European Journal of Cancer 195 (2023) 113386

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Original Research

Clinical activity of nivolumab in combination with eribulin in HER2-negative metastatic breast cancer: A phase IB/II study (KCSG BR18-16)

Se Hyun Kim [a,1], Seock-Ah Im [b,1], Koung Jin Suh [a], Kyung-Hun Lee [b], Min Hwan Kim [c], Joohyuk Sohn [c], Yeon Hee Park [d], Ji-Yeon Kim [d], Jae Ho Jeong [e], Kyoung Eun Lee [f], In Sil Choi [g], Kyong Hwa Park [h], Hee-Jun Kim [i], Eun Kyung Cho [j], So Yeon Park [k], Milim Kim [k,l], Jee Hyun Kim [a,*]

[a] Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea
[b] Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University, College of Medicine, Seoul, South Korea
[c] Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea
[d] Hematology-Oncology, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, South Korea
[e] Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea
[f] Department of Hematology and Oncology, Ewha Womans University Hospital, Seoul, South Korea
[g] Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, South Korea
[h] Division of Medical Oncology/Hematology, Department of Internal Medicine, Korea University Anam Hospital, Seoul, South Korea
[i] Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, South Korea
[j] Division of Medical Oncology, Department of Internal Medicine, Gil Medical Center, Gachon University College of Medicine, Incheon, South Korea
[k] Department of Pathology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea
[l] Department of Pathology, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

ARTICLE INFO

Keywords:
Advanced breast cancer
Metastatic breast cancer
Nivolumab
Immune checkpoint inhibitors
Eribulin
Clinical trial
Luminal breast cancer

ABSTRACT

Aim: We evaluated the efficacy and safety of nivolumab and eribulin combination therapy for metastatic breast cancer (BC) in Asian populations.

Methods: In this parallel phase II study, adult patients with histologically confirmed recurrent/metastatic hormone receptor-positive/HER2-negative (HR+HER2-) or triple-negative BC (TNBC) were prospectively enroled from 10 academic hospitals in Korea (ClinicalTrials.gov Identifier: NCT04061863). They received nivolumab (360 mg) on day 1 plus eribulin (1.4 mg/m^2) on days 1 and 8 every 3 weeks until disease progression or intolerable toxicity. The primary endpoint was the investigator-assessed 6-month progression-free survival (PFS) rate in each subtype. Secondary endpoints included investigator-assessed objective response rate (ORR) as per Response Evaluation Criteria in Advanced Solid Tumors version 1.1, disease control rate, overall survival, and treatment toxicity. The association between PD-L1 expression and efficacy was investigated.

Results: Forty-five patients with HR+HER2- BC and 45 with TNBC were enroled. Their median age was 51 (range, 31–71) years, and 74 (82.2%) received one or two prior treatments before enrolment. Six-month PFS was 47.2% and 25.1% in the HR+HER2- and TNBC cohorts, respectively. Median PFS was 5.6 (95% confidence interval [CI]: 5.3–7.4) and 3.0 (95% CI: 2.1–5.2) months in the HR+HER2- and TNBC groups, respectively. ORRs were 53.3% (complete response [CR]: 0, partial response [PR]: 24) and 28.9% (CR: 1, PR: 12). Patients with PD-L1+ tumours (PD-L1 expression ≥1%) and PD-L1- tumours (ORR 50% versus 53.8% in HR+HER2-, 30.8% versus 29.0% in TNBC) had similar ORRs. Neutropenia was the most common grade 3/4 adverse event; the most common immune-related adverse events (AEs) were grades 1/2 hypothyroidism and pruritus. Five patients discontinued therapy because of immune-related AEs.

* *Correspondence to*: Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173 beon-gil, Bundang-gu, Seongnam 13620, South Korea.
E-mail address: jhkimmd@snu.ac.kr (J.H. Kim).
[1] These authors contributed equally to this study.

https://doi.org/10.1016/j.ejca.2023.113386
Received 10 July 2023; Received in revised form 13 September 2023; Accepted 6 October 2023
Available online 14 October 2023

Conclusion: Nivolumab plus eribulin showed promising efficacy and tolerable safety in previously treated HER2-metastatic BC.
Trial registration: NCT04061863

1. Introduction

Despite recent breakthroughs in systemic therapy, metastatic breast cancer (MBC) remains an incurable disease with a 5-year survival of approximately 25% and the leading cause of cancer-related death worldwide [1,2]. MBC survival is strongly related to its subtype, which is determined by gene expression signature or protein expression profile. Major improvements have been observed in patients with Human epidermal growth factor receptor 2 (HER2)-positive MBC after the introduction of various HER2-targeting agents, although cytotoxic chemotherapy remains the standard of care for hormone receptor (HR)-positive BC that progresses after prior endocrine treatment and triple-negative breast cancer (TNBC) [2].

