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Authors

Blum, Joanne L
Laird, A Douglas
Litton, Jennifer K
[et al.](#)

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Determinants of Response to Talazoparib in Patients with HER2-Negative, Germline *BRCA1/2*-Mutated Breast Cancer



Joanne L. Blum¹, A. Douglas Laird², Jennifer K. Litton³, Hope S. Rugo⁴, Johannes Ettl⁵, Sara A. Hurvitz⁶, Miguel Martin⁷, Henri H. Roché⁸, Kyung-Hun Lee⁹, Annabel Goodwin¹⁰, Ying Chen², Silvana Lanzalone¹¹, Jijumon Chelliserry², Akos Czibere¹², Julia F. Hopkins¹³, Lee A. Albacker¹³, and Lida A. Mina¹⁴

ABSTRACT

Purpose: PARP inhibitors (PARPi) have demonstrated efficacy in tumors with germline breast cancer susceptibility genes (*gBRCA*) 1 and 2 mutations, but further factors influencing response to PARPi are poorly understood.

Experimental Design: Breast cancer tumor tissue from patients with *gBRCA1/2* mutations from the phase III EMBRACA trial of the PARPi talazoparib versus chemotherapy was sequenced using FoundationOne CDx.

Results: In the evaluable intent-to-treat population, 96.1% (296/308) had ≥ 1 tumor *BRCA* (*tBRCA*) mutation and there was strong concordance (95.3%) between *tBRCA* and *gBRCA*

mutational status. Genetic/genomic characteristics including *BRCA* loss of heterozygosity (LOH; identified in 82.6% of evaluable patients), DNA damage response (DDR) gene mutational burden, and tumor homologous recombination deficiency [assessed by genomic LOH (gLOH)] demonstrated no association with talazoparib efficacy.

Conclusions: Overall, *BRCA* LOH status, DDR gene mutational burden, and gLOH were not associated with talazoparib efficacy; however, these conclusions are qualified by population heterogeneity and low patient numbers in some subgroups. Further investigation in larger patient populations is warranted.

Introduction

DNA double-strand break repair is a key process in maintaining genomic stability (1). Breast cancer susceptibility genes (*BRCA*) 1 and 2 are tumor-suppressing genes that play a critical role in this process via homologous recombination repair (2). Germline *BRCA1/2* mutations (*gBRCA1/2mut*) are associated with an increased susceptibility to breast, ovarian, prostate, and pancreatic cancer (3). Cancer cells with

BRCA1/2mut have homologous recombination deficiency (HRD) and become more reliant on PARP 1 and 2, which mediate base excision repair of single-strand DNA (ssDNA) breaks (2, 4–6).

PARP inhibitors act via direct catalytic inhibition and there is evidence that they trap PARP on sites of DNA damage, hindering transcription and inducing replication fork collapse (2, 7, 8). Inhibition of PARP results in persistent ssDNA breaks, culminating in accumulation of double-stranded DNA breaks and therefore, in cells with HRD, ultimately inducing synthetic lethality stemming from irreparable DNA damage (2).

The PARP inhibitor talazoparib has demonstrated efficacy in cancers with *gBRCAmut* (9–11), and has also shown higher PARP-trapping activity *in vitro* compared with other PARP inhibitors (2, 8, 12). In the phase III EMBRACA trial (NCT01945775), talazoparib significantly improved median progression-free survival (PFS) compared with chemotherapy in patients with HER2-negative locally advanced/metastatic breast cancer (LA/mBC) and a *gBRCAmut* [8.6 months; 95% confidence interval (CI), 7.2–9.3 vs. 5.6 months; 95% CI, 4.2–6.7; HR for disease progression or death 0.54; 95% CI, 0.41–0.71; $P < 0.001$]; ref. 9]. On the basis of the EMBRACA results, talazoparib (oral; 1 mg, once daily) is approved in the United States, European Union, and other countries for patients with HER2-negative LA/mBC with *gBRCA1/2mut* (13, 14). Similarly, multiple guidelines recommend the use of PARP inhibitors in patients with *gBRCA1/2mut* and advanced HER2-negative breast cancer, as an alternative to chemotherapy, with the National Comprehensive Cancer Network (NCCN) guidelines including treatment with talazoparib or olaparib, as a category 1, preferred option for patients with *gBRCA1/2mut* (15, 16).

While the efficacy of PARP inhibitors in patients with *gBRCA1/2mut* HER2-negative advanced breast cancer has been demonstrated in clinical trials (9–11), little is known about tumor-related factors that might influence response to PARP inhibitors in such patients. The purpose of these analyses was to evaluate samples of tumor tissue from patients enrolled in EMBRACA to explore the

¹Baylor Charles A. Sammons Cancer Center, Texas Oncology, US Oncology, Dallas, Texas. ²Pfizer Inc., La Jolla, California. ³The University of Texas MD Anderson Cancer Center, Houston, Texas. ⁴University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, California. ⁵Department of Obstetrics and Gynecology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany. ⁶University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, California. ⁷Instituto de Investigación Sanitaria Gregorio Marañón, CIBERONC, GEICAM, Universidad Complutense, Madrid, Spain. ⁸Institut Claudius Regaud, Institut Universitaire du Cancer Toulouse, Toulouse, France. ⁹Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea. ¹⁰Concord Repatriation General Hospital, Sydney, Australia. ¹¹Pfizer Inc., Milan, Italy. ¹²Pfizer Inc., Cambridge, Massachusetts. ¹³Foundation Medicine Inc., Cambridge, Massachusetts. ¹⁴Banner MD Anderson Cancer Center at Banner Gateway Medical Center, Gilbert, Arizona.

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Corresponding Author: Joanne L. Blum, Baylor Charles A. Sammons Cancer Center, Texas Oncology, US Oncology, 3410 Worth Street, Suite 400, Dallas, TX 75246. Phone: 214-370-1050; E-mail: joanne.blum@usoncology.com

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Translational Relevance

While the efficacy of the PARP inhibitor talazoparib has been demonstrated in patients with germline breast cancer susceptibility gene (*gBRCA1/2*)-mutated HER2-negative locally advanced or metastatic breast cancer, less is known about tumor-related factors that might influence response to talazoparib. This retrospective analysis evaluated tumor tissue samples from patients enrolled in the EMBRACA study to explore potential tumor mutational and genomic factors that may influence response to talazoparib. The results from this analysis show that genetic/genomic characteristics, including *BRCA* loss-of-heterozygosity status, DNA damage response gene mutational burden, and tumor homologous recombination deficiency, demonstrate no association with talazoparib efficacy among patients with germline *BRCA1/2* mutations. Further research is warranted and will be important in identifying patients in the clinic who may maximally benefit from talazoparib treatment.

prevalence of tumor *BRCA1/2*mut (*tBRCA*mut) in patients with a *gBRCA1/2*mut, the concordance of *BRCA* mutation between germline and tumor samples, and *tBRCA* zygosity. Non-*BRCA* DNA damage response (DDR) mutations; other common, mechanistically pertinent, non-*BRCA* mutations; and HRD as assessed by genomic loss of heterozygosity (gLOH) were also evaluated. In addition, potential associations of these factors with patient outcomes were assessed.

