Combination of Olaparib, Durvalumab, and Fulvestrant in Patients with Advanced ER+/HER2− Breast Cancer and Selected Genomic Alterations: Results of the DOLAF Trial

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ABSTRACT

Purpose: Previous data suggest synergy between PARP inhibition and immune checkpoint blockade in different genetic settings. The estrogen receptor (ER) pathway remains a key target in metastatic breast cancer regardless of genomic context. This study assesses the activity of the combination of PARP, ER, and PD-L1 inhibition among patients with metastatic breast cancer and relevant genomic alterations.

Patients and Methods: In this multicenter, single-arm, phase II clinical trial, we used a Simon two-stage design to evaluate the activity and safety of a combination of durvalumab, olaparib, and fulvestrant as second or third line in patients with ER+/HER2− metastatic breast cancer. Patients with either somatic or germline mutations of a homologous recombination repair gene, a microsatellite instability status, or an endocrine resistance–related mutation were eligible. Primary endpoint was 24-week progression-free survival rate.

Results: The 172 (100%) patients included received prior endocrine therapy for metastatic breast cancer and 86% received a CDK4/6 inhibitor, and 67 (39%) had a previously documented germline *BRCA1/2* mutation (g*BRCA1/2*m). The 24-week progression-free survival rate was 66.7% [95% confidence interval (CI), 58.6–74.1] in the evaluable population and 76.3% (95% CI, 63.4–86.4) in g*BRCA1/2*m patients. The median progression-free survival was 9.3 months (95% CI, 7.5–12.7) and 12.6 months (95% CI, 8.2–16.7) in the intention-to-treat and g*BRCA1/2*m populations, respectively. The median overall survival was 30 months (95% CI, 26.6–not reached). Most common adverse events of any grade were nausea (59%) and asthenia (43%). No new toxicity warning was detected.

Conclusions: In patients with ER+/HER2− metastatic breast cancer and selected genomic alterations, this triplet combination was active and had an acceptable toxicity profile (NCT04053322).

Introduction

BRCA1 and *BRCA2* are high-penetrance breast cancer predisposition genes, mutated in approximately 2.5% of all patients with breast cancer (1, 2). About 50% to 60% of all germline deleterious variants of the *BRCA1/2* gene [germline *BRCA1/2* mutations (g*BRCA1/2*m)]–related breast cancer are estrogen receptor (ER)–positive (ER+) and HER2-negative (HER2−) tumors (3, 4). BRCA1 and BRCA2 proteins are involved in the homologous recombination DNA repair (HRR) pathway, which carries out high-fidelity repair of DNA double-strand breaks spontaneously arising during DNA replication or after exposure to chemicals or UV radiations (5). Based on a synthetic lethality mechanism, g*BRCA1/2*m-related breast cancer is specifically sensitive to several DNA repair–targeted compounds, notably PARP inhibitors, like olaparib and talazoparib (6, 7). Beyond g*BRCA1/2*m, other genomic alterations at the tumor level in *BRCA1/2* and several other genes involved in HRR have been suggested to lead to the tumor

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Translational Relevance

The DOLAF trial was designed to evaluate the efficacy and safety of a new combination co-targeting the estrogen receptor (ER) pathway, homologous recombination repair (HRR), and PD-L1 as second- or third-line treatment in patients with ER+/HER2− metastatic breast cancer and selected genomic alterations. The combination of fulvestrant, olaparib, and durvalumab led to a 66% (95% confidence interval, 58.6–74.1) progression-free survival rate at 24 weeks in a population largely pretreated with CDK4/6 inhibitors. Progression-free survival rate was highest among germline *BRCA2* carriers [84.4% (70.5–93.5)] and lowest among germline *BRCA1* and non-HRR non–microsatellite instability tumor mutation carriers. Our results suggest that (i) the triplet combination was active among patients selected for this study based on a central tumor next-generation sequencing testing, (ii) several HRR alterations may drive sensitivity to PARP inhibition beyond germline *BRCA*, and (iii) germline *BRCA1* and germline *BRCA2* alterations lead to different outcomes among patients with ER+ metastatic breast cancer.

"BRCAness" phenotype, including sensitivity to PARP inhibitors. These genes include *ATM*, *ATR*, *CHEK1*, *CHEK2*, *RAD51C*, *RAD51D*, *BRIP1*, *NBN*, *PALB2*, and the Fanconi anemia family of genes (*FANCA*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, and *FANCL*; refs. 1, 2).

Genomic studies demonstrated high mutation frequency of several genes, including *AKT1*, *ESR1*, *FGFR1*, *FGFR2*, *FGFR3*, and *PIK3CA*, in ER+/HER2− breast cancer. These mutations are involved in resistance to endocrine therapies (8–10). Although loss of the *BRCA* gene function is a key driver of oncogenesis in g*BRCA1/2*m-related breast cancer, the ER pathway seems to remain a critical therapeutic target for these patients (11, 12). Our group has previously shown that about 15% of patients with ER+/HER2− metastatic breast cancer had hypermutated tumors enriched in coincident mutations in both DNA damage repair and ER signature genes (9), and those gene mutations were associated with poor overall survival (OS; ref. 13). The high mutational load observed in certain ER+/HER2− metastatic breast cancer could increase their sensitivity to immune checkpoint inhibitors (ICI) because of the increased number of mutations and neoantigens (9, 10, 14). Barroso-Sousa and colleagues (14) reported that hypermutation occurs in 5% of all breast cancer with a higher prevalence in metastatic tumors. In the phase II TAPUR basket trial, pembrolizumab showed antitumor activity in heavily pretreated patients with metastatic breast cancer with a high tumor mutational burden (15). Microsatellite instability (MSI) is rare in breast cancer (~1%) but may result in a high mutational burden because of mismatch repair deficiency caused by alterations in *MLH1*, *MSH2*, *MSH6*, or *PMS2* genes. These deficiencies introduce a myriad of mutations in downstream genes, including *MRE11*, involved in HRR (16). Moreover, convincing preclinical and clinical data have demonstrated that defect in the mismatch repair pathway is highly predictive of PD-1 inhibitors' treatment efficacy (17).