MBC subtypes are distinct based on the expression of targetable receptors and their immunological phenotypes, such as tumour-associated antigens, Programmed death ligand 1 (PD-L1) expression, number of tumour-infiltrating lymphocytes (TILs), and tumour mutational burden. Observation of high PD-L1 expression in the tumour microenvironment of TNBC led to the success of clinical trials in this aggressive tumour type [3]. Pembrolizumab has received FDA approval for use in combination with first-line chemotherapy for PD-L1-positive (combined positive score of 10 or higher) metastatic TNBC based on the clinical benefits observed in the KEYNOTE-355 trial [4]. In previous studies using The Cancer Genome Atlas data that analysed distinct genomic immune profiles across intrinsic BC subtypes, none were identified as immunologically quiet, reinforcing the possibility of leveraging the pre-existing host immunity to boost the immune response against MBC [5,6]. Clinical trials investigating immunotherapeutic agents for MBC have been growing exponentially over the past few years.

Eribulin, a non-taxane inhibitor of microtubule dynamics, is distinct from other tubulin-targeting drugs, such as vinca alkaloids and taxanes. In a phase III trial of eribulin (EMBRACE, Eisai metastatic breast cancer study assessing physician's choice versus E7389), an increase in survival was observed in patients with MBC after eribulin treatment, without an improvement in disease-free survival [7]. In addition to the direct cytotoxic effect of eribulin, its immune-modulating effect has been demonstrated in experimental studies using cancer cells and tumour tissues [8,9]. These unique profiles have led investigators to conduct prospective clinical trials combining immune checkpoint inhibitors with eribulin in patients with MBC [10–12].

Ethnicity and related germline variants can affect immune function. Thus, East Asian patients with MBC may have a unique immunological profile, including APOBEC3B polymorphism [13–15]. However, the efficacy of eribulin and immune checkpoint inhibitors in Asian populations might be underrepresented, as most participants of the aforementioned studies were of non-Asian descent. Therefore, herein (Korean Cancer Study Group (KCSG) BR18-16 or KORNELIA trial), we evaluated the efficacy and safety of nivolumab and eribulin combination therapy in Asian patients with HER2-negative MBC.

2. Material and methods

2.1. Study design and patient population

The KORNELIA trial was a multicenter, parallel-design, open-label phase 2 trial conducted in 10 academic hospitals in Korea. The eligibility criteria included provision of informed consent before any study-specific procedures, being at least 20 years old, diagnosed with HER2-negative BC as defined by the American Society of Clinical Oncology–College of American Pathologists guidelines version 2013 [16], having at least one measurable lesion based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [17] as assessed by the investigator, metastatic disease treated with anthracycline and/or taxane unless contraindicated (patients who received anthracycline and/or taxane-based chemotherapy in either the neoadjuvant, adjuvant, or metastatic setting and experienced disease progression on or after taxane-based chemotherapy in the metastatic setting), an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, less than three prior lines of cytotoxic chemotherapy for metastatic disease (prior chemotherapy within 1 year after completion of (neo) adjuvant anthracycline and taxane-based chemotherapy was counted as one prior line of treatment; endocrine therapy was not counted as a prior line of treatment), and adequate organ function for study treatment.

The key exclusion criteria included previous treatment with eribulin mesylate or any anti-PD-1, PD-L1, or PD-L2 therapy; the presence of active autoimmune disease or central nervous system metastases or carcinomatous meningitis (previously treated patients who were stable for at least 4 weeks were permitted); history of human immunodeficiency virus and active hepatitis B or C infection; any other malignancy requiring treatment during the 3 years prior to enrolment; history of cardiac dysfunction; diagnosis of immunodeficiency or receiving systemic steroid therapy exceeding 10 mg of corticosteroids; history of pneumonitis requiring steroids or interstitial lung disease; and receipt of a live-virus vaccination within 30 days before initiation of the study therapy.

The trial was performed in accordance with the standards of Good Clinical Practice and the Declaration of Helsinki. The trial protocol and all amendments were approved by the Institutional Review Board (IRB) of the participating institutions, including Seoul National University Bundang Hospital (IRB no. B-1811-505-004). All patients provided written informed consent before undergoing protocol-related activities. The trial protocol was published online and is available at Clinicaltrials.gov (Identifier: NCT04061863).

2.2. Treatment schedule

As the safety profile of eribulin plus nivolumab combination therapy has not been evaluated in patients with BC, a safety run-in was adopted to ensure that no severe adverse events occurred during the study. In the run-in phase, three patients were enroled and treated with nivolumab 360 mg on day 1 combined with eribulin 1.4 mg/m^2 on days 1 and 8 every 21 days. If no dose-limiting toxicity (DLT) occurred in any of these participants, additional participants were enroled in each cohort (phase 2). If DLT was observed in any of these participants, accrual of three more patients with a reduced dose of eribulin (1.1 mg/m^2) was planned. DLT was monitored by the Steering Committee 21 days after the first dosing of the first cycle of protocol treatment.

