

# Efficacy and Safety of Ixabepilone in Metastatic Breast Cancer After Multiple Treatments: Analysis Based on Real-World Data

<sup>1b</sup> Goncağul AKDAĞ<sup>a</sup>, <sup>1b</sup> Özkan ALAN<sup>b</sup>, <sup>1b</sup> Akif DOĞAN<sup>a</sup>, <sup>1b</sup> Sedat YILDIRIM<sup>a</sup>, <sup>1b</sup> Oğuzcan KINIKOĞLU<sup>a</sup>,  
<sup>1b</sup> Nargiz MAJIDOVA<sup>c</sup>, <sup>1b</sup> İbrahim Vedat BAYOĞLU<sup>c</sup>, <sup>1b</sup> Caner KAPAR<sup>d</sup>, <sup>1b</sup> Eda ERÇİN<sup>e</sup>,  
<sup>1b</sup> Zeynep ALACA TOPÇU<sup>f</sup>, <sup>1b</sup> Murad GULIYEV<sup>g</sup>, <sup>1b</sup> Deniz IŞIK<sup>a</sup>, <sup>1b</sup> Özlem Nuray SEVER<sup>a</sup>,  
<sup>1b</sup> Hatice ODABAŞ<sup>a</sup>, <sup>1b</sup> Mahmut Emre YILDIRIM<sup>a</sup>, <sup>1b</sup> Nedim TURAN<sup>a</sup>

<sup>a</sup>University of Health Science Kartal Dr. Lütfi Kırdar City Hospital, Division of Medical Oncology, İstanbul, Türkiye

<sup>b</sup>Koç University Faculty of Medicine, Division of Medical Oncology, İstanbul, Türkiye

<sup>c</sup>Marmara University Pendik Training and Research Hospital, Division of Medical Oncology, İstanbul, Türkiye

<sup>d</sup>Bakırköy Sadi Konuk Training and Research Hospital, Clinic of Medical Oncology, İstanbul, Türkiye

<sup>e</sup>Ümraniye Training and Research Hospital, Clinic of Medical Oncology, İstanbul, Türkiye

<sup>f</sup>Medeniyet University Faculty of Medicine, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Division of Medical Oncology, İstanbul, Türkiye

<sup>g</sup>İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Division of Medical Oncology, İstanbul, Türkiye

**ABSTRACT Objective:** Patients with metastatic breast cancer (MBC) with a history of treatment with anthracyclines and taxanes exhibit improvement with ixabepilone, a semi-synthetic analog of epothilone B. The present study, therefore, aimed to evaluate the safety and effectiveness of ixabepilone in patients with MBC who have previously received multiple lines of treatment **Material and Methods:** Patients with MBC who were treated with ixabepilone were included in the present study, which was designed as a retrospective multicenter analysis. Radiological responses were evaluated based on the RECIST criteria, and overall survival (OS) and progression-free survival (PFS) were calculated. The Common Terminology Criteria for Adverse Events version 5.0 was adopted to evaluate adverse events. **Results:** The analysis of 34 patients revealed a median OS of 10.0 months, a median PFS of 4.2 months, and an objective response rate (ORR) of 28%. The patients treated with ixabepilone prior to the fifth line of treatment exhibited a significantly better response (ORR 50%). In the subgroup analysis based on receptor status, ER+ and human epidermal growth factor receptor-2 (HER2+) patients presented the longest median PFS of 6.2 months. **Conclusion:** Ixabepilone demonstrated effectiveness in patients with MBC who had received multiple lines of treatments previously. The results suggest that early treatment regimens or targeted therapy for HER2+ patients could lead to better therapeutic outcomes when ixabepilone is administered. Ixabepilone is, therefore, a viable option for MBC patients who have received extensive treatment previously while maintaining a good performance status.

**Keywords:** Ixabepilone; metastatic breast cancer; overall survival; progression-free survival

Breast cancer (BC) and lung cancer are the most frequently reported cancers in women and men, respectively, in terms of both numbers of cases and deaths.<sup>1</sup> It is estimated that 6%-10% of BC cases present as *de novo* metastatic at the time of diagnosis,

and between 25% and 30% of BC cases experience metastatic recurrence.<sup>2</sup> While no definitive cure for metastatic breast cancer (MBC) is available to date, the advent of novel systemic therapies has enhanced survival outcomes in patients with this condition.

