ORIGINAL RESEARCH

Phase II study of eribulin in combination with gemcitabine for the treatment of patients with locally advanced or metastatic triple negative breast cancer (ERIGE trial). Clinical and pharmacogenetic results on behalf of the Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC)

B. Pellegrino[1,2,3], L. Cavanna[4], D. Boggiani[1,2], C. Zamagni[5], A. Frassoldati[2,6], A. Schirone[6], A. Caldara[7], A. Rocca[8], S. Gori[9], F. Piacentini[10], R. Berardi[11], A. A. Brandes[12], J. Foglietta[13], F. Villa[14], R. Todeschini[2], M. Tognetto[15], N. Naldi[1], B. Bortesi[1], F. Montemurro[16], A. Ardizzoni[15], L. Boni[17] & A. Musolino[1,2,3*]

[1]Medical Oncology and Breast Unit, University Hospital of Parma, Parma; [2]Italian Oncology Group for Clinical Research (GOIRC), Parma; [3]Department of Medicine and Surgery, University of Parma; [4]Hospital of Piacenza, Piacenza; [5]SSD Oncologia Medica Addarii, Policlinico S.Orsola-Malpighi, Bologna; [6]Medical Oncology Unit, University Hospital of Ferrara, Ferrara; [7]Medical Oncology Unit, Ospedale Santa Chiara, Trento; [8]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola (FC), Italy; [9]Sacro Cuore-Don Calabria Hospital, Negrar (VR); [10]Medical Oncology Unit, University Hospital of Modena, Modena; [11]Ancona University Hospital, Ancona; [12]Department of Medical Oncology, Azienda USL, Bologna; [13]Hospital of Perugia, Perugia; [14]Hospital of Lecco, Lecco; [15]Oncologia Medica, Azienda Ospedaliero-Universitaria di Bologna, Bologna; [16]Multidisciplinary Oncology Outpatient Clinic, Candiolo Cancer Institute, FPO-IRCCS, Candiolo; [17]Clinical Epidemiology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

Background: The combination of a microtubule inhibitor (eribulin) with a nucleoside analog (gemcitabine) may synergistically induce tumor cell death, particularly in triple negative breast cancer (TNBC) characterized by high cell proliferation, aggressive behavior, and chemo-resistance.

Patients and methods: This is an open-label, multicenter phase II study evaluating the combination of eribulin (0.88 mg/m^2) plus gemcitabine (1000 mg/m^2) on days 1 and 8 of a 21-day cycle as either first- or second-line treatment of locally advanced or metastatic TNBC. The primary endpoint was the objective response for evaluable patients. A prospective, molecular correlative study was carried out to assess the role of germinal BRCA pathogenic variants and single nucleotide polymorphisms (SNPs) in predicting efficacy and toxicity of the combination regimen.

Results: From July 2013 to September 2016, 83 evaluable patients were enrolled. They received a median number of six cycles of treatment. An overall response rate (ORR) of 37.3% (31 patients) was observed, with a complete response rate of 2.4% and a partial response rate of 34.9%; the clinical benefit rate was 48.8%. With a median follow-up of 28.8 months, the median response duration was 6.6 months, the median progression-free survival (PFS) was 5.1 months, and the median overall survival (OS) was 14.5 months. The most common grade 3-4 adverse events were aminotransferase elevation (in 25% of the patients) and neutropenia (in 23.8%). Women with *BRCA1/2* pathogenic variants were associated with worse ORR, PFS, and OS than *BRCA1/2* wild-type carriers. *CYP3A4* and *FGD4* SNPs were associated with increased risk of liver toxicity. Three different SNPs in *CDA*2*, *RRM1*, and *CYP2C8* genes were significantly associated with poorer OS.

Conclusions: The combination of eribulin and gemcitabine showed promising activity and a moderate toxicity profile in metastatic TNBC. BRCA status and pharmacogenetics tests may help identify patients with high probability of response with negligible toxicity.

EudraCT number: 2012-003505-10.