In phase 2, 360 mg of nivolumab was administered on day 1 and eribulin on days 1 and 8 of each 21-day cycle at the recommended phase 2 dose from the run-in part of the study. Subjects received treatment for a maximum of 2 years or until disease progression, unacceptable toxicity, or withdrawal of consent, whichever occurred first. Dose reduction of nivolumab was not permitted; pre-specified dose modifications of eribulin were permitted to manage toxicity. Tumour assessment using computed tomography or magnetic resonance imaging was performed at baseline and every 6 weeks (±7 days) until progressive disease as per RECIST version 1.1. After week 54, the participants who remained on treatment underwent response assessment every 12 weeks (±7 days). Beyond progression, treatment according to iRECIST criteria was permitted if the investigator deemed it necessary after the initial

radiographic progressive disease. Safety assessments were performed on the first day of each study treatment and documented using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

2.3. Exploratory analysis for biomarkers

Baseline tumour biopsy from metastatic or recurrent lesions was mandatory, and use of archival tumour samples taken within 24 months before enrolment was permitted. Peripheral blood samples were collected at baseline, cycle 3, day 1, and time of disease progression. TIL and PD-L1 expression was determined by two breast pathologists (Park SY and Kim ML). TILs were manually counted on hematoxylin/eosin-stained slides according to previously published guidelines [18]. TIL counts were categorised as high (≥10%) and low (<10%). PD-L1 expression was determined using SP142 (Ventana Medical Systems, Tucson, AZ, USA) and SP263 (Ventana Medical Systems) antibodies. The pathologists were certified to interpret the Ventana assay findings and independently evaluated the percentages of tumour cells (TCs) and immune cells (ICs) that stained positive at any intensity for PD-L1 expression. Discernible PD-L1 staining in TC and/or IC of any intensity covering ≥1% of the tumour area was considered PD-L1 positive.

2.4. Primary and secondary endpoints

The primary endpoint of this study was a 6-month progression-free survival (PFS) rate in HR+HER2- and TNBC subtypes; PFS was defined as the time from study treatment to disease progression according to RECIST 1.1, or death due to any cause, whichever occurred first. Secondary endpoints were the objective response rate (ORR) as per RECIST v1.1, disease control rate (DCR), PFS, overall survival (OS), and safety of combination treatment.

2.5. Statistical analysis

Sample size of the phase II run-in part was calculated based on the hypothesis of a higher 6-month PFS rate from eribulin plus nivolumab (36%) versus eribulin monotherapy (18%) [7] using the Kaplan–Meier estimation method. Enroling 45 patients in each cohort provided 80% power (with an expected 10% drop-out rate) with a one-sided alpha value of 0.05. Variables are described as frequencies (%) or means and medians including the range. Independent two-sample t-tests were used to analyse continuous variables, and Fischer's exact tests were used for categorical variables. The Kaplan–Meier method was used to estimate PFS and OS, and log-rank tests were used to investigate differences between the groups. R (version 4.2.0) was used for statistical analyses, and statistical significance was set at $P < 0.05$ (two-sided).

3. Results

3.1. Baseline characteristics

Ninety patients were enrolled between August 2019 to June 2021: 45 in the HR+HER2- cohort and 45 in the TNBC cohort (Fig. 1). Table 1 shows the demographic and baseline characteristics of the study participants. The median age was 51 (range 31–71) years and 63 (70%) patients had an ECOG performance status of 1. Approximately one-quarter (22 patients, 24.4%) of the patients had *de novo* MBC. The most common site of metastasis was the lungs (41 patients, 45.6%), followed by bones (33 patients, 40%). Thirty-nine (86.7%) and eight (17.8%) patients in the HR+HER2- and TNBC cohort, respectively, received prior endocrine treatment. Seventy-three (81.1%) participants had received one (46 patients, 51.1%) or two (27 patients, 30%) prior lines of cytotoxic chemotherapy. Nearly all participants (86 patients, 95.6%) had received taxane-based chemotherapy before enrolment.

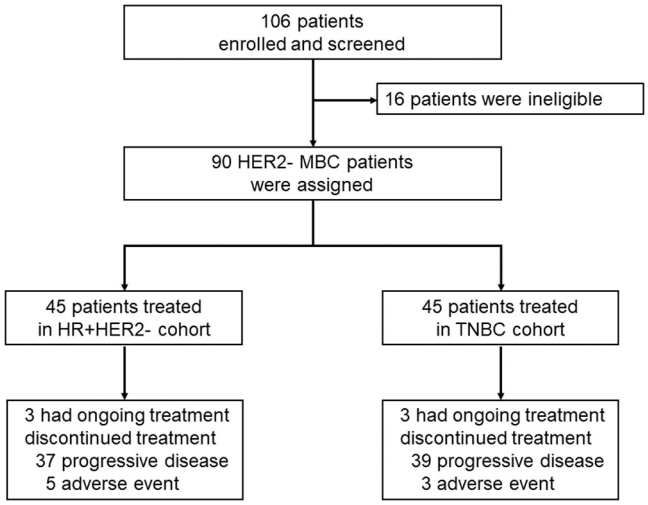

Fig. 1. Flowchart of study inclusion and design. MBC, metastatic breast cancer; HR, hormone receptor; TNBC, triple-negative breast cancer.

