TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes

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abstract

PURPOSE Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi), is approved for the treatment of human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer (MBC) in germline (g)*BRCA1/2* mutation carriers. Olaparib Expanded, an investigator-initiated, phase II study, assessed olaparib response in patients with MBC with somatic (s)*BRCA1/2* mutations or g/s mutations in homologous recombination (HR)–related genes other than *BRCA1/2*.

METHODS Eligible patients had MBC with measurable disease and germline mutations in non-*BRCA1/2* HR-related genes (cohort 1) or somatic mutations in these genes or *BRCA1/2* (cohort 2). Prior PARPi, platinum-refractory disease, or progression on more than two chemotherapy regimens (metastatic setting) was not allowed. Patients received olaparib 300 mg orally twice a day until progression. A single-arm, two-stage design was used. The primary endpoint was objective response rate (ORR); the null hypothesis (≤ 5% ORR) would be rejected within each cohort if there were four or more responses in 27 patients. Secondary endpoints included clinical benefit rate and progression-free survival (PFS).

RESULTS Fifty-four patients enrolled. Seventy-six percent had estrogen receptor–positive HER2-negative disease. Eighty-seven percent had mutations in *PALB2,* s*BRCA1/2*, *ATM,* or *CHEK2*. In cohort 1, ORR was 33% (90% CI, 19% to 51%) and in cohort 2, 31% (90% CI, 15% to 49%). Confirmed responses were seen only with g*PALB2* (ORR, 82%) and s*BRCA1/2* (ORR, 50%) mutations. Median PFS was 13.3 months (90% CI, 12 months to not available/computable [NA]) for g*PALB2* and 6.3 months (90% CI, 4.4 months to NA) for s*BRCA1/2* mutation carriers. No responses were observed with *ATM* or *CHEK2* mutations alone.

CONCLUSION PARP inhibition is an effective treatment for patients with MBC and g*PALB2* or s*BRCA1/2* mutations, significantly expanding the population of patients with breast cancer likely to benefit from PARPi beyond g*BRCA1/2* mutation carriers. These results emphasize the value of molecular characterization for treatment decisions in MBC.

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INTRODUCTION

Breast cancers in germline *BRCA1* and *BRCA2* mutation carriers (g*BRCA1/2* carriers) have a defect in homologous recombination (HR) and are therefore sensitive to therapies that create DNA double-strand breaks or stalled replication forks (eg, poly [ADP-ribose] polymerase [PARP] inhibitors [PARPi]). PARPi (olaparib and talazoparib) are approved for the treatment of human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer (MBC) in g*BRCA1/2* carriers. Compared with nonplatinum chemotherapy, PARPi result in significantly better progression-free survival (PFS), objective response rate (ORR), and quality of life.[1,2] PARPi also have activity in the neoadjuvant setting,[3] although their benefit in the treatment of early-stage breast cancer is still being investigated (eg, ClinicalTrials.gov identifier: NCT02032823).

The identification of patients beyond g*BRCA1/2* carriers whose cancers may be sensitive to PARP inhibition remains an important goal. Several genes other than *BRCA1* and *BRCA2* function in the DNA damage response and HR pathways to repair DNA double-strand breaks; germline mutations in these genes also confer increased cancer susceptibility. Studies in prostate cancer have suggested that some patients with mutations in HR-related genes other than *BRCA1/2* may benefit from PARPi, although which genes are consistently associated with response is not yet clear.[4-6] In addition, ovarian cancer studies have demonstrated benefit for PARPi in women with a somatic (s)*BRCA1/2* mutation.[7]

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) have been approved for the treatment of germline BRCA (gBRCA) mutation carriers with metastatic breast cancer (MBC). In addition, PARPi have demonstrated efficacy in patients with ovarian cancer with somatic BRCA1 or BRCA2 (sBRCA1/2) mutations. Other genes also function in the homologous recombination (HR)–related DNA repair pathway. This study examined whether patients with MBC with either germline mutations in HR-related genes other than BRCA1/2 or sBRCA1/2 mutations respond to the PARPi olaparib.

Knowledge Generated

The response rate to olaparib was 82% in patients with gPALB2 mutations and 50% in patients with sBRCA1/2 mutations; progression-free survival was 13.3 and 6.3 months, respectively. Responses were seen in all breast cancer subtypes. No responses were seen in patients with only ATM or CHEK2 mutations.

Relevance

The population of patients with MBC who can derive benefit from PARPi extends beyond gBRCA1/2 mutation carriers and includes patients with gPALB2 and sBRCA1/2 mutations.

Olaparib Expanded (TBCRC 048) is an investigator-initiated, phase II proof-of-principle trial designed to test the hypothesis that olaparib would have at least a 20% ORR in patients with MBC with a germline or somatic mutation in an HR-related gene other than *BRCA1/2,* or with a s*BRCA1/2* mutation.

METHODS

Patients

Eligible patients were at least 18 years old and had MBC with at least one measurable lesion by RECIST 1.1 criteria. Patients had to have a somatic pathogenic or likely pathogenic variant, (ie, mutation) in *BRCA1/2* in the absence of a g*BRCA1/2* mutation, or a germline or somatic mutation in one of the following DNA repair genes: *ATM*, *ATR*, *BAP1*, *BARD1*, *BLM*, *BRIP1*, *CHEK1*, *CHEK2*, *CDK12*, *FANCA*, *FANCC*, *FANCD2*, *FANCF, MRE11A*, *NBN*, *PALB2*, *RAD50*, *RAD51C*, RAD51D, or *WRN*.[8] Somatic mutations could be identified from genomic profiling of metastatic tumor tissue or blood (ie, circulating tumor DNA). Germline testing was required only to exclude a g*BRCA1/2* mutation if a s*BRCA1/2* mutation was present. Eligible patients had not progressed on more than two previous chemotherapy regimens in the metastatic setting. There was no limit on the number of prior hormone, immune, or targeted therapies allowed. Patients with prior PARPi use or platinum-refractory disease (progression on a platinum-based regimen or development of metastatic disease within 12 months of receiving platinum chemotherapy) were not eligible. Patients with treated CNS metastases were eligible, provided the disease was stable. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance-status score of 0 to 1 and adequate organ function.