Key words: breast cancer, TNBC, eribulin, gemcitabine, metastatic, pharmacogenetics

INTRODUCTION

Triple negative breast cancer (TNBC) is a heterogeneous disease characterized by high cell proliferation, chemo-resistance, and unfavorable prognosis.[1] In the early setting, neoadjuvant and adjuvant chemotherapy containing anthracyclines and taxanes are the standard of care.[2,3]

None the less, almost 40% of TNBC patients relapse after local surgery and neo/adjuvant therapies,[4] whereas about 6%-10% of patients with newly diagnosed TNBC present with stage IV disease.[5] Patients who develop a metastatic disease have a very poor prognosis with a median survival of approximately 1 year.[6]

The systematic use of pre- and post-operative chemotherapy administered in patients with TNBC prompts

Correspondence to: Prof. Antonino Musolino, Medical Oncology and Breast Unit, University Hospital of Parma, via Gramsci 14, 43126 Parma, Italy. Tel: +39-0521-702316; Fax: +39-0521-995448

E-mail: antoninomusolino@hotmail.com (A. Musolino).

malignant cells to be exposed early to anti-cancer drugs and may render tumors resistant to them by the time the disease recurs. Therefore, using more active chemotherapy drugs in the early setting may reduce the number of therapeutic options for metastatic disease, making novel and ground-breaking approaches necessary for the treatment of advanced TNBC patients.[7,8] Gemcitabine is a nucleoside (pyrimidine) analogue that replaces one of the building blocks of cytidine, a nucleic acid, during DNA replication, causing the stall of the replication fork.[9] Gemcitabine is an active drug against chemotherapy-naive and chemotherapy-pretreated breast cancer (BC) with response rates, as a single agent, of 12%-33% and favorable toxicity profile.[9] Gemcitabine has also shown activity in metastatic TNBC in various combination regimens, particularly in combination with taxanes.[9] Eribulin mesylate (E7389, Eisai Research Institute, Andover, MA) is a synthetic analogue of the macrolide halichondrin B, which is a large polyether macrolide found in a rare Japanese sponge, *Halichondria okadai*.[10,11] Like halichondrin B, eribulin inhibits tubulin polymerization by binding the β-tubulin subunit. This activity explains its ability to overcome taxane resistance conferred by β-tubulin mutations.[12] Three phase II trials and one phase III trial have demonstrated the efficacy of eribulin in patients with metastatic breast cancer[13-16]; furthermore, the pooled analysis, conducted by Pivot et al., has shown that the drug is particularly active in metastatic TNBC.[17]

A single phase I study has evaluated the combination of eribulin and gemcitabine in 21 pretreated patients with advanced solid tumors.[18] Eribulin and gemcitabine were given on days 1 and 8 of a 21-day cycle. Best responses were as follows: partial response (PR) in two patients (ovarian cancer and head and neck cancer), stable disease (SD) in eight patients {minor response: 4 [non-small-cell lung cancer (NSCLC) 2, endometrial cancer 1, head and neck cancer 1]}, progressive disease (PD) in seven patients; four patients were not evaluable. According to this trial, the investigators recommended the following dosing regimen for further investigation: eribulin mesylate 1.0 mg/m^2 (equivalent to 0.88 mg/m^2 eribulin) plus gemcitabine 1000 mg/m^2, on days 1 and 8 every 21 days.[18]

Based on these considerations, the objective of this multicenter, single-arm, phase II trial was to assess the activity and safety of eribulin in combination with gemcitabine in patients with locally advanced BC or TNBC (ERIGE trial; EudraCT number: 2012-003505-10). The impact of genetic and pharmacogenetic profiles of enrolled patients on clinical outcomes and toxicity was also evaluated.

PATIENTS AND METHODS

Patient selection

Patients with locally advanced and/or metastatic TNBC were enrolled. Eligibility criteria included previous neoadjuvant and/or adjuvant chemotherapy containing an anthracycline and a taxane (unless one or both were clinically contra-indicated), ≥ 1 measurable tumor lesion according to RECIST 1.1,[19] Eastern Cooperative Oncology Group (ECOG) status ≤ 2, and adequate organ function. The study protocol and three protocol amendments, which included the permission to enroll patients previously treated with no more than one line of therapy for metastatic disease and/or with treated/stable brain metastases, were approved by the independent local ethics committee of each participating hospital. The study was conducted according to the Declaration of Helsinki and ICH-GCP guidelines. All patients gave informed consent before any study-related procedure.

