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ORIGINAL RESEARCH

A phase II study of pembrolizumab plus carboplatin in *BRCA*-related metastatic breast cancer (PEMBRACA)

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Background: *BRCA1/2*-related metastatic breast cancers (mBC) are sensitive to DNA-damage agents and show high tumor-infiltrated lymphocytes. We hypothesized that the association between pembrolizumab and carboplatin could be active in *BRCA*-related mBC.

Patients and methods: In this phase II Simon's design multicenter single-arm study, *BRCA1/2*-related mBC patients received carboplatin at area under the curve 6 every 3 weeks for six courses associated with 200 mg pembrolizumab every 3 weeks until disease progression or unacceptable toxicity. The primary aim at first stage was overall response rate (ORR) $\geq$70%. Disease control rate (DCR), time to progression (TTP), duration of response (DOR), and overall survival (OS) were the secondary aims.

Results: Among 22 patients enrolled at the first stage, 5 *BRCA1* and 17 *BRCA2*, 16 (76%) were luminal tumors and 6 (24%) triple-negative BC (TNBC). In 21 patients, ORR and DCR were 43% and 76% (47% and 87% in luminal, 33% and 50% in TNBC), respectively. TTP was 7.1 months, DOR was 6.3 months, and median OS was not reached. Grade $\geq$3 adverse events (AEs) or serious AEs occurred in 5/22 patients (22.7%). Since the primary aim was not met, the study was terminated at the first stage.

Conclusions: Although the primary aim was not reached, data on efficacy and safety of pembrolizumab plus carboplatin in first-line visceral disease *BRCA*-related luminal mBC were provided and they need to be further investigated.

Key words: *BRCA1*, *BRCA2*, pembrolizumab, carboplatin, phase II

INTRODUCTION

Despite efforts in targeted therapeutic approaches over the past 20 years, metastatic breast cancer (mBC) remains a lethal disease with a median overall survival (OS) of 39 months and the need for further development in personalized medicine.[1] About 3%-6% of all BCs may present genetic alterations in *BRCA1/2* with higher prevalence for triple-negative BC (TNBC) (15.4%), with respect to hormone receptors-positive (HR+)/HER2-negative BC (5.2%).[2] Both *BRCA1* and *BRCA2* are required for DNA double-strand break repair by homologous recombination.[3,4] Inherited mutations in *BRCA1* and *BRCA2* inactivate one of the two alleles, and in cancer cells the wild-type allele is almost invariably lost, leading to a defect in homologous recombination DNA repair in the cancer. Platinum chemotherapy generates interstrand cross-links that can only be adequately repaired by homologous recombination DNA repair, and consequently *BRCA1*-deficient and *BRCA2*-deficient cells are highly sensitive to platinum chemotherapy both *in vitro* and *in vivo*. Many studies showed an impressive overall response rate (ORR) to platinum-derived drugs in mBC with germline *BRCA* (g*BRCA*) mutations ranging between 54.5% and 68%.[5,6] Another important characteristic of *BRCA*-mutated BC is represented by an elevated rate of programmed death-ligand 1 (PD-L1), as compensatory up-regulation of the mechanism of inhibiting T-cell activation at tumor sites, related to the genomic instability, and subsequent tumor surface neoantigen expression that leads to an increase in tumor-infiltrating immune cells. The PD-L1 expression in *BRCA1* and *BRCA2* mutations differs, being higher in *BRCA1* than in *BRCA2* BC.[7,8] Pembrolizumab was

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administered in combination with poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) in *BRCA*-mutated patients affected by metastatic TNBC (mTNBC).[9] The TOPACIO trial provided, in g*BRCA*-mutated TNBC, an ORR and disease control rate (DCR) of 47% and 80%, respectively.

Based on the improvement of progression-free survival (PFS) derived from the platinum-derived drugs and also based on a median PFS of 8.3 months provided by pembrolizumab and niraparib in *BRCA1/2*-mutated patients, we designed the PEMBRACA phase II study with carboplatin plus pembrolizumab in metastatic HER2-BC with g*BRCA1/2* mutation. The primary aim was to evaluate the ORR; secondary objectives were to assess the time to progression (TTP), duration of response (DOR), DCR, and OS. The exploratory analyses regarded the CD8/tumor-infiltrated lymphocytes (TILs) and PD-L1 evaluation in the metastatic biopsy and/or on primary surgical specimen, and they will not be reported in this paper.