Study Design, Treatments, and Endpoints

Olaparib Expanded was an open-label, nonrandomized, multicenter phase II trial. Cohort 1 included patients with a germline mutation in an HR-related gene (but not g*BRCA1/2*), and cohort 2, those with a somatic mutation in these same genes (including *BRCA1/2*).

Olaparib was administered orally at a dose of 300 mg twice a day continuously until disease progression, unacceptable toxicity, or withdrawal of consent. Patients with progression of disease were allowed to remain in the trial if the treating physician felt the patient was receiving clinical benefit.

The primary endpoint was ORR, defined as confirmed complete response (CR) and partial response (PR) according to modified RECIST, version 1.1. Secondary endpoints were clinical benefit rate (CBR; ie, confirmed CR or PR or stable disease (SD) $\geq$ 18 weeks), PFS (ie, time from initiation of olaparib until progression or death from any cause), duration of response (DOR; ie, time from initial response [subsequently confirmed] to progression or death from any cause), and toxicity. Adverse events were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Restaging scans were performed every 6 weeks until week 24, then every 12 weeks thereafter. Patients were examined every cycle (ie, 3 weeks). On January 21, 2020, an amendment allowed visits to occur every 6 weeks after week 24. Laboratory values were monitored every 3 weeks, and decisions to withhold or reduce dose were made as outlined in the Methods section of the Protocol (online only).

Trial Oversight

The study was conducted within the Translational Breast Cancer Research Consortium and was approved by the research ethics committee at each participating site. Data were collated and analyzed by the Clinical Trials Office at the Dana-Farber Cancer Institute. A Data and Safety Monitoring Committee reviewed the safety data twice

yearly. The manuscript was written by the first and last authors without industry medical-writing support. All authors reviewed the manuscript and affirm the accuracy and completeness of the data.

Statistical Analysis

For each cohort, the null hypothesis that the true response rate was ≤ 5% was tested against a one-sided alternative using a Simon minimax study design at a type I error rate of 5%. For each cohort, 13 patients were accrued in the first stage. If there were no responses in the cohort, the study would be stopped for that cohort. If at least one response was observed, 14 additional patients would be accrued to that cohort, for a total of 27 patients. The null hypothesis would be rejected for that cohort if four or more responses were observed. Under an alternative hypothesis that the true response rate was 20%, this design provided 80% power to reject the null hypothesis.[9-11]

A two-sided exact binomial 90% CI was calculated for the response rate using the Atkinson- Brown method to account for the two-stage design.[12] For estimating the objective response, patients who received at least one cycle (3 weeks) of olaparib or who went off treatment because of progression were considered evaluable. Patients who received less than one cycle and went off treatment for reasons other than progression were not evaluable.

In each cohort, the CBR was reported with 90% binomial exact CI. PFS and durations of response and SD were calculated using the method of Kaplan-Meier and are reported using the median with a 90% CI. Data cutoff was June 5, 2020.

RESULTS

Study Patients

From March 2018 through January 2020, 55 patients were enrolled. One patient withdrew after signing consent but before receiving study treatment and was replaced per protocol. All other patients received at least one cycle of olaparib. One patient treated in cohort 2 with a s*BRCA2* mutation was subsequently found to have a g*BRCA2* mutation and was excluded from efficacy analyses but included in demographics and safety analyses. All patients without disease progression had at least three response assessments with the following exceptions: one patient who was lost to follow-up, one who came off the study because of toxicity, and one who withdrew from the study. Two patients had their third response assessment before week 18 and were therefore excluded from CBR assessment.

Table 1 summarizes the baseline characteristics of the patients. Of participants enrolled, 87.5% had a mutation in one of the following genes: *ATM*, *CHEK2*, *PALB2*, s*BRCA1*, or s*BRCA2*. Seventy-six percent had estrogen receptor (ER)–positive (ER+) HER2-negative breast cancer. Only 6% had received prior platinum chemotherapy. Appendix Tables A1 and A2 (online only) provide details about each patient, including specific gene variants, genetic testing performed, therapies received, and sites of metastatic disease.

Efficacy

Both cohorts passed the initial stage. The median follow-up was 4.2 months (range, 1-19.8 months).

For cohort 1 (germline mutation other than g*BRCA1/2*), the ORR was 33% (90% CI, 19% to 51%), with nine patients having confirmed PR; the CBR at 18 weeks was 50% (90% CI, 33% to 67%; Table 2). All responses were in patients with a g*PALB2* mutation (Fig 1A). Thus, for g*PALB2* mutation carriers, the ORR was 82% (90% CI, 53% to 96%) and the CBR was 100% (90% CI, 74% to 100%; Table 2). Responses of longer than 1 year were observed (Fig 1B), and median PFS was 13.3 months (90% CI, 12 months to not available/computable (NA)). There were no responses in patients with any other germline mutations; one patient with a g*RAD50* mutation had SD for 6 months before progression (Fig 1).

For cohort 2 (somatic mutations in HR-related genes), the ORR was 31% (90% CI, 15% to 49%), with eight patients having a confirmed PR (Table 2); the CBR at 18 weeks was 48% (90% CI, 30% to 66%). All confirmed responses were in patients with a s*BRCA1* or s*BRCA2* mutation (Fig 2A). Three additional patients had an unconfirmed PR and were analyzed as having SD: one patient each with a somatic mutation in *BRCA1*, *CDK12,* and *BLM*. Thus, for s*BRCA1/2* mutation carriers, the ORR was 50% (90% CI, 28% to 72%) and the CBR was 66% (90% CI, 42% to 85%; Table 2). Responses lasting as long as 18 months were observed (Fig 2); median PFS was 6.3 months (90% CI, 4.4 months to NA). Two patients with s*PALB2* mutations were enrolled; one had disease progression at 12 weeks, and the other was lost to follow-up after the first assessment with SD with response in skin and circulating tumor markers (Fig 2). Kaplan-Meier curves for PFS and DOR for cohorts 1 and 2 are found in Appendix Figures A1 and A2 (online only).

