European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2024.
https://doi.org/10.58600/eurjther2151

Original Research

Prognostic and Predictive Significance of HER2-low Expression in Metastatic Hormone Receptor Positive Breast Cancer Patients Receiving CDK4-6 Inhibitor Therapy

Hacı Arak [1,*], Tulay Kuş [2]

[1] Department of Medical Oncology, Gaziantep City Hospital, Gaziantep, Türkiye
[2] Department of Medical Oncology, Faculty of Medicine, Gaziantep Universit, Gaziantep, Türkiye

Received: 2024-04-18 **Accepted:** 2024-05-23 **Published Online:** 2024-05-23

Corresponding Author
Hacı Arak, MD.
Address: Department of Medical Oncology, Gaziantep City Hospital, 27310, Gaziantep, Türkiye
E-mail: harak63@hotmail.com

ABSTRACT

Objective: This study aimed to analyze the predictive and prognostic value of HER2-low expression in hormone receptor (HR) positive human epidermal growth factor receptor-2 (HER2) negative metastatic breast cancer patients receiving cyclin-dependent kinase-4/6 inhibitor (CDK4/6i) therapy.

Methods: This retrospective study included patients who received CDK4/6i plus endocrine therapy (ET). The pathological and clinical characteristics and survival times of the patients were compared and analyzed.

Results: Our study included 122 patients. There were HER2-zero 88(72%) and HER2-low 34 (28%) patients. The median progression free survival (mPFS) of all patients who received CDK4/6i+ET was 21 (95% confidence interval (CI),18.5–23.5) months, while mPFS was not reached in the HER2-zero group, and mPFS in the HER2-low group was 12 (95%CI, 6.8–17.1) months (p=0.001). The mPFS was shorter in patients with primary endocrine resistance (6 vs. 21 months, p=0.001). There was a change in the HER2-low status of 26(45%) patients with recurrence compared to the first biopsy. In the HER2-zero and HER2-low groups, 22(25%) and 24(71%) patients, respectively, progressed with CDK4/6i+ET (p=0.001). Estrogen receptor (ER) levels less than and greater than 50% resulted different mPFS (6 and 21 months, respectively) (p=0.025). Median PFS differed based on CDK4/6i+ET combination, treatment line, and best treatment response (all p=0.001). In multivariate analysis, HER2 status(p=0.018), chemotherapy status(p=0.006), best response status with CDK4/6i (p=0.001) for PFS, and best response status with CDK4/6i therapy (p=0.007) for OS were significant.

Conclusions: In patients with HR+HER- metastatic breast cancer receiving CDK4/6i therapy, the duration of mPFS was lower in the HER2-low group than that in the HER2-zero group. HER2-low expression is a predictive biomarker of response to CDK4/6 inhibitor therapy.

Keywords: Breast cancer, Endocrine resistance, Cyclin-Dependent Kinases, Her2-low.

INTRODUCTION

Breast cancer is the most common and important cancer in women [1]. Breast cancer is divided into four groups according to HER2, HR and ki-67 proliferation index [2]. Currently, it is difficult to routinely assess gene expression profiles, and the treatment and management of patients are based on the HR and HER2 status.

HER2 expression is reported according to College of American Pathologists (CAP) guidelines [3]. HER2 expression status was further discussed after trastuzumab deruxtecan showed superior efficacy in the DESTINY-Breast-04 trial [4]. In this study, HER2 immunohistochemistry (IHC) score1+ or 2+ but in situ hybridization (ISH) negative patients are defined as "HER2-low". HER2-low expression is present in 30% of patients with triple-negative breast cancer [5], 43% of patient with non-metastatic breast cancer [6]. The HER2-low ratio was 48% in the HR-negative group and 67% in the HR-positive group [7]. There are differences in the results of previous studies regarding the prognostic significance of HER2-low status in breast cancer. HER2-low expression in early-stage breast cancer were associated with better survival [7]. In metastatic triple negative patients, HER2 expression had no prognostic significance [5].

A complex bidirectional double crosstalk mechanism between the ER and HER2 pathways has been implicated in endocrine resistance in patients with luminal-B breast cancer [8]. Therefore, it is important to investigate the predictive and prognostic value of HER2-low expression in HR+HER2-patients receiving CDK4/6i therapy. Douganiotis G et al. found that there was no significant difference in PFS in patients receiving CDK4/6i treatment; However, PFS was shorter in HER2-low patients [9].

Main Points;

- HER-2 low status is present in approximately half of all breast cancers patients.
- HER2 expression is dynamic and can change with disease progression.
- In patients with HR+HER-metastatic breast cancer receiving CDK4/6i therapy, the duration of mPFS was lower in the HER2-low group than that in the HER2-zero group.
- HER2-low expression is a predictive biomarker of response to CDK4/6 inhibitor therapy.

Carlino et al. found that HER2-low or HER2-zero expression had no significant effect on patients receiving palbociclib [10]. Bao et al. showed that PFS was significantly shorter in HER2-low patients who received CDK4/6i [11].

Different results have been obtained by studies on the predictive and prognostic value of HER2-low expression in patients with HR+ and HER2- metastatic breast cancer receiving CDK4/6i therapy. This study aimed to comprehensively evaluate the prognostic and predictive value of HER2-low expression in patients with HR positive HER2 negative metastatic breast cancer receiving CDK4/6i therapy at a single center.

MATERIALS AND METHODS

Study Design

This study was conducted at the Oncology Clinic of the Gaziantep University Faculty of Medicine (Ethics Committee of the Gaziantep University Faculty of Medicine, no.2023/48). Inclusion criteria: Patients age older 18 years, who received CDK4/6i treatment for HR positive and HER2 negative metastatic breast cancer, and for whom follow-up and treatment-related information could be obtained. Patients diagnosed with male breast cancer, second malignancy, performance score (PS)>2, and those with no information regarding treatment or response were excluded from the study.

Patients who received CDK4/6i treatment between May 2020 and February 2023 were screened retrospectively at a single center. A total of 122 patients who met the inclusion criteria were included in this study. Parameters such as age at diagnosis, sex, PS, HER2 status at diagnosis, PR, ER levels and, ki-67 proliferation index in biopsy, stage at diagnosis, endocrine treatment received, endocrine resistance status, luminal type, treatments received before or after CDK4/6i treatment, date of progression, last control, and mortality date were obtained from the patient files or electronic systems.