PATIENTS AND METHODS

Patients and study design

PEMBRACA was a single-arm, open-label, multicenter, phase II study built with a two-stage Simon's design (NCT03732391).[10] The CONSORT diagram is represented in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101207. All patients provided written informed consent. Eligible patients were $\geq$18 years (males and females) with HER2-mBC g*BRCA1/2*-mutated, previously treated with no more than one line of chemotherapy for advanced BC. They needed to have received anthracycline and/or taxane in a (neo)adjuvant or metastatic setting; carboplatin could be offered in the (neo)adjuvant setting without progression under treatment. In case of luminal BC, a first-line hormonal treatment for mBC can be administered before. Patients had a *BRCA1/2* deleterious germline mutation (C4-C5 by ENIGMA classification) or with unknown significance (C3 classification). Main exclusion criteria included benign g*BRCA1/2* variants (C1-C2 classification), having received more than one line of chemotherapy for mBC, prior therapy with an anti-programmed cell death protein 1 (PD-1), anti-PD-L1 or anti-PD-L2 agent, contraindication to immunotherapy, $<$14 days from radiotherapy, chemotherapy or target small-molecule therapy, symptomatic or progressive brain metastases and/or carcinomatous meningitis, previous history of pneumonitis/interstitial lung disease that required steroids, hematopoietic function, or organ impairment. The local ethics committee approved the study.

Procedure and assessments

Patients were treated with carboplatin intravenous (i.v.) at area under the curve 6 every 3 weeks for six courses in combination with 200 mg pembrolizumab i.v. every 3 weeks until disease progression, unacceptable toxicity, or patient refusal. Subjects were prohibited from other concomitant therapy while starting and during the study treatment, (chemotherapy, hormonal therapy, immunotherapy, and radiotherapy, with the exception for symptomatic solitary lesion or brain). Live vaccines were prohibited within 30 days before the first dose of trial treatment and while participating in the trial, whereas administration of killed vaccines and RNA vaccines was allowed. Finally, systemic glucocorticoids for modulating symptoms from an event of clinical interest of suspected immunologic etiology could be permitted.

Toxicity management and dose reduction followed a summary of product characteristic recommendations and local standard practice. Clinical and laboratory examinations were carried out every 3 weeks after treatment initiation. The safety was assessed and graded by the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5 (NCI-CTCAE v.5.0) every 3 weeks from treatment initiation until the end of treatment. Assessment of response to treatment was based on investigator-reported measurements on target and non-target lesions and carried out according to RECIST v1.1[11] and irRECIST v.1.1 (as exploratory analysis in which changes in two dimensions are used for target lesions)[12] with computed tomography (CT) scans or magnetic resonance imaging repeated every 9 weeks along the combination therapy and every 12 weeks along the maintenance treatment.

Germline BRCA1/2 *mutations, tumor immunostaining*

The *BRCA1/2* germline analysis was carried out at the different centers that provided us the report. The immunostaining was carried out on primary breast cancer tissue, and when available on metastatic biopsy at the local laboratory too. Immunohistochemical assessment was carried out to evaluate: HR measured by estrogen receptors (ER) and progesterone receptors (PgR), HER2, and Ki67 expression. HR+ were considered with ER and/or PgR $\geq$ 10%.