Study treatment

Patients received eribulin (0.88 mg/m^2) as an intravenous (i.v.) infusion over 2-5 min on days 1 and 8 of every 21-day cycle and gemcitabine (1000 mg/m^2) as an i.v. infusion over 30 min after eribulin administration on days 1 and 8 of every 21-day cycle. The treatment was administered for three cycles (9 weeks) and in case of objective response or stabilized disease at that time, the same therapy was given for three additional courses (9 weeks). After a minimum of six courses (18 weeks) of chemotherapy, patients could continue the treatment until disease progression, unacceptable toxicity, or any other reason for discontinuation.

Molecular analyses

BRCA1/2 genetic testing. Genomic DNA was isolated from peripheral blood lymphocytes. DNA library preparation and sequencing were carried out using the Illumina MiSeq platform as specified by the manufacturer's instructions.[20] All sequence variants were named according to the nomenclature used by the Human Genome Variation Society (HGVS) guidelines,[21] and classification of *BRCA1/2* variants was also provided using the ClinVar variation report and interpretation.[22]

Pharmacogenetics. We investigated a panel of 10 single nucleotide polymorphisms (SNPs) in seven genes involved in either eribulin or gemcitabine metabolism pathway: *RRM1* (ribonucleotide reductase catalytic subunit M1), *CDA1* (cytidine deaminase 1), *CDA2*, *ABCB1* (ATP binding cassette subfamily B member 1), *CYP3A4* (cytochrome P450 family 3 subfamily A member 4), *CYP2C8* (cytochrome P450 family 2 subfamily C member 8), and *FGD4* (FYVE, RhoGEF, and PH domain containing 4). Genotyping was carried out using pre-designed TaqMan® probes according to the manufacturer's instructions.[23] FcγRIIa and FcγRIIIa polymorphisms were evaluated in study patients as negative controls.[24] Genotyping was carried out by researchers blinded to clinical outcome and toxicity data. SNP genotypes were assessed for Hardy—Weinberg equilibrium.[25,26]

Statistical analysis

The primary endpoint of this multicenter, single-arm, phase II trial was the objective response, defined as the best response identified by RECIST 1.1 criteria,[19] and recorded from the start of the trial until disease progression or death occurred, or the patient discontinued study intervention. Overall response rate (ORR) was defined as the proportion

of patients who achieved a complete or partial response as their best overall response. The Simon's two-stage optimal design[27] was planned to test the null hypothesis that the ORR would be 20% or less against a one-sided alternative (i.e. before the investigators could proceed to stage 2 of the study, at least 9 of 37 patients had to have a response). We calculated that a sample size of 83 patients would have yielded a one-sided type I error rate of 5% and power of 90% if the true response rate is 35%. The exact method was used to calculate the two-sided 90% confidence intervals for the response rate. Secondary endpoints were the response duration, progression-free survival (PFS), overall survival (OS), clinical benefit rate (disease response plus stable disease lasting $\geq$6 months), and safety. Adverse events were recorded at each visit and classified according to the National Cancer Institute-Common Terminology Criteria (NCI-CTCAE) version 4.0.[28] The response duration was defined as the time from documentation of tumor response to disease progression. PFS was defined as the time between the date of enrolment to progression or death due to any cause or last contact the patient was known to be progression-free or alive. OS was measured from the start of treatment to the date of death or the last follow-up at which the patient was known to be alive. Survival curves were estimated according to the Kaplan—Meier method.[29] All efficacy and toxicity endpoints were updated in August 2018.

The association of genetic factors with binary endpoints was tested with the chi-square test for heterogeneity,[26] or the Fisher's exact test[30] when appropriate. The association of genetic factors with survival endpoints was tested with the log-rank test.[31] All reported P values are two-sided; P values $\leq$ 0.05 were considered statistically significant. SAS System version 9.2 was used in all analyses.

RESULTS

Patient characteristics

From July 2013 to September 2016, 89 patients were registered in the trial at 22 centers in Italy. Five out of these were not eligible because of severe violations of inclusion/exclusion criteria, and one patient was registered two times in the web-based registration database by mistake. Therefore, the modified intention-to-treat efficacy population, as predefined in the study protocol, was composed of 83 eligible and evaluable patients. One out of the five non-eligible patients received study drugs and, therefore, was included in the safety analysis population of 84 patients.