Efficacy by various clinical and tumor characteristics was explored (Table 3). Responses were observed in all breast cancer subtypes. Among the 27 g*PALB2* and s*BRCA1/2* mutation carriers enrolled, responses occurred in 12 of 20 (60%) with ER+ HER2-negative disease, in four of six (67%) with triple-negative breast cancer (TNBC), and in one patient with HER2-positive disease. Responses also occurred in 11 of 19 patients (58%) treated previously with a prior CDK4/6 inhibitor. On the date of data cutoff, 14 patients were still receiving olaparib in the study, and 12 had not had disease progression.

Safety

The median duration of olaparib treatment was 18.3 weeks (range, 4-86 weeks). The average delivered-dose intensity

TABLE 1. Patient and Tumor Characteristics

Characteristic	Total (N = 54)	Cohort 1 (n = 27)	Cohort 2[a] (n = 27)
Age, years, mean (range)	59 (30-87)	54 (30-87)	59 (34-79)
Subtype[b]			
ER+ HER2−[c]	41 (76)	23 (85)	18 (67)
TNBC	10 (19)	2 (7)	8 (30)
HER2+	3 (6)	2 (7)	1 (4)
No. of lines of prior chemotherapy in metastatic setting, mean (range)	1 (0-4)	0 (0-2)	1 (0-4)[d]
No prior chemotherapy	10 (19)	6 (22)	4 (15)
Prior platinum	3 (6)	0 (0)	3 (11)
Prior CDK 4/6i among ER+ HER2−	38 (93)	22 (96)	16 (89)
Genes (n = 1 unless specified)	*ATM* (8)	*CHEK2* (8)[e]	*BRCA1* (6)[f]
	BARD1	*ATM* (4)	*BRCA2* (10)[a]
	BLM	ATM & *CHEK2* (2)	*ATM* (4)[g]
	BRIP1	*PALB2* (11)[h]	*PALB2* (2)
	s*BRCA1* (6)[e]	*BARD1*	*CDK12* (2)
	s*BRCA2* (10)	*RAD50*	*BRIP1*
	CDK12 (2)		*BLM*
	CHEK2 (8)[i]		*FANCA*
	ATM & *CHEK2* (2)		
	FANCA		
	PALB2 (13)		
	RAD50		

Note. Values are presented as No. (%) unless otherwise indicated.

Abbreviations: CDK4/6i, CDK4/6 inhibitor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer.

[a]One patient in cohort 2 with a somatic *BRCA2* (s*BRCA2*) mutation was ineligible and was excluded from efficacy analyses.

[b]Subtype defined from primary tumor.

[c]ER > 1%, with the exception of one patient each in cohorts 1 and 2 with ER immunohistochemical (IHC) staining 1% to 10%; for all others, ER IHC > 10%.

[d]Patients may have received more than two chemotherapy regimens in the metastatic setting, provided they did not progress on more than two (ie, stopping for toxicity did not count towards chemotherapy limit).

[e]One patient in cohort 1 with a germline missense *CHEK2* mutation was found to also have a somatic *BRCA1* (s*BRCA1*) mutation (not counted as an sBRCA1 patient in this table but included in efficacy analyses for s*BRCA1/2*).

[f]One patient with s*BRCA1* mutation also had somatic ataxia telangiectasia, mutated (s*ATM*) mutation (not listed with *ATM* group).

[g]One patient with a s*ATM* mutation also had a somatic Fanconi anemia group F (s*FANCF*) mutation.

[h]One patient with a germline Partner and Localizer of *BRCA2* (*gPALB2*) mutation also had a germline ATM (g*ATM*) mutation (not listed with ATM group).

[i]*CHEK2* mutations: five missense, five frameshift/truncating.

was 297.1 mg twice a day (range, 200-300 mg). Olaparib was generally well tolerated; the observed toxicity profile was consistent with those of previous reports (Appendix Table A3, online only). Nine percent of patients had grade 2 nausea (none ≥ grade 3), 26% of patients had > grade 1 anemia (13% ≥ grade 3), and two patients (4%) had grade 2 alopecia. Eight patients (15%) required a dose reduction, and two patients (4%) came off study because of olaparib toxicity.

DISCUSSION

In this proof-of-principle study, the primary endpoint was met in both cohorts. Olaparib was effective in patients with MBC and germline or somatic mutations in HR-related genes. Responses were gene specific; confirmed responses were observed only in patients with somatic mutations in *BRCA1/2* or germline mutations in *PALB2* but not in those with mutations in *ATM* or *CHEK2* alone. This strongly suggests a differential response to PARPi for mutations in different HR-related genes. To our knowledge, this is the first report of PARPi response in patients with breast cancer with s*BRCA1/2* mutations and the largest in patients with cancer with germline mutations in a single gene other than *BRCA1* or *BRCA2*. In the current trial, the ORR and median PFS with olaparib for g*PALB2* and s*BRCA1/2* mutation carriers were 82% and 13.3 months, and 50% and 6.2 months, respectively. The latter are broadly similar to the ORR and median PFS with PARPi of 60% and 7-8.6 months reported in g*BRCA1/2* carriers in the OLYMPIAD and EMBRACA trials.[1,2]

