Predictive Roles of Ki 67 level & mPEPI Score for Neoadjuvant 'Chemotherapy' Efficacy in Locally Advanced ER(+)/HER2(-) Breast Cancer

Mutlu DOGAN[1], Cengiz KARACIN[1], Omur KAMAN[1], Zarife Melda BULUT[2], Gamze KIZILTAN[3], Berna OKSUZOGLU[1], Lutfi DOGAN[3]

[1] University of Health Sciences, Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Medical Oncology

[2] University of Health Sciences, Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Pathology

[3] University of Health Sciences, Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of General Surgery & Surgical Oncology

ABSTRACT

Neoadjuvant chemotherapy (NAC) & modified preoperative endocrine prognostic index (mPEPI) score after NAC role is unclear in locally advanced ER+/HER2(-) breast cancer (LA-HnLBC). We aimed to evaluate prognostic & predictive factors including mPEPI score for NAC in LA-HnLBC, retrospectively. 142 LA-HnLBC patients were classified as pCR(n:26) & non-pCR (n: 116) & categorized for PR/ki67/ki67 decline/mPEPI score patients were included. Median age was 53 years. pCR rate was 18.3%. Median ER/PR/ki67 were as 90% / 40% / 40%. Median basal & postoperative ki67 level was 40. pCR group had more T2(73%), grade 3 (69%) & non-pCR had more T3(21%), grade 2(46%) tumors (p= 0.03,p= 0.03). pCR group had lower mPEPI score (3.5 vs 5,p= 0.05). 5y-DFS was 69% (pCR 93.8%,non-pCR 63.4%, p= 0.012). 5y-OS was 77% (pCR 100%,non-pCR 72%, p= 0.018). In univariate analysis, high basal/postoperative ki67 levels, ki67 decline & mPEPI score were significant poor prognostic factors for DFS (p= 0.01, p< 0.001, p= 0.017, p< 0.001) & OS (p= 0.006, p= 0.003, p= 0.05, p= 0.001) in non-pCR goup. Prognostic cut-offs were as 40 for basal ki67 (DFS & OS), 20 for postoperative ki67 (DFS), 4 for mPEPI (DFS) & 30 for ki67 decline (OS). Favorable prognostic factors were defined as lower basal ki67 level (< 40%) & higher ki67 decline (ki67 <30%) for OS; lower basal ki67 (<40%), po ki 67 (< 20%) & mPEPI score (< 4) for DFS after NAC in LA HnLBC. Different prognostic cut-offs for basal & postoperative ki 67 is striking. mPEPI score may also have prognostic significance after NAC in LA-HnLBC patients.

Keywords: ER+/HER2- breast cancer, Locally advanced breast cancer, Luminal-like breast cancer, mPEPI score, Neoadjuvant treatment

INTRODUCTION

Breast cancer is the most common cancer in females with a decline in mortality rate due to well-established screening models and early diagnosis, besides novel therapeutic options in recent years. It is a heterogeneous malign complex with various biological molecular subtypes rather than a simple histopathological diagnosis.

Prognosis of breast cancer depends on clinical & pathological features such as age, tumor size, nodal involvement, grade, ki 67, estrogen receptor (ER), progesteron receptor (PR) and human epidermal growth receptor 2 (HER2) overexpression.[1] According to 'The St Gallen International Breast Cancer Conference (2013)', breast cancer intrinsic subtypes were defined as luminal A-like (ER positive, PR positive, ki67 low and HER2 negative), luminal B-like HER2 negative (ER positive, HER2 negative, PR negative/low and/or ki 67 high) and luminal B-like HER2 positive (ER positive, HER2 positive, any PR, any ki 67), HER2 positive nonluminal (ER & PR negative, HER2 positive) and basal-like (ER, PR& HER2 negative) breast cancer.[2,3]

Luminal-like breast cancer has favorable prognosis, however PR and/or ki 67 differ for luminal A-like & luminal B-like breast cancer subtypes, in terms of both prognosis and therapeutic options. Optimal cut-off values for PR and ki 67 (i.e. high and low levels) in luminal B-like HER2 (-) breast cancer are not well-defined. Ono et al., determined a significant negative correlation between PR & ki 674. They reported 20% as a significant cut-off value for ki 67, regardless from cut-off values for PR (10%, 20% and 30%). It indicates that lower PR and higher ki 67 (> 20%) had poor outcomes (p< 0.01, p< 0.001, p: 0.003, respectively).[4] Prognosis is more favorable in luminal A-like breast cancer. Luminal B-like HER2 negative disease has also favorable outcomes depending on PR rate and ki 67 level, as well.

Multigene molecular genomic tests, such as 21-gene assay (Oncotype Dx®), 70-gene assay (Mammaprint®), 12-gene assay (Endopredict®), 50-gene assay (PAM50®) and Breast Cancer Index® are prognostic in early stage ER(+) / HER2(–) breast cancer. Of these, Oncotype Dx is also predictive for adjuvant chemotherapy of ER(+) / HER2(-) early breast cancer patients with tumor size (>5 mm) and (0-3) lymph node.[5-8] Mammaprint has also been reported to have prognostic and predictive significance, especially for younger premenopausal genomic and clinical discordant ER(+) / HER2(-) breast cancer patients.[9,10] However, prognostic and predictive values of these molecular genomic tests for 'neoadjuvant' treatment is not so clear.