Variables and Outcome Definition

In Turkey, ribociclib and palbociclib were included on the list of reimbursement agencies in May 2020. However, abemaciclib is not included in the list. All patients in the study were at stage-4; some had de novo metastasis while some had metastasis with recurrence during follow-up. Some patients received cytotoxic chemotherapy during the neoadjuvant phase, whereas others received cytotoxic chemotherapy before or after CDK4/6i treatment during the metastatic phase. Before CDK4/6i was

included in the scope of reimbursement, some patients received cytotoxic chemotherapy prior to CDK4/6i treatment during the metastatic period, regardless of tumor burden.

For standardization, ER, PR, HER2, and ki-67 proliferation index values in breast biopsies at the time of diagnosis were analyzed. In patients who were diagnosed at the local stage and developed recurrence during follow-up, a repeat biopsy was usually performed for metastatic lesions. Patients who were HER2 positive in the control biopsy were excluded from the study. The discordance in HER2 status between diagnostic and repeat biopsies of patients with recurrence was also analyzed.

HER2-zero was defined as an IHC score 0, and HER2-low was defined as IHC score 1 or 2++ but with ISH-negative results. For ER, <1% was defined as negative, 1–9% as weakly positive, 10–49% as moderately positive, and 50–100% as strongly positive. PR and ki-67 were analyzed by dividing into two groups: between 1% and 20%, and ≥20%.

During CDK4/6i treatment, response evaluation is usually performed using physical examination, radiological evaluation, hemogram, biochemistry, and tumor markers. The patients' best responses to treatment were screened retrospectively. Endocrine resistance was analyzed as a factor that may affect the PFS duration of patients treated with CDK4/6 inhibitors. Endocrine resistance, and endocrine sensitivity were analyzed according to the advanced breast cancer (ABC) 4 guidelines [12].

PFS was defined as the time from initiation of CDK4/6i treatment to the date of progression, last control, or mortality. OS was defined as the time from CDK4/6i initiation to the date of the last follow-up or mortality.

Statistical Analysis

The distribution pattern and descriptive characteristics of the variables were analyzed. Since the variables are generally non-parametric, the Mann-Whitney U test was often used for comparison. The association between HER2 status and clinicopathological features was evaluated using the chi-squared or Fisher's exact test. Survival of HER2 groups was analyzed using the Kaplan-Meier method. The multivariate Cox model included HER2 expression status, ER-positive levels, combination of CDK4/6i and ET, chemotherapy status, and best response to CDK4/6i treatment. Data were recorded in the SPSS program (SPSS Inc., Chicago, IL, USA) and statistical analysis were performed. $p<0.05$ was accepted for significance.

RESULTS

Patient Characteristics

A total of 122 eligible patients were included. Among these patients, 88 (72%) were HER2-zero and 34 (28%) were HER2-low. Among the HER2-low patients, 19 (16%) had an IHC score1+ and 15 (12%) had an IHC score2++/ISH-negative. The median age of the study cohort was 48 (27–87)years. Ribociclib and palbociclib were administered to 81 (66%) and 41 (34%) patients respectively. While 72 (59%) patients had de novo metastasis, 50 (41%) had recurrence. Among patients with recurrence, 47 patients received adjuvant ET before recurrence. The HER2 groups were compared according to the patients' baseline characteristics (**Table-1**). The baseline characteristics were similar between the groups. However, a higher proportion of patients in the HER2-zero group did not receive cytotoxic chemotherapy (HER2-zero group: 39.8%; HER2-low group: 8.8%) (p=0.004).

In patients with recurrence, the conversion from HER2-zero at diagnosis to HER2-low at recurrence was 16%, the conversion from HER2-low at diagnosis to HER2-zero at recurrence was 29%, while the HER2 status remained unchanged in 55% of patients. HER2 groups were compared in terms of ER level, PR level, ki-67 proliferation index, tumor grade, luminal type, histological type, and CDK4/6i+ET combination (**Table-2**). The frequency of lung, liver, brain, lymph node, and bone metastases was similar between HER2 groups (all $p>0.05$). A significant correlation was observed between the best response to CDK4/6i treatment and endocrine resistance. While three patients with complete response were endocrine sensitive, 9 of the 11 patients who progressed had secondary endocrine resistance (p=0.028). There were no correlations between the development of endocrine resistance and the PR level, ER level, ki-67 proliferation index, or HER2 expression status (all $p>0.05$).

In the HER2-zero group, 52 (59%) patients received first-line treatment and 19 (21%) patients received third-line treatment and subsequent CDK4/6 inhibitor therapy, while in the HER2-low group, 9 (26%) patients received first-line treatment and 18 (52%) patients received third-line treatment and subsequently underwent CDK4/6 treatment (p=0.001). In the HER2-zero and HER2-low groups, 22 (25%) and 24 (71%) patients, respectively, progressed with CDK4/6i+ET (p=0.001). The HER2 expression status did not affect the best response to CDK4/6i+ET treatment (p=0.497). Prior to CDK4/6i treatment, 40 (33%) patients had a median history of 17.5(3–65) months of ET during metastasis.

Table 1. Patient and treatment characteristics of HER2-zero and HER2-low patients