TABLE 2. Responses by Cohort

Response	Cohort 1 (germline)		Cohort 2 (somatic)	
	All	gPALB2 Mutations	All	sBRCA1/2[a] Mutations
Best response				
(Confirmed) CR	0	0	0	0
(Confirmed) PR	9	9	8	8
SD	8	2	10	6
PD	10	0	8	2
ORR, % (90% CI)	33 (19 to 51)	82 (53 to 96)	31 (15 to 49)	50 (28 to 72)
CBR, % (90% CI)	50 (33 to 67)	100 (74 to 100)	48 (30 to 66)	66 (42 to 85)
DOR, months, median (90% CI)	9 (7.5 to NA)	9 (7.5 to NA)	6.3 (3.1 to NA)	6.3 (3.1 to NA)
PFS, months, median (90% CI)	4.5 (1.7 to 12)	13.3 (12 to NA)	4.1 (2.8 to 6.3)	6.3 (4.4 to NA)
Time to onset of response, weeks, median (90% CI)	12.1 (11.4 to 20.8)	12.1 (11.4 to 20.8)	10.3 (8.4 to 11.9)	10.3 (8.4 to 11.9)

Abbreviations: CBR, clinical benefit rate; CR, complete response; DOR, duration of response; g, germline; NA, upper limit of the 90%-CI was not available/computable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; s, somatic; SD, stable disease.

[a]Includes patient from cohort 1 with g*CHEK2* and s*BRCA1* mutations.

These findings underscore the importance of performing germline and tumor genomic profiling in patients with MBC to identify those who might benefit from PARPi, and they highlight the need for additional investigation in other tumors. To our knowledge, this is the first study to report responses in a meaningful number of g*PALB2* mutation carriers. Our results are consistent with reports of two confirmed responses to talazoparib in patients with breast cancer with g*PALB2* mutations treated in a basket trial.[13] Germline mutations in *PALB2* (partner and localizer of BRCA2), a gene encoding a protein that functions in the HR complex, confer a 35% to 58% lifetime risk of breast cancer. Because g*PALB2* mutations also predispose to pancreatic and ovarian cancer,[14] our results may have significant implications for the treatment of other g*PALB2*-associated cancers.

Our findings have the potential to affect many patients with breast cancer. Approximately 2 million women are diagnosed with breast cancer annually; 5% to 10% are diagnosed with MBC initially, and an additional 20% to 30% will recur with MBC. g*BRCA1/2* mutations occur in 2% to 5% of patients with breast cancer.[15-19] Germline mutations in *PALB2* occur in approximately 1% of patients with breast cancer.[16,20,21] Somatic mutations in *BRCA1/2*, in the absence of a g*BRCA* mutation, occur in an additional 3% to 4% of patients with breast cancer, although the prevalence in patients with MBC is unknown because studies have generally analyzed primary tumors.[22,23] Thus, our findings demonstrate that through genomic assessment, a significantly larger population of patients with MBC, beyond g*BRCA1/2* carriers, who may benefit from PARPi can be identified.

In the current trial, responses were observed across all breast cancer subtypes. Because *BRCA1*-associated breast cancers are usually triple negative,[24] early trials focused on non-*BRCA* carriers with TNBC who might respond to PARPi.[25] Less attention was paid to ER+ breast cancers, even though 70% of *BRCA2*-associated breast cancers are ER+.[24] Of note, all of the participants with a g*PALB2* mutation and 71% of those with a response in our trial had ER+ disease, underscoring the importance of including these patients when searching for breast cancers with HR deficiency (HRD). Responses were seen after progression on a CDK4/6 inhibitor and in a patient with HER2-positive breast cancer, populations not represented in the OLYMPIAD or EMBRCA trials for g*BRCA1/2* carriers.[1,2]

In our trial, no confirmed responses were observed in patients with mutations in other HR-related genes. This may be because of the specific genes and variants included in this study, or because of the sample size. The lack of response to olaparib in patients with mutations in *ATM* or *CHEK2,* the more commonly mutated HR-related genes in breast cancer, is consistent with the findings of studies demonstrating the lack of *BRCA*-associated mutational signatures in breast cancers associated with mutations in these genes.[22,26] We did observe tumor regression in one patient with an s*CDK12* mutation who had SD for 6 months before progression. *CDK12* is a positive regulator of *BRCA* genes.[27,28] We also report an unconfirmed PR in a patient with an s*BLM* mutation, and SD for 6 months in a patient with a g*RAD50* mutation.

In patients with castrate-resistant prostate cancer (CRPC), responses to PARPi have been reported in patients other than those with *BRCA1/2* mutations.[4-6] Initial studies observed responses in patients with somatic mutations in *ATM*,[4] but this was not confirmed in subsequent studies.[5,29] In the PROfound trial, superior outcomes were found with