Materials and Methods

Study design and patients

EMBRACA was an open-label, randomized, international, phase III trial comparing the efficacy and safety of talazoparib with chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine), assigned in a 2:1 ratio, in patients with HER2-negative and *gBRCA*-mutated LA/mBC. Details of the study have been previously published (9). Briefly, eligible patients were 18 years of age or older and had received ≤ 3 previous cytotoxic regimens for advanced breast cancer, and had been previously treated with a taxane, an anthracycline, or both, unless these treatments were contraindicated. The primary endpoint was radiographic PFS by blinded independent review facility (IRF) using RECIST version 1.1.

The trial protocol was approved by an independent ethics committee at each site before initiation of the trial, and the study was conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonisation Guideline for Good Clinical Practice, the U.S. Code of Federal Regulations, and/or other national and local regulations. Written informed consent was obtained from each patient before entering the patient into the study.

Next-generation sequencing and mutational analysis

Molecular eligibility for enrollment in EMBRACA was supported by germline testing using the BRACAnalysis CDx test (Myriad Genetic Laboratories, Inc.; ref. 9). In this analysis, mandated tumor tissue samples from primary or metastatic sites from patients enrolled in EMBRACA were tested using FoundationOne CDx (Foundation Medicine Inc.). Mutations were defined as known/likely pathogenic single-nucleotide variants (SNV), insertions, deletions, or rearrangements. Copy-number alterations (CNA) were analyzed separately as these alterations often reflect larger genomic changes that are not

necessarily associated with a specific gene (17, 18). Furthermore, non-*BRCA* DDR genes (*ARID1A*, *ATR*, *ATM*, *BARD1*, *BRD4*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *FANCC*, *FANCG*, *NBN*, *PALB2*, *RAD51B*, and *STAG2*) present in tumor tissue were included in a subset of correlative analyses based on their role in homologous recombination-mediated DNA response and/or demonstrated potential for these mutations to sensitize to PARP inhibitors in various nonclinical models (19–22), and based on the presence of mutations in these genes in the FoundationOne CDx dataset. gLOH and somatic-germline-zygosity (SGZ) assessments were performed by Foundation Medicine Inc. gLOH was used to evaluate HRD at the genome level (23, 24). SGZ was used to predict the homozygous versus heterozygous state of the *BRCA* mutations (25). Finally, germline versus tumor sequence comparisons were used to determine whether tumor *BRCA* mutations were of germline or somatic origin.

Patient populations included in biomarker analysis

The evaluable intent-to-treat (ITT) population included all patients in the ITT population with tumor samples suitable for analysis by FoundationOne CDx testing. Subsets of the ITT population were used for different analyses (Supplementary Fig. S1) and included the *tBRCA*-mutated ITT population: patients with ≥ 1 *tBRCA*mut (i.e., alterations consisting of known or likely pathogenic SNVs, insertions, deletions, or rearrangements, but excluding CNAs) identified by FoundationOne CDx; ITT population evaluable for *BRCA* zygosity: a subset of the *tBRCA*-mutated ITT population evaluable for zygosity by SGZ; and ITT population evaluable for gLOH: a subset of the evaluable ITT population in which gLOH could be assessed.

Clinical efficacy endpoints assessed in correlative analyses

Clinical efficacy endpoints assessed in correlative analyses included the clinical benefit rate [defined as a complete response (CR), partial response (PR), or stable disease (SD) lasting for ≥ 24 weeks (CBR24) per RECIST 1.1 by investigator assessment] and PFS per RECIST 1.1 by IRF assessment. Best percent change of sum of longest diameters of target lesions from baseline over time by investigator assessment, with best overall response assessed as CR, PR, SD, or progressive disease, was also evaluated. Patients with samples that were not evaluable due to tissue availability, sample quality, or tumor-cell fraction were excluded from these analyses.

Data availability statement

Pfizer will provide access to individual deidentified participant data and related study documents [e.g., protocol, statistical analysis plan (SAP), clinical study report (CSR)] upon request from qualified researchers, and subject to certain criteria, conditions, and exceptions.

Results

Patients

A total of 431 patients were included in the overall ITT population. This comprised 287 patients in the talazoparib arm and 144 patients in the chemotherapy arm. Tumor tissue was evaluable from 308 patients (71.5%) forming the evaluable ITT population for this analysis: 201 patients (70.0%) receiving talazoparib and 107 patients (74.3%) receiving chemotherapy. A summary of baseline characteristics in the overall ITT population and evaluable ITT population is presented in Supplementary Table S1, which demonstrates similar overall characteristics between these populations. Whether tumor tissue was taken

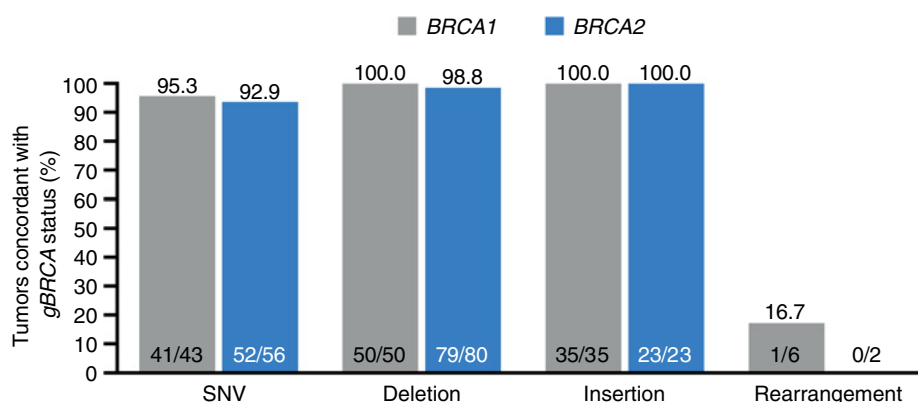


Figure 1.