3.2. Efficacy of eribulin plus nivolumab

In the safety run-in, three (2 HR+HER2-, 1 TNBC) patients were enroled. As no DLT was observed during the first cycle, the recommended phase 2 dose was determined as nivolumab 360 mg on day 1 combined with eribulin 1.4 mg/m^2 on days 1 and 8 every 21 days. With a median follow-up time of 22.8 months by reverse Kaplan-Meier method, 75 (83.3%) patients experienced progressive disease and 54 (60.0%) died. Six (6.7%) patients were treated without disease progression. The median PFS was 5.6 (95% confidence interval [CI], 5.3–7.4) and 3.0 (95% CI, 2.1–5.2) months in the HR+HER2- and TNBC cohorts, respectively; 6-month PFS rates were 47.2% (95% CI, 34.4–64.8) and 25.1% (95% CI, 14.9–42.1) (Fig. 2) and those at 12 months were 22.7% (95% CI, 12.7–40.1) and 17.2% (95% CI, 8.8–33.8), respectively. Three HR+HER2- and three TNBC patients achieved 24 months without disease progression.

Objective tumour responses are summarised in Table 2. Treatment with eribulin plus nivolumab resulted in an ORR of 41.1% (36 of 90 patients; 95% CI: 30.8–52.0) in the overall population; ORR was 53.3% (24 of 45 patients; 95% CI: 37.9–68.3) and 28.9% (13 of 45 patients; 95% CI: 16.4–44.3) in the HR+HER2- and TNBC cohorts, respectively (Supplementary Fig. 1). Excluding nine unconfirmed partial responses (eight in HR+HER2- and one in TNBC cohort), 16 (35.6%) and 12 (26.7%) patients in the HR+HER2- and TNBC cohorts had confirmed responses, respectively. One patient in the TNBC cohort achieved a complete response. The median duration of response according to RECIST version 1.1 was 6.9 (95% CI: 5.6–18.3) and 12.9 (95% CI: 6.9–not available) months in the HR+HER2- and TNBC cohorts, respectively (log-rank, $P = 0.31$; Supplementary Fig. 2).

The median OS was 17.9 (95% CI: 15.1–not available) and 15.7 (95% CI: 11.0–21.9) months in the HR+HER2- and TNBC cohorts, respectively (log-rank, $P = 0.26$; Supplementary Fig. 3).

In exploratory analyses, high TIL count was found in eight (17.8%) and nine (20.5%) patients in the HR+HER2- and TNBC cohorts, respectively (Table 1). Tumours with PD-L1 expression (at least 1%) were observed in 18 (20.0%) and 13 (14.4%) of the 89 patients with sufficient tumour samples for both SP142 Ab and SP263 Ab, respectively. More tumours with PD-L1 expression were found in the TNBC (28.9% with SP142 Ab, 22.2% with SP263 Ab) cohort than in the HR+HER2- (13.3% with SP142 Ab, 6.7% with SP263 Ab) cohort.

Objective tumour responses stratified by HR and PD-L1 expression status are shown in Table 3. Among patients in the HR+HER2- cohort, the ORR was similar regardless of PD-L1 expression status (50% in PD-L1+ versus 53.8% in PD-L1-; Chi-square, $P = 0.967$). In patients in the

Table 1
Baseline characteristics of the study participants.

	ER+HER2- (n = 45)		ER-HER2- (n = 45)		Total (n = 90)		P-value
	N	(%)	N	(%)	N	(%)	
Age (median, range)	52	31–71	49	34–71	51	31–71	0.637
Menopause							1.000
Premeno	12	26.7	13	28.9	25	27.8	
Postmeno	33	73.3	32	71.1	65	72.2	
ECOG performance status							0.358
0	16	35.6	11	24.4	27	30	
1	29	64.4	34	75.6	63	70	
Pathology							0.755
IDC	39	86.7	41	91.1	80	88.9	
ILC	4	8.9	3	6.7	7	7.8	
Others	2	4.4	1	2.2	3	3.3	
Type of MBC							0.806
Recurrence	33	73.3	35	77.8	68	75.6	
De novo	12	26.7	10	22.2	22	24.4	
Lung metastasis							0.090
Yes	16	35.6	25	55.6	41	45.6	
No	29	64.4	20	44.4	49	54.4	
Liver metastasis							0.029
Yes	22	48.9	11	24.4	33	36.7	
No	23	51.1	34	75.6	57	63.3	
Bone metastasis							0.001
Yes	26	57.8	10	22.2	36	40.0	
No	19	42.2	35	77.8	54	60.0	
Prior Endocrine treatment							<0.018
Yes	39	86.7	8	17.8	47	52.2	
No	6	13.3	37	82.2	43	47.8	
Prior lines of CT for MBC							1.000
0	8	17.8	8	17.8	16	17.8	
1	23	51.1	23	51.1	46	51.1	
2	14	31.1	14	31.1	28	31.1	
Prior taxane based CT							1.000
Yes	43	95.6	43	95.6	86	95.6	
No	2	4.4	2	4.4	4	4.4	
Prior anthracycline based CT							0.653
Yes	29	64.4	31	68.9	60	66.7	
No	16	35.6	14	31.1	30	33.3	
Exploratory central testing (TIL and PD-L1)							
TIL							0.018
negative (0%)	25	55.6	12	27.3	37	41.6	
low (1–9%)	12	26.7	23	52.3	35	39.3	
high (≥10%)	8	17.8	9	20.5	17	19.1	
PD-L1 status by SP142 Ab							0.158
positive[a]	6	13.3	12	26.7	18	20.0	
negative	39	86.7	32	71.1	71	78.9	
not available	0	0	1[b]	2.2	1	1.1	
PD-L1 status by SP263 Ab							0.060
positive[a]	3	6.7	10	22.2	13	14.4	
negative	42	93.3	34	75.6	76	84.4	
not available	0	0	1[b]	2.2	1	1.1	

CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; MBC, metastatic breast cancer;
[a] Defined as ≥1%.
[b] PD-L1 status was not evaluable in one patient because of low tumour cellularity.