Demographics		**All (n:122) n (%)**	**Her2-zero (n:88) n(%)**	**Her2-low (n:34) n(%)**	**p value**
Age(years)	(median (min-max))	48(27-87)	49 (27-85)	47.5 (29-87)	0.444
	<65	100(82)	71 (80.7)	29 (85.3)	0.552
	≥65	22(18)	17 (19.3)	5 (14.7)	
Performance score(PS)	PS-0	64(52.5)	50 (56.8)	14 (41.2)	0.323
	PS-1	53(43.4)	35(39.8)	18 (52.9)	
	PS-2	5(4.1)	3(3.4)	2 (5.9)	
Stage at diagnosis	Stage-1	2(1.6)	2(2.3)	0 (0)	0.648
	Stage-2	11(9)	7 (8)	4 (11.8)	
	Stage-3	38(31.1)	26(29.5)	12 (35.3)	
	Stage-4	71(58.2)	53(60.2)	18 (52.9)	
Adjuvant endocrine therapy	Tamoxifen	11(23.4)	8(23.5)	3 (23.1)	0.766
	Tamoxifen+GnRH	18(38.3)	14(41.2)	4 (30.8)	
	Aromatase inhibitor(Aİ)	17(36.2)	11 (32.4)	6 (46.2)	
	Aİ+ GnRH	1(2.1)	1 (2.9)	0 (0)	
Menopause status	Premenopause	47(38.5)	33 (37.5)	14 (41.2)	0.887
	Perimenopause	13(10.7)	10 (11.4)	3 (8.8)	
	Postmenopause	62(50.8)	45 (51.1)	17 (50)	
Metastasis status	Recurrence patients	50(41)	35 (39.8)	15 (44.1)	0.662
	De novo metastasis	72(59)	53 (60.2)	19 (55.9)	
Chemotherapy status	Neo/adjuvant received	46(37.7)	30 (34.1)	16 (47.1)	***0.004***
	Received in the metastatic stage	38(31.1)	23 (26.1)	15 (44.1)	
	Did not receive	38(31.1)	35 (39.8)	3 (8.8)	
Radiotherapy status	Palliative	28(23)	17 (19.3)	11 (32.4)	0.202
	Adjuvant	37(30.3)	26 (29.5)	11 (32.4)	
	Did not receive	57(46.7)	45 (51.1)	12 (35.3)	
CDK4-6i	Ribociclib	81(66.4)	61 (69.3)	20 (58.8)	0.271
	Palbociclib	41(33.6)	27 (30.7)	14 (41.2)	
Endocrine resistance	Endocrine sensitive	58(47.5)	42 (47.7)	16 (47.1)	0.874
	Primary resistance.	15(12.3)	10 (11.4)	5 (14.7)	
	Secondary resistance.	49(40.2)	36 (40.9)	13 (38.2)	

GnRH: Gonadotropin-releasing hormone, CDK4/6i:Cyclin-dependent kinase 4 and 6 inhibitors.

Table 2. Distribution of tumor characteristics and combination of CDK4/6i and endocrine therapy in both groups

Demographics		**All (n:122) n(%)**	**Her2-0 (n:88) n(%)**	**Her2-low (n:34) n(%)**	**p value**
Histological Type	Invasive ductal carcinoma	84(68.9)	58 (65.9)	26 (76.5)	0.435
	Invasive lobular carcinoma	15(12.3)	11 (12.5)	4 (11.8)	
	NOS	23(18.9)	19 (21.6)	4 (11.8)	
Percentage of ER	1-9%	2(1.6)	0 (0)	2 (5.9)	0.071
	10-49%	7(5.7)	5 (5.7)	2 (5.9)	
	50-100%	113(92.6)	83 (94.3)	30 (88.2)	
Percentage of PR	Negative	10(8.2)	6 (6.8)	4 (11.8)	0.589
	1-20 %	19(15.6)	13 (14.8)	6 (17.6)	
	≥20%	93(76.2)	69 (78.4)	24 (70.6)	
ki-67 proliferation index	Unknown	22(18)	14 (15.9)	8 (23.5)	0.506
	0-20%	36(29.5)	28 (31.8)	8 (23.5)	
	≥20%	64(52.5)	46 (52.3)	18 (52.9)	
Grade	grade-1	8(6.6)	7 (8)	1 (2.9)	0.726
	grade-2	59(48.4)	42 (47.7)	17 (50)	
	grade-3	21(17.2)	14 (15.9)	7 (20.6)	
	Unknown	34(27.9)	25 (28.4)	9 (26.5)	
Luminal type	luminal-A	33(27)	26 (29.5)	7 (20.6)	0.318
	luminal-B	89873)	62 (70.5)	27 (79.4)	
Combination of CDK4/6i and endocrine therapy	Palbociclib+letrozole	24(19.7)	16 (18.2)	8 (23.5)	0.737
	Ribociclib+letrozole	47(38.5)	35 (39.8)	12 (35.3)	
	Palbociclib+fulvestrant	17(13.9)	11 (12.5)	6 (17.6)	
	Ribociclib+fulvestrant	34(27.9)	26 (29.5)	8 (23.5)	
Concomitant endocrine therapy	Aromatase inhibitor	71(58.2)	51 (58)	20 (58.8)	0.930
	Fulvestrant	51(41.8)	37 (42)	14 (41.2)	

NOS: No Specific Type, ER: Estrogen receptor, PR: Progesterone receptor,CDK4/6i: Cyclin-dependent kinase 4 and 6 inhibitors

Survival Analysis

There were differences in the duration of mPFS in subgroups based on HER2 status, best response to CDK4/6i treatment, concomitant ET, CDK4/6i treatment line, ER level, and chemotherapy status (Table-3). In the HER2-zero group, median PFS duration was not reached. Median PFS was 12 (95% CI, 6.8–17.1) months in the HER2-low group and 21 (95% CI, 18.5–23.5) months in all patients (p=0.001) (Figure-1A). Median PFS was 20 (95% CI, 9.2–30.8) months in the IHC score1+ group and 6 (95% CI, 3.4–8.6) months in the IHC score2++/ISH negative group (p=0.001). In the multivariate analysis, HER2 status at diagnosis, cytotoxic chemotherapy status, and best response to CDK4/6i+ET treatment were significant parameters for PFS (p = 0.018, p = 0.006, p = 0.001, respectively) (Table-4). At the time of analysis, 46 (38%) patients had progressed with CDK4/6i+ET therapy and 76 (62%) patients were on CDK4/6i+ET therapy.