Tumor sequencing and concordance with germline *BRCA* status—evaluable ITT population. The proportion of patients with a known *gBRCA*mut by Central lab who have a *BRCA1/2*mut (defined as known or likely pathogenic variant, CNAs excluded) detected in a tumor using FoundationOne CDx. All patients showing concordant *BRCA1* or *BRCA2* mutational status exhibited the same mutation in tumor as originally detected in germline, as evidenced by mapping to a common Variation ID in ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar>) or other comparative means, with one exception (1 patient who exhibited a distinct *BRCA2*mut in germline and tumor). A total of 14 patients were discordant: 2 patients—same germline variants used to support enrollment were classified by the FoundationOne CDx test as pathogenicity unknown; 7 patients exhibited *gBRCA* deletion impacting one or multiple exons and were hence mapped to Rearrangement category. These patients exhibited alterations classified as pathogenic *BRCA* CNAs by FoundationOne CDx in the corresponding *BRCA* genes; 2 patients—*gBRCA2*mut, *tBRCA1*mut; 1 patient—*gBRCA1*mut, *tBRCA2*mut; 2 patients—no *tBRCA* variant detected.

from primary or metastatic sites was not recorded in the case report form.

Tumor molecular profiling

Among the 308 patients in the evaluable ITT population, 296 (96.1%) had ≥ 1 *tBRCA*mut: 135 (43.8%) had ≥ 1 *tBRCA1*mut with no *tBRCA2*mut, 157 (51.0%) had ≥ 1 *tBRCA2*mut with no *tBRCA1*mut, 4 (1.3%) had both *tBRCA1*mut and *tBRCA2*mut, and 12 (3.9%) did not have either *tBRCA1*mut or *tBRCA2*mut in tumor samples (Supplementary Fig. S2A). Known or likely pathogenic CNAs in *BRCA1* and *BRCA2* (not counted as *BRCA* mutations) were observed in 6 of 308 (1.9%) and 3 of 308 (1.0%) of the evaluable ITT population tumors, respectively.

Of the 12 patients recorded as lacking a *tBRCA1* or *tBRCA2* mutation (Supplementary Table S2), 3 were found to have *tBRCA2* SNVs classified by FoundationOne CDx as “pathogenicity unknown”; for 2 of these 3, the same variants were originally identified in germline testing and used to support molecular eligibility for enrollment of these patients. Seven patients had *tBRCA* CNAs that were classified as pathogenic by FoundationOne CDx. Further analysis showed that these samples harbored partial deletions of *BRCA* genes, and *gBRCA* enrollment testing (BRACAnalysis CDx test) showed deletions in the corresponding *gBRCA* genes for these patients. Three patients lacked any *tBRCA* variants, including 2 with central *gBRCA1/2*mut used to support molecular eligibility for enrollment and one with no *gBRCA1/2*mut detected by Central testing, who was enrolled on the basis of local *gBRCA* test results. Clinical outcomes for patients who were recorded as lacking *tBRCA*mut are shown in Supplementary Table S2.

Concordance between *gBRCA* and *tBRCA* mutational status was assessed in 295 patients. A total of 281 of 295 (95.3%) patients exhibited concordance (Fig. 1). However, a majority (9) of the 14 patients described as nonconcordant were found to have the same/similar underlying variants in both the germline and tumor tests, and were only classified as nonconcordant due to differences in variant classification/nomenclature between tests (Fig. 1). Hence, the concordance rate would be 290 of 295 (98.3%) if these variant classifica-

tion/nomenclature differences were factored into this concordance assessment. In addition to patients listed as lacking a *tBRCA1/2*mut, 3 patients had different *gBRCA* and *tBRCA* mutations (2 patients had a *gBRCA2* but a *tBRCA1* mutation and 1 patient had a *gBRCA1* but a *tBRCA2* mutation).

Of the 296 patients in the *tBRCA*-mutated ITT population, 236 (79.7%) were evaluable for *BRCA* zygosity and 236 of 308 (76.6%) of the evaluable ITT population were evaluable for gLOH. *BRCA* LOH, with retention of a mutant *BRCA* allele, was predicted in 195 of 236 (82.6%) patients including 1 patient with mutations in both *BRCA1* and *BRCA2* with LOH predicted for both genes. Forty-one patients had a *tBRCA1/2*mut with no LOH (Supplementary Fig. S2B). Baseline characteristics of these patients are presented in Supplementary Table S3.

In the evaluable ITT population, non-*BRCA* mutations within the tumor were found in *ARID1A* (2.3%); *CHEK2* and *FANCA* (each 1.6%); *NBN* (1.3%); *ATM* and *BRIP1* (each 1.0%); *ATR*, *BRD4*, *FANCC*, *PALB2*, and *RAD51B* (each 0.6%); and *BARD1*, *CDK12*, *FANCG*, and *STAG2* (each 0.3%). The most common non-*BRCA* mutations ($\geq 10\%$) were *TP53* and *PIK3CA* in both the evaluable ITT population (51.6% and 10.4%) and the *tBRCA*-mutated population (52.0% and 10.8%), respectively. *TP53* mutations were more commonly observed with *tBRCA1*mut while *PIK3CA* mutations were more frequently observed in *BRCA2*-mutated tumors (Table 1). Known/likely pathogenic CNAs with a prevalence of $\geq 10\%$ in the evaluable ITT population were *MYC* (21.4%) and *RAD21* (21.1%) with similar values observed in the *tBRCA*-mutated ITT population (20.9% and 21.3%, respectively; Table 1).

In EMBRACA, median (range) gLOH scores were 21.8% (0.0–52.7) and 20.5% (0.2–40.5) for the talazoparib and chemotherapy arms, respectively. An analysis from the Foundation Medicine Insights database found similar gLOH scores in patients with HER2-negative *BRCA1/2*-mutated breast cancer (median 22.6%, based on $N = 1,471$ tumors), but gLOH was lower in the overall breast cancer population (median 12.5%, based on $N = 17,261$ tumors). The relationship between *BRCA* LOH and gLOH was also explored. In both treatment arms, gLOH was significantly higher in tumors exhibiting *BRCA* LOH

Table 1. Most commonly mutated non-*BRCA1/2* tumor tissue genes in patients with *tBRCAmut* (evaluable ITT population).