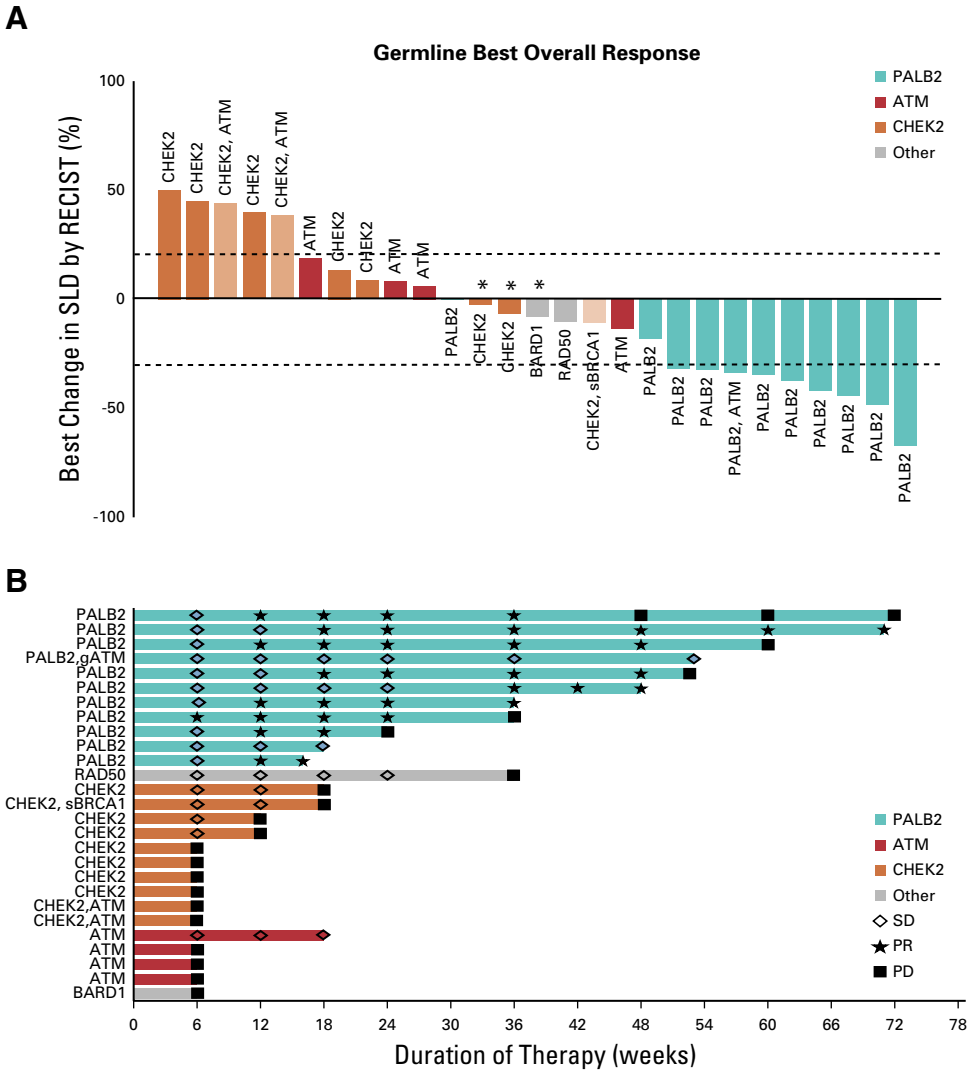

FIG 1. Best response and duration of responses for patients in cohort 1 (germline mutations). (A) Best change from baseline in patients in cohort 1, according to genes. (B) Responses and duration of responses for patients in cohort 1, according to genes. (*) Progressive disease (PD) because of growth or appearance of new metastases. PR, partial response; SD, stable disease.

olaparib than with hormonal agents for a cohort of patients with *BRCA1*, *BRCA2,* or *ATM* mutations, although patients with *ATM* mutations did not seem to have better outcomes.[30] PARPi responses in patients with CRPC and s*CDK12* mutations have also been inconsistent.[5,6,30] Limited responses with mutations in other HR-related genes have been reported, although results vary on the basis of response criteria (ie, radiographic, prostate-specific antigen (PSA), or circulating tumor cells).[4-6]

A strength of our study is that all variants were reviewed by an executive committee composed of clinicians with expertise in germline and somatic genomics (N.M.T., J.E.G., M.E.R., S.D., G.M.W., A.D., and N.W.) to ensure variant pathogenicity. For somatic variants in particular, data needed to determine pathogenicity are often limited, and consistency in calling a variant pathogenic is lacking. Among our study limitations was the lack of significant numbers of individuals with mutations in less common HR-related genes, such as *RAD51C, RAD51D*, and *BARD1*, which limited our ability to assess responses in patients with other HR-related gene mutations. In addition, there were only two patients with somatic mutations in *PALB2*, preventing adequate assessment of olaparib response in this population. Another limitation is that for patients in cohort 2, germline testing was only required to exclude a g*BRCA* mutation in patients with an s*BRCA* mutation (Appendix Table A2). However, this likely did not affect the results, because the only patients in cohort 2 with confirmed responses were those with s*BRCA1/2* mutations.

The difficulties of adequately assessing the activity of PARPi in patients with mutations in every HR-related gene underscore the need to identify predictors of response to therapies that target HRD, whether mutational signatures,[22,26] functional studies,[31-33] biallelic inactivation,[34] or other biomarkers. Given the challenge of assessing rare mutations, such biomarkers could serve to ensure that small numbers of responses for less common genes are neither overlooked nor overemphasized.