Baseline characteristics are summarized in Table 1.

Median age at baseline was 56 years; the majority of the patients (80%) were pretreated with anthracyclines and/or taxanes in the (neo)adjuvant setting. Sixty-six and 17 patients were in first- and second-line treatment, respectively. Median interval from the end of (neo)adjuvant treatment to the time of initiation of first-line therapy was 14 months [interquartile range (IQR) 6.9 to 24.9].

Sixty-eight out of the 83 (82%) eligible patients enrolled in the trial were successfully genotyped. Genotyping was not

Table 1. Clinical characteristics of the patients at baseline

Parameter	Evaluable population (total, $n = 83$) n (%)
Age, years	
Median	56
Range	23-81
BRCA1/2 status	
Pathogenic variant	15 (18)
Wild type	53 (64)
Untested	15 (18)
ECOG performance status	
0	74 (89)
1	9 (11)
Prior neoadjuvant chemotherapy	
Anthracycline	18 (22)
Taxane	18 (22)
Platinum salts	2 (2)
Prior adjuvant chemotherapy	
Anthracycline	48 (58)
Taxane	48 (58)
Platinum salts	4 (5)
Prior lines of chemotherapy for metastatic disease	
0	66 (80)
1[a]	17 (20)
Sites of metastatic disease	
1 site	11 (13)
$\geq$2	66 (80)
Bone and visceral	21 (25)
Visceral only	57 (69)
Brain	7 (8)

ECOG, Eastern Cooperative Oncology Group; n, number.
[a] Capecitabine, seven patients; carboplatin, six patients; vinorelbine/other, four patients.

carried out for the remaining patients due to the following reasons: patient's informed refusal ($n = 8$), lack of informed proposal ($n = 5$), and consent withdrawal ($n = 2$). There was no significant difference in pretreatment characteristics between genotyped patients and the whole study population (data not shown). Germline pathogenic BRCA mutations (9 *BRCA1* and 6 *BRCA2*) were detected in 15 (22%) out of 68 tested patients (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2020.100019). Frameshift mutations were detected in eight women: five in *BRCA1* and three in *BRCA2*. Four nonsense, two splice, and one missense mutations were also reported. The same pathogenic variant *BRCA1* c.5030_5034del was detected in two women. All these mutations result in loss of function of the protein product and are considered to be clinically significant.

Treatment administration

Eighty-four patients received at least one dose of the study treatment. The median number of cycles administered was six (range 1-27). With an estimated median follow-up of 28.8 months (IQR 16.8-38.9), all patients discontinued therapy. Reasons for treatment discontinuation included progression of disease in 62 patients, patient or investigator decision for 18 patients, and adverse events in four patients.

Fifty-two (62%) and 49 (58%) patients required a dose reduction for eribulin and gemcitabine, respectively.

Therapy delays occurred for 60 (71%) patients in 142 (22%) out of 645 cycles.

Efficacy

Based on the predefined interim analysis conducted at the completion of the first stage, enrollment was allowed to continue, as per protocol. A total of 83 eligible and evaluable patients (37 in the first stage, 46 in the second stage) were included in the efficacy analysis. Three out of 83 patients interrupted study treatment before first tumor evaluation (two for toxicity and one for withdrawal of consent) and were considered non-responders. The response rate for all patients was 37.3% [90% confidence interval (CI), 28.5 to 46.9], with 2.4% of patients having a complete response and 34.9% having a PR (Table 2).

The clinical benefit rate was 48.8% (90% CI 39.2 to 58.4). For the 31 patients who had a response at the time of data analysis, the estimated median response duration was 6.1 months (95% CI 4.1 to 7.2). The estimated median PFS among all patients was 5.1 months (95% CI 4.1 to 6.9). The median OS for this study was 14.5 months (95% CI 10.1 to 19.8) (Table 2).