	Talazoparib <i>n/N</i> (%)	Chemotherapy <i>n/N</i> (%)	Combined <i>n/N</i> (%)
Mutations			
<i>TP53</i>			
<i>tBRCA1mut</i> only	76/90 (84.4)	39/45 (86.7)	115/135 (85.2)
<i>tBRCA2mut</i> only	23/102 (22.5)	16/55 (29.1)	39/157 (24.8)
<i>tBRCA1mut</i> and <i>tBRCA2mut</i>	0/1 (0.0)	0/3 (0.0)	0/4 (0.0)
<i>tBRCA1mut</i> or <i>tBRCA2mut</i>	99/193 (51.3)	55/103 (53.4)	154/296 (52.0)
<i>PIK3CA</i>			
<i>tBRCA1mut</i> only	6/90 (6.7)	1/45 (2.2)	7/135 (5.2)
<i>tBRCA2mut</i> only	16/102 (15.7)	9/55 (16.4)	25/157 (15.9)
<i>tBRCA1mut</i> and <i>tBRCA2mut</i>	0/1 (0.0)	0/3 (0.0)	0/4 (0.0)
<i>tBRCA1mut</i> or <i>tBRCA2mut</i>	22/193 (11.4)	10/103 (9.7)	32/296 (10.8)
Known/likely pathogenic CNAs			
<i>MYC</i>			
<i>tBRCA1mut</i>	16/90 (17.8)	12/45 (26.7)	28/135 (20.7)
<i>tBRCA2mut</i>	21/102 (20.6)	11/55 (20.0)	32/157 (20.4)
<i>tBRCA1mut</i> and <i>tBRCA2mut</i>	0/1 (0.0)	2/3 (66.7)	2/4 (50.0)
<i>tBRCA1mut</i> or <i>tBRCA2mut</i>	37/193 (19.2)	25/103 (24.3)	62/296 (20.9)
<i>RAD21</i>			
<i>tBRCA1mut</i>	10/90 (11.1)	13/45 (28.9)	23/135 (17.0)
<i>tBRCA2mut</i>	23/102 (22.5)	16/55 (29.1)	39/157 (24.8)
<i>tBRCA1mut</i> and <i>tBRCA2mut</i>	0/1 (0.0)	1/3 (33.3)	1/4 (25.0)
<i>tBRCA1mut</i> or <i>tBRCA2mut</i>	33/193 (17.1)	30/103 (29.1)	63/296 (21.3)

Note: *tBRCA*-mutated ITT population includes all patients with tumor samples suitable for the genomic evaluation and analyzed using FoundationOne CDx who have *BRCA* mutations (variants with known or likely pathogenic impact, excluding CNAs). Genes shown exhibit mutations (known/likely pathogenic variant, CNAs excluded) or known/likely pathogenic CNAs in $\geq 10\%$ of patients in combined arms.

than in tumors not exhibiting *BRCA* LOH: median (minimum, maximum): 22.8% (0.1, 52.7) and 12.7% (0.0, 21.2), $P < 0.0001$, for talazoparib; median (minimum, maximum): 21.8% (0.2, 40.5) and 15.8% (1.6, 23.6), $P = 0.0028$, for chemotherapy (Supplementary Fig. S3).

Correlative analysis

CBR24 was generally comparable for tumors with *BRCA1/2mut*: in the talazoparib arm; CBR24 was 64% ($n/N = 58/90$; 95% CI, 54–74) and 76% ($n/N = 78/102$; 95% CI, 67–84) for *tBRCA1mut* and *tBRCA2mut*, respectively. In the chemotherapy arm, CBR24 was 36% ($n/N = 16/45$; 95% CI, 22–51) and 31% ($n/N = 17/55$; 95% CI, 19–45) for *tBRCA1mut* and *tBRCA2mut*, respectively. In patients with or without *tBRCA1/2* LOH treated with talazoparib, CBR24 was 74.6% ($n/N = 91/122$) and 66.7% ($n/N = 18/27$), respectively.

In the talazoparib arm, no significant differences in median PFS were observed between the 122 patients with *tBRCA* LOH and the 27 patients without *tBRCA* LOH [9.0 months vs. 6.9 months; HR (95% CI) = 0.868 (0.512–1.470); $P = 0.597$; **Table 2**]. Similarly, no significant difference in median PFS was observed between patients with or without *tBRCA* LOH in the chemotherapy arm [5.8 vs. 5.6 months; HR (95% CI) = 1.797 (0.751–4.298); $P = 0.179$; **Table 2**]. Differences in PFS between patients with and without *tBRCA* LOH were also evaluated by lines of prior chemotherapy and tumor subtype where subgroup sample size was ≥ 10 patients. In the talazoparib arm, a trend favoring patients with *tBRCA* LOH was observed in the hormone receptor–positive subgroup [median PFS: 13.0 months vs. 8.5 months; HR (95% CI) = 0.542 (0.285–1.032); $P = 0.058$; **Table 2**]; however, the triple-negative breast cancer (TNBC) subgroup was not evaluable for this analysis as most evaluable patients (56/60, 93.3%) exhibited *BRCA* LOH.

Additional analyses explored the relationship between number of DDR mutations with tumor response in the evaluable ITT population and the impact of alteration status on commonly altered non-DDR genes on PFS in patients with *tBRCAmut*. No association was observed between the total number of DDR mutations (1 vs. ≥ 2) and best overall response to talazoparib or chemotherapy [OR (95% CI): 0.76 (0.31–1.87), $P = 0.55$ for talazoparib; 0.98 (0.27–3.51), $P = 0.97$ for chemotherapy; Supplementary Fig. S4]. In the talazoparib group, PFS was significantly shorter in patients with *TP53* mutations than in those without [HR (95% CI) = 1.693 (1.186–2.418); $P = 0.0033$]. In the chemotherapy group, PFS was shorter in patients with *TP53* mutations than in those without; however, this did not reach statistical significance [HR (95% CI) = 1.439 (0.859–2.411); $P = 0.1614$]. *PTEN*, *PIK3CA*, *RAD21*, and *MYC* mutational and/or CNA status were not associated with PFS in either arm (Supplementary Table S4).

In either treatment arm, no differences in gLOH were observed between patients who did and did not achieve a clinical benefit, and no relationship was evident between gLOH and best overall response category based on the Jonckheere–Terpstra trend test (Supplementary Fig. S5 and S6; **Table 3**). The association between gLOH and clinical benefit was also investigated in subgroups of patients by lines of prior chemotherapy and tumor subtype (TNBC or hormone receptor–positive breast cancer) where subgroup sample size was ≥ 30 patients (**Table 3**). No association was observed between gLOH and clinical benefit with talazoparib by lines of prior chemotherapy. In patients with TNBC, gLOH was significantly higher in patients who had clinical benefit versus no clinical benefit in the talazoparib arm. No association between gLOH and clinical benefit was observed in patients with hormone receptor–positive breast cancer in either study arm. In both treatment arms, patients with gLOH more than

Table 2. PFS of patients with *BRCA*-mutant tumors: *BRCA1* or *BRCA2* LOH versus no *BRCA1* or *BRCA2* LOH (*tBRCA*-mutant ITT population evaluable for *BRCA* zygosity).