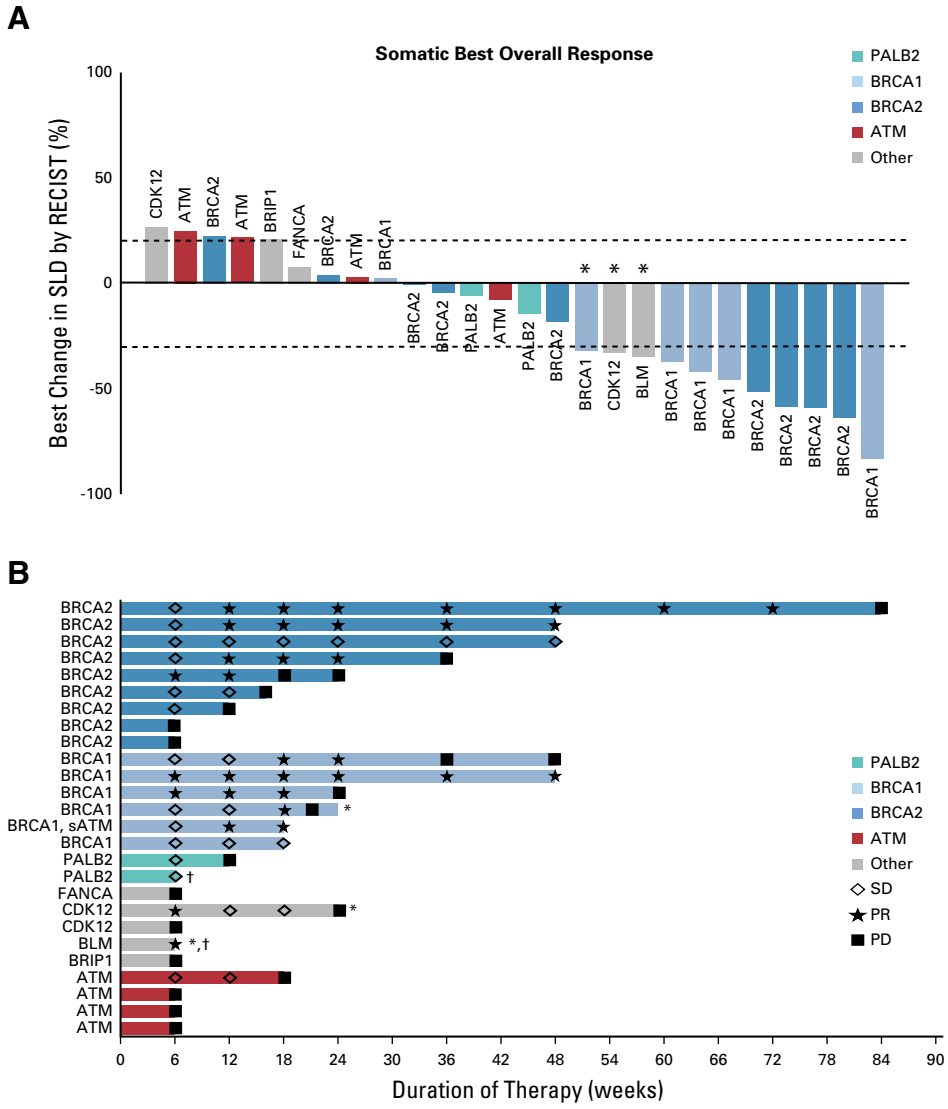

FIG 2. Best response and duration of responses for patients in cohort 2 (somatic mutations). (A) Best change from baseline in patients in cohort 2 (somatic mutations), according to genes. (B) Responses and duration of responses for patients in cohort 2, according to genes. (*) Stable disease (SD) because of lack of confirmation of partial response (PR) on subsequent scan. (†) Patient came off study after first assessment. PD, progressive disease.

TABLE 3. Efficacy by Patient and Tumor Characteristics

Clinical Factor	g*PALB2* Responders of Total (n = 9 of 11)	s*BRCA1/2* Responders of Total (n = 8 of 16)[a]
Tumor subtype[b]		
ER+ HER2−	8 of 10	4 of 10
TNBC	—	4 of 6
HER2+	1 of 1	—
Any prior chemotherapy	7 of 8	7 of 15
No prior chemotherapy	2 of 3	1 of 1
Prior CDK 4/6 inhibitor	7 of 9	4 of 10

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; ER, estrogen receptor; g, germline; HER2, human epidermal growth factor receptor 2; s, somatic; TNBC, triple-negative breast cancer.

[a]Includes patient from cohort 1 with g*CHEK2* and s*BRCA1* mutations.

[b]Primary tumor.

In conclusion, we report that PARP inhibition is an effective treatment for patients with MBC and g*PALB2* or s*BRCA1/2* mutations. This significantly expands the population of patients with breast cancer likely to benefit from PARPi beyond those with g*BRCA* mutations, including those with subtypes other than TNBC. An important but still preliminary finding is that patients with breast cancer with only *ATM* or *CHEK2* mutations do not seem to respond to PARPi. Because two thirds of the germline mutations in non-*BRCA1/2* genes identified in patients with breast cancer are in *ATM*, *CHEK2*, or *PALB2*,[16] clarifying the role of PARPi in patients with these mutations would significantly affect the treatment of breast cancer. Our findings underscore the importance of performing genomic profiling in patients with MBC to identify those who may benefit from PARPi.

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APPENDIX

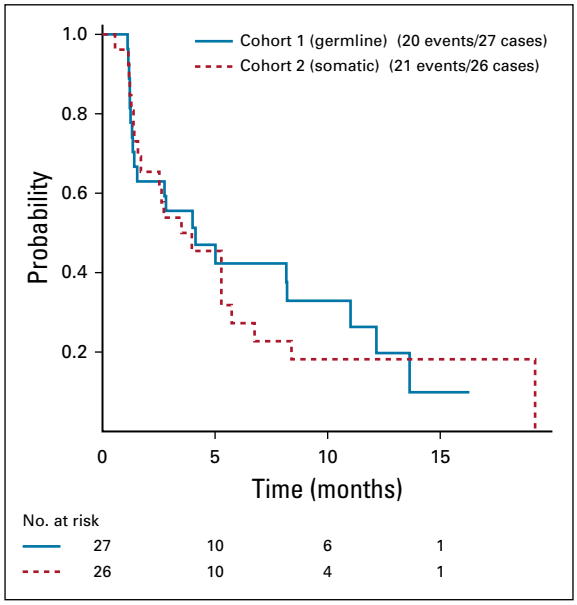

FIG A1. Kaplan-Meier estimate of progression-free survival in patients in cohort 1 (germline mutations) and cohort 2 (somatic mutations).

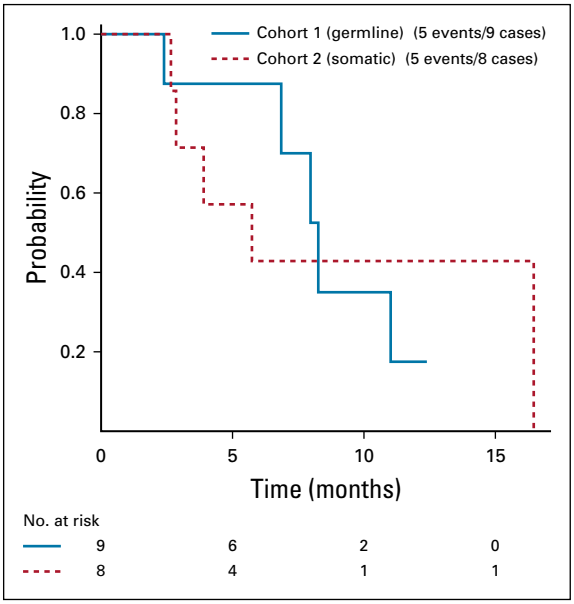

FIG A2. Kaplan-Meier estimate of duration of response in patients in cohort 1 (germline mutations) and cohort 2 (somatic mutations).