Safety

The majority of the adverse events observed in the 84 patients who received at least one dose of study drugs were grade 1 or 2. The most common nonhematologic adverse events occurring in more than 10% of patients were fatigue (in 66.7% of patients), elevation of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) (in 58.3%), nausea (in 36.9%), alopecia (in 23.8%), diarrhea (in 19.0%), constipation (in 17.9%), peripheral neuropathy (in 14.3%), rash (in 14.3%), vomiting (in 11.9%), and oral mucositis (in 10.7%) (Table 3).

Grade 3 and 4 hematologic adverse events included neutropenia (in 23.8% of patients), thrombocytopenia (in 2.4%), and anemia (in 1.2%); two patients (2.4%) had grade 3/4 febrile neutropenia.

An adverse event leading to discontinuation of therapy occurred in four patients (4.7%). No patient died during treatment due to an adverse event.

Efficacy and safety by BRCA status and pharmacogenetics

Among the 68 genotyped patients, the response rate was 41.5% (90% CI 30.0-53.7) and 26.7% (90% CI 9.7-51.1) for BRCA wild-type and BRCA-mutated subgroups, respectively ($P = 0.375$) (Table 2). Furthermore, the clinical benefit rate was 57.7% (90% CI 45.4-69.3) in wild-type patients and only 26.7% (90% CI 9.7-51.1) in BRCA-mutated ones ($P = 0.043$). Similarly, subjects with BRCA pathogenic variants were associated with significantly worse response duration, PFS, and OS than non-carriers (Table 2; Figure 1). No correlation was observed between toxicity and BRCA status (data not shown).

Genotyped patients were also evaluated using a panel of 10 SNPs in seven genes involved in either eribulin or gemcitabine metabolism pathway. All SNP genotypes were in Hardy–Weinberg equilibrium; none of them were associated with treatment response (data not shown). Conversely, the CYP3A4*1B (392A>G) SNP, which is involved in the hepatic metabolism of both eribulin and gemcitabine, was associated with grade 3/4 AST and ALT elevations {23% in AA genotype [variant frequency (VF): 94%] versus 75% in AG/GG genotypes [VF: 6%]; $P = 0.05$}. The same association was also reported for the FGD4 (2044236G>A) SNP, which is involved in the regulation of actin cytoskeleton assembly and cell shape: the rates of grade 3/4 hypertransaminasemia were 20% in AA/AG genotypes (VF: 85.5%) versus 60% in GG genotype (VF: 14.5%;

Table 2. Efficacy results by BRCA status					
Variable	BRCA pathogenic variants (n = 15)	BRCA wild type (n = 53)	BRCA untested (n = 15)	P^a	All patients (N = 83)
Response n (%)[b]					
Overall	4 (26.7)	22 (41.5)	5 (33.3)	0.375	31 (37.3)
Complete	0	1 (1.9)	1 (6.7)		2 (2.4)
Partial	4 (26.7)	21 (39.6)	4 (26.7)		29 (34.9)
None[c]	11 (73.3)	31 (58.5)	10 (66.6)		52 (62.7)
Clinical benefit rate[d]	4 (26.7)	30 (57.7)	6 (40)	0.043	40 (48.8)
Response duration[e] months					
Median	2.4	6.6	5.1	0.008	6.1
95% CI	2.0-6.1	4.1-8.4	2.0-7.1		4.1-7.2
Progression-free survival months					
Median	2.6	6.4	5.1	<0.001	5.1
95% CI	2.0-4.5	4.4-9.3	2.4-6.9		4.1-6.9
Overall survival months					
Median	9.6	17.9	13.0	0.020	14.5
95% CI	2.6-11.3	11.1-21.5	4.6-20.1		10.1-19.8

CI, confidence interval; n/N, number.
[a] Fisher's exact test or log-rank test for the comparison between BRCA-mutated and wild-type patients.
[b] First stage results of 37 patients: overall response: 16/37 (43.2%), complete response: 0, partial response: 16/37; no response: 21/37 (56.8%).
[c] No response was defined as stable, progressive, or non-assessed disease.
[d] One BRCA wild-type patient was not evaluable for clinical benefit rate because they were not assessed for short (<6 months) versus long (≥6 months) stable disease duration.
[e] Response duration was defined as the time from documentation of tumor response to disease progression.