Table 3. Comparison of groups with different PFS and overall survival by Kaplan–Meier method

		PFS		OS	
Variables		**Median(95%CI) month**	**p value**	**Mean(95%CI) month**	**p value**
HER2 status	HER2-zero	NR	**0.001**	25.7(23.3-28.2)	0.195
	HER2-low	12(6.8-17.2)		30.3(24.3-36.4)	
	All patients	21(18.5-23.5)		32.9(9.5-36.4)	
CDK4/6i	Ribociclib	20(17.4-22.6)	0.530	33.4(29.3-37.6)	0.631
	Palbociclib	21(10.9-31)		23.5(20-26.9)	
Change in HER2 status	Her2-zero then became Her2-low	NR	**0.001**	25.4(20.7-30.2)	**0.031**
	Her2-low then became Her2-zero	9(4-13.9)		20.2(15.2-25.3)	
	Her2 unchanged	17(10.8-23.2)		21.5(16.8-26.2)	
	There was no repeat biopsy	NR		36.7(32.5-41)	
Metastasis status	Recurrence	17(8.5-25.5)	0.052	22.6(19.1-26.2)	**0.018**
	De novo metastatic	27(18.8-35.2)		35.1(31-39.3)	
Best response to CDK4/6i	partial response	23(18.2-27.8)	**0.001**	37.5(33.8-40.9)	**0.001**
	stable disease	9(7.2-10.7)		21.8(17.2-26.5)	
	progressive disease	3(1.9-4.1)		8.3(4.5-12)	
Progression with CDK4/6i	No			29.6(28.1-31.1)	**0.001**
	Yes			25.3(20-30.5)	
Concurrent endocrine therapy	aromatase inhibitor	NR	**0.01**	36.3(32-40.8)	**0.003**
	Fulvestrant	18(8.3-27.7)		21(17.5-24.8)	
CDK4/6i therapy line	1.line	NR	**0.001**	26.3(23.5-29)	0.527
	2.line	NR		24.2(19.5-28.8)	
	3.line	12(7.4-16.6)		32.4(24.6-40.2)	
	4.line and later	9(3.9-14)		17.9(13.6-22.3)	
Primary endocrine resistance	No	21(14.5-27.5)	**0.001**	34(31.4-38)	**0.001**
	Yes	6(4.7-7.2)		16(10-22.9)	
Estrogen receptor status	1-9%	NR	**0.025**	10(0.3-19.7)	0.172
	10-49%	6(2.1-9.8)		18.7(9.8-27.5)	
	50-100%	21(18.7-23.2)		33.5(30-37)	
CDK4-6i plus endocrine therapy	Palbociclib+letrozole	NR	**0.001**	28.7(26.3-31)	**0.001**
	Ribociclib+letrozole	NR		34(28-39.9)	
	Palbociclib+fulvestrant	7(4.7-9.2)		14.4(8.6-20)	
	Ribociclib+fulvestrant	19(13.9-24)		24.1(20-28)	
chemotherapy status	Did not receive	NR	**0.001**	21.3(17.9-24.8)	**0.047**
	Received in the metastatic stage	12(0-25.2)		31(25-37)	
	Neoadjuvant received	17(8.8-25.2)		28.9(26-31.6)	

PFS: Progression-free survival, OS: Overall survival, NR: Not reached,CDK4/6i: Cyclin-dependent kinase 4 and 6 inhibitors

Table 4. Univariable and multivariable analysis of parameters affecting mPFS duration

		Univariable		Multivariable	
Variables		**HR(95% CI)**	**p value**	**HR(95% CI)**	**p value**
HER2	Score-0	Reference	**0.001**	Reference	**0.018**
	Score-(+1)	1.8(0.9-3.8)		2.08(0.90-4.79)	
	Score-(+2)/ISH(-)	4.3(2.1-8.8)		3.21(1.38-7.44)	
ER	≥50%	Reference	**0.05**	Reference	0.223
	10-49%	5.5(1.3-23)		4.59(0.76-27.8)	
	1-9%	1.4(0.5-3.9)		1.60(0.49-5.12)	
CDK4-6i+ET	Palbociclib+letrozole	Reference	**0.015**	Reference	0.753
	Ribociclib+letrozole	1.3(0.5-3.5)		1.32(0.46-3.77)	
	Palbociclib+fulvestran	4.1(1.5-11.2)		1.68(0.54-5.16)	
	Ribociclib+fulvestrant	2(0.8-5.2)		1.05(0.38-2.88)	
chemotherapy status	Did not receive	Reference	**0.003**	Reference	**0.006**
	Received in the metastatic stage	10.8(2.5-46)		3.56(0.69-18.3)	
	Neoadjuvant received	12.1(2.8-51.6)		8.99(1.77-45)	
CDK4-6i+ET best response	partial regression	Reference	**0.001**	Reference	**0.001**
	stable disease	3(1.5-6)		2.98(1.38-6.44)	
	progressive disease	54(19-149)		83.5(21.9-318)	

ER: Estrogen receptor, CDK4/6i: Cyclin-dependent kinase 4 and 6 inhibitors, ET: Endocrine therapy, ISH:in situ hybridization

There was no significant difference in mPFS between patients receiving ribociclib and those receiving palbociclib (p=0.530). The mPFS was 6 (95% CI, 4.8–72) months in patients with primary endocrine resistance and 21 (95% CI, 14.5–27.4) months in patients without primary endocrine resistance (p=0.001) (Figure-1B). The mPFS was not reached in patients receiving CDK4/6i concomitant letrozole, while mPFS was 18 (95%CI,8.3–27.7) months in patients receiving fulvestrant (p=0.01) (Figure-2A). The mPFS was 21 (95% CI, 18.8–23.2) months in patients with ER levels >50% and 6(95% CI, 2.1–9.8) months in patients with ER levels<50% (p=0.025). There was a difference in mPFS based on the best response to CDK4/6i+ET treatment and the treatment line in which cytotoxic chemotherapy was administered (all p<0.001) (Figure-2B). There was a difference in mPFS between CDK4/6i+ET combinations, for example, mPFS at 7 (95% CI, 4.7–9.3) months in the fulvestrant+palbociclib group and 19 (95% CI, 14–24) months in the fulvestrant+ribociclib group (p=0.001) (Figure-3A).

In patients with discordance between diagnosis and repeat biopsy, the duration of mPFS could not be reached in patients who were HER2-zero initially and then became HER2-low. In patients whose HER2 status did not change in the second biopsy, mPFS was 17 (955 CI, 10.8–23.2) months. The mPFS was 9 (95% CI,4.1–13.9) months in patients who were initially HER2-low and then became HER2-zero (p=0.001) (**Figure-3B**).