TNBC cohort, a higher rate of progressive disease was observed in patients with PD-L1-; however, the difference was not significant (23.1% in PD-L1+ versus 41.9% in PD-L1-; chi-square, P = 0.242). A decrease in target lesion size was observed in both cohorts regardless of PD-L1 status (Fig. 3). There was a trend toward improved PFS in the TNBC cohort when patients were stratified based on TILs, with a >10% cut-off and PD-L1 expression by SP142 Ab (Supplementary Fig. 2). This trend was not observed following the analysis of the HR+HER2- cohort. Exploratory subset analyses, including clinical characteristics, line of therapy, PD-L1 status, TIL, and Neutrophil-lyphocyte ratio (NLR), also did not show any specific population with a significant improvement in PFS (Supplementary Fig. 3).

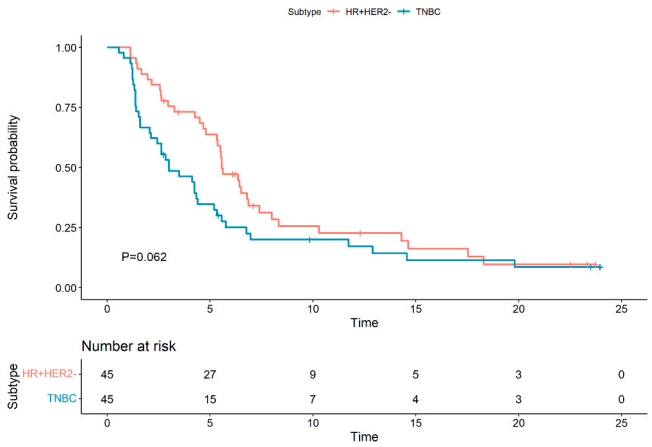

Fig. 2. Kaplan–Meier survival estimates for progression-free survival.

Table 2
Best objective response in breast cancer with nivolumab plus eribulin treatment.

	Total	HR+HER2- cohort	TNBC cohort
	n = 90	n = 45	n = 45
ORR, %	41.1	53.3	28.9
(95% CI)	(30.8–52.0)	(37.9–68.3)	(16.4–44.3)
DCR, %	73.3	82.2	64.4
(95% CI)	(63.0–82.1)	(67.9–92.0)	(48.8–78.1)
Best overall response, %			
Complete response	1 1.1	0 0	1 2.2
Partial response	36 40.0	24 53.3	12 26.7
Stable disease	29 32.2	13 28.9	16 35.6
Progressive disease	24 26.7	8 17.8	16 35.6
Median duration of response (range), months[†]	7.8 (2.6 to 24.0+)	6.9 (2.6 to 23.7+)	12.9 (4.0 to 24.0+)

The best objective response was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1. NR denotes not reached.
[†] Indicates ongoing response evaluation.

3.3. Adverse events (AEs) of eribulin plus nivolumab

Treatment-related AEs occurred in 96.7% (87) of patients in both arms, and the rate of grade 3 or 4 AEs was 65.6% (59 patients); those observed in >10 patients are listed in Table 4. The most common grade 3/4 AE was neutropenia (52/90, 57.8%), and the most common immune-related AEs were grades 1/2 hypothyroidism (18/90, 21.1%) and pruritus (16/90, 17.8%). Five patients discontinued the study treatment because of immune-related AEs (three pneumonitis, one hepatitis, and one skin rash). No treatment-related deaths occurred during the study.

4. Discussion

In this open-label, parallel-arm, phase II study, the combination treatment of eribulin plus nivolumab was well-tolerated and demonstrated encouraging antitumour efficacy in HER2-negative MBC. The safety profile of eribulin plus nivolumab was comparable to that in previous studies without any unexpected AEs. Grade 3/4 neutropenia was observed in approximately half of the patients in our study; a similar rate was reported in the EMBRACE study (grade 3/4 neutropenia, 45%).

Considering the limitations of cross-study comparison, the confirmed ORR of 35.6% in the HR+HER2- cohort was comparable to that reported in previous trials that combined eribulin with pembrolizumab for the treatment of HR+HER2- MBC [10,12]. In a phase II trial of eribulin plus pembrolizumab, ORR of 40.9% and median PFS of 6.1 months were achieved in HR+HER2- MBC in a second- and third-line (2–3L) therapy

Table 3
Best objective response in breast cancer with nivolumab plus eribulin treatment according to PD-L1 (SP142 IHC).