Table 3. Adverse events[a]

Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	No. of patients with event (%)				
Hematologic event					
Neutropenia	8 (9.5)	22 (26.2)	14 (16.7)	6 (7.1)	50 (59.5)
Anemia	23 (27.4)	12 (14.3)	1 (1.2)	0	36 (42.9)
Thrombocytopenia	18 (21.4)	6 (7.1)	2 (2.4)	0	26 (30.9)
Nonhematologic event					
Fatigue	25 (29.8)	26 (30.9)	5 (5.9)	0	56 (66.6)
Elevation of AST/ALT	14 (16.7)	14 (16.7)	21 (25.0)	0	49 (58.3)
Nausea	20 (23.8)	10 (11.9)	1 (1.2)	0	31 (36.9)
Alopecia	10 (11.9)	7 (8.3)	2 (2.4)	1 (1.2)	20 (23.8)
Diarrhea	12 (14.3)	4 (4.8)	0	0	16 (19.0)
Constipation	12 (14.3)	2 (2.4)	1 (1.2)	0	15 (17.9)
Peripheral neuropathy	8 (9.5)	3 (3.6)	1 (1.2)	0	12 (14.3)
Rash	8 (9.5)	2 (2.4)	2 (2.4)	0	12 (14.3)
Vomiting	8 (9.5)	1 (1.2)	1 (1.2)	0	10 (11.9)
Oral mucositis	6 (7.1)	3 (3.6)	0	0	9 (10.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; no., number.
[a] The safety analysis set included the 84 patients who received at least one dose of study drugs.

$P = 0.04$). Moreover, after adjustment for BRCA status, three different SNPs were significantly and independently associated with poorer over survival (Figure 2): CDA*2 (79A>C) and RRM1 (2455A>G), which are involved in the metabolism of nucleoside analogues, and the CYP2C8 (416G>A) SNP involved in the hepatic metabolism of both eribulin and gemcitabine.

DISCUSSION

The ERIGE trial is a multicenter, Italian study enrolling a homogenous population of patients with advanced TNBC, testing a novel treatment regimen that combines eribulin with gemcitabine.

The combination therapy showed a remarkable best ORR of 37.3% and a clinical benefit rate of 48.8%. Adverse events of the trial were consistent with the known safety profiles of the two drugs. The administration of eribulin and gemcitabine revealed a manageable safety profile and the most common grade 3/4 toxicities were liver toxicity and

neutropenia without febrile neutropenia. At a median follow-up of 28.8 months, the median PFS was 5.1 months and the median OS was 14.5 months.

For patients with metastatic breast cancers, both combination and sequential, single-agent chemotherapy are reasonable options.[2] Current guidelines recommend sequential monotherapy as the preferred choice. Combination chemotherapy should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control. In patients pretreated (in the adjuvant and/or metastatic setting) with an anthracycline and a taxane, single-agent capecitabine, carboplatin, vinorelbine, or eribulin may be offered.[3]

The combination of eribulin with gemcitabine used in the ERIGE trial seems to increase the activity of eribulin monotherapy, which accounts for an ORR of 12%, according to the results of the EMBRACE trial in heavily pretreated patients with metastatic breast cancer.[16] Furthermore, the activity of eribulin plus gemcitabine observed in our trial was almost higher compared with the first-line monotherapies tested in the triple negative breast cancer trial (TNT),[32] i.e. carboplatinum and taxotere, showing an ORR of 31% and 34%, respectively.[32] Some studies were conducted in patients with metastatic TNBC evaluating other combination regimens, such as carboplatin/gemcitabine,[33] iniparib plus carboplatin/gemcitabine,[34] gemcitabine/paclitaxel,[35] ixabepilone/capecitabine,[36] and cisplatin/gemcitabine.[37] In summary, those combination treatments revealed response rates of 23%-36%, median PFS times of 4.1-6.0 months, and median OS times of 11-12 months. With an ORR of 37.3%, PFS of 5.1 months, and OS of 14.5 months, the combination of eribulin and gemcitabine compares well with those results. For interpretation purposes, it is however important to take into account that the ERIGE study did not perform independent central reviews of neither triple negative status nor survival endpoints.