The median PFS was 20 months in tumor histologica grade 1 and 2 patients and 7 (95% CI,3.3–10.6) months in grade 3 patients (p=0.120). The ORR was 69% and the DCR was 90%. In 12 patients, treatment was newly initiated or the best-response status could not be reached. The mPFS decreased significantly with increasing CDK4/6i+ET treatment line (p=0.001).

In the HER2-zero group, the 24-month survival was 95% and the 36-month survival was 86%, while in the HER2-low group, the 24-month survival was 93% and the 36-month survival was 89% (p=0.578). There were differences in mOS between the subgroups, discordance in HER2 status, metastasis status, CDK4-6i+ET combinations, primary endocrine resistance, chemotherapy status, concurrent ET agent, best response to CDK4/6i, and progression with CDK4/6i treatment (**Table-3**).

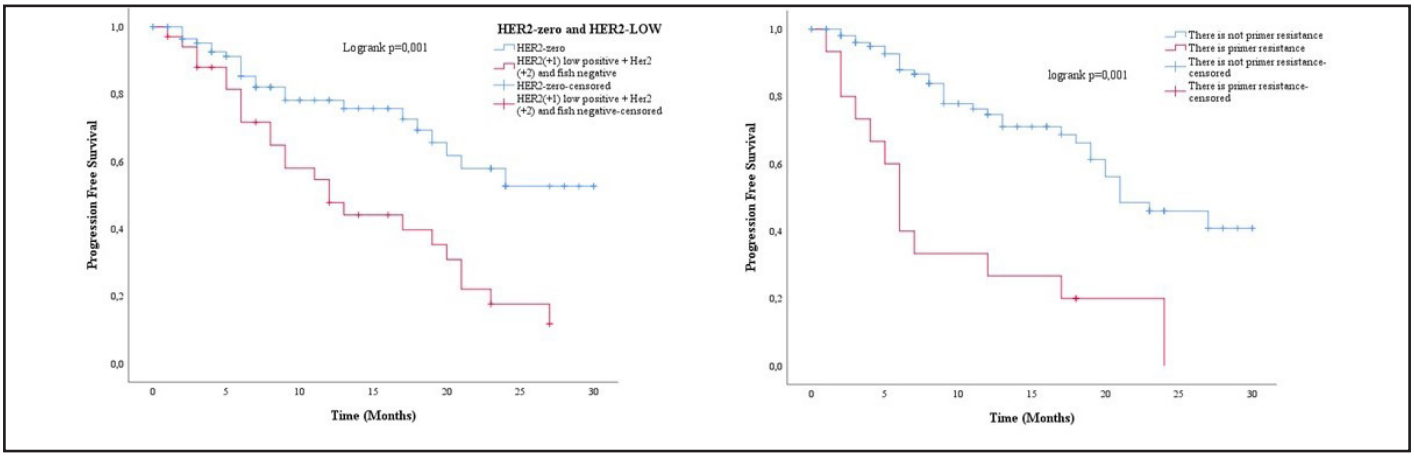

Figure 1.A. Median PFS is significantly longer in HER2-zero than that in HER2-low patients. **B)** Median PFS was significantly shorter in patients with primary endocrine resistance.

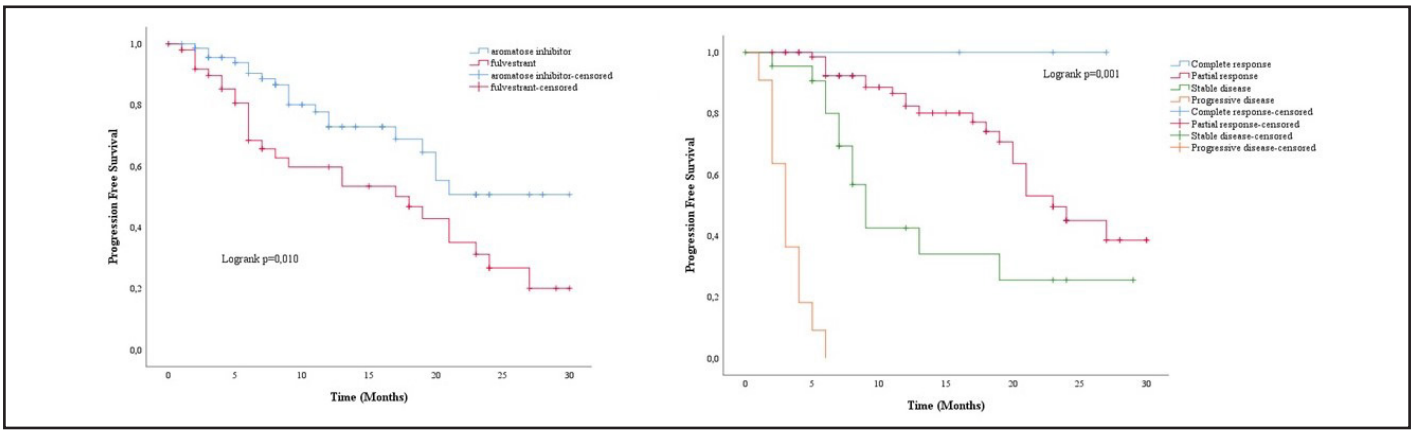

Figure 2.A. Regardless of the CDK4/6i agent, mPFS was different according to concomitant letrozole or fulvestrant treatment. **B)** The best response status obtained with CDK4/6i+ET combination predicted the duration of mPFS.