Finally, preclinical data suggest synergistic activity of PARP and ICIs (18), with encouraging results from early-phase clinical trials (19, 20). In the phase II MEDIOLA basket trial, the combination of olaparib and durvalumab was assessed in 34 patients with germline *BRCA* mutation (g*BRCA*m) HER2− metastatic breast cancer (20). The disease control rate was 80% and 50% at 12 and 28 weeks, respectively (20).

Based on these data, we evaluated the efficacy and safety of the triple combination of durvalumab plus olaparib plus fulvestrant (DOLAF) in patients with g*BRCA1/2*m or selected sporadic ER+, HER2− advanced breast cancer with HRR deficiency, MSI, or mutations on actionable genes involved in endocrine resistance.

Patients and Methods

Study design and eligibility

This study was designed as a single-arm, phase II, non–threshold-crossing, Simon two-stage trial. Patients aged ≥18 years with pathologically documented ER+ (≥10%), HER2– metastatic or locally advanced breast cancer and an Eastern Cooperative Oncology Group performance status score 0 or 1 were eligible. Patients had to have a somatic or germline pathogenic variant in *BRCA1/BRCA2* or other HRR genes (*ATM*, *ATR*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCA*, *FAND2*, *FANCL*, *MRE11A*, *NBN*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*), MSI tumor status, or mutation in other actionable genes (*AKT1*, *ESR1*, *FGFR1*, *FGFR2*, *FGFR3*, and *PIK3CA*). After an amendment in May 2021, patients with alterations solely in these other actionable genes could no longer be included. Eligibility criteria also included prior treatment with at least one line of endocrine therapy, which must have included a CDK4/6 inhibitor (CDK4/6i), after an amendment in April 2022, and no more than one line of chemotherapy in the metastatic setting. Patients who previously received fulvestrant or mTOR inhibitors, patients with symptomatic or uncontrolled brain metastases, or those with an active documented autoimmune disease within the past 2 years were excluded.

Treatment

Olaparib was administered orally at a dosage of 300 mg twice daily and fulvestrant as two intramuscular injections of 250 mg each on days 1 and 15 of cycle 1 and day 1 of each subsequent 28-day cycle. In premenopausal women and men, goserelin was added (one subcutaneous injection of 3.6 mg every 28 days). Intravenous durvalumab was started 4 weeks after the first dose of olaparib at a fixed dosage of 1,500 mg, every 4 weeks. Patients received treatment until disease progression, unacceptable toxicity, death, or withdrawal of consent. In case of olaparib-related toxicity, the olaparib dosage could be reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. Clinical and radiologic responses were evaluated every 8 weeks until disease progression or patient death.

Central tumor genomic assessment

Biological samples for central next-generation sequencing (NGS) analysis were collected from the patient's most recent formalin-fixed paraffin-embedded tumor sample available, preferably from a metastatic site (excluding bone metastases).

The analyses were carried out in the French National Cancer Institute molecular genetics platforms in the Biopathology departments of Centre Léon Bérard (Lyon) and Institut de Cancérologie de l'Ouest (Angers). The panel-based NGS methodology and MSI assessment procedures are detailed in Supplementary Appendix S1. Patients who had previously documented personal g*BRCA*m and those who had previously documented deleterious germline or somatic alterations of HRR pathway or an MSI status could be

included in the study without waiting for the central results, after review of the analysis report by the molecular genetics platforms. Depending on the type of alterations found during the screening phase, genetic counseling was recommended.

A non-decisional analysis of the tumor PD-L1 expression status was performed using the VENTANA PD-L1 (SP263) assay (Roche; details in the Supplementary Appendix S1) and the tumor proportion score (percentage of PD-L1–positive tumor cells in relation to viable tumor cells in the studied sample) with a cutoff for positivity of 1% or higher.

Study endpoints

The primary endpoint was the progression-free survival rate (PFSR) at 24 weeks, defined as the percentage of patients alive without disease progression 24 weeks after inclusion according to the local investigator's evaluation, under RECIST v1.1. We chose PFSR at 24 weeks as the primary outcome, although not specifically validated in ER+/HER2− breast cancers, as it has been shown to be a good surrogate for 12-month OS in clinical trials with ICIs in other tumor types and triple-negative breast cancer (TNBC; ref. 21). More traditional breast cancer trial outcomes such as progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), OS, and safety and tolerability (according to NCI Common Terminology Criteria for Adverse Events v5.0) were selected as secondary endpoints to facilitate comparison with results from other relevant trials. All these endpoints were assessed in the intention-to-treat (ITT) population and in the g*BRCA*m population. PFSR at 24 weeks in g*BRCA*m patients was also reported. Exploratory analyses were carried out in the subgroups of patients with or without prior CDK4/6i treatment and with positive or negative PD-L1 expression.

Statistical considerations

Sample size calculation

This trial was designed according to an optimum Simon two-stage design, with a one-sided type 1 error α of 2.5% and β of 5%. Success was defined as a patient without progression at 24 weeks. With a maximal inefficiency of PFSR of 50% (p0) and a minimum efficiency of PFSR of 65% (p1), a total of 149 evaluable patients were required (64 and 85 during the first and the second step, respectively). Expecting 10% of patients to be lost to follow-up or non-evaluable, 166 patients needed to be included. Evaluable patients were eligible patients who received at least one dose of the triplet and with a tumor evaluation at inclusion (within 28 days ± 3 days before first treatment) and at 24 weeks (±14 days) or patients who died before 24 weeks. The combination was to be considered interesting if a minimum of 87 successes were observed during the second stage.