Statistical analysis

This phase II study was planned according to the two-step Simon's design: assuming as minimal interesting activity an ORR of 70%, 12 objective responses among the first 20 enrolled patients were necessary for the first step; to verify the hypothesis of ORR 70%, another 33 patients had to be enrolled in the second step, with 34 objective responses among the total 53 patients enrolled being necessary. The null hypothesis (p0) has been set equal to 0.55 with a type I (alfa) error of 0.10 (10%) and a type II (beta) error of 0.20 (power = 80%). In case the combination was unsatisfactory, the adopted design allowed to stop the study at stage one with a probability of 59%. By reaching an ORR of 70% at the end of the trial, the probability error to declare the combination inefficacious was 19.8%, and the probability to stop the study at stage one was 1.13%. We choose an alfa error of 0.10 rather than 0.05, since the specific population is very rare (*BRCA* mutation carriers). Furthermore, the rate of non-responder patients could be reduced by the increased number of CT scan due to the pseudoprogression phenomenon typical of immunotherapy treatments. We considered that the study by Isakoff,[5] carried out with platinum-derived drugs in first- or second-line

BRCA-related mTNBC, provided an ORR equal to 54.6% whereas the KEYNOTE-012 study reported an ORR of 18.5% in patients with mTNBC treated only by pembrolizumab.[13] Our study hypothesis was generated to provide an ORR equal to 70% as the sum of benefits from these two drugs.

The ORR, TTP, DOR, and DCR were based on the investigator's evaluation using the per-protocol population, by which patients were excluded if they did not receive at least three courses of treatment (for reasons other than progressive disease). The TTP was defined for each patient as the time from the first cycle until objective tumor progression (TTP does not include deaths) and was considered positive with at least 5 months. The other secondary objectives were the DOR, measured from the first ORR to the date of progression, and it was considered positive with 5 or more months, the DCR, considered as the percentage of patients with ORR and stable disease (SD) with an expected positivity rate of $\geq$80%, and OS, defined as the time from the first cycle of treatment until death from any cause (expected as at least 15 months). OS was calculated by Kaplan—Meier plots and summarized by median and confidence intervals.

The safety of the combination was evaluated as the secondary endpoint too, based on the intent-to treat population according to the toxicity grade reported throughout the whole treatment period. The toxicity descriptions and grading scales for adverse event (AE) reporting were using the revised CTCAE v. 5.0).[14]

RESULTS

Patient demographics

From December 2019 to May 2022, 23 consecutive, unselected patients were screened for the study. One patient did not enter into the study due to screening failure (Table 1). Among the 22 eligible patients for the study, the male/female ratio was 1/21; median age, 50 years (35-69 years); Eastern Cooperative Oncology Group performance status 0, 22/22; *BRCA1/2*, 5/17; HR+/HR-16/6; metastatic sites: liver 12 patients (29.2%), lung 7 patients (17.1%), lymph nodes 7 patients, (17.1%); local recurrence 1 patient (2.4%), bone 10 patients (24.4%), others 5 patients (12.2%). Metastatic site was single in 9 patients (41%) and multiple in 13 patients (59%). Single metastatic sites were: bone (two patients), lymph nodes (two patients), lung (two patients) and liver (three patients). Lines of chemotherapies for mBC: 7 patients (32%) received a second-line treatment after taxane (3 patients) or anthracycline (2 patients) or capecitabine (2 patients), whereas 15 received experimental therapy as first line (68%). Totally, six patients received a previous hormonal treatment for mBC, four with and two without cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (27%).

Activity and efficacy

The preliminary analysis of efficacy was conducted among the first 21 patients (one patient was excluded for G3 hepatotoxicity after one cycle of treatment). The ORR was 43% (nine objective responses): eight partial responses (89%) and one complete response (11%). The study was terminated in the first stage according to the statistical plan. The DCR was equal to 76%: seven SD; five patients progressed (24%) (Figure 1A). The ORR in luminal patients (76%) was equal to 47% (7/15) with a DCR equal to 87% (13/15), whereas in case of TNBC (24%) the ORR and DCR were 33% and 50%, respectively (Figure 1B). The ORR and DCR in first-line therapy for mBC were 50% (7/14) and 100% (14/14), respectively, whereas in the second line the ORR