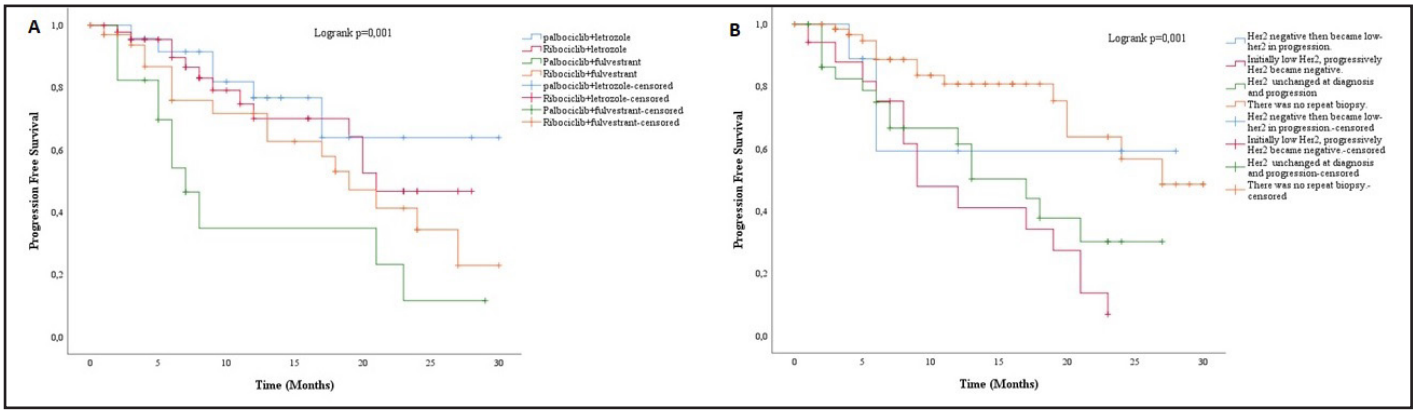

Figure 3.A. A difference was observed in the duration of mPFS across different treatment combinations. Similar mPFS was observed in patients treated with CDK4-6i plus letrozole combination, while its was significantly lower in those treated with fulvestrant+palbociclib combination. **B**) Moreover,differences were found in the mPFS times in patients whose HER2 status changed between biopsy specimen obtained at diagnosis and at recurrence. Patients with HER2-zero in the initial biopsy had significantly longer mPFS than those with HER2-low in the initial biopsy (p=0.001).

In the multivariate analysis, best response to CDK4/6i alone was an independent parameter affecting OS duration (p=0.007). Following progression with CDK4/6i+ET, patients received subsequent treatments: 4 (11%) received ET alone, 9 (25%) received chemotherapy and ET, and 23 (64%) received chemotherapy only. In these patients, the mOS was 9 (95%CI, 3.8–14.2) months and the best mOS was observed in the group that received chemotherapy and ET (p=0.001).

DISCUSSION

In this study, the duration of mPFS with CDK4/6i+ET was lower in the HER2-low group than in the HER2-zero group (p=0.001). Similarly, the mPFS duration was significantly lower in patients with an IHC score2++/ISH- than in patients with IHC score1+ (6 vs. 20 months). In a study by Bao et al., mPFS was 8.9 months in HER2-low patients receiving CDK4/6i+ET treatment, whereas mPFS was 18.8 months in HER2-zero patients (p=0.01) [11]. In another study, the duration of mPFS was lower in HER2-low patients receiving CDK4/6i therapy than that in HER2-zero patients (1.74 vs.3.35 years), but the difference was not significant [9]. In a study by Francesca et al., there was no difference in mPFS between HER2 groups who received palbociclib treatment alone [10]. The results of our study is consistent with that of two of three similar studies in the literature. HER2-low expression is a negative predictive biomarker in patients treated with CDK4/6i+ET.

The incidence of HER2-low expression varies among breast cancer studies. While the incidence of HER2-low was 28% in our study, it occurred at different rates (30–77%) in other studies [9-11]. In a database study analyzing 65,000 patients, the incidence of HER2-low status in the ER+ cohort was 65%, while that in the ER- cohort was 38% [13]. Differences in the incidence of HER2-low expression may be related analytical processes, ethnicity, and patient group. In the DESTINY-Breast04 study, trastuzumab deruxtecan was compared with physician-selected chemotherapy in previously treated HER2-low patients, and mPFS was found to be 10.1 months vs. 5.4 months in both patients with IHC score1+ and score2++/ISH [4]. HER2-low expression is present in nearly half of breast cancer patients and is a predictive biomarker for the response to antibody-drug conjugates (ADCs).

In our study, there was a change in the HER2-low status of 26 (45%) patients with recurrence compared to the first biopsy. While the mPFS duration could not be reached in those who changed from HER2-zero to HER-low, it was 9 months in those who changed from HER-low to HER-zero. In other words, the mPFS duration of patients with discordance between biopsies was determined using the HER2 expression status in the first biopsy. In a study conducted in China, changes in HER2-low status were analyzed in 247 patients with recurrent breast cancer. The twenty-five (49%) patients who were initially HER2-zero and 19 (27%) who were initially HER2-positive converted to HER2-low. Changes in HER2 status were observed in up to 20% of all study patients [14]. The HER2-low expression status is dynamic, similar to the hormone profile in breast cancer, and may change during progression. Tissue sampling during disease progression is essential to detect the potential benefits of ADC and dynamic HER2 expression.

In our study, patients with complete response to CDK4/6i+ET treatment were endocrine sensitive, whereas patients with progressive disease with CDK4/6i+ET treatment often had secondary endocrine resistance. If the patient had secondary endocrine resistance, the expected response and duration of response to CDK4/6i+ET treatment were reduced compared to those in endocrine-sensitive patients. There are common pathways involved in the mechanisms of endocrine resistance and resistance to CDK4/6i therapy [15]. Furthermore, in our study, 25% of the patients in the HER2-zero group and 71% of the patients in the HER2-low group progressed with CDK4/6i+ET (p=0.001). The presence of HER2-low expression, such as in endocrine resistance, decreased the efficacy of CDK4/6i+ET treatment and more patients progressed. The role of HER2 activation in endocrine resistance in patients with HR+HER- breast cancer has only been demonstrated in a limited number of preclinical studies [16].

The mPFS was lower in patients with tumor histological grade-3 tumors than that in patients with grades 1-2 tumors (6 vs. 20 months). This may be related to the low efficacy of CDK4/6 inhibitors, especially in high-grade and aggressive tumors [17]. There was no difference between the median PFS of our patients who received ribociclib or palbociclib treatment. In a study in which real-life data were analyzed, the PFS times were similar for palbociclib and ribociclib (28 and 29 months, respectively) [18]. In our study, mPFS was significantly different between patients who received cytotoxic chemotherapy before CDK4/6 in the metastatic period and those who received CDK4/6i treatment as first-line treatment [19]. In a similar study, PFS with CDK4/6i was shorter in patients with recurrence and visceral metastases. Although the reason for this is not clear, because patients with

recurrence usually receive ET as an adjuvant treatment, endocrine resistance may develop in these patients; therefore, the response to CDK4/6i+ET treatment is reduced.