TABLE A1. Additional Information on Enrolled Patients: Cohort 1 (germline)

Pt ID	Gene Variant(s)	Tumor Genomic Profiling Performed (Y/N)	Additional Somatic Alterations in HR Genes	Tumor Hormone Receptor Status (ER/PR/HER2)[a]	(Neo) Adjuvant Chemotherapy Received (Y/N)	No. of Lines of Prior Chemotherapy in Met Setting	Prior Platinum (Y/N)	Prior CDK 4/6 Inhibitor (Y/N)	Best Response (change in size of target lesions, %)	No. of Cycles of Olaparib	Visceral Disease (Y/N)[b]	Reason for Coming Off Study
003	*CHEK2* c.444+aG>A ATM c.3993+1G>A	Y		+/−/−	N	0	N	Y	PD (38.3)	2	Y	PD
005	*PALB2* del exons 4-7 ATM c.538C>T	Y	Additional s*PALB2* PV	+/−/−	N	0	N	Y	PR (−33.8)	18	Y	PD
006	*CHEK2* c.349A>G	Y		+/−/−[c]	N	1	N	Y	SD (−6.5)	4	Y	PD
007	*ATM* c.3802delG	Y		+/−/−	Y	1	N	Y	PD (8.7)	2	Y	PD
009	*PALB2* c.3549C>A	Y	Additional s*PALB2* PV	+/−/+	N	2	N	N	PR (−42.1)	27	Y	Active
010	*PALB2* c.1031delA	Y		+/−/−	Y	0	N	N	PR (−34.8)	26	Y	Active
011	*CHEK2* c.1100delC ATM c.8266A>T	Y	g*CHEK2* variant not identified	+/+/−	N	1	N	Y	PD (44)	2	Y	PD
012	*CHEK2* c.470T>C	Y		+/−/−	Y	2	N	Y	SD (13.4)	6	Y	PD
013	*PALB2* del exons 7-8	N		+/+/−	N	0	N	Y	SD (0)	22	N	Active
014	*BARD1* c.1854_1855dup	N		−/−/−	Y	1	N	N	PD (−8)	2	Y	PD
017	*CHEK2* c.1020_1096-215del889	Y		+/+/−	Y	0	N	Y	PD (39.9)	2	Y	PD
019	*PALB2* c.3256C>T	Y		+/−/−	Y	1	N	Y	PR (−44.4)	20	Y	PD
020	*CHEK2* c.565A>G	Y		+/−/−	Y	0	N	Y	PD (−2.67)	2	Y	PD
021	*ATM* c.5290delC	Y		+/+/+	N	2	N	Y	PD (18.6)	2	Y	PD
022	*PALB2* c.2368C>T	N		+/+/−	Y	0	N	Y	PR (−44.5)	7	Y	PD
024	*PALB2* c.1479delC	Y		+/−/−	Y	0	N	Y	PR (−32.2)	19	Y	Active
028	*RAD50* c.2718+1_2718+5delGTAAG	N		−/−/−	N	1	N	N	SD (−10.4)	11	N	PD
031	*CHEK2* c.1100delC	Y		+/+/−	Y	1	N	Y	SD (8.7)	4	Y	Toxicity, PD
033	*PALB2* del exon 11	N		+/−/−[d]	Y	0	N	Y	PR (−37.2)	15	N	Active
034	*PALB2* c.2257C>T	N		+/+/−	N	1	N	Y	PR (−67)	12	Y	PD
035	*CHEK2* c.1100delC	Y		+/+/−	Y	0	N	Y	PD (50)	2	Y	PD
039	*CHEK2* c.1283C>T	Y		+/+/−	N	0	N	Y	PD (45)	2	N	PD
043	*CHEK2* c.470T>C	Y	s*BRCA*	+/+/−	N	2	N	Y	SD (−10.7)	6	Y	PD
049	*ATM* c.7951C>T	Y		+/−/−	Y	1	N	Y	PD (6)	2	Y	PD
052	*PALB2* c.3116del	Y		+/+/−	N	0	N	Y	PR (−32)	7	N	Active
053	*PALB2* c.3113G>A	Y	Additional s*PALB2* PV	+/+/−	Y	0	N	Y	SD (−18.2)	7	Y	Active
055	*ATM* c.3996delT	Y		+/+/−	N	0	N	Y	SD (−13.5)	7	Y	Active

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, homologous recombination; Met, metastatic; N, No; PD, progressive disease; PR, progesterone receptor; PR, partial response; Pt, patient; PV, pathogenic variant; SD, stable disease; Y, Yes.

[a]On the basis of the primary tumor.

[b]Visceral disease includes metastases to brain, lung, liver, adrenal gland, ovary; nonvisceral disease includes metastases to skin, breast, lymph nodes, bone.

[c]ER weakly positive (< 10%).

[d]Biopsy of metastatic site was triple-negative breast cancer.