Table 1. Characteristics of patients at baseline

Patients	Age	Sex	ECOG PS	*BRCA1/2*	Phenotype	Metastatic site	Previous therapies for mBC
1	45	F	0	1	TNBC	Lymph nodes	None
2	50	F	0	2	Luminal	Liver, bone	HT + CDK4/6i
3	54	F	0	2	Luminal	Lung	Taxane
4	47	F	0	2	Luminal	Liver	None
5	50	F	0	2	Luminal	Lung	None
6	57	F	0	2	Luminal	Liver, lung, bone, lymph nodes	None
7	46	F	0	2	Luminal	Liver, bone	HT + CDK4/6i
8	63	F	0	2	Luminal	Lung, liver, lymph nodes, bone	Taxane
9	46	F	0	2	Luminal	Lung, liver, pericardial effusion, bone	None
10	40	F	0	1	TNBC	Breast, lymph nodes	None
11	53	F	0	2	Luminal	Liver, pleural effusion, bone	None
12	59	F	0	2	Luminal	Lymph nodes	None
13	51	F	0	2	Luminal	Bone	Capecitabine
14	60	F	0	2	Luminal	Liver, bone	Anthracycline
15	69	F	0	2	TNBC	Pleura, peritoneum	Capecitabine
16	46	F	0	2	Luminal	Liver, bone	HT + CDK4/6i
17	35	F	0	1	TNBC	Liver	Anthracycline
18	50	F	0	1	Luminal	Liver	HT + CDK4/6i
19	69	M	0	2	Luminal	Bone	HT
20	44	F	0	2	Luminal	Liver, lung	HT
21	29	F	0	1	TNBC	Lymph nodes, lung, pleura	Taxane
22	47	F	0	2	TNBC	Lymph nodes	None
23 (s.f.)	34	F	0	2	Luminal	Bone	HT

CDK4/6i, cyclin-dependent kinase4/6 inhibitors; ECOG PS, Eastern Cooperative Oncology Group Performance Scale; F, female; HT, hormonal therapy; M, male; mBC, metastatic breast cancer; s.f., screening failure; TNBC, triple-negative breast cancer.

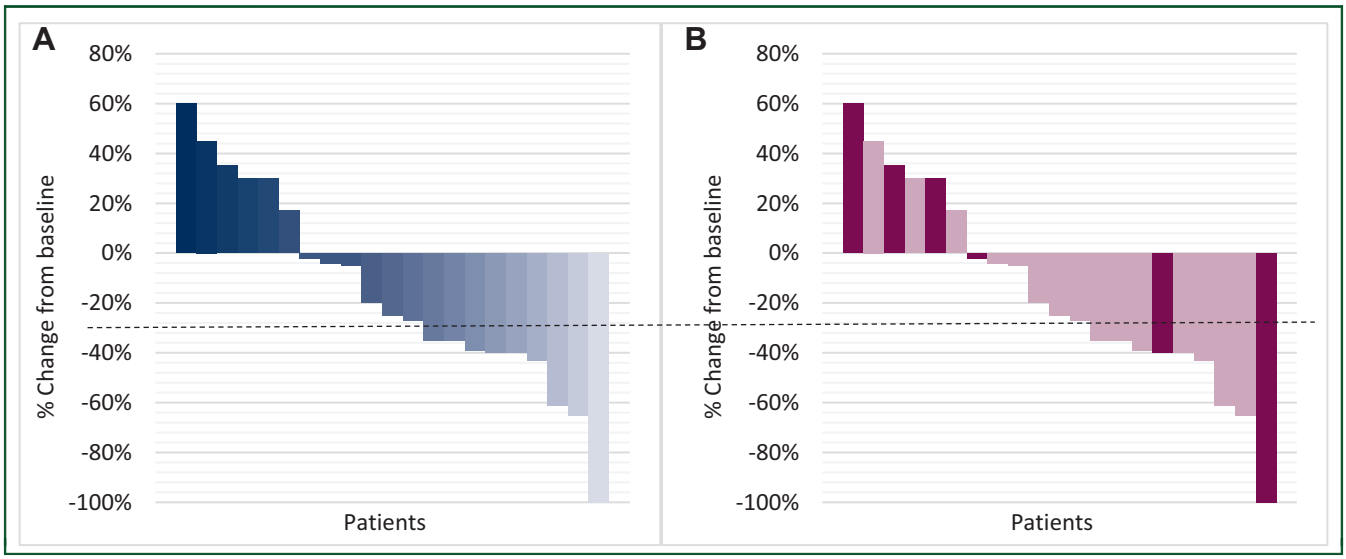

Figure 1. Overall response rate and disease control rate in all patients and according to phenotype. Waterfall plot of maximum changes in tumor size (diameter) from baseline in all individual patients (A) and according to tumor phenotype (B) during the treatment. Pink bars represent TNBC, violet bars represent luminal BC. The dash line represents -30% of change from baseline.