Almost 40% of patients with metastatic TNBC, which express the programmed death-ligand 1 (PD-L1) on immune cells of the tumor microenvironment, are currently treated in
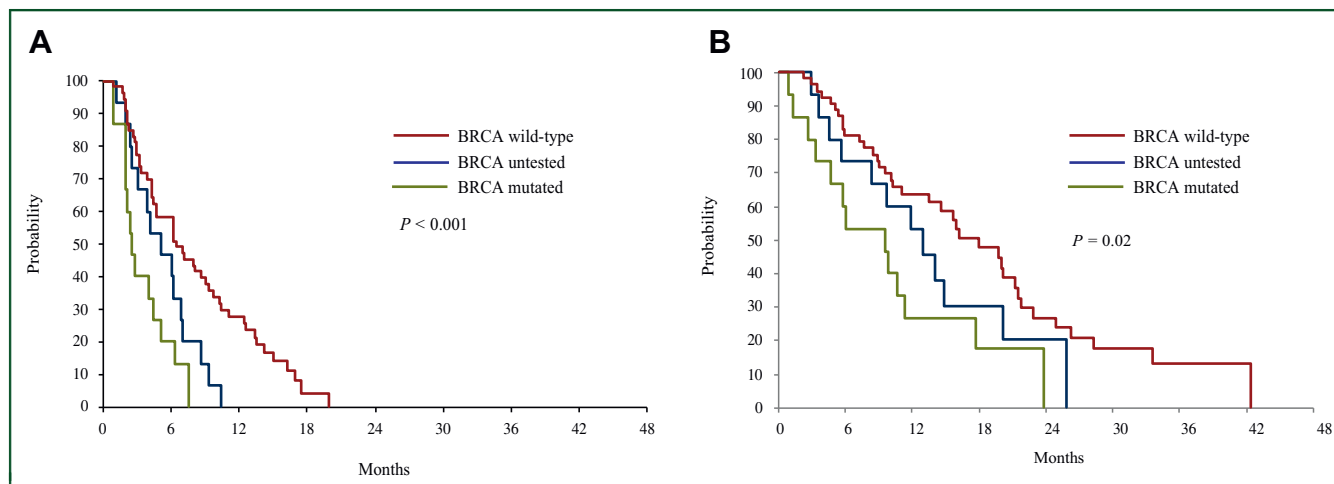

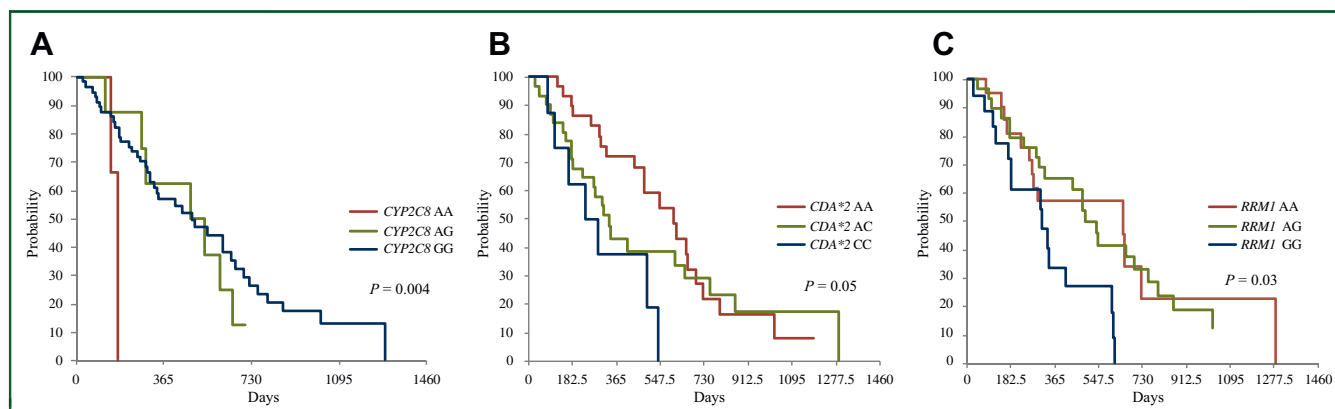**Figure 1. Progression-free survival (A) and overall survival (B) according to the BRCA1/2 status.**