	TOTAL				HR+HER2-				TNBC cohort			
	PD-L1+		PD-L1-		PD-L1+		PD-L1-		PD-L1+		PD-L1-	
CR	1	5.60%	0	0%	0	0%	0	0%	1	7.70%	0	0%
PR	5	27.80%	31	43.70%	3	50%	21	53.80%	3	23.10%	9	29.00%
SD	8	44.40%	20	28.20%	2	33.30%	11	28.20%	6	46.20%	9	29.00%
PD	4	22.20%	20	28.20%	1	16.70%	7	17.90%	3	23.10%	13	41.90%

The best objective response was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1. Abbreviation: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

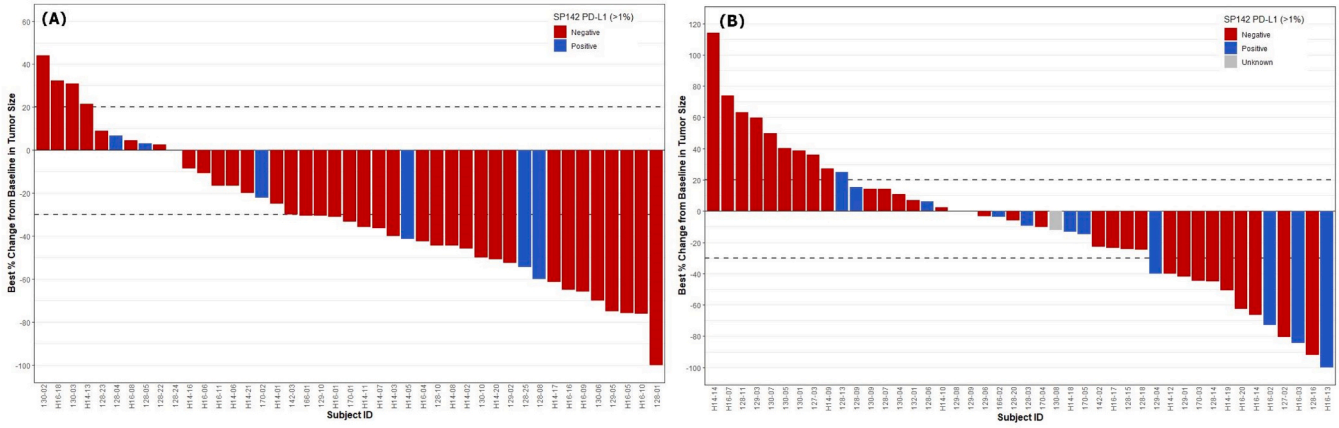

Fig. 3. Maximum percentage change from baseline to postbaseline nadir in total sum of target lesion diameters in HR+HER2- cohort (A) and TNBC cohort (B). This analysis included evaluable patients with both baseline and at least 1 postbaseline target lesion assessment. (Blue: PD-L1 positive by SP142 test, Red: PD-L1 negative by SP142 test, Grey: not available).

Table 4
Treatment-related adverse events that were observed in >10 patients.

AE name	Any grade, n	(%)	Grade 3–4, n	(%)
Neutrophil count decreased	52	57.8	50	55.6
Fatigue	33	36.7	2	2.2
Fever	32	35.6	0	0.0
Anorexia	24	26.7	0	0.0
Myalgia	24	26.7	0	0.0
AST increased	23	25.6	4	4.4
Mucositis	21	23.3	1	1.1
ALT increased	19	21.1	1	1.1
Hypothyroidism	18	20.0	0	0.0
Pruritus	16	17.8	1	1.1
Pain	15	16.7	1	1.1
Headache	14	15.6	0	0.0
Nausea	13	14.4	0	0.0
Alopecia	12	13.3	0	0.0
Back pain	12	13.3	0	0.0
Cough	12	13.3	0	0.0
Peripheral sensory neuropathy	12	13.3	0	0.0

setting [12]. The other randomised phase II trial failed to demonstrate clinical improvement in either ORR or PFS, compared with eribulin alone in HR+HER2- MBC [10]. The study reported a lower ORR (27%) in the combination arm than in the eribulin-alone arm (34%). Although anti-tumour efficacy in most patients was driven by eribulin, the presence of some patients who had prolonged responses seen in our study (22.7% patients lasting more than 12 months, 3 patients lasting 24 months) might support the role of immune checkpoint inhibitors in the treatment of HR+HER2- breast cancer. Therefore, further clinical investigations are required to determine the activity of ICIs against this type of tumour.

In the TNBC cohort, the 6-month PFS rate was 25.1%, and the primary endpoint point was not reached. The ORR of 28.9% (confirmed ORR of 26.7%) in the TNBC cohort is similar to that reported in the study of eribulin plus pembrolizumab (25.8% for first-line, 21.8% for 2–3L) [11]. The study reported a median PFS of 4.1 months and poor predictive power of PD-L1 score in a 2–3L therapy setting, supporting our study results. Considering that PD-1 monotherapy did not show clinical improvement compared with cytotoxic treatment, strategies to combine various drugs and select optimal patients via PD-L1 screening are currently being investigated in metastatic TNBC [19]. Although early-stage TNBC can be treated with anti-PD-1 antibody regardless of PD-L1 status, 60–70% of patients with metastatic TNBC and low (combined positive score <10) or negative PD-L1 scores are not considered candidates for pembrolizumab. Eribulin, a standard treatment for TNBC, has a promising immune modulation effect toward a favourable tumour microenvironment via the reversal of epithelial–mesenchymal transition and normalisation of tumour vasculature [8]. It also downregulates the immunosuppressive cytokine transforming growth factor-β in responders of MBC [9]. These immune modulatory effects may partly contribute to the conversion of immunologically “cold” tumours into “hot” tumours, enhancing the antitumour efficacy of nivolumab in patients with TNBC without PD-L1 expression. As the currently available data, including those from the present study, are not sufficiently large to draw conclusions regarding eribulin plus nivolumab or pembrolizumab treatment, further clinical investigations with a larger number of patients with TNBC should be conducted.