#### TO CITE THIS ARTICLE:

Akdağ G, Alan Ö, Doğan A, Yıldırım S, Kınıkoğlu O, Majidova N, Bayoğlu İV, Lapaç C, Erçin E, Alaca Topçu Z, Guliyev M, Işık D, Sever ÖN, Odabaş H, Yıldırım ME, Turan N. Efficacy and Safety of Ixabepilone in Metastatic Breast Cancer After Multiple Treatments: Analysis Based on Real-World Data. Journal of Oncological Sciences. 2024;10(2):89-96.

**Correspondence:** Goncağul AKDAĞ

University of Health Science Kartal Dr. Lütfi Kırdar City Hospital, Division of Medical Oncology, İstanbul, Türkiye

**E-mail:** akdaggoncagul@gmail.com

Peer review under responsibility of Journal of Oncological Sciences.

**Received:** 14 Feb 2024

**Received in revised form:** 07 May 2024

**Accepted:** 23 May 2024

**Available online:** 04 Jun 2024

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In MBC, tumors tend to develop resistance, leading to disease progression and necessitating frequent changes in the therapeutic regimen. Chemotherapy treatments that are administered repeatedly to MBC patients, particularly those involving the use of taxane-based regimens as adjuvants (e.g., docetaxel and paclitaxel), place great pressure on tumor cells to evolve and develop both genetic and non-genetic characteristics that would assist these cells in resisting the effects of chemotherapy.<sup>3</sup> The identification of the best order of anticancer drugs to be used when encountering such treatment resistance is a challenge encountered during the management of MBC patients.

Epothilones are a novel class of anticancer drugs that act by interfering with the function of microtubules.<sup>4</sup> Specifically, these 16-membered macrolides bind to tubulin, leading to apoptosis. Epothilones are potent inducers of microtubule stabilization and have demonstrated efficacy against taxane-sensitive and taxane-resistant tumors both *in vitro* and *in vivo*.<sup>5,6</sup> Ixabepilone is a semi-synthetic analog of epothilone B that has been licensed for the treatment of resistant BC. It has demonstrated success in both monotherapy and combination therapy along with capecitabine for the treatment of metastatic breast tumors that have been previously treated using anthracyclines and taxanes.<sup>7</sup> In two multinational, randomized Phase III trials, patients with metastatic or locally advanced BC who had been previously treated with or were resistant to anthracyclines and taxanes were evaluated for the effects of using capecitabine alone and in combination with ixabepilone. It was observed that compared to the use of capecitabine alone, the combination of ixabepilone and capecitabine resulted in a doubled objective response rate (ORR) and markedly improved progression-free survival (PFS) in both trials.<sup>8,9</sup>

In the above context, the present study aimed to evaluate the safety and effectiveness of ixabepilone in patients with MBC who have previously received multiple lines of treatment and, in addition, explore the parameters determining the treatment response. The objective was to provide a reference for therapeutic agent selection in nations where reimbursement conditions are suboptimal and, therefore, continued reliance on intensive chemotherapy exists.

## MATERIAL AND METHODS

### PATIENTS

MBC patients treated with ixabepilone in Türkiye between the years 2018 and 2023 were included in the present study, which was designed as a retrospective, multicenter investigation. The eligible participants had received a histological diagnosis of MBC, undergone treatment with ixabepilone, and possessed comprehensive medical records. All participants were aged above 18 years. The patients with a secondary malignancy or without a complete medical record were excluded from the study. Patient demographic data, including age, performance status, pathological subtype, receptor status, menopausal status, and chemotherapy history, were extracted from medical charts.

### RESPONSE CRITERIA

Radiological responses were assessed based on the RECIST Criteria for solid tumors.<sup>10</sup> The duration between the first administered dose of ixabepilone and the date of radiological progression, death, or the last documented visit was defined as PFS. The duration between the first administered dose of ixabepilone to the date of death due to any cause or the last visit was referred to as the overall survival (OS). Adverse events were sourced from patient records, graded, and categorized according to the Common Terminology Criteria for Adverse Events version 5.0.<sup>11</sup> The ORR and disease control rate (DCR) were calculated as follows:

ORR: Complete response (CR)+partial response (PR)

DCR: CR+PR+stable disease

### Chemotherapy

Patients received ixabepilone intravenously, for three hours at a time, beginning with a dose of 40 mg/m<sup>2</sup>, every three weeks.