and DCR were equal to 29% (2/7) (Figure 2A). Finally, the ORR and DCR in visceral disease were equal to 43% (6/14) and 79% (11/14), respectively, whereas in the non-visceral metastasis the ORR and DCR were 43% (3/7) and 72% (5/7), respectively (Figure 2B).

After a median follow-up of 19 months, two patients are still on treatment. The median TTP was 7.1 months (1.7-18.9 months): 19 events occurred and one patient (6%) was progression-free for >12 months (Figure 3A). The DOR was measured on 16 patients, excluding 5 patients who progressed at the first evaluation. The median DOR was equal to 6.3 months (1.2-17 months). Of the 10 responders, 1 patient had a response duration longer than 1 year; 6 patients (two with ongoing treatment) had a response duration of 6-10 months; and 3 additional patients had a response duration of <6 months. Two of seven patients with SD continued without progression for >6 months (Figure 3B). The median duration of treatment with carboplatin and pembrolizumab was 4 months, whereas the median maintenance therapy with pembrolizumab alone was 3.1 months. The median OS was not reached: 5 patients died (23%) and 17 patients (77%) are still alive; 45% of patients (10 patients) were alive >18 months.

Safety

All 22 patients were assessable for safety. The overall incidence of AEs of any grade was 100% (22/22 patients), and the incidence of grade ≥3 AEs or serious AEs (SAEs) was

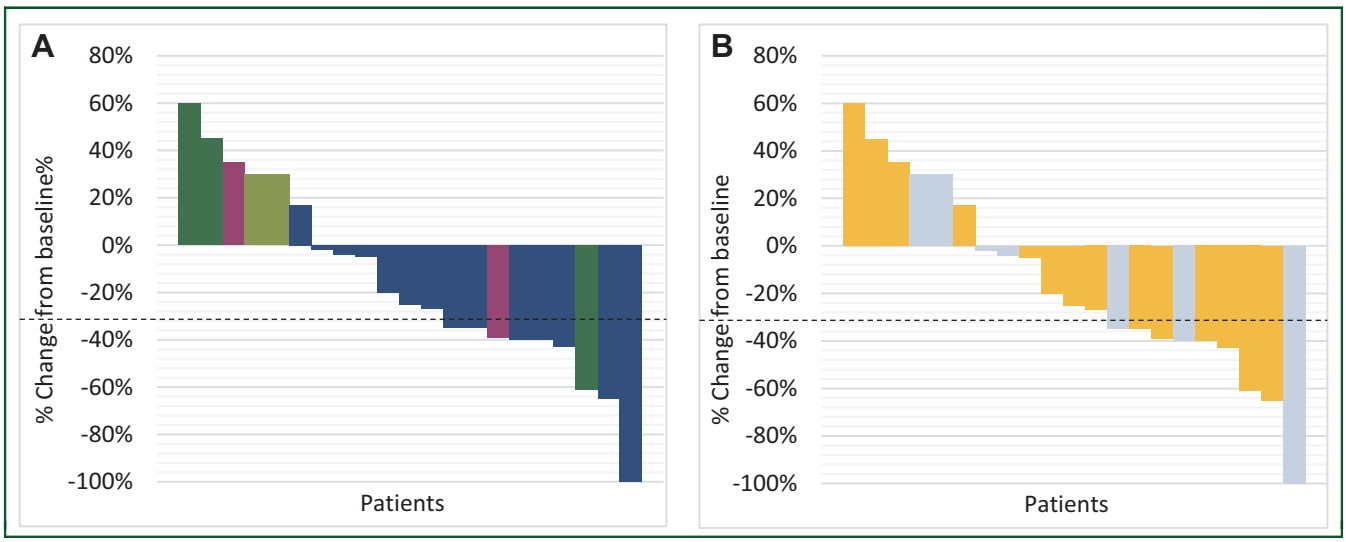

Figure 2. Overall response rate and disease control rate according to the line of treatment and to the metastatic site. Waterfall plot of maximum changes in tumor size (diameter) from baseline according to the line of treatment (A) and to the metastatic sites (B). The blue bars represent the first line of treatment for the experimental therapy, the green bars correspond to second line of treatment after taxane, the pink bars after anthracyclines, and the violet bars after capecitabine. The yellow bars represent visceral disease and the gray bars, the non-visceral metastasis.