In our study, we found that the duration of mPFS increased significantly as the estrogen receptor levels increased. Similarly, previous studies have shown that the benefits of ET increase as estrogen and progesterone receptor expression increases [20]. The improvement in PFS duration with increasing ER levels may be attributed to the increased efficacy of ET used concomitantly with CDK4/6i. Similarly, because fulvestrant is generally used in cases of endocrine resistance, the PFS time of patients receiving fulvestrant was shorter than that of patients receiving letrozole. In our patients receiving palbociclib+fulvestrant had a mPFS of 7 months, similar to the PFS of 9.5 months in the PALOMA-3 study [21]. In our patients who received ribociclib+fulvestrant combination therapy, mPFS was 19 months, similar to the mPFS of 20.5 months in the MONALEESA-3 study [22].

In our study, the best response status of patients predicted the benefit of CDK4/6i+ET treatment (p=0.001) (Table-5). The ORR was 69% and the DCR was 90%; in PALOMA-2, a prospective study, the ORR was 56% and the DRC was 87%, with similar rates [23]. In our study, the use of CDK4/6 inhibitors in the first step resulted in a significant difference in mPFS compared to the use of CDK4-6 inhibitors in subsequent steps. In other studies, longer mPFS durations were observed with first-line CDK4/6i therapy [21, 22].

In an Austrian study, HER2-low expression was frequent in metastatic HR+ breast cancer and had no effect on prognosis [24]. HER2-low expression in early-stage breast cancer was considered a good prognostic biomarker in both HR positive and HR negative patients [7]. As tumor biology, resistance mechanisms, and mutations observedin the early and metastatic stages of breast cancer may differ, HER2 expression may have a different prognostic value. The CDK4/6i-dependent mOS of patients with recurrence was significantly shorter than that of patients with denovo metastasis. As patients with recurrence usually receive adjuvant ET before CDK4/6i and CDK4/6i therapy during the endocrine resistance period, the benefits provided by CDK4/6i are reduced. In our study, the CDK4/6i-dependent mOS duration was shorter in patients with primary endocrine resistance and those receiving fulvestrant treatment. In our study, the prognostic value of HER2-low expression for OS duration was not found. The survival times were consistent with those reported in previous studies [21].

The step in which CDK4/6i+ET was administered was significant for mPFS but not for mOS. Patients who progressed with CDK4/6I+ET treatment received ET or chemotherapy, and their mPFS was 9 months. In the DESTINYBreast-04 study, the mPFS was 10 months with trastuzumab deruxtecan treatment after 70% of the patients received CDK4/6i treatment [4]. Administration of trastuzumab deruxtecan after progression with CDK4/6i in HER2-low patients may prolong overall survival in this patient group. The best response to CDK4/6i+ET treatment was an independent parameter affecting OS duration in our study.

Table 5. Response rates, Endocrine resistance status, and mPFS duration of patients with the best response to CDK4-6i and endocrine therapy combination treatment

Best response status	n(%)	mPFS (95%CI) month	Endocrine resistance status		
			Endocrine sensitive, n(%)	primary resistance n(%)	secondary resistance n(%)
complete response	3(2.5%)	NR	3(100)	-	-
partial regression	73(60%)	23(18.2-27.8)	33(45.2)	28(38.4)	12(16.4)
stable disease	23(19%)	9(7.3-10.7)	14(60.9)	7(30.4)	2(8.7)
progressive disease	11(9%)	3(1.9-4)	2(18.2)	9(81.8)	-
Overall	110	20(17.7-22.3)	52(47.3)	44(40)	14(12.7)

mPFS: median Progression-free survival, NR: Not reached

Limitations

Retrospective design, the fact that CDK4/6i+ET treatment was applied at different steps, and relatively limited number of patients are the limitations of the study. Nevertheless, this is one of the few studies investigating the HER2-low expression in patients receiving CDK4/6i+ET treatment. Factors that may affect patient survival were comprehensively analyzed. The difference between this and other studies is that we also investigated the relationship between endocrine resistance and HER2-low status.

CONCLUSION

HER2-low expression is present in nearly half of the patients with breast cancer and may change during disease progression. HER2-low patients progressed more with CDK4/6i treatment, and their mPFS was lower than that of the HER2-zero group. Independent parameters affecting mPFS duration were HER2-low status, best response to CDK4/6i+ET treatment, and cytotoxic chemotherapy status. HER2-low expression was not a prognostic factor for OS but a predicted response to CDK4/6i treatment. Randomized studies are required to determine the predictive value of HER2-low expression in patients receiving CDK4/6i.

Informed Consent: Obtained from patients or their legal representatives.

Conflict of interests: The authors declare no conflicts of interest regarding the publication of this paper.

Funding: This study received no external funding.

Ethical Approval: This study was approved by Gaziantep University Faculty of Medicine Ethics Committee **(no.2023/48).**

Author Contributions: Conception: **H,A;T,K.**- Design: **H,A;T,K.** Supervision: **H,A;T,K.**- Fundings: **H,A;T,K.** Materials: **H,A;T,K.**- Data Collection and/or Processing: **H,A.**- Analysis and/or Interpretation: **H,A.** - Literature: **H,A.** Review: **H,A;T,K** - Writing: **H,A;T,K** Critical Review: **H,A;T,K**

REFERENCES

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A (2022) Cancer statistics, 2022. CA Cancer J Clin 72:7-33. https://doi.org/10.3322/caac.21708

[2] Prat A, Pineda E, Adamo B, Galvan P, Fernandez A, Gaba L, et al. (2015) Clinical implications of the intrinsic molecular subtypes of breast cancer. Breast 24 Suppl 2:S26-35. https://doi.org/10.1016/j.breast.2015.07.008

[3] Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. (2018) Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med 142:1364-1382. https://doi.org/10.5858/arpa.2018-0902-SA

[4] Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga et al. (2022) Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med 387:9-20. https://doi.org/10.1056/NEJMoa2203690

[5] Gampenrieder SP, Dezentje V, Lambertini M, de Nonneville A, Marhold M, Le Du F, Cortes Salgado A, et al. (2023) Influence of HER2 expression on prognosis in metastatic triple-negative breast cancer-results from an international, multicenter analysis coordinated by the AGMT Study Group. ESMO Open 8:100747. https://doi.org/10.1016/j.esmoop.2022.100747