### STATISTICAL ANALYSIS

IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis of all data. Descriptive statistics were

used for the assessment of the frequency distributions of collected data. Categorical data were presented as frequencies and percentages. Continuous variables were presented as median values with ranges (minimum-maximum). The overall and PFS values were calculated using the Kaplan-Meier approach. A two-sided p-value of less than 0.05 indicated statistical significance, and a 95% confidence interval (CI) was adopted.

## ETHICAL APPROVAL

The study followed the Helsinki Declaration of 1964, its later amendments, and comparable ethical standards. In addition, the institutional and national research committees' ethical standards were followed when performing all techniques involving human subjects. The study was also approved by the Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital in İstanbul, Türkiye (date: August 28, 2023, no: 2023/514/256/15). Patient data, were obtained retrospectively from patient records after obtaining written informed consent from the patients or their relatives.

## RESULTS

The data of 34 female patients who had received ixabepilone (monotherapy) treatment for MBC between November 2019 and April 2023 were evaluated. The age range of these patients at the time of diagnosis was 29 to 85 years, with a median age of 50.5 years. The follow-up period ranged from 1 to 25.9 months, with a median of 6.3 months. Thirteen of these patients presented initially with a diagnosis of Stage 4 illness. Half of the participants (n=17) were postmenopausal. Most of the patients (56%) had MBC that was both human epidermal growth factor receptor-2 (HER2)-negative and hormone receptor-positive. Notably, a significant proportion of the patients had undergone extensive treatments previously; 65% of the patients had been administered a minimum of five lines of chemotherapy in the metastatic context. Ixabepilone was introduced between the second and the twelfth line of treatment, with the fifth line of treatment being the median. Detailed demographic and clinicopathologic data are presented in [Table 1](#).

**TABLE 1:** Demographic and clinicopathological findings.

Findings		n=34 (%)
Age (years)		50.5 (minimum 29-maximum 85)
ECOG status	ECOG PS 0	19 (56)
	ECOG PS 1	13 (38)
	ECOG PS 2	2 (6)
Menopause status	Premenopausal	17 (50)
	Postmenopausal	17 (50)
Body mass index (median)		27.3 (minimum 18.4-37.4)
Receptor status	ER+, HER-2 negative	19 (56)
	ER+, HER-2 positive	7 (21)
	ER-, HER-2 positive	3 (9)
	ER-, HER-2 negative	5 (14)
Ixabepilone treatment line	Median	5 (minimum 2-maximum 12)
	<5. line	12 (35)
	≥5. line	22 (65)
Ixabepilone treatment cycle (median)		4 (minimum 1-maximum 19)
Progression (n=32)	Present	26 (81)
	Absent	6 (19)
Status	Alive	18 (53)
	Exitus	16 (47)

ECOG: Eastern Cooperative Oncology Group; ER: Estrogen receptor; HER-2: Human epidermal growth factor receptor-2.

Response evaluations were conducted for 32 patients, and during the study period, disease progression was observed in 26 patients, accounting for 81% of this subset of included patients. Considering the patients' best radiological responses to treatment, the DCR was 47% and the ORR was 28%. When ORR and DCR were determined based on the treatment sequence, the ORR was 50% versus 15% between the two groups (<5. line versus ≥5. line, respectively), with the difference being statistically significant. Specifically, the patients who had received treatment prior to the fifth line of treatment presented a better response (p=0.03). The DCR was 67% versus 35% between the groups (<5. line versus ≥5. line, respectively), although this numerical difference was not statistically significant (p=0.08). Detailed data are listed in [Table 2](#).

In the entire study period, 16 patients, representing 47% of the cohort, succumbed to their illness. The median OS was ten months (95% CI: 8.1-11.9) ([Figure 1](#)). The median PFS was 4.2 months (95% CI: 3.9-4.4) ([Figure 2](#)). Patients who had received treatment prior to the fifth line of treatment had a median OS of 12.5 months, while those treated during or

**TABLE 2:** Radiological response of ixabepilone.

n=32*	All patients	<5. line (n=12)	≥5. line (n=20)
Complete response	1 (3%)	0	1 (5%)
Partial response	8 (25%)	6 (50%)	2 (10%)
Stable disease	6 (19%)	2 (17%)	4 (20%)
Progressive disease	17 (53%)	4 (33%)	13 (65%)
Objective response rate	28%	50%	15%
Disease control rate	47%	67%	35%

\*Response evaluations have not been performed in two patients.