Given the lack of safety data for this association, a safety run-in of a minimum of six patients and a maximum of nine patients was planned. Details on the statistical hypotheses about the safety run-in stage and the subgroup of patients with g*BRCA*m are described in the Supplementary Appendix S2.

Statistical methods

Usual descriptive statistical analyses were performed. Time-to-event endpoints were estimated using the Kaplan–Meier method; effect size for subgroup analyses was performed using a Cox proportional hazards model. The latter analyses were performed according to the ITT principles: all patients included after the screening phase, whether treated or not and eligible or not.

The primary endpoint was analyzed for the evaluable population. Patients who withdrew because of drug-related toxicity, clinical deterioration, or death between the start of study treatment and week 24 were included in the evaluable population and were considered as failures. Patients lost to follow-up before week 24 or patients who withdrew their consent without known reason were considered as non-evaluable. Additionally, a sensitivity analysis of the 24-week PFSR was performed in patients who received at least one dose of the triplet but lacked either baseline or week 24 RECIST evaluations, considering them as failures.

The study database was locked for statistical analyses on December 22, 2023. Statistical analyses were performed with the SAS 9.4 software.

Legal and ethical aspects and data protection

This study was conducted in accordance with the Declaration of Helsinki and the European Guidelines on Good Clinical practice. The protocol underwent independent peer review, including a patient advocate committee. The protocol is registered on ClinicalTrials.gov under the ID NCT04053322. The study was approved by the competent authorities and national ethics committees of each participating country. All patients provided written informed consent.

The intermediate results (at the end of the first stage of the Simon design) were reviewed by an Independent Data Monitoring Committee to allow the trial continuation. All authors reviewed the article and affirmed the accuracy and completeness of the data.

Results

Patient and tumor characteristics

From August 2019 to March 2023, 172 of 552 patients screened from 41 centers in France, Spain, and Belgium were included in the study (**Fig. 1**). Patient and primary tumor characteristics of the ITT population are summarized in **Table 1**. The median age was 49 years (Q1, 42; Q3, 60) and 109 (64.1%) were postmenopausal women. The vast majority of patients had received prior CDK4/6i (85.5%) with a median duration of treatment of 12 months (min, 1; max, 62 months). Only four (2.3%) patients received prior platinum-based chemotherapy (only one in the metastatic setting). Baseline characteristics of the evaluable population were similar to the ITT population (Supplementary Table S1).

Sixty-seven (39%) patients had a previously documented g*BRCA1*m ($N = 15$) or g*BRCA2*m ($N = 52$) and had been included directly (without waiting for the NGS results). Characteristics of the previously documented g*BRCA*m patients are summarized in Supplementary Table S2. Among the 164 patients with central NGS analysis available (mainly made on primary breast tumor, 67.8% of cases), 43 (26.2%) patients had been included because of a non-*BRCA* HRR alteration, one patient because of an MSI status only, and 47 (28.6%) patients had been included solely based on a mutation of a non-HRR non-MSI actionable gene (**Table 2**). The different types of mutations are described in **Table 2**. Details of the genetic counseling recommended following NGS analysis are provided in Supplementary Appendix S3. A study representativeness table is provided in the supplementary data (Supplementary Table S3).

Efficacy

For the primary endpoint analysis, 153 patients were evaluable (**Fig. 1**). The 24-week PFSR was 66.7% [95% confidence interval (CI), 58.6–74.1] with 102 successes, allowing the rejection of the null hypothesis (**Table 3**). The reasons for the end of treatment before 24 weeks

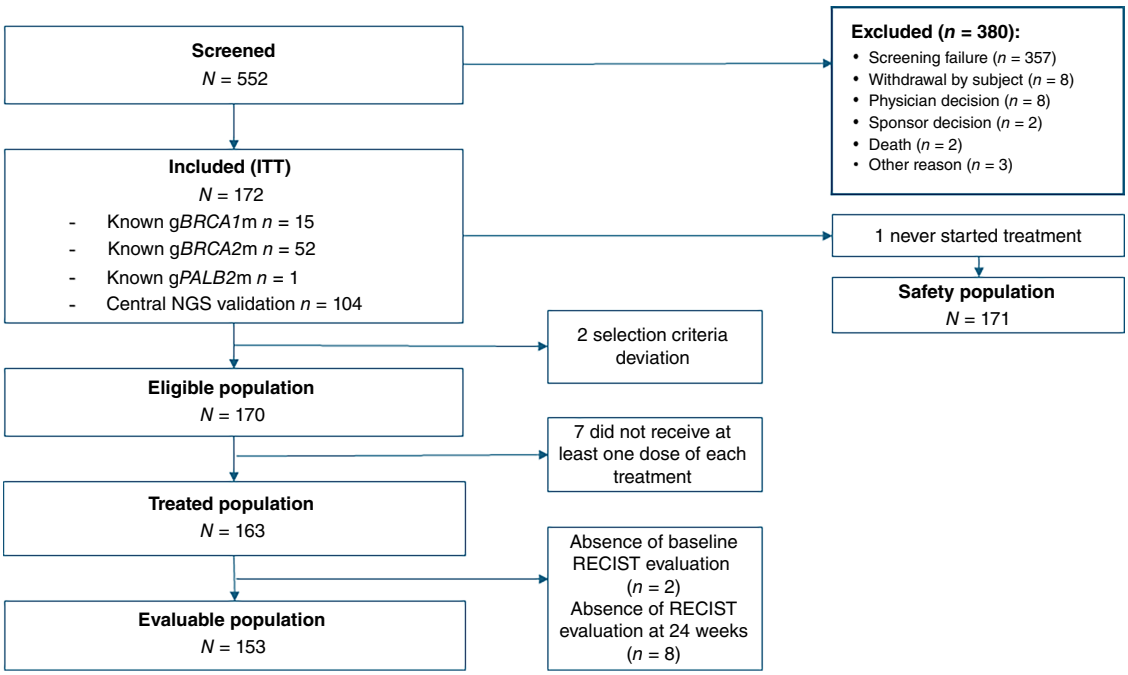

Figure 1.
Study flowchart. g*PALB2*m, germline *PALB2* mutation.

were disease progression ($N = 48$), death ($N = 2$), or treatment toxicity ($N = 2$). The sensitivity analysis, which considered patients without either baseline ($n = 2$) or week 24 ($n = 8$) RECIST evaluations as failures, showed a 24-week PFSR of 62.6% (95% CI, 54.7–70.0).