Group	Evaluable for <i>BRCA</i> zygosity, <i>n</i>	<i>BRCA1</i> or <i>BRCA2</i> LOH, <i>n</i>	No <i>BRCA1</i> or <i>BRCA2</i> LOH, <i>n</i>	Median PFS, ^a mo		HR (95% CI)	<i>P</i> value
				<i>BRCA1</i> or <i>BRCA2</i> LOH	No <i>BRCA1</i> or <i>BRCA2</i> LOH		
Talazoparib arm							
ITT	149	122	27	9.0	6.9	0.868 (0.512–1.470)	0.597
1 prior line of chemotherapy	56	40	16	6.9	5.8	0.879 (0.407–1.899)	0.740
HR ⁺ BC	89	66	23	13.0	8.5	0.542 (0.285–1.032)	0.058
Chemotherapy arm							
ITT	87	73	14	5.8	5.6	1.797 (0.751–4.298)	0.179
1 prior line of chemotherapy	26	23	3	3.6	5.6	0.809 (0.177–3.702)	0.783
HR ⁺ BC	54	45	9	6.7	5.6	0.696 (0.238–2.030)	0.500

Note: Cox proportional hazards model with no *BRCA1/2* LOH as the reference group was used to calculate HR and 95% CI. HR < 1 indicates better PFS in the *BRCA1* or *BRCA2* LOH group, whereas HR > 1 indicates better PFS in the no *BRCA1* or *BRCA2* LOH group. Log-rank two-sided test was performed to compare between the two groups. Evaluable ITT population includes all patients with tumor samples suitable for the genomic evaluation and analyzed using FoundationOne CDx who have known or likely pathogenic *BRCA*mut (*BRCA* CNAs excluded) and who are evaluable for *BRCA* zygosity. Subgroups shown are of the evaluable ITT population defined by previous line of chemotherapy or cancer subtype. PFS is per RECIST 1.1 by IRF assessment.

Abbreviations: HR⁺ BC, hormone receptor-positive breast cancer; mo, months.
^aBased on Kaplan–Meier estimates.

or equal to the median exhibited PFS similar to that seen in patients with gLOH below the median: HR (95% CI) = 1.247 (0.828–1.879) for talazoparib; 1.238 (0.693–2.211) for chemotherapy (Fig. 2). In patients with TNBC, PFS was similar between patients with gLOH ≥ median and patients with gLOH less than median treated with talazoparib [HR (95% CI) = 0.913 (0.526–1.587)] (Supplementary Fig. S7). In patients treated with chemotherapy, a numerically longer PFS was observed in patients with gLOH less than median versus in patients with a gLOH ≥ median, although CIs overlapped with 1.0 [HR (95% CI) 2.036 (0.838–4.950)]. Finally, when gLOH was assessed in a stratified Cox regression model with treatment and gLOH as the covariates, no association between gLOH and PFS was evident (Supplementary Table S5).

Discussion

In the EMBRACA study, 96.1% of patients with evaluable tumor samples exhibited ≥1 *tBRCA1*mut or *tBRCA2*mut. Strong concordance

(95.3%) between *tBRCA* mutational status based on FoundationOne CDx and *gBRCA* mutational status based on the Myriad BRACAnalysis CDx test was observed. When factoring in differences in classification/nomenclature between the two tests, the concordance rate was 98.3%. Strong concordance was also observed in the phase II ABRAZO trial in which 96.7% of patients had ≥1 *BRCA1* or *BRCA2* tumor mutation, and 96.4% of patients exhibited concordance between *tBRCA* and *gBRCA* mutational status (11, 26). This is unsurprising given the importance of *BRCA* mutations in breast cancer. However, it should be acknowledged that high positive concordance of tumor to germline *BRCA* mutational status might not translate in patients not preselected for *gBRCA*mut.

No differences in clinical benefit for tumors with *BRCA1*mut compared with *BRCA2*mut were noted in these analyses. The potential for clinical benefit observed in the small fraction of patients lacking *tBRCA*mut may have been due to the fact that the majority of patients classified as lacking *tBRCA*mut (*n* = 12) did in fact have a known/likely pathogenic *tBRCA* or *gBRCA* alteration: 7 patients who exhibited

Table 3. Clinical benefit by gLOH for talazoparib and chemotherapy by line of therapy or breast cancer subtype—ITT population evaluable for clinical benefit and gLOH.

	Talazoparib			Chemotherapy		
	gLOH (%) for clinical benefit—yes Median (range), <i>n</i>	gLOH (%) for clinical benefit—no Median (range), <i>n</i>	<i>P</i> value	gLOH (%) for clinical benefit—yes Median (range), <i>n</i>	gLOH (%) for clinical benefit—no Median (range), <i>n</i>	<i>P</i> value
Evaluable ITT	21.3 (0.0–52.7), 100	22.5 (0.0–45.1), 40	0.9762	20.1 (0.3–35.9), 26	20.9 (0.2–40.5), 55	0.4917
No prior lines of chemotherapy	22.0 (0.3–52.7), 44	26.4 (11.0–45.1), 10	0.1022	26.3 (0.3–35.9), 10	19.2 (0.2–40.5), 21	0.5771
1 prior line of chemotherapy	20.4 (0.5–45.2), 33	18.7 (0.0–31.9), 16	0.1872	Not shown (total <i>n</i> < 30)		
2 prior lines of chemotherapy	23.1 (0.0–50.3), 21	22.7 (10.9–28.1), 11	0.5406	Not shown (total <i>n</i> < 30)		
HR ⁺ BC	18.1 (0.0–50.3), 62	18.91 (6.33–31.9), 15	0.8171	19.1 (1.6–35.9), 21	17.5 (0.2–39.0), 24	0.2633
TNBC	30.8 (0.3–52.7), 37	23.0 (0.0–45.1), 27	0.0456	23.6 (0.3–31.3), 5	26.7 (0.2–40.5), 32	0.3445

Note: Clinical benefit is based on target, nontarget, and new lesions per RECIST 1.1, and confirmation of CR, PR, and SD is not required. Clinical benefit is defined as best overall response of CR, PR, or SD lasting ≥24 weeks from randomization per RECIST 1.1 as determined by investigator. Subgroups shown are subgroups of the evaluable ITT population defined by previous lines of chemotherapy or cancer subtype. *P* value from two-tailed *t* test.