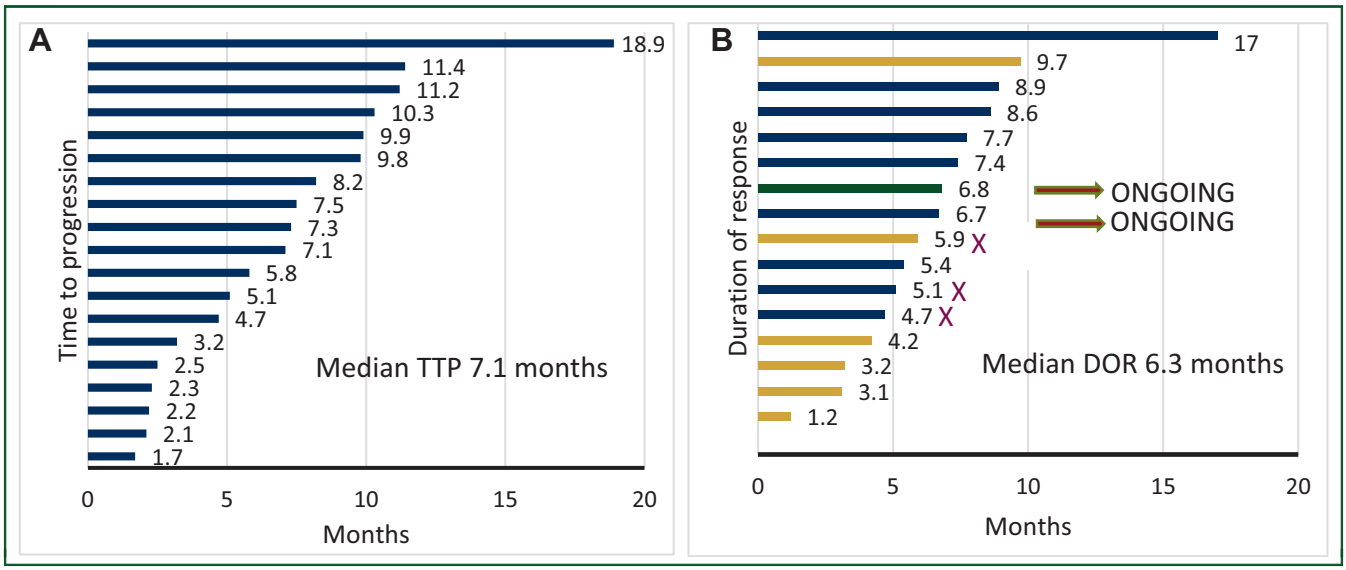

Figure 3. Time to progression and duration of response. The TTP is shown on the left bar graph (A). The median TTP was 7.1 months. The duration of response is shown on the right bar graph (B). The green bar represents the CR, the blue bars represent the PR, and the orange bars, the SD. The pink crosses represent death. Two patients, one with CR and one with PR, are still on treatment after 6.8 and 6.7 months, respectively. The median DOR was 6.3 months.
CR, complete response; DOR, duration of response; PR, partial response; SD, stable disease; TTP, time to progression.

22.7% (5/22 patients). The most common toxicities were the increase in alanine transaminase (ALT) and/or aspartate transaminase (AST) (27.3%), followed by nausea (22.7%), fatigue (13.6%), and vomiting (13.6%) (Table 2). One patient with grade 3 vomiting along chemotherapy required dose reduction. One patient with grade 3 hepatotoxicity interrupted treatment after the first cycle of treatment, whereas one patient showed a grade 3 autoimmune nephritis SAE after three courses of chemo-immunotherapy, leading to a permanent discontinuation. Finally, one patient showed a grade 2 interstitial lung disease along pembrolizumab maintenance, treated by prednisone for 1 month at a de-escalating dosage and resumed (still ongoing).