In the ITT population and after a median follow-up of 24.6 months (95% CI, 19.3–28), the median PFS was 9.3 months (95% CI, 7.5–12.7; **Fig. 2A**), the PFSR at 2 years was 20.6% (95% CI, 13.8–28.4), and the median OS was 30 months (95% CI, 26.6–not reached; **Fig. 2B**). Among the 160 patients with at least one RECIST evaluation at inclusion and at least another evaluation, the ORR was 41% (95% CI, 33.5–49.3). The median DoR was 12.1 months (95% CI, 6.8–18.4; **Table 3**).

At the time of analysis, 36 patients (20.9%) were still on treatment. Similar results were found in the population that previously received CDK4/6i, but with a shorter DoR of 9.2 months (95% CI, 5.6–14.7). There was no significant difference according to the PD-L1 status (data not shown), but very few patients had a positive PD-L1 tumor (9.3%).

Among the 59 evaluable patients with previously documented g*BRCA*m, the 24-week PFSR was 76.3% (95% CI, 63.4–86.4). With a median follow-up of 16.6 months (95% CI, 13.1–23.2), the median PFS was 12.6 months (95% CI, 8.2–16.7), the PFSR at 2 years was 17% (95% CI, 5.6–33.7), and the median OS was 29.3 months (95% CI, 22.2–not reached; Supplementary Fig. S1A and S1B).

Full efficacy data are reported in **Table 3**, including all prespecified subgroups of interest. Of note, patients with g*BRCA2*m and g*BRCA1*m had a median PFS of 12.9 and 6.3 months and a median OS of 29.3 and 17.8 months, respectively (Supplementary Fig. S2A and S2B).

Safety

No dose-limiting toxicity was observed during the safety run-in. Overall, 171 patients were evaluable for safety (**Fig. 1**). The most common drug-related adverse events (AE) were nausea (59.6%), asthenia (43.3%), anemia (26.3%), and diarrhea (25.1%), the vast majority of which were grade 1 and 2. Forty-one (23.9%) patients presented at least one AE of grade ≥3, mainly anemia (9.4%). Details of all drug-related AEs, including immune-related AEs, are listed in **Table 4**. With regard to the immune-related AEs, the most common were endocrine disorders, with 20 (11.7%) patients having hypothyroidism and 12 (7%) hyperthyroidism, all grade 1 and 2. No new toxicity warning has been detected.

Sixteen (9.3%) patients had at least one treatment-related serious AE: four patients had grade 3 to 4 anemia and one had grade 3 vomiting (related to olaparib), three patients had grade 2 or 3 thrombo-embolic events (considered related to fulvestrant), and five had events related to durvalumab (one acute grade 3 pancreatitis, one grade 3 colitis, one grade 3 renal failure, one immuno-induced grade 2 rheumatism, and one grade 4 adrenal insufficiency). All these events recovered. A grade 3 thrombotic microangiopathy and a villous tumor of the sigmoid were described as possibly related to treatment, although possibly due to disease progression and a new cancer, respectively. Two patients had a grade 5 nontreatment-related AE: one patient with multifocal digestive ischemia as a complication of aortobifemoral bypasss surgery and one patient died of hepatic failure most likely because of disease progression, but for whom, an associated autoimmune hepatitis related to durvalumab could not be ruled out.

Six (3.5%) patients completely discontinued all study drugs because of AEs. Fifty-nine (34.7%) patients required a dose reduction of olaparib. Thirteen patients (7.6%) received red blood cell transfusions, among whom one had a microangiopathic thrombopenia. To date, no myelodysplastic syndrome or acute leukemia has been reported during or after treatment. Safety data among the g*BRCA*m population did not differ from the whole cohort.

Table 1. Baseline patient and tumor characteristics (ITT).

Characteristic	ITT population *N* = 172
Age, median (Q1; Q3)	49 (42; 60)
Sex, *n* (%)	
Female	170 (98.8)
Male	2 (1.2)
Menopausal status (female patients), *n* (%)	
Premenopausal	60 (35.3)
Postmenopausal	109 (64.1)
Unknown	1 (0.6)
ECOG at inclusion, *n* (%)	
0	106 (62)
1	65 (38)
Missing	1
Histologic type, *n* (%)	
No special type	143 (83.6)
Lobular	22 (12.9)
Mixed (ductal + lobular)	5 (2.9)
Other	1 (0.6)
Missing	1
Prior CDK4/6i in the metastatic setting, *n* (%)	147 (85.5)
Prior chemotherapy in the metastatic setting, *n* (%)	13 (7.6)
Previously documented germline *BRCA* pathogenic variant, *n* (%)	67 (39.0)
Included after NGS analysis, *n* (%)	104 (60.5)[a]
PD-L1 status, *n* (%)	
Negative	140 (81.4)
Positive	16 (9.3)
Missing	16 (9.3)
Disease status, *n* (%)	
Distant metastases	166 (96.5)
Locally advanced	6 (3.5)
Metastatic sites (several possible), *n* (%)	
Bone	135 (81.3)
Nodes	76 (45.8)
Liver	63 (38.0)
Lung	35 (21.1)
Other	21 (12.7)
Pleura	15 (9.0)
Peritoneum	5 (3.0)
Central nervous system	3 (1.8)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Q, quartile.
[a]One patient was included with previously known germline *PALB2* mutation.