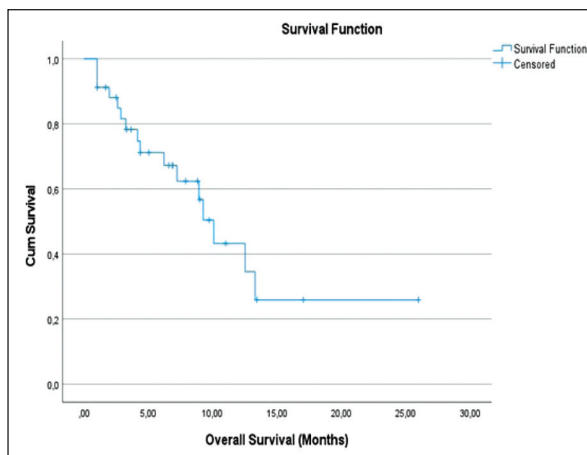


FIGURE 1: Kaplan-Meier survival curves for overall survival of patients.

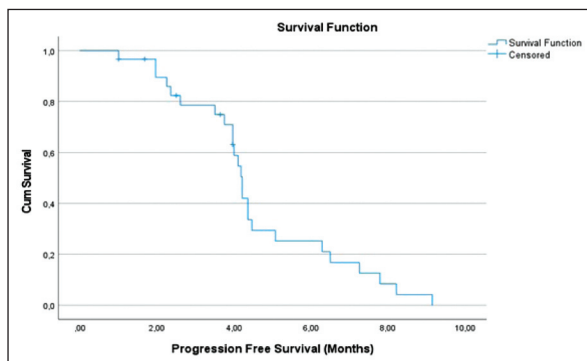


FIGURE 2: Kaplan-Meier survival curves for progression-free survival of patients.

after the fifth line of treatment had a median OS of 9.2 months. A numerical difference in OS was noted between these groups, although this difference was not statistically significant ( $p=0.61$ ) (Figure 3). The median PFS was similar for patients treated prior to and after the fifth line of treatment, with values of 4.2 months and 4.1 months, respectively (Figure 4, Table 3).

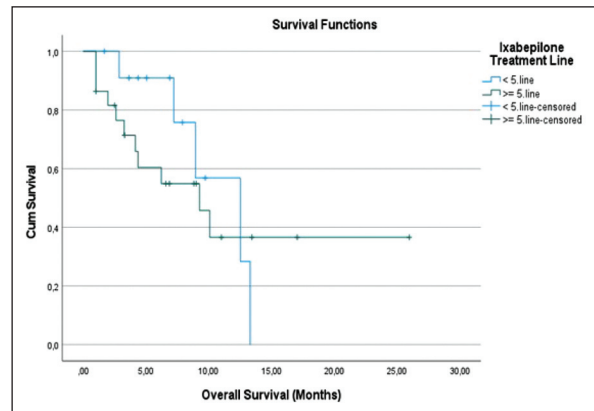


FIGURE 3: Kaplan-Meier survival curves for overall survival by ixabepilone treatment line of patients.

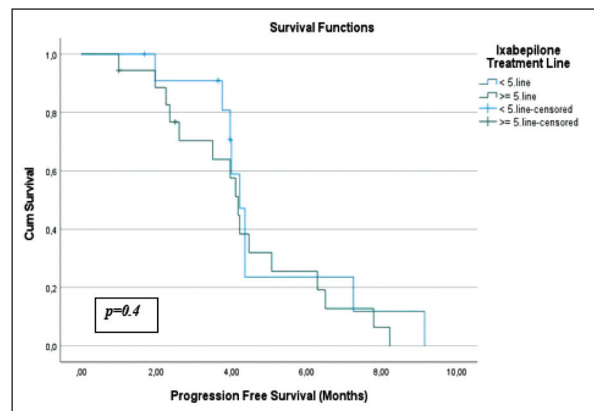


FIGURE 4: Kaplan-Meier survival curves for progression-free survival by ixabepilone treatment line of patients.