Abbreviation: HR⁺ BC, hormone receptor-positive breast cancer.

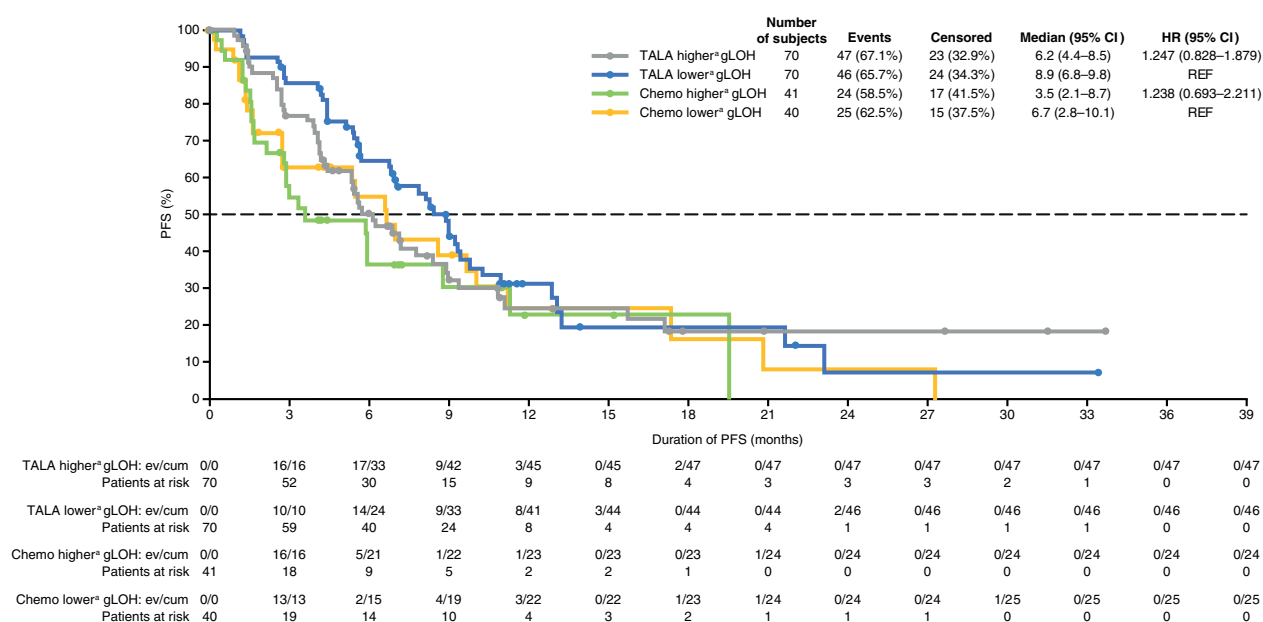


Figure 2.

Kaplan–Meier curves for duration of radiographic PFS by IRF assessment—ITT population evaluable for PFS and gLOH. Chemo, chemotherapy; cum, cumulative; ev, events; REF, reference; TALA, talazoparib. ^aHigher and lower indicate that gLOH is above or below the median, respectively. HR is based on unstratified Cox regression model and is relative to talazoparib gLOH < median or chemotherapy gLOH < median with <1 favoring higher gLOH.

deleterious *gBRCA* deletions per BRCAAnalysis CDx had known/likely pathogenic CNAs (losses) in the corresponding *BRCA* genes per Foundation Medicine nomenclature; 3 patients lacked any *tBRCA* variants, and 2 patients each had a *tBRCA* variant defined as being of unknown pathogenicity per Foundation Medicine with identical corresponding *gBRCA* variants defined as known/likely pathogenic per Myriad.

Overall, 82.6% of patients with evaluable *tBRCA*mut exhibited *BRCA* LOH, which is consistent with previous reports that also showed a high prevalence of LOH for *BRCA1/2*mut (27, 28). In a study that analyzed whole-genome sequences of 560 breast cancer samples, 88.9% of samples with a germline or somatic *BRCA1/2*mut exhibited LOH (27). In another analysis, *BRCA* LOH was seen in 90.2% of *BRCA1* carriers compared with 54.3% of *BRCA2* carriers (28). A high rate of *BRCA* LOH (85.1%) was also observed in the evaluable *tBRCA*-mutated population in ABRAZO (11, 26). The high frequency of LOH in the above studies demonstrates the strong selective drive in breast cancer tumors to retain mutated *gBRCA* alleles and lose the wildtype allele, although mechanisms such as *BRCA1* promoter methylation may also contribute to silencing the wildtype *BRCA* allele (27–29). Therefore, the absence of *BRCA* LOH is not necessarily a robust indicator of *BRCA* functionality in tumors. However, in both treatment arms of EMBRACA, gLOH was significantly higher in tumors exhibiting *BRCA* LOH than in those not exhibiting *BRCA* LOH. This relationship between *BRCA* LOH status and HRD is consistent with similar associations documented by others (28). Nonetheless, although there were some differences in PFS within the gLOH high versus low groups, particularly notable in the chemotherapy-treated group (median PFS 3.5 vs. 6.7 months), numbers of patients at risk were small, with wide CIs on median PFS, and no statistically significant association was found between PFS and *BRCA* LOH status. In addition, a trend in PFS appeared to favor patients with *tBRCA* LOH in the hormone

receptor–positive subgroup, although this association did not reach statistical significance ($P = 0.058$). Overall, this may suggest a lack of predictive utility of *BRCA* LOH status in patients with HER2–negative LA/mBC and a *gBRCA*mut.

Mutations in non-*BRCA* genes implicated in homologous recombination, DDR, and/or sensitization to PARP inhibitor detected in this analysis included, but were not limited to, *ARID1A*, *ATR*, *BARD1*, *BRD4*, *BRIP1*, *CHEK2*, *FANCC*, and *STAG2*. The presence of these non-*BRCA* DDR mutations did not appear to be associated with differential sensitivity to talazoparib in patients with *tBRCA*mut; however, due to small patient numbers in this subgroup, confirmation in a larger study is warranted.