Table 2. Mutation assessment according to central NGS analyses.

Central tumor NGS analysis	*N* = 164[a] *n* (%)
Patients with previously documented g*BRCA*m	62 (37.8)
Patients with HRR mutation (excluding patients with previously documented g*BRCA*m):	53 (32.3)
Tumor mutation *BRCA2*	8 (4.9)
Tumor mutation *BRCA1*	2 (1.2)
Other mutation	43 (26.2)
Patients with mutation of only a non-HRR non-MSI actionable gene	47 (28.6)[b]
Patient included based only on MSI status	1 (0.6)
Type of mutations in the HRR pathway[c]	
BRCA2	56 (34.1) including 48 (29.3) with g*BRCA2*m
BRCA1	16 (9.8) including 14 (8.5) with g*BRCA1*m
PALB2	13 (7.9)
ATM/ATR	11 (6.7)
CHEK2	7 (4.3)
NBN	5 (3)
FANCA	4 (2.4)
RAD51B	2 (1.2)
RAD51C	2 (1.2)
FAND2	2 (1.2)
RAD51D	1 (0.6)
BRIP1	1 (0.6)
BARD1	1 (0.6)
FANCL	1 (0.6)
MRE11A	1 (0.6)
CHEK1	0
CDK12	0
PPP2R2A	0
RAD54L	0
MSI status[c]	3 (1.8)
Other actionable genes[c]	
PIK3CA	60 (36.6)
ESR1	14 (8.5)
AKT1	7 (4.3)
FGFR1	1 (0.6)
FGFR2	1 (0.6)
FGFR3	1 (0.6)
TP53 mutations[c]	44 (26.8)

[a]One patient has been included according to a germline *PALB2* mutation and with only TP53 mutation on the NGS analysis.
[b]Including 30 (63.8%) patients included with *PIK3CA* mutation only.
[c]Several possible mutations.

Discussion

The combination of olaparib, durvalumab, and fulvestrant evaluated in this study as second- to third-line treatment was active, with 66.7% (95% CI, 58.6–74.1) 24-week PFSR in a population of largely CDK4/6i-pretreated patients with metastatic breast cancer. This result, as well as a median PFS of 9.3 months, a PFSR at 2 years of 20.6%, and a median OS of 30 months, compares very well with other recent therapeutic approaches in this post-CDK4/6i setting. Although this trial was non-randomized, it opens the path for the development of this strategy and confirms the preclinical and clinical data suggesting the potential of this combination.

Our results were particularly striking among g*BRCA*m carriers as expected, given their exquisite sensitivity to olaparib, although non-carriers also showed notable effects. Indeed, two pivotal randomized trials testing the PARP inhibitors olaparib and talazoparib in patients with g*BRCA*m HER2– metastatic breast cancer in the first- to third-line metastatic setting have demonstrated PFS benefits over standard chemotherapy and an improvement of the quality of life, while they failed to demonstrate OS benefits (6, 7). In the OlympiAD pivotal trial, the median PFS with olaparib was 7 versus 4.2 months for patients who received physician's choice of chemotherapy (hazard ratio = 0.58, $P < 0.001$; ref. 6). In the subgroup of patients with hormone receptor–positive (HR+) tumors, the median PFS was 10.0 months (versus 4.2 months in the control arm, hazard ratio = 0.52; ref. 22). Results of the study testing talazoparib in the same setting were very close (23). In the LUCY study, in which only 18.6% had received a CDK4/6i, the median PFS was

Table 3. Efficacy data.

		Evaluable population *N* = 153					
24-week PFSR, % (95% CI)		66.7 (58.6–74.1)					
		Patients with previously documented g*BRCA*m[c]			Patients with HRR or MSI mutation (excluding patients with previously documented g*BRCA*m)[d]	Patients with HRR (excluding patients with g*BRCA*m, t*BRCA*m, and *PALB2*m)[e]	Patients with mutation solely of a non-HRR non-MSI actionable gene[f]
	ITT population[a,b] *N*=172	*gBRCA1m* *N* = 15	g*BRCA2m* *N* = 52	All g*BRCAm* *N* = 67	*N* = 55	*N* = 30	*N* = 47
24-week PFSR, % (95% CI)	68.1 (60.4–74.5)	50.0 (23–77)	84.4 (70.5–93.5)	76.3 (63.4–86.4)	67.3 (52.9–79.7)	64.3 (44.1–81.4)	51.2 (35.1–67.1)
2-year PFSR, % (95% CI)	20.6 (13.8–28.4)	11.1 (0.8–37.2)	16.5 (3.6–37.7)	17 (5.6–33.7)	22.8 (11.2–36.8)	22.7 (8.5–41.0)	19.1 (9.3–31.7)
Median PFS, months (95% CI)	9.3 (7.5–12.7)	6.3 (2.8–13.8)	12.9 (9.3–20.4)	12.6 (8.2–16.7)	9.2 (7.2–16.4)	8.7 (5.5–16.8)	7.3 (5.3–10.8)
Median OS, months (95% CI)	30 (26.6–NR)	17.8 (11.7–NR)	29.3 (23.6–NR)	29.3 (22.2–NR)	29.5 (26.6–NR)	NR (29,5–NR)	30.0 (18.7–NR)
MPP	*N* = 160	*N* = 15	*N* = 48	*N* = 63	*N* = 53	*N* = 29	*N* = 43
ORR, % (95% CI)	41 (33.5–49.3)	60 (32.3–83.7)	56.3 (41.2–70.5)	57.1 (44–69.5)	37.7 (24.8–52.1)	20.7 (8.0–39.7)	23.3 (11.8–38.6)
Partial response, *n* (%)	55 (83.3)	5 (55.6)	24 (88.9)	29 (80.6)	18 (90)	6 (100)	8 (80)
Complete response, *n* (%)	11 (16.7)	4 (44.4)	3 (11.1)	7 (19.4)	2 (10)	0	2 (20)
If partial or complete response, median DoR, months (95% CI)	12.1 (6.8–18.4)	12.1 (1.5–NR)	24.7 (5.8–NR)	13.3 (5.8–NR)	9.1 (3.7–14.7)	6.8 (3.7–NR)	18.4 (2.6–NR)