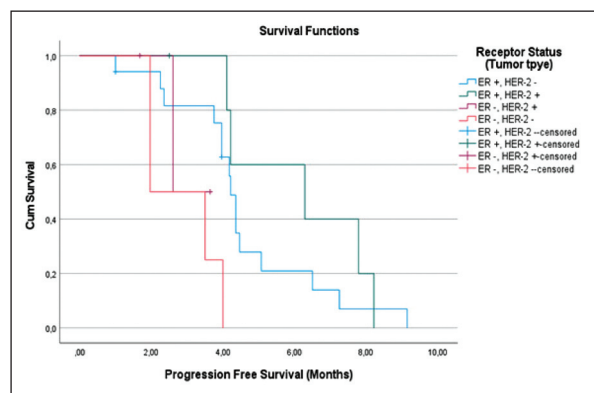


FIGURE 5: Kaplan-Meier survival curves for progression-free survival by receptor status of patients.

ER: Estrogen receptor; HER-2: Human epidermal growth factor receptor-2.

The subgroup analysis based on receptor status revealed that ER<sup>+</sup> and HER2<sup>+</sup> patients presented the longest median PFS of 6.2 months, followed by ER<sup>+</sup>

**TABLE 3: Survival outcomes.**

		Progression free survival (months) (median)	Overall survival (months) (median)
All patients		4.2 (95% CI: 3.9-4.4)	10.0 (95% CI: 8.1-11.9)
Treatment line	<5. line	4.2 (95% CI: 3.8-4.5)	12.5 (95% CI: 6.9-18.0)
	≥5. line	4.1 (95% CI: 3.7-4.5)	9.2 (95% CI: 3.3-15.1)
	p value	0.42	0.61
Receptor status	ER+, HER-2 negative	4.2 (95% CI: 4.0-4.4)	12.5 (95% CI: 6.0-18.9)
	ER+, HER-2 positive	6.2 (95% CI: 1.8-10.7)	10.0 (95% CI: 8.3-11.7)
	ER-, HER-2 positive	2.6 (95% CI: Not calculated)	2.6 (95% CI: Not calculated)
	ER-, HER-2 negative	1.9 (95% CI: Not calculated)	4.1 (95% CI: 0.0-8.8)
	p value	<b>0.008</b>	0.20

\*ER: Estrogen receptor; HER-2: Human epidermal growth factor receptor-2; CI: Confidence interval.

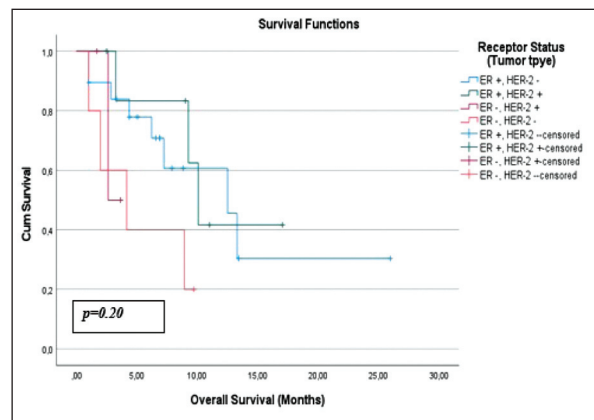
and HER2 patients with a median PFS of 4.2 months. Notably, the patients with triple-negative breast cancer (TNBC) exhibited a significantly shorter median PFS ( $p=0.008$ ) (Figure 5). In the log-rank test for PFS, statistical difference was noted relative to the TNBC group ( $ER^+ HER2^+$  vs. TNBC,  $p=0.002$  and  $ER^+HER2^-$  vs. TNBC,  $p=0.01$ ). However, no statistically significant difference was observed in the OS based on receptor status ( $p=0.20$ ) (Figure 6).

**TOXICITIES**

No Grade 4 adverse events were revealed in the patients’ hematological toxicity profiles. However, Grade 3 adverse events, such as neutropenia, anemia, leukopenia, or thrombocytopenia, were noted for each patient. The most frequently observed side effect was anemia, which presented as a Grade 1 adverse event in 54% of the patients. Further details are provided in Table 4.

