein product is involved in repairing chromosomal damage. Although structurally different from *BRCA1*, *BRCA2* has cellular functions similar to *BRCA1*. *BRCA2* binds to RAD51 to fix DNA breaks caused by irradiation and other environmental agents. Also known as the breast cancer 2 early onset gene.

poly (ADP-ribose) polymerase (PARP): a family of nuclear enzymes that facilitate DNA repair via poly (ADP-ribose)ylation of histones and DNA repair enzymes.

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Appendix

Table A1. Response Rate by *BRCA1* Versus *BRCA2* Mutation Status and Tumor Type

	Ovarian		Breast		Pancreatic		Prostate		Other		Total	
Response Status	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
BRCA1												
Response	44	29.7	5	13.5	1	20.0	1	100.0	1	14.3	52	26.3
95% CI	22.5 to 37.8		4.5 to 28.8		0.5 to 71.6		2.5 to 100.0		0.4 to 57.9		20.3 to 33.0	
Nonresponse	104	70.3	32	86.5	4	80.0	0	0.0	6	85.7	146	73.7
95% CI	62.2 to 77.5		71.2 to 95.5		28.4 to 99.5		0.0 to 97.5		42.1 to 99.6		67.0 to 79.7	
Total	148		37		5		1		7		198	
BRCA2												
Response	16	36.4	3	12.0	4	23.5	3	42.9	0	0.0	26	26.5
95% CI	22.4 to 52.2		2.5 to 31.2		6.8 to 49.9		9.9 to 81.6		0.0 to 52.2		18.1 to 36.4	
Nonresponse	28	63.6	22	88.0	13	76.5	4	57.1	5	100.0	72	73.5
95% CI	47.8 to 77.6		68.8 to 97.5		50.1 to 93.2		18.4 to 90.1		47.8 to 100.0		63.6 to 81.9	
Total	44		25		17		7		5		98	
BRCA1 and *BRCA2*												
Response	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
95% CI	0.0 to 97.5		0.0 to 100.0		0.0 to 95.0		0.0 to 100.0		0.0 to 100.0		0.0 to 84.2	
Nonresponse	1	100.0	0	0.0	1	100.0	0	0.0	0	0.0	2	100.0
95% CI	2.5 to 100.0		0.0 to 100.0		5.0 to 100.0		0.0 to 100.0		0.0 to 100.0		15.8 to 100.0	
Total	1		0		1		0		0		2	