Abbreviations: MPP, modified per-protocol population (patients with at least one RECIST evaluation at inclusion and at least another evaluation); NR, not reached; t*BRCA*m, tumor *BRCA* mutation.
[a]One patient never started treatment, and two patients were non-eligible because of a platform error.
[b]Including 153 evaluable patients.
[c]Including 59 evaluable patients.
[d]Including 52 evaluable patients.
[e]Including 28 evaluable patients.
[f]Including 42 evaluable patients.

8.38 months (95% CI, 7.92–10.55) among the 134 patients with HR+ tumors (24). In our more chemo-naïve (only 8.7% received previous chemotherapy for metastatic breast cancer) but more CDK4/6i pretreated (76.1%) population with HR+/HER2− g*BRCA*m with a short duration of previous CDK4/6i (median, 11 months; min, 7; max, 15 months), the median PFS with the combined treatment was 12.6 months. It is important to note that our primary endpoint (24-week PFSR) differs from that used in the OlympiAD and EMBRACA studies, making direct comparisons challenging. Furthermore, the patient populations in these two pivotal phase III trials differed from ours, as OlympiAD and EMBRACA included TNBC and patients more heavily pretreated with chemotherapy (6, 7). In the subgroup analysis of OlympiAD, the median PFS was 8.1 months in patients without prior chemotherapy in the metastatic setting (22). With regard to the ORR in our g*BRCA1/2*m subgroup, it is slightly lower than that observed in OlympiAD and EMBRACA trials using single-agent PARP inhibitor: 57% versus 63% with olaparib or talazoparib in the HR+/HER2− subgroups (7, 22).

Despite the demonstrated efficacy of PARP inhibitor in g*BRCA1/2*m-associated breast cancers, primary resistance has been reported (25). Genomic studies have suggested that a subset of g*BRCA1/2*m-associated tumors may not have BRCA locus–specific loss of heterozygosity (LOH; refs. 26, 27) and thus, not complete loss of BRCA1 or BRCA2 function. The absence of locus-specific LOH could be a biomarker of primary resistance to PARP inhibitors. Maxwell and colleagues (26) reported that among 76 patients with g*BRCA1/2* breast cancers, 10% of *BRCA1* carriers and 46% of *BRCA2* carriers lacked locus-specific LOH. Unfortunately, we do not have these data in our HR+ population, with a majority of g*BRCA2*m. Hence, we cannot correlate LOH status with outcomes and determine whether these patients derive less benefit from treatment with olaparib.

Second-line endocrine therapy after progression on first line with endocrine therapy and CDK4/6i remains a challenge. Studies that tested switching endocrine therapy while maintaining a CDK4/6i have shown median PFS between 4.6 and 5.3 and between 2.8 and 4.8 months in the experimental arm and the control arm (endocrine therapy only), respectively (28–30). Few data are available with regard to the endocrine therapy benefit beyond the first line in patients harboring HRR-related gene alterations. In a retrospective study, Bruno and colleagues (31) reported a median PFS of 6.8 months (95% CI, 2.2–14.6) among patients treated with CDK4/6i in the second- or subsequent-line setting and harboring a g*BRCA1/2*, *ATM*, or *CHEK2* mutation. In the present study, we report a median PFS of 9.3 months for a population mainly composed of patients pretreated with CDK4/6i and harboring g*BRCA*m or other HRR-related gene alteration. This outcome compares well with previously reported second-line treatment options. Patients harboring solely mutations of several genes involved in resistance to endocrine therapies (8–10)