Mutational profiles of non-*BRCA* genes in EMBRACA differed between *tBRCA1*- and *tBRCA2*-related cancers. *TP53* mutations were very frequent in *BRCA1*-mutated tumors (85.2%), but less frequent in *BRCA2*-mutated tumors (24.8%), similar to the mutational profiles observed in ABRAZO (75.9% for *BRCA1*- and 14.3% for *BRCA2*-mutated tumors; ref. 26). This difference may be due in part to the high prevalence of both *TP53* and *BRCA1* mutations in TNBC (30, 31). Conversely, *PIK3CA* mutations were more commonly seen in *BRCA2*-mutated tumors than in *BRCA1*-mutated tumors, which may be attributed to the relatively high prevalence of both *PIK3CA* mutations (32) and *BRCA2* mutations in hormone receptor–positive mBC (33, 34).

No associations were evident between the alteration status of non-*BRCA* genes and PFS, with the exception of *TP53* where the presence of *TP53* mutations appeared to be associated with shorter PFS in the talazoparib arm, with a similar, albeit nonsignificant, trend evident in the chemotherapy arm; the significance of this finding could have been limited by the lower number of patients in the chemotherapy arm. While the prognostic significance of *TP53* mutations is variable according to tumor type (35), *TP53* mutations are associated with worse outcomes in metastatic breast cancer (36), which may reflect the

close association between *TP53* and *BRCA1* mutations, and in turn reflect a common association with TNBC (30, 31).

In this analysis, gLOH was assessed as a genomic-level marker of HRD. gLOH scores in EMBRACA patients were similar to those found in HER2-negative *BRCA1/2*-mutant breast cancer from the Foundation Medicine Insights database and were much higher than those seen for the overall breast cancer population, reflecting HRD associated with *BRC*Amut. In both treatment arms, patients with gLOH greater than or equal to median exhibited PFS similar to that seen in patients with gLOH less than median. However, in the talazoparib arm, gLOH was higher in patients with TNBC who exhibited clinical benefit than in those who did not. Caution is needed when drawing a direct relationship between biological variation and clinical significance, as other, still unknown, parameters could be involved in the final response. Therefore, this observation would need to be confirmed in additional studies because of the relatively small numbers of patients in the EMBRACA subgroup being compared and the wide interpatient variability in gLOH scores. Overall, based on these retrospective, exploratory analyses from EMBRACA, there is no clear evidence that gLOH is associated with clinical benefit in this patient population, with the potential exception of the subgroup of patients with TNBC.

The limitations of the EMBRACA study have been previously reported (9). Regarding this analysis, the DNA sequencing used cannot detect sequence-independent functional deficiencies in DDR genes (e.g., promoter methylation). It was also not possible to analyze data based on whether tumor samples were collected from primary or metastatic sites as this information was not recorded in the study and, therefore, may have compromised our ability to resolve potential contributions of *BRCA* LOH status or gLOH to efficacy since these might change during tumor progression. Similarly, all patients in the EMBRACA study had to have a germline mutation in *BRCA1* or *BRCA2* to enroll; therefore, efficacy based on somatic-only mutations could not be assessed. Finally, small patient numbers in some mutational subpopulations warrant further investigation in larger datasets.

In summary, 96% of tumors exhibited ≥ 1 *BRCA1/2*mut and there was 95% concordance between known *gBRCA* and *tBRCA* mutational status. Genetic and genomic characteristics, including *BRCA* LOH status (with *BRCA* LOH evident in 83% of evaluable patients) and DDR gene mutational burden, demonstrated no apparent differential association with talazoparib efficacy. There was also no clear evidence that tumor HRD (as assessed by gLOH) was associated with clinical benefit, with the potential exception of the subgroup of patients with TNBC, although this subgroup was small and there was high interpatient variability. Taken together, these results showing high concordance between *gBRCA* and *tBRCA* mutations, high prevalence of *BRCA* LOH, and overall lack of association of *BRCA* LOH or HRD with outcomes in patients with *gBRCA* mutations are consistent with recent findings from the OlympiAD trial (37).

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Authors' Contributions

J.L. Blum: Conceptualization, data curation, formal analysis, writing–review and editing. A.D. Laird: Data curation, formal analysis, writing–review and editing. J.K. Litton: Data curation, formal analysis, writing–review and editing. H.S. Rugo: Conceptualization, data curation, formal analysis, writing–review and editing. J. Ettl: Conceptualization, formal analysis, writing–review and editing. S.A. Hurvitz: Data curation, formal analysis, writing–review and editing. M. Martin: Data curation, formal analysis, writing–review and editing. H.H. Roché: Data curation, formal analysis, writing–review and editing. K.-H. Lee: Data curation, formal analysis, writing–review and editing. A. Goodwin: Data curation, formal analysis, writing–review and editing. Y. Chen: Formal analysis, writing–review and editing. S. Lanzalone: Conceptualization, data curation, formal analysis, writing–review and editing. J. Chelliserry: Data curation, writing–review and editing. A. Czibere: Conceptualization, data curation, formal analysis, writing–review and editing. J.F. Hopkins: Formal analysis, writing–review and editing. L.A. Albacker: Formal analysis, writing–review and editing. L.A. Mina: Data curation, formal analysis, writing–review and editing.