Table 2. Summary of AEs of pembrolizumab also in association with chemotherapy

	Any grade $N = 22$ (%)	*N* Grade ≥3 (%)
Any AE	22 (100)	5 (22.7)
AST/ALT increase	6 (27.3)	1 (4.5)[a]
Nausea	5 (22.7)	0
Fatigue	3 (13.6)	0
Vomiting	3 (13.6)	1 (4.5)[a]
Abdominal pain	2 (9.1)	0
Headache	2 (9.1)	0
Systemic allergic reaction	1 (4.5)	0
Cutaneous rash	1 (4.5)	0
Arthralgia	1 (4.5)	0
Autoimmune nephritis	1 (4.5)	1 (4.5) (SAE)[b]
Diarrhea	1 (4.5)	1 (4.5)
Interstitial lung disease	1 (4.5)	1 (4.5)[c]

AE, adverse event; AST, aspartate transaminase; ALT, alanine transaminase; SAE, serious adverse event.
[a]AE leading to dose reduction.
[b]AE leading to treatment interruption.
[c]AE leading to treatment delay.

DISCUSSION

Chemo-immunotherapy has been shown to significantly prolong survival in first-line metastatic or locally advanced TNBC.[15-17] In the IMpassion-130 trial, adding atezolizumab to nab-paclitaxel in the first line significantly improved OS of mTNBC patients with PD-L1 ≥1, compared with chemotherapy alone (median OS 25.4 months versus 17.9 months).[15,16] In the KEYNOTE-355 study, adding pembrolizumab to nab-paclitaxel, paclitaxel, or gemcitabine—carboplatin in advanced TNBC patients significantly increased OS over chemotherapy alone in patients with or without PD-L1 overexpression (median OS 23 months versus 16 months),[17,18] regardless of *BRCA1/2* mutation status.[8] Data on platinum-derived drugs in *BRCA*-related mTNBC have shown an impressive ORR, also compared to taxane.[5,6] These results suggest a synergistic action of immunotherapy in association with chemotherapy in mTNBC, but no trial for *BRCA1/2*-mutated patients, regardless of the phenotype, was designed.

To our knowledge, this is the first prospective multicenter phase II study evaluating efficacy and toxicity of pembrolizumab in combination with carboplatin, in the first- and second-line setting in metastatic *BRCA* patients, in both TNBC and luminal. Our study was interrupted at the time of the first-stage analysis because the primary endpoint was not achieved (43% versus expected 70%). The ORR of 70% may have been too ambitious. We hypothesized more consecutively enrolled TNBC, but surprisingly they were very few. In our series, 76% of patients were luminal, more than the prevalence usually reported in the literature (50% in the OlympiAD and 56% in the EMBRACA trials, respectively).[19,20] However, in the luminal cancers the ORR was greater than that in the TNBC subgroup (47% versus 33%). In the KEYNOTE-028 study, single-agent pembrolizumab exhibited

modest activity (ORR = 12%) in a subset of patients with PD-L1-positive, HR+, HER2− mBC.[21] Data in favor of better ORR in luminal metastatic *BRCA*-related tumors were found in the MEDIOLA phase I/II trial, evaluating olaparib + durvalumab in patients with g*BRCA1/2* mBC. The ORR in HR+ was equal to 69% (all partial responses) compared to 59% (nine partial and one complete responses) in TNBC.[7] Furthermore, the DCR in our HR+ patients was 87%, which was higher than that in TNBC patients (50%), as in the case of the MEDIOLA data (92% versus71%). Data provided by our study and MEDIOLA trial seem support the hypothesis that g*BRCA*m could drive the response to pembrolizumab in HR+ BC, combined with chemotherapy or PARP inhibitors (PARPi). Studies on PD-L1 expression and TILs count are ongoing and could provide more information on immunoresponse in g*BRCA*-HR+ tumors.