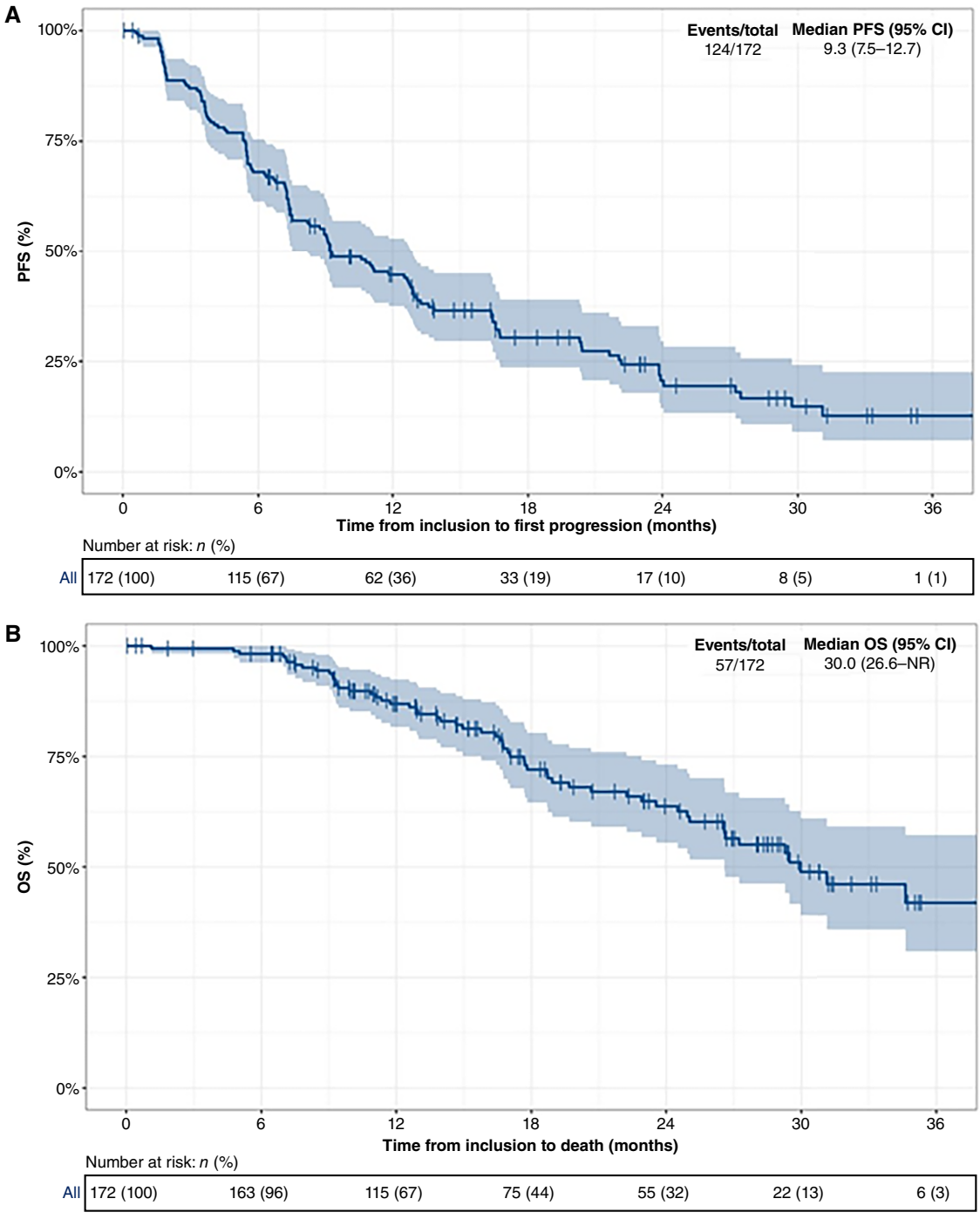

Figure 2.
PFS (**A**) and OS (**B**; ITT population).

were initially allowed in the study until an amendment excluded them based on the most recent literature showing that these alterations would not confer specific sensitivity to PARP inhibition or immune checkpoint blockade. About 28% of patients were included solely on this criterion, mostly because of *PI3KCA* mutations, and the median PFS in this subgroup was 7.3 months (95% CI, 5.3–10.8). Rugo and colleagues (32) reported that among patients harboring a *PI3KCA* mutation, and who received an association of alpelisib plus fulvestrant following progression during CDK4/6i plus aromatase inhibitor, the median PFS was 7.3 months (95% CI, 5.6–8.3) with a distinct safety profile compared with our combination. Once again, our results compare

Table 4. AEs (NCI-CTCAE V5.0).

AEs	Any grade *N* (%)	Grade ≥3 *N* (%)[a]
Any treatment-related AEs	160 (93.5%)	41 (23.9%)
Treatment-related occurring in >10% of patients		
Nausea	102 (59.6%)	3 (1.7%)
Asthenia	74 (43.3%)	4 (2.3%)
Anemia	45 (26.3%)	16 (9.4%)
Diarrhea	43 (25.1%)	3 (1.7%)
Headache	24 (14.0%)	0
Hot flushes	24 (14.0%)	0
Arthralgia	22 (12.9%)	0
Vomiting	19 (11.1%)	1 (0.6%)
Decreased appetite	19 (11.1%)	0
Fatigue	19 (11.1%)	1 (0.6%)
Injection site pain	18 (10.5%)	0
Immune related		
Hypothyroidism	20 (11.7%)	0
Hyperthyroidism	12 (7.0%)	0
Drug hypersensitivity	2 (1.2%)	0
Myositis	2 (1.2%)	0
Renal failure	2 (1.2%)	1 (0.6%)
Rheumatic disorder	1 (0.6%)	0
Hepatic failure	1 (0.6%)	1 (0.6%)
Colitis	1 (0.6%)	1 (0.6%)
Acute pancreatitis	1 (0.6%)	1 (0.6%)
Adrenal insufficiency	1 (0.6%)	1 (0.6%)
Number of treatment-related SAEs[b]	16 (9.3%)	
Number of grade 5 AEs (non–treatment related)	2 (1.2%)	

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious AE.
[a]No grade 5.
[b]Any grade.

favorably with the current comparators, although unfortunately no formal conclusion can be drawn from this observation.

Several studies suggested that patients with tumors harboring alterations of the HRR pathway beyond g*BRCA1/2*m, including non-germline alterations of *BRCA1/2*, may benefit from PARP inhibitors, but the data remain relatively sparse and do not reach a formal clinical demonstration (33–35). In the study of Tung and colleagues (33), confirmed responses were only seen among patients with gemline *PALB2* mutations or somatic *BRCA1/2*m. In our study, in patients without g*BRCA*m but with mutations in one of the HRR genes or with an MSI status, the median PFS was 9.2 months. Furthermore, after excluding patients with somatic *BRCA1/2*m and *PALB2* mutations from this subgroup, the median PFS was 8.7 months (95% CI, 5.5–16.8). These results are well beyond what would be expected with fulvestrant single agent and are therefore consistent with an efficacy of PARP inhibitors in HR+/HER2− metastatic breast cancer that have homologous recombination–associated mutations beyond *BRCA1/2*. Future translational research will help to determine which molecular features might predict response to any of these therapies in each patient.