**DISCUSSION**

The present study underscores the effectiveness of ixabepilone in genuine clinical settings. Numerous novel agents are under investigation for their effec-



**FIGURE 6:** Kaplan-Meier survival curves for overall survival by receptor status of patients.

tiveness in treating BC in the current medical landscape. However, despite recent improvements in the treatment of MBC, several patients exhibit drug resistance during the course of their care. Ixabepilone has exhibited activity in patients resistant to taxanes.<sup>12</sup> Ixabepilone has been authorized by the Food and Drug Administration for use in the treatment of patients with MBC who exhibit progression following anthracycline and taxane therapy. However, in Türkiye, the prescription of ixabepilone currently ne-

**TABLE 4: Patient adverse events related to ixabepilone.**

	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia (n=24)	9 (37%)	2 (8%)	1 (4%)	0
Neutropenia (n=23)	7 (30%)	2 (9%)	1 (5%)	0
Anemia (n=24)	13 (54%)	5 (21%)	1 (4%)	0
Thrombocytopenia (n=22)	9 (41%)	1 (5%)	1 (5%)	0

Adverse events were categorized, and graded as per the Common Terminology Criteria for Adverse Events, version 5.0.

cessitates progression after treatments with anthracycline, taxane, and gemcitabine. Consequently, all the patients included in the study were those who had been treated with anthracycline, taxane, and gemcitabine prior to receiving ixabepilone. A previous study reported that administering ixabepilone as a monotherapy led to 19% ORR, a mean PFS of 3.1 months, and a mean OS of 8.6 months.<sup>13</sup> Another previous study conducted in Türkiye compared the weekly and three-weekly administration of ixabepilone and reported the mOS of 12 months, mPFS of 5 months, and an ORR of 32% for patients who were administered the drug every three weeks.<sup>14</sup> The cohort in the present study comprised patients with MBC who had received extensive prior treatment. The patients exhibited an ORR of 28%, a median PFS of 4.2 months, and a median OS of 10.0 months. The response rates and median PFS values were consistent with those reported in the literature, and the median OS was superior to the previously reported values. The summary of a comparative analysis between the previously reported studies involving patients receiving ixabepilone monotherapy and the present study is provided in Table 5.

In the current therapeutic landscape for BC, in which treatment is primarily based on receptor status, ixabepilone has been approved irrespective of the hormone receptor status. In a Phase II trial, patients with HER2-positive MBC who received both trastuzumab and ixabepilone exhibited improved efficacy.<sup>15</sup> Another Phase II trial evaluated patient response based on whether the patients had received a first-line or a non-first-line treatment. In this trial, the overall response rate was 44%, and Cohort 1 (first-line) exhibited a statistically greater response rate (73%) compared to Cohort 2 (non-first-line), which exhibited a response rate of 25%. The fact that the response rate of Cohort 1 was higher could be attributed to the lack of prior trastuzumab or chemotherapy for MBC in Cohort 1.<sup>16</sup> In the present study, a statistically significant difference ( $p=0.03$ ) was noted in the ORR rates between the two groups of patients treated with ixabepilone prior to and after the fifth line of treatment, with the corresponding values of 50% and 15%. The lower response rate after the fifth line of treatment was probably due to the development of chemotherapy resistance. In addition, among the HER2-positive patients included in the present study, those with an ER<sup>+</sup> status presented the longest mPFS, followed by the ER<sup>+</sup> HER2<sup>-</sup> patients. TNBC patients presented the shortest PFS. The differences between the groups were statistically signifi-

**TABLE 5:** Summary of clinical trials with ixabepilone in breast cancer and key efficacy measurements from our study.

Design	Patients, n	Population	Treatment	Efficacy	Study
Phase II	65	Patients with MBC previously treated with adjuvant anthracycline	Ixabepilone 40 mg/m <sup>2</sup> IV Q3W	ORR: 41.4% (95% CI, 29.4-54.4%); mTTP: 4.8 mo; mOS: 22.0 mo	Roche et al. <sup>20</sup>
Phase II	126	Patients with MBC who progressed during treatment with an anthracycline, taxane, and capecitabine	Ixabepilone 40 mg/m <sup>2</sup> IV Q3W	ORR (IRF): 11.5% (95% CI, 6.3-18.9%), ORR (INV): 18.3%; mPFS: 3.1 mo; mOS: 8.6 mo; mDoR: 5.7 mo	Perez et al. <sup>13</sup>
Phase II	49	Patients with MBC who progressed during or within four mo of taxane therapy	Ixabepilone 40 mg/m <sup>2</sup> or 50 mg/m <sup>2</sup> IV Q3W	ORR (INV): 12% (95% CI, 4.7-26.5%); mDoR: 10.4 mo; mTTP: 2.2 mo; mOS: 7.9 mo	Thomas et al. <sup>7</sup>
Phase II	52	Patients with MBC resistant to taxanes and previously treated with anthracyclines	Ixabepilone 40 mg/m <sup>2</sup> IV Q3W	ORR (IRF): 11.5% (95% CI 4.2-23.4%); mDoR: 3.6 mo; mTTP: 2.8 mo; mOS: 12.4 mo	Aogi et al. <sup>22</sup>
Retrospective	36	Patients with MBC who progressed during treatment with an anthracycline, taxane, and gemcitabine	Ixabepilone 40 mg/m <sup>2</sup> IV Q3W	ORR (INV): 28%; mPFS: 4.2 mo; mOS: 10.0 mo	Our study