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References

1. Scully R, Panday A, Elango R, Willis NA. DNA double-strand break repair-pathway choice in somatic mammalian cells. *Nat Rev Mol Cell Biol* 2019;20:698–714.
2. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. *Science* 2017;355:1152–8.
3. Ashworth A. A synthetic lethal therapeutic approach: poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. *J Clin Oncol* 2008;26:3785–90.
4. Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. *Mol Oncol* 2011;5:387–93.
5. Javle M, Curtin NJ. The potential for poly (ADP-ribose) polymerase inhibitors in cancer therapy. *Ther Adv Med Oncol* 2011;3:257–67.
6. Morales J, Li L, Fattah FJ, Dong Y, Bey EA, Patel M, et al. Review of poly (ADP-ribose) polymerase (PARP) mechanisms of action and rationale for targeting in cancer and other diseases. *Crit Rev Eukaryot Gene Expr* 2014;24:15–28.
7. Murai J, Huang SN, Das BB, Renaud A, Zhang Y, Doroshow JH, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. *Cancer Res* 2012;72:5588–99.
8. Murai J, Huang SY, Renaud A, Zhang Y, Ji J, Takeda S, et al. Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. *Mol Cancer Ther* 2014;13:433–43.
9. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee K-H, et al. Talazoparib in patients with advanced breast cancer and a germline *BRCA* mutation. *N Engl J Med* 2018;379:753–63.
10. de Bono J, Ramanathan RK, Mina L, Chugh R, Glaspy J, Rafii S, et al. Phase I, dose-escalation, two-part trial of the PARP inhibitor talazoparib in patients with advanced germline *BRCA1/2* mutations and selected sporadic cancers. *Cancer Discov* 2017;7:620–9.
11. Turner NC, Telli ML, Rugo HS, Mailliez A, Ettl J, Grischke EM, et al. A Phase II study of talazoparib after platinum or cytotoxic nonplatinum regimens in patients with advanced breast cancer and germline *BRCA1/2* mutations (ABRAZO). *Clin Cancer Res* 2019;25:2717–24.
12. Zandarashvili L, Langelier MF, Velagapudi UK, Hancock MA, Steffen JD, Billur R, et al. Structural basis for allosteric PARP-1 retention on DNA breaks. *Science* 2020;368:eaax6367.
13. European Medicines Agency. TALZENNA[®] (talazoparib) summary of product characteristics. November 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/talzenna-epar-product-information_en.pdf.
14. U.S. Food and Drug Administration. TALZENNA[®] (talazoparib) prescribing information. 2021. Available from: <http://labeling.pfizer.com/ShowLabeling.aspx?id=11046>.
15. Tung NM, Boughey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, et al. Management of hereditary breast cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology guideline. *J Clin Oncol* 2020;38:2080–106.
16. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]): Breast cancer. Version 5. 2020. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf.
17. Ooi A, Inokuchi M, Horike SI, Kawashima H, Ishikawa S, Ikeda H, et al. Amplicons in breast cancers analyzed by multiplex ligation-dependent probe amplification and fluorescence in situ hybridization. *Hum Pathol* 2019;85:33–43.
18. Kneissig M, Bernhard S, Storchova Z. Modelling chromosome structural and copy number changes to understand cancer genomes. *Curr Opin Genet Dev* 2019;54:25–32.
19. Heeke AL, Pishvaian MJ, Lynce F, Xiu J, Brody JR, Chen WJ, et al. Prevalence of homologous recombination-related gene mutations across multiple cancer types. *JCO Precis Oncol* 2018;2018:PO.17.00286.
20. Sun C, Yin J, Fang Y, Chen J, Jeong KJ, Chen X, et al. BRD4 inhibition is synthetic lethal with PARP inhibitors through the induction of homologous recombination deficiency. *Cancer Cell* 2018;33:401–16.
21. Chung JH, Dewal N, Sokol E, Mathew P, Whitehead R, Millis SZ, et al. Prospective comprehensive genomic profiling of primary and metastatic prostate tumors. *JCO Precis Oncol* 2019;3:PO.18.00283.
22. Mondal G, Stevers M, Goode B, Ashworth A, Solomon DA. A requirement for *STAG2* in replication fork progression creates a targetable synthetic lethality in cohesin-mutant cancers. *Nat Commun* 2019;10:1686.
23. Sokol ES, Pavlick D, Khiabani H, Frampton GM, Ross JS, Gregg JP, et al. Pan-cancer analysis of *BRCA1* and *BRCA2* genomic alterations and their association with genomic instability as measured by genome-wide loss of heterozygosity. *JCO Precis Oncol* 2020;4:442–65.
24. Swisher EM, Lin KK, Oza AM, Scott CL, Giordano H, Sun J, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2017;18:75–87.
25. Sun JX, He Y, Sanford E, Montesin M, Frampton GM, Vignot S, et al. A computational approach to distinguish somatic vs. germline origin of genomic alterations from deep sequencing of cancer specimens without a matched normal. *PLoS Comput Biol* 2018;14:e1005965.
26. Turner NC. Next-generation DNA sequencing (NGS) results for tumors from Phase 2 ABRAZO study of talazoparib after platinum or cytotoxic nonplatinum regimens in patients (pts) with advanced breast cancer (ABC) and germline *BRCA1/2* (*gBRCA*) mutations. In: Proceedings of the European Society for Medical Oncology 2019 Congress; 2019 Sept 27–Oct 1; Barcelona, Spain. Lugano, Switzerland: Annals of Oncology; 2019. Abstract nr 2575.
27. Nik-Zainal S, Davies H, Staaf J, Ramakrishna M, Glodzik D, Zou X, et al. Landscape of somatic mutations in 560 breast cancer whole-genome sequences. *Nature* 2016;534:47–54.
28. Maxwell KN, Wubbenhorst B, Wenz BM, De Sloover D, Pluta J, Emery L, et al. *BRCA* locus-specific loss of heterozygosity in germline *BRCA1* and *BRCA2* carriers. *Nat Commun* 2017;8:319.
29. Polak P, Kim J, Braunstein LZ, Karlic R, Haradhavala NJ, Tiao G, et al. A mutational signature reveals alterations underlying deficient homologous recombination repair in breast cancer. *Nat Genet* 2017;49:1476–86.
30. Holstege H, Joosse SA, van Oostrom CT, Nederlof PM, de Vries A, Jonkers J. High incidence of protein-truncating *TP53* mutations in *BRCA1*-related breast cancer. *Cancer Res* 2009;69:3625–33.
31. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature* 2012;490:61–70.
32. Mollon L, Aguilar A, Anderson E, Dean J, Davis L, Warholak T, et al. Abstract 1207: A systematic literature review of the prevalence of *PIK3CA* mutations and mutation hotspots in HR+/HER2- metastatic breast cancer. *Cancer Res* 2018;78:1207.
33. Atchley DP, Albarracín CT, Lopez A, Valero V, Amos CI, Gonzalez-Angulo AM, et al. Clinical and pathologic characteristics of patients with *BRCA*-positive and *BRCA*-negative breast cancer. *J Clin Oncol* 2008;26:4282–8.
34. Comen E, Davids M, Kirchoff T, Hudis C, Offit K, Robson M. Relative contributions of *BRCA1* and *BRCA2* mutations to "triple-negative" breast cancer in Ashkenazi Women. *Breast Cancer Res Treat* 2011;129:185–90.
35. Olivier M, Hollstein M, Hainaut P. *TP53* mutations in human cancers: origins, consequences, and clinical use. *Cold Spring Harb Perspect Biol* 2010;2:a001008.
36. Meric-Bernstam F, Zheng X, Shariati M, Damodaran S, Wathoo C, Brusco L, et al. Survival outcomes by *TP53* mutation status in metastatic breast cancer. *JCO Precis Oncol* 2018;2018:PO.17.00245.
37. Hodgson D, Lai Z, Dearden S, Barrett JC, Harrington EA, Timms K, et al. Analysis of mutation status and homologous recombination deficiency in tumors of patients with germline *BRCA1* or *BRCA2* mutations and metastatic breast cancer: OlympiAD. *Ann Oncol* 2021;32:1582–9.