Figure 2. Overall survival according to *CYP2C8 (416G>A)* (A), *CDA*2 (79A>C)* (B), and *RRM1 (2455A>G)* (C) single nucleotide polymorphisms.

the first-line setting with the anti-PD-L1 monoclonal antibody atezolizumab in combination with nab-paclitaxel.[38] Furthermore, the 20% of patients with TNBC who harbored *BRCA1/2* pathogenic variants and had previously received ≤2 lines of chemotherapy for metastatic disease obtained benefit from PARP inhibitors (PARPi), such as olaparib and talazoparib.[39-41] Nevertheless, ~50% of TNBC do not present biomarkers predictive of response to targeted therapies and, in this population, there is no general agreement on the best first- or second-line treatment to provide for metastatic disease, especially if patients already received adjuvant regimens including anthracyclines and taxanes (+/− carboplatin).[42] Considering the complementary mechanisms of action of eribulin and gemcitabine, the activity of their combination observed in the ERIGE trial, and the manageable toxicity, we propose the use of our regimen in patients with 'biomarker-orphan', metastatic TNBC.

Looking at the results of our pre-planned genetic and pharmacogenetic analyses, the study regimen partially lost its efficacy in patients harboring *BRCA1/2* pathogenic variants, showing an ORR of 26.7% and a median PFS and OS of 2.6 and 9.6 months, respectively. Interestingly, in the PARP inhibitor OlympiAD and EMBRACA trials, pretreated patients with BRCA-mutated, HER2-negative metastatic breast cancer who were treated with treatment of physician's choice (TPC) as control arm (i.e. eribulin, gemcitabine, capecitabine, or vinorelbine) showed comparable response rates of 27%-29% and a median PFS of 4.2-5.6 months.[39,40] Furthermore, the TNT trial demonstrated that docetaxel was less active than carboplatin in BRCA-mutated tumors.[32] Taking into account all these data, we can hypothesize that therapeutic agents such as microtubule inhibitors and nucleotide analogues, which, unlike platinum salts and PARPi, do not exploit the vulnerability of impaired DNA damage repair mechanism in BRCA-mutant cancers, do not get the most therapeutic benefit in this group of patients. Our data confirm the current guideline statement that *BRCA1/2* germline testing has proven clinical utility and therapeutic impact in metastatic breast cancer and should be carried out as early as possible.[3]

Pharmacogenomic studies are conducted to investigate biomarkers that can predict the toxicity or efficacy of chemotherapies. A relatively limited number of pharmacogenomic studies have been conducted to investigate these biomarkers in BC with inadequate accumulated evidence to warrant specific dosing or chemotherapy regimens. Apart from the guidelines regarding dihydropyrimidine dehydrogenase (DPYD) genetic testing before fluoropyrimidine use, there are no other guidelines related to other chemotherapeutic agents used in BC.[42] To our knowledge, the ERIGE trial is the first trial prospectively investigating the role of SNPs involved in the metabolism of eribulin and gemcitabine in predicting toxicities and efficacy of those drugs. SNPs in *CYP3A4* and *FGD4* genes were associated with increased risk of liver toxicity. Moreover, three different SNPs in *CDA*2*, *RRM1*, and *CYP2C8* genes were significantly associated with poorer OS. For all that, additional data from large-scale, prospective randomized clinical trials are required.

Conclusion

The combination of eribulin and gemcitabine demonstrated promising antitumor activity as first- or second-line therapy for advanced TNBC. The treatment was well-tolerated with manageable toxicity. The pre-planned subgroup analysis indicated that this combination regimen was particularly efficacious in BRCA wild-type patients. Pharmacogenetic testing was encouraging, suggesting that SNP data analysis may represent for this disease setting a reliable and affordable approach in the precision medicine scenario.

ETHICS STATEMENT

This study was approved by the local independent ethics committee (IEC). The patients provided informed written consent for participation in the trial publication of clinical data and images.

DISCLOSURE

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DISCLAIMER

Any views, opinions, findings, conclusions, or recommendations expressed in this material are those solely of the authors and do not necessarily reflect those of ESMO, Roche, or Eisai.

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