MBC: Metastatic breast cancer; IV: Intravenous; Q3W: Every three weeks; ORR: Objective response rate; CI: Confidence interval; mTTP: Median time to progression; mo: Month; mOS: Median overall survival; IRF: Independent radiology facility or committee; INV: Investigator-assessed; mPFS: Median progression-free survival; mDoR: Median duration of response.

cant. However, the difference in mOS was numerically and not statistically significant. The difference in the PFS of ER<sup>+</sup> patients could be attributed to the contribution of the anti-hormonal treatment.

Rugo et al. compared the safety and effectiveness of administering ixabepilone plus capecitabine (I+C) with those achieved using capecitabine alone (C) in TNBC patients with few treatment options and poor prognosis.<sup>17</sup> Among the 443 TNBC patients evaluated in the study, 213 were treated with the I+C combination therapy and 230 were treated with C alone therapy. The PFS in the I+C group was considerably longer than that in the C alone group (hazard ratio, 0.64; 95% CI, 0.52-0.78; p<0.0001) at 4.2 months versus 1.7 months, respectively. Consistent with the literature, the present study revealed that TNBC patients presented the worst PFS with a median of 1.9 months. Since capecitabine had been used previously to treat these patients, ixabepilone was used as monotherapy.

Toxicity has to be evaluated essentially in BC patients who have received extensive treatment. Various meta-analyses have demonstrated that sequential single-agent chemotherapy exhibits greater effectiveness and lower toxicity compared to combination chemotherapy MBC patients. Since no cure is currently available for MBC, any therapy for MBC aims to just increase survival and improve the quality of life of patients.<sup>18-20</sup> Therefore, the primary objective is to use the least toxic and most effective treatment plan with equally effective agents. In the present study, implementing the ixabepilone regimen for patients with MBC who have received extensive treatment previously did not result in Grade 4 side effects, which indicated the tolerability and low toxicity of this drug.

As with all research, the present study also has certain limitations, such as the retrospective nature of the study, the small-sized cohort, and the heterogeneous design. In addition, the types of chemotherapy

and hormonal treatments previously received varied among patients.

## CONCLUSION

The present study underscores the effectiveness of using ixabepilone for the treatment of patients with MBC who have received multiple treatments previously. The result data suggest a higher ORR in the earlier stages, indicating that administering ixabepilone in combination with the anti-HER2 therapy for HER2-positive patients or along with capecitabine for TNBC patients during the early stages could result in a more favorable therapeutic response. Ixabepilone is, therefore, a viable option to treat MBC patients who have received multiple drugs and for maintaining a good performance status.

### Source of Finance

*During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.*

### Conflict of Interest

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

### Authorship Contributions

**Idea/Concept:** Goncagül Akdağ, Özkan Alan; **Design:** Özlem Nuray Sever, Deniz Işık; **Control/Supervision:** Nedim Turan, Hatice Odabaş, Mahmut Emre Yıldırım; **Data Collection and/or Processing:** Goncagül Akdağ, Murad Guliyev, Vaner Kapar, Eda Erçin; **Analysis and/or Interpretation:** Oğuzcan Kınıkoğlu, Goncagül Akdağ; **Literature Review:** Akif Doğan, Sedat Yıldırım, İbrahim Vedat Bayoğlu; **Writing the Article:** Goncagül Akdağ; **Critical Review:** Goncagül Akdağ; **References and Fundings:** Nargiz Majidova, Zeynep Alaca Topçu; **Materials:** Goncagül Akdağ, Arif Doğan, Sedat Yıldırım.

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