Neither high TIL count nor PD-L1 expression was a significant predictor of eribulin plus nivolumab in either cohort in this study. Although a trend toward a higher number of progressive diseases was observed in patients with TNBC without PD-L1 expression, the difference was not significant. This result is in line with those from previous studies and recent FDA approvals; metastatic TNBC with PD-L1 expression may benefit from immunotherapy plus chemotherapy in first-line therapy settings. In HR+HER2- MBC, the predictive value of PD-L1 expression remains uncertain. PD-L1 expression is not associated with clinical

outcomes, such as ORR and PFS, in a phase II trial [20]. Further translational research to identify robust biomarkers that precisely predict immune response in HR+HER2 MBC is needed.

Our study has several limitations. First, our results must be interpreted with caution because of the small number of subjects and heterogeneity of prior treatment. One-third of included patients were not exposed to anthracycline, potentially affecting the response rate of study treatment. Second, OS data were immature owing to the relatively short follow-up duration. However, the 6-month PFS rate is suggested as a surrogate endpoint in immune checkpoint inhibitor trials [21]. Third, since our study was analysed with one-sided alpha, we may have missed potential detrimental effects derived from the addition of nivolumab. Finally, we did not include HER2-positive MBC in our study. Therefore, these results are not representative of the entire MBC population.

In conclusion, in this parallel phase II clinical trial, the addition of nivolumab to eribulin showed promising efficacy and tolerable safety profiles in previously treated HER2- MBC. Considering the taxane exposure rate of our study population, eribulin can be a valuable addition to immune checkpoint inhibitors used in treating HER2- MBC with prior taxane treatment. Further "omics" analyses based on sequencing data and immunobiology testing are ongoing and may reveal who would derive optimal benefits from eribulin and nivolumab combination therapy.

Funding

Ono Pharmaceutical Co. provided the study drug (nivolumab) and provided funding to Seoul National University Bundang Hospital for the study conduct. Eisai Korea inc. provided the study drug (eribulin) for study conduct.

This work was supported by the National R&D Program for Cancer Control through the National Cancer Center (NCC) funded by the Ministry of Health & Welfare, Republic of Korea [HA22C0012].

CRediT authorship contribution statement

SHK: Conceptualization, Writing protocol, Writing – original draft. **KJS:** Methodology, Project administration. **SI** and **JHK:** Conceptualization, Supervision, Funding acquisition. All authors were involved in the planning, conducting (investigation), and data acquisition of the work described in this article. JHK is responsible for the overall content as guarantor. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ono Pharmaceutical Co. provided the study drug (nivolumab) and provided funding to Seoul National University Bundang Hospital for study conduct. Eisai Korea inc. provided the study drug (eribulin) for study conduct. The companies were not involved in trial data analysis and manuscript writing.

SHK has a consulting or advisory role with Ono Pharmaceutical. SI reports receiving research grant from AstraZeneca, Daewoong Pharm, Eisai, Roche, and Pfizer and personal consultation fees from AstraZeneca, Eisai, GSK, Hanmi, Lilly, MSD, Idience, Novartis, Roche, and Pfizer. The research group received drugs from Eisai and Boryung. KL reports receiving honorarium from AstraZeneca, Daiichi-Sankyo, Eli Lilly, Novartis, Pfizer, Roche. JS reports receiving research funding from MSD, Roche, Novartis, Lilly, Pfizer, Daiichi Sankyo, AstraZeneca, GlaxoSmithKline, Sanofi, and Boehringer Ingelheim. KHP has a consulting or advisory role with Eisai, Eli Lilly, Novartis, Daiichi Sankyo/Astra Zeneca, Pfizer, IMBDx, Celltrion and Roche and has received research funding from Astra Zeneca. JHK has a consulting or advisory role with Bixink, Eisai, Yuhan, Novartis, Daiichi Sankyo/Astra Zeneca, Pfizer, and Roche and has received research funding from Ono Pharmaceutical and Roche. All remaining authors have declared no conflicts of interest.

Data availability

Data are available from the corresponding author upon reasonable request.

Acknowledgements

This manuscript was presented in part at the Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, IL, June 2–7, 2022, as a poster.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113386.

References

[1] DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, et al. Breast cancer statistics, 2019. CA Cancer J Clin 2019;69:438–51. https://doi.org/10.3322/caac.21583.

[2] Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020;31:1623–49. https://doi.org/10.1016/j.annonc.2020.09.010.

[3] Emens LA. Breast cancer immunotherapy: facts and Hopes. Clin Cancer Res 2018;24:511–20. https://doi.org/10.1158/1078-0432.CCR-16-3001.