TABLE A2. Additional Information on Enrolled Patients: Cohort 2 (somatic)

Pt ID	Gene Variant(s)	Germline Testing? (Y/N)	Additional Alterations in HR Genes	Tumor Hormone Receptor Status (ER/PR/HER2)[a]	(Neo) Adjuvant Chemotherapy Received (Y/N)	No. of Lines of Prior Chemotherapy in Met Setting	Prior Platinum (Y/N)	Prior CDK 4/6 Inhibitor (Y/N)	Best Response (change in size of target lesions)	No. of Cycles of Olaparib	Visceral Disease[b] (Y/N)	Reason for Coming Off Study
001	*BRCA2* c.1308_1309del	Y		+/+/−	N	3	N	Y	PD[c] (−18.2)	2	Y	PD
002	*BRCA2* c.217C>T	Y		+/+/−	Y[d]	1	N	Y	PR (−63.7)	29	Y	PD
004	*BRCA2* c.8716G>T	Y		+/−/−	N	0	N	Y	PR (−55.6)	16	Y	PD
008	*CDK12* p.S1236fs*55	Y		−/−/−	N	1	N	N	SD[e] (−33)	8	Y	PD
015	*ATM* c.4246C>T	Y	*FANCF*	+/−/−	Y	2	Y	Y	PD (25)	2	Y	PD
016	*BRIP1* inversion	Y		+/−/−	N	0	N	Y	PD (21.1)	2	Y	PD
018	*BRCA2* p.S3133*	Y		+/−/−	Y	1	N	Y	PD (22.5)	2	Y	PD
023	*BRCA2* c.3195delT	Y		+/+/−	N	1	N	Y	SD (−4.6)	19	N	Active
025	*BRCA1*c.3496del	Y		+/+/−	N	3	N	Y	SD[e] (−32)	8	Y	PD
026	*BRCA2* del exon 1-10	Y		−/−/−	Y	1	N	Y	PR (−59.2)	18	N	Active
027	*BRCA1* loss of exons 2-3	Y		−/−/−	Y	0	N	N	PR (−83.3)	18	Y	Active
029	*BRCA1* c.1341delT	Y		−/−/−	N	1	N	N	PR (−42)	7	Y	PD
030	*ATM* c.1010G>A	N		+/+/−	Y	3	N	Y	PD (−8)	2	Y	PD
032	*BRCA1* c.2215A>T	Y		−/−/−	N	3	Y	N	PR (−37.2)	15	Y	Active
036	*ATM* c.7181C>T	N		+/+/−	N	0	N	N	SD (3)	7	Y	Toxicity, PD
037	*CDK12* intronic rearrangement	Y		−/−/+	Y	2	Y	N	PD (26.7)	2	Y	PD
038	*BRCA2* c.5130T>G	Y		+/+/−	N	2	N	Y	N/A	2	Y	Ineligible
040	*PALB2* c.347T>A	N		+/−/−	N	0	N	Y	SD (−14.4)	2	N	LTF
042	*BRCA2* c.5645C>A	Y		+/−/−[f]	N	1	N	N	PR (−51.6)	8	Y	Active
044	*BLM* c.1536delA	N		+/−/−	Y	2	N	Y	SD[e] (−35)	3	Y	Withdrew from study
045	*BRCA2* c.5909C>A	Y		+/−/−	Y	0	N	Y	SD (4)	4	Y	PD
046	*PALB2* c.886_887insA	N		+/+/−	Y	1	N	Y	SD (−6.1)	4	N	PD

(continued on following page)

TABLE A2. Additional Information on Enrolled Patients: Cohort 2 (somatic) (continued)

Pt ID	Gene Variant(s)	Germline Testing? (Y/N)	Additional Alterations in HR Genes	Tumor Hormone Receptor Status (ER/PR/HER2)[a]	(Neo) Adjuvant Chemotherapy Received (Y/N)	No. of Lines of Prior Chemotherapy in Met Setting	Prior Platinum (Y/N)	Prior CDK 4/6 Inhibitor (Y/N)	Best Response (change in size of target lesions)	No. of Cycles of Olaparib	Visceral Disease[b] (Y/N)	Reason for Coming Off Study
047	*ATM* splice site SNV	N		+/+/−	Y	0	N	Y	PD (21.7)	2	Y	PD
048	*FANCA* p.D202fs	N		−/−/−	Y	1	N	N	PD (7.8)	2	N	PD
050	*BRCA2* p.L2929*	Y		−/−/−	Y	4	N	N	SD (−0.5)	5	N	PD
051	*BRCA1* intronic rearrangement	Y	s*ATM* c.9022C>T	+/+/−	N	3	N	Y	PR (−45.9)	7	Y	Active
054	*BRCA1* rearrangement intron 12	Y		−/−/−	N	1	N	N	SD (2.4)	7	Y	Active

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, homologous recombination; LTF, lost to follow-up; Met, metastatic; N, No; PD, progressive disease; PR, progesterone receptor; PR, partial response; Pt, patient; PV, pathogenic variant; SD, stable disease; Y, Yes.

[a]On the basis of the primary tumor.

[b]Visceral disease includes metastases to brain, lung, liver, adrenal gland, ovary; nonvisceral disease includes metastases to skin, breast, lymph nodes, bone.

[c]PD because of mixed response, appearance of new lesions despite tumor regression in target lesions.

[d]Patient had one regimen in adjuvant setting (cyclophosphamide, methotrexate, and fluorouracil), then two additional chemotherapy regimens for local recurrence (doxorubicin, cyclophosphamide-paclitaxel, and capecitabine).

[e]SD because of lack of confirmation scan.

[f]ER weakly positive (< 10%).

TABLE A3. Treatment-Related Adverse Events (Grade ≥ 2)

	Olaparib (n = 54)	
Toxicity	**Grade 2 (% patients)**	**Grade 3/4 (% patients)**
Fatigue	6	2
GI		
Nausea	9	0
Vomiting	2	0
Diarrhea	6	2
Anorexia	6	0
Reflux	4	0
Constipation	2	0
Abnormal AST/ALT	0	4
Mucositis	2	0
Extremity discomfort or weakness	2	0
Dyspnea	2	2
Alopecia	4	0
Hematologic		
Anemia	13	13
Lymphopenia	4	4
Neutropenia	2	2
Thrombocytopenia	2	0
Hypocalcemia	2	0

NOTE. Eight patients (15%) required dose reductions: four for anemia, three for nausea, and one for limb weakness/pain. Two patients (4%) came off study because of toxicity: one for ↑ liver function tests and one for anemia.