[6] Tan R, Ong WS, Lee KH, Lim AH, Park S, Park YH, et al. (2022) HER2 expression, copy number variation and survival outcomes in HER2-low non-metastatic breast cancer: an international multicentre cohort study and TCGA-METABRIC analysis. BMC Med 20:105. https://doi.org/10.1186/s12916-022-02284-6

[7] Ergun Y, Ucar G, Akagunduz B (2023) Comparison of HER2-zero and HER2-low in terms of clinicopathological factors and survival in early-stage breast cancer: A systematic review and meta-analysis. Cancer Treat Rev 115:102538. https://doi.org/10.1016/j.ctrv.2023.102538

[8] Giuliano M, Trivedi MV, Schiff R (2013) Bidirectional Crosstalk between the Estrogen Receptor and Human Epidermal Growth Factor Receptor 2 Signaling Pathways in Breast Cancer: Molecular Basis and Clinical Implications. Breast Care (Basel) 8:256-262. https://doi.org/10.1159/000354253

[9] Douganiotis G, Kesisis G, Lalla E, Korantzis I, Boukovinas I, Papazisis K (2022) Prognostic Significance of Low HER2 Expression in Patients With Metastatic Hormone Receptor-

positive Breast Cancer Treated With First Line CDK4/6 Inhibitors: A Greek Multicenter Real-world Data Analysis. Cancer Diagn Progn 2:585-591. https://doi.org/10.21873/cdp.10146

[10] Carlino F, Diana A, Ventriglia A, Piccolo A, Mocerino C, Riccardi F, et al. (2022) HER2-Low Status Does Not Affect Survival Outcomes of Patients with Metastatic Breast Cancer (MBC) Undergoing First-Line Treatment with Endocrine Therapy plus Palbociclib: Results of a Multicenter, Retrospective Cohort Study. Cancers (Basel) 14. https://doi.org/10.3390/cancers14204981

[11] Bao KKH, Sutanto L, Tse SSW, Man Cheung K, Chan JCH (2021) The Association of ERBB2-Low Expression With the Efficacy of Cyclin-Dependent Kinase 4/6 Inhibitor in Hormone Receptor-Positive, ERBB2-Negative Metastatic Breast Cancer. JAMA Netw Open 4:e2133132. https://doi.org/10.1001/jamanetworkopen.2021.33132

[12] Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, Andre F, et al. (2018) 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4) dagger. Ann Oncol 29:1634-1657. https://doi.org/10.1093/annonc/mdy192

[13] Baez-Navarro X, van Bockstal MR, Andrinopoulou ER, van Deurzen CHM (2023) HER2-Low Breast Cancer: Incidence, Clinicopathologic Features, and Survival Outcomes From Real-World Data of a Large Nationwide Cohort. Mod Pathol 36:100087. https://doi.org/10.1016/j.modpat.2022.100087

[14] Shi Q, Yu J, Liu D, Ren F, Wu J, Shen K (2023) Distribution, dynamic evolution, and clinical outcomes of patients with advanced breast cancer according to HER2 expression. BMC Cancer 23:173. https://doi.org/10.1186/s12885-023-10634-7

[15] Stanciu IM, Parosanu AI, Orlov-Slavu C, Iaciu IC, Popa AM, Olaru CM, et al. (2023) Mechanisms of Resistance to CDK4/6 Inhibitors and Predictive Biomarkers of Response in HR+/HER2-Metastatic Breast Cancer-A Review of the Literature. Diagnostics (Basel) 13. https://doi.org/10.3390/diagnostics13050987

[16] Mazumder A, Shiao S, Haricharan S (2021) HER2 Activation and Endocrine Treatment Resistance in HER2-negative Breast Cancer. Endocrinology 162. https://doi.org/10.1210/endocr/bqab153

[17] Hu Y, Gao J, Wang M, Li M (2021) Potential Prospect of CDK4/6 Inhibitors in Triple-Negative Breast Cancer. Cancer Manag Res 13:5223-5237. https://doi.org/10.2147/CMAR.S310649

[18] Buller W, Pallan L, Chu T, Khoja L (2023) CDK4/6 inhibitors in metastatic breast cancer, a comparison of toxicity and efficacy across agents in a real-world dataset. J Oncol Pharm Pract 29:1825-1835. https://doi.org/10.1177/10781552231163121

[19] Knudsen ES, Schultz E, Hamilton D, Attwood K, Edge S, O'Connor T, et al. (2022) Real-World Experience with CDK4/6 Inhibitors for Metastatic HR+/HER2- Breast Cancer at a Single Cancer Center. Oncologist 27:646-654. https://doi.org/10.1093/oncolo/oyac089

[20] Bartlett JM, Brookes CL, Robson T, van de Velde CJ, Billingham LJ, Campbell FM, et al. (2011) Estrogen receptor and progesterone receptor as predictive biomarkers of response to endocrine therapy: a prospectively powered pathology study in the Tamoxifen and Exemestane Adjuvant Multinational trial. J Clin Oncol 29:1531-1538. https://doi.org/10.1200/JCO.2010.30.3677

[21] Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, Colleoni M, et al. (2016) Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 17:425-439. https://doi.org/10.1016/S1470-2045(15)00613-0

[22] Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. (2018) Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol 36:2465-2472. https://doi.org/10.1200/JCO.2018.78.9909

[23] Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. (2015) The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/

TRIO-18): a randomised phase 2 study. Lancet Oncol 16:25-35. https://doi.org/10.1016/S1470-2045(14)71159-3

[24] Gampenrieder SP, Rinnerthaler G, Tinchon C, Petzer A, Balic M, Heibl S, et al. (2021) Landscape of HER2-low metastatic breast cancer (MBC): results from the Austrian AGMT_MBC-Registry. Breast Cancer Res 23:112. https://doi.org/10.1186/s13058-021-01492-x

How to Cite;

Arak H, Kuş T (2024) Prognostic and Predictive Significance of HER2-low Expression in Metastatic Hormone Receptor Positive Breast Cancer Patients Receiving CDK4-6 Inhibitor Therapy. Eur J Ther. https://doi.org/10.58600/eurjther2151