In our study, an improvement in ORR (50%) and DCR (100%) was observed when the combination was offered in the first compared to the second line of treatment for mBC. As recently reported by the JBCRG 22 TR study, patients with *BRCA* mutations who received neoadjuvant treatment with eribulin plus capecitabine lost TILs compared to those treated with eribulin plus carboplatin.[22] Based on this evaluation, capecitabine could have reduced the subsequent immunocompetence to pembrolizumab in both patients who progressed along treatment with chemo-immunotherapy combination. On the other side, patients with *BRCA* mutations seem to be more sensitive to drugs affecting the homologous recombination repair system, like carboplatin or PARPi, when offered in the first line, as shown in the OlympiAD trial, where olaparib provided a significant improvement in OS.[23]

Our study firstly evaluates the maintenance therapy after a chemotherapy induction with immunotherapy, in the mBC *BRCA*-related tumors. In the same population, the BROCADE-3 study with veliparib and carboplatinum/taxane and maintenance with PARPi had shown a significantly better PFS for the maintenance arm compared to chemotherapy alone (19.3 months versus 13.5 months).[24] Also, in the neoadjuvant setting for TNBC patients, the combination of chemotherapy and immunotherapy followed by maintenance with pembrolizumab provided a statistically significant benefit in event-free survival compared to chemotherapy alone (84.5% versus 76.8%), particularly in patients who did not obtain the pathological complete response to the preoperative treatment.[25] The results of these trials force us to consider whether a strategy of platinum-based induction combination chemotherapy followed by maintenance treatment might ultimately lead to superior outcomes for this group of patients, regardless of HR expression.

Comparing our study to the TOPACIO trial,[9] where tumoral *BRCA*-mutated mTNBC patients were treated with pembrolizumab plus niraparib, the TTP (equivalent to PFS, since no death for other causes were registered), was similar (TTP 7.1 months versus PFS 8.3 months). After exclusion of seven patients with SD and two other patients who are still under combination treatment, the DOR of >6 months is slightly inferior to that in the TOPACIO trial (71% versus 90%, respectively). Our results are probably limited by the low number of cases in study. Finally, although the OS data were not mature at the time of this analysis, 50% of alive patients overcame 18 months, confirming the expected hypothesis of 15 months.

Although 59% of patients had two or more metastatic sites at diagnosis and, most importantly, 29% of patients had liver metastases that are associated with a poor prognosis,[26] the best ORR and DCR were obtained in visceral disease rather than in non-visceral. Our results are likely opposite to those obtained with pembrolizumab plus chemotherapy in non-small-cell lung cancer, where liver metastases are associated with shorter OS and PFS compared to other metastatic sites.[27,28] Once again, g*BRCA* mutation could guide unexpected responses with respect to *BRCA*wt conditions, providing a better prognosis for this poor setting of patients.

Adverse effects were modest, with grade 3 and 4 events reported in 22.7% of patients, mostly attributable to chemotherapy than to the immunotherapy. We mainly observed hepatotoxicity (27.3%) that usually is rare for the pembrolizumab-alone treatment (1%-2%), but it can increase until 15% in case of combination regimens.[29] However, only one grade 3 hepatotoxicity led to permanent treatment discontinuation, whereas in five other 1/2 grades, the delay week and AST/ALT monitoring, as Care Step Pathways suggest,[30] were enough for recovering therapy. The only grade 3 vomiting was due to carboplatin therapy, recovered with dose reduction at 75%. The grade 2 interstitial pneumonitis accounted for 1.5% of all patients treated with pembrolizumab according to literature data and required administration of corticosteroid for 1 month to restart immunotherapy without consequences. The SAE due to nephritis was related to pembrolizumab treatment, as already reported in literature data,[31] causing permanent discontinuation.

In summary, this trial, although did not meet the primary endpoint, provides data on some efficacy of immunotherapy plus carboplatin in *BRCA*-mutated HR+ mBC. The benefit appears particularly evident in first-line chemotherapy for mBC and in case of visceral disease. The limit of this study was represented by the low number of enrolled patients and by the lack of comparison with PARPi.

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DISCLOSURE

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ROLE OF THE FUNDING SOURCE

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