[4] Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im SA, Yusof MM, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020;396:1817–28. https://doi.org/10.1016/S0140-6736(20)32531-9.

[5] Netanely D, Avraham A, Ben-Baruch A, Evron E, Shamir R. Expression and methylation patterns partition luminal-A breast tumors into distinct prognostic subgroups. Breast Cancer Res 2016;18:74. https://doi.org/10.1186/s13058-016-0724-2.

[6] Zhu B, Tse LA, Wang D, Koka H, Zhang T, Abubakar M, et al. Immune gene expression profiling reveals heterogeneity in luminal breast tumors. Breast Cancer Res 2019;21:147. https://doi.org/10.1186/s13058-019-1218-9.

[7] Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet 2011;377:914–23. https://doi.org/10.1016/S0140-6736(11)60070-6.

[8] Kashiwagi S, Asano Y, Goto W, Takada K, Takahashi K, Hatano T, et al. Mesenchymal–epithelial transition and tumor vascular remodeling in eribulin chemotherapy for breast cancer. Anticancer Res 2018;38:401–10. https://doi.org/10.21873/anticanres.12236.

[9] Kashiwagi S, Asano Y, Goto W, Takada K, Morisaki T, Kouhashi R, et al. Validation of systemic and local tumour immune response to eribulin chemotherapy in the treatment of breast cancer. Anticancer Res 2020;40:3345–54. https://doi.org/10.21873/anticanres.14317.

[10] Tolaney SM, Barroso-Sousa R, Keenan T, Li T, Trippa L, Vaz-Luis I, et al. Effect of eribulin with or without pembrolizumab on progression-free survival for patients with hormone receptor–positive, ERBB2-negative metastatic breast cancer: a randomized clinical trial. JAMA Oncol 2020;6:1598–605. https://doi.org/10.1001/jamaoncol.2020.3524.

[11] Tolaney SM, Kalinsky K, Kaklamani VG, D'Adamo DR, Aktan G, Tsai ML, et al. Eribulin plus pembrolizumab in patients with metastatic triple-negative breast cancer (ENHANCE 1): a phase Ib/II StudyPhase. Clin Cancer Res 2021;27:3061–8. https://doi.org/10.1158/1078-0432.CCR-20-4726.

[12] Pérez-García JM, Llombart-Cussac A, Gion M, Curigliano G, López-Miranda E, Alonso JL, et al. Pembrolizumab plus eribulin in hormone-receptor–positive, HER2-negative, locally recurrent or metastatic breast cancer (KELLY): an open-label, multicentre, single-arm, phase II trial. Eur J Cancer 2021;148:382–94. https://doi.org/10.1016/j.ejca.2021.02.028.

[13] Wen WX, Soo JS-S, Kwan PY, Hong E, Khang TF, Mariapun S, et al. Germline APOBEC3B deletion is associated with breast cancer risk in an Asian multi-ethnic cohort and with immune cell presentation. Breast Cancer Res 2016;18:56. https://doi.org/10.1186/s13058-016-0717-1.

[14] Kidd JM, Newman TL, Tuzun E, Kaul R, Eichler EE. Population stratification of a common APOBEC gene deletion polymorphism. PLOS Genet 2007;3:e63. https://doi.org/10.1371/journal.pgen.0030063.

[15] Kim SH, Ahn S, Suh KJ, Kim YJ, Park SY, Kang E, et al. Identifying germline APOBEC3B deletion and immune phenotype in Korean patients with operable breast cancer. Breast Cancer Res Treat 2020;183:697–704. https://doi.org/10.1007/s10549-020-05811-2.

[16] Wolff AC, Hammond MEH, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast

cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Arch Pathol Lab Med 2014;138:241–56. https://doi.org/10.5858/arpa.2013-0953-SA.

[17] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47. https://doi.org/10.1016/j.ejca.2008.10.026.

[18] Salgado R, Denkert C, Demaria S, Sirtaine N, Klauschen F, Pruneri G, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann Oncol 2015;26:259–71. https://doi.org/10.1093/annonc/mdu450.

[19] Winer EP, Lipatov O, Im SA, Goncalves A, Muñoz-Couselo E, Lee KS, et al. Pembrolizumab versus investigator-choice chemotherapy for metastatic triple-negative breast cancer (KEYNOTE-119): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:499–511. https://doi.org/10.1016/S1470-2045(20)30754-3.

[20] Keenan TE, Guerriero JL, Barroso-Sousa R, Li T, O'Meara T, Giobbie-Hurder A, et al. Molecular correlates of response to eribulin and pembrolizumab in hormone receptor-positive metastatic breast cancer. Nat Commun 2021;12:5563. https://doi.org/10.1038/s41467-021-25769-z.

[21] Kok PS, Cho D, Yoon WH, Ritchie G, Marschner I, Lord S, et al. Validation of progression-free survival rate at 6 months and objective response for estimating overall survival in immune checkpoint inhibitor trials: a systematic review and meta-analysis. JAMA Netw Open 2020;3:e2011809. https://doi.org/10.1001/jamanetworkopen.2020.11809.