Our hypotheses were based on the increasing evidence suggesting an interaction between PARP inhibitor–induced DNA damage and the immune system (36, 37). In the MEDIOLA study, the median PFS in the HR+ subgroup was 9.9 months (95% CI, 6.2–21.5) and median OS was 22.4 months (95% CI, 14.4–25.5; ref. 20). Our results, with the addition of fulvestrant, compare favorably with a median PFS of 12.6 months and a median OS of 29.3 months in the g*BRCA*m subgroup, suggesting that ER signal inhibition remains important in this setting. In the TOPACIO phase II study, the combination of niraparib and pembrolizumab demonstrated clinical benefit in metastatic TNBC with numerically higher response rates in those with *BRCA*m tumors (ORR of 47% vs. 11% in *BRCA* wild type; ref. 38). In the phase II non-comparative DORA trial, 45 patients were randomized to receive olaparib monotherapy or in combination with durvalumab, as maintenance therapy for advanced TNBC sensitive to platinum-based chemotherapy (39). The median PFS was 4 months with olaparib and 6.1 months with the combination, both significantly longer than the historical control (primary objective). The 1-year PFS rates were 10% with olaparib alone and 33% with the combination (39). Only eight patients had a known g*BRCA*m (one *BRCA2* in the olaparib group and seven *BRCA1* in the combination group) and 18 patients were not tested. As this trial was not designed to compare the two experimental regimens, no definitive conclusion can be drawn about the added value of durvalumab to olaparib in this setting. In the randomized phase II trial of Fanucci and colleagues (40), the addition of atezolizumab to olaparib in 78 patients with metastatic breast cancer (including 23 TNBC) and *BRCA*m did not significantly increase the PFS (about 7 months in the two arms, $P = 0.92$). These negative results could be partly explained by the choice of the ICI (40). Currently, pembrolizumab is the only ICI approved in combination with chemotherapy for the treatment of patients with metastatic TNBC with a PD-L1 expression based on the combined positive score (≥10; ref. 41). Response rates in the TOPACIO study and OS in the MEDIOLA study were numerically higher among patients with a PD-L1–positive tumor (combined positive score ≥1 in the TOPACIO study and PD-L1 positive on tumor or immune cells ≥1% in MEDIOLA; refs. 20, 38). In our study, no significant difference in outcomes was observed according to the PD-L1 status, maybe because of the very low number of PD-L1–positive tumors or the choice of the assay used. Given the non-randomized design, we cannot exclude the possibility that durvalumab provided only a limited additional PFS benefit.

Clinical trials and current international guidelines for breast cancer consider that *BRCA1*- and *BRCA2*-associated tumors are a unique biological and clinical entity. However, there is accumulating evidence that they are two distinct entities, which may respond differently to treatment (42–44). BRCA1 and BRCA2 interact differently with the ERα pathway (44). Estrogen can promote BRCA1-deficient tumor initiation and progression by stimulation of cell proliferation and activation of epithelial–mesenchymal transition, which are dependent on AKT activation and independent of ER (45). These data may suggest that treatment based on endocrine therapy is more effective in cases of *BRCA2* mutation. Preclinical data suggest a higher sensitivity to ICIs in *BRCA2*-mutated TNBCs (43). In our study, patients with g*BRCA2*m had a longer PFS compared with patients with g*BRCA1*m, with no difference in ER expression level (Supplementary Table S2). These results should be interpreted with caution given the small number of patients with g*BRCA1*m. Nevertheless, this information may be relevant to further trials, which should be designed to specifically investigate the efficacy of ICI in HR+/HER2− and g*BRCA2*m patients.

The combination of olaparib, durvalumab, and fulvestrant was well tolerated over the follow-up period. The safety profile of the triplet is comparable with that of olaparib or durvalumab alone and

acceptable in this setting. No new safety signals, including immune-mediated AEs, were observed.

One strength of our study is its design. Thanks to the safety run-in phase and the optimum Simon two-stage design, we were able to obtain reassuring safety data and promising efficacy data in one study. Our results remain robust even after sensitivity analysis corresponding to the worst-case scenario, considering patients without RECIST evaluation at baseline or at 24 weeks as failures. This analysis showed a 24-week PFSR rate close to that of the primary analysis, exceeding the threshold of 50% corresponding to our hypothesis of maximum inefficacy and close to 65% corresponding to our hypothesis of minimum efficacy.

A limitation is that it was a single-arm study without a comparative arm, making it difficult to evaluate the relative contribution of olaparib, durvalumab, or the combination to the observed results. Moreover, the trial design does not allow for formal biomarker validation. A prospective randomized trial with appropriate stratification or biomarker-based randomization is needed to establish predictive value of specific gene alterations. The DOLAF trial was specifically designed to detect early efficacy and safety signals rather than to validate predictive biomarkers.

Altogether, our results suggest that (i) ER signal inhibition remains important in g*BRCA*m patients in addition to PARP inhibitor and immune checkpoint inhibition, (ii) PARP inhibitors (± ICI) could improve the outcome of patients with HRR-related gene mutation beyond g*BRCA*m, and (iii) patients with only mutations on actionable genes involved in endocrine resistance could benefit from the addition of ICI to endocrine therapy. Further research is needed to determine whether these combinations could improve the outcome of these patients and which specific subgroups could benefit most from the triplet.

In conclusion, in patients with ER+/HER2− metastatic breast cancer enriched in molecular abnormalities predicting sensitivity to PARP inhibitors, a combination of olaparib, durvalumab, and fulvestrant as second- to third-line treatment showed promising efficacy and compared well with current standards, with an acceptable toxicity profile. Further studies are needed to compare this combination with standard of care in a randomized setting.

Data Availability

All data generated or analyzed during the DOLAF study are included in this published article and its supplementary materials. Unicancer will grant access to all study data upon reasonable request sent to b-juzyna@unicancer.fr.

The NGS data have been deposited in the European Genome-phenome Archive platform with accession number EGAD50000001665.

Authors' Disclosures

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Authors' Contributions

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Note

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