Neoadjuvant treatment is standard in locally advanced stage disease, especially for those with nodal involvement. The patients who have pathological complete response (pCR) after neoadjuvant treatment have better survival outcomes. It is also preferred for selected patients (>T1c) without nodal involvement in triple negative breast cancer and HER2 positive breast cancer. Locally advanced stage luminal A-like breast cancer patients are candidates for neoadjuvant endocrine therapy. However, neoadjuvant treatment'modality' (i.e. chemotherapy or endocrine therapy) is controversial for luminal B-like HER2 negative ones, especially for those with lower PR rate and/or higher ki 67 level. Therefore, we need predictive factors for choosing best candidates for neoadjuvant 'chemotherapy' among ER(+) / HER2(-) breast cancer patients.

Current approaches for prediction of neoadjuvant endocrine treatment sensitivity in luminal-like breast cancer are generally based on molecular tests and pathological prognostic indices, such as preoperative endocrine prognostic index (PEPI) & modified preoperative endocrine prognostic index (mPEPI).[11-13] In ALTERNATE trial, the patients with mPEPI score 0 (pT1-2, pN0, ki67 <2.7%) after neoadjuvant endocrine therapy were reported to have lower risk of recurrence without adjuvant chemotherapy.[12.13] However, there is no well-established data for prediction of relapse after neoadjuvant'chemotherapy' in 'luminal-like' breast cancer. Therefore, the role of mPEPI score for neoadjuvant chemotherapy efficacy & recurrence prediction is not clear.

In present study, we aimed to evaluate the prognostic & predictive roles of mPEPI score & ki 67 decline rate for neoadjuvant 'chemotherapy' in locally advanced'HER2 negative luminal-like' breast cancer.with neoadjuvant chemotherapy, besides ideal cut-off values for basal PR & ki 67 as prognostic and predictive factors in this population.

PATIENTS AND METHODS

The patients who had neoadjuvant chemotherapy for locally advanced stage HER2 (-) luminal breast cancer followed-up at our center were evaluated retrospectively. Patients' demographics, clinical and pathological features were recorded from our registration database. All patients had doxorubicin +/- taxane as neoadjuvant chemotherapy. They were classified for pathologic response rates (A: pCR & B: non-pCR) & categorized for pathological features, such as PR, ki67, ki67 decline & mPEPI score. mPEPI score was calculated according to the formula including pathological characteristics (pT, pN, ER & ki67).[12]

Since optimal cut-off value for ki 67 is not well-established, we considered to evaluate the patients according two different cut-off values, such as 20 (i.e. by literature) in Model 1 and median value in Model 2, if it was different from literature. Postoperative ki 67 level as less than 30% with neoadjuvant chemotherapy was accepted as 'prominent' ki 67 decline.

Table 1. Clinical and pathological features according to the pathological response after neoadjuvant chemotherapy

		Total n: 142	Non-pCR n: 116	pCR n: 26	p
Age, year (mean ± SD)	52±11.7	53±12.1	51±9.9	0.484	
Menopause status, (%)	premenopausal	64 (45.1)	53 (45.7)	11 (42.3)	0.754
	postmenopausal	78 (54.9)	63 (54.3)	15 (57.7)	
T stage, (%)	T1	20 (14.1)	15 (12.9)	5 (19.2)	0.037
	T2	78 (54.9)	59 (50.9)	19 (73.1)	
	T3	27 (19.0)	25 (21.6)	2 (7.7)	
	T4	17 (12.0)	17 (14.7)	0 (0)	
N stage, (%)	N0	7 (3.9)	6 (5.2)	1 (3.8)	0.922
	N1	52 (36.6)	43 (37.1)	9 (34.6)	
	N2	83 (58.5)	67 (57.8)	16 (61.5)	
Grade, (%)	1	7 (4.9)	6 (5.2)	1 (3.8)	0.035
	2	60 (42.3)	54 (46.6)	6 (23.1)	
	3	62 (43.7)	44 (37.9)	18 (69.2)	
	X	13 (9.2)	12 (10.3)	1 (3.8)	
ER, median (IQR)	90 (70-95)	90 (75-95)	90 (70-95)	0.904	
ER, categorical (%)	< 10	14 (9.9)	12 (10.3)	2 (7.7)	1.000
	≥ 10	128 (90.1)	104 (89.7)	24 (92.3)	
PR, median (IQR)	40 (10-80)	40 (10-80)	55 (10-70)	0.985	
PR, categorical (%)	< 20	47 (33.1)	38 (32.8)	9 (34.6)	0.856
	≥ 20	95 (66.9)	78 (67.2)	17 (65.4)	
Ki-67, median (IQR)	40 (25-60)	40 (25-60)	43 (30-70)	0.173	
Ki-67, categorical (%)	< 20	19 (13.4)	17 (14.6)	2 (7.7)	0.740
	≥ 20	112 (78.9)	92 (79.4)	20 (76.9)	
	Unknown	11 (7.7)	7 (6.0)	4 (15.4)	
mPEPI score, median (IQR)	5.0 (4.0-7.0)	5.0 (4.0-7.0)	3.5 (2.0-4.5)	0.052	
mPEPI, categorical, n: 97* (%)	< 5	55 (45.5)	30 (31.6)	25 (96.2)	<0.001
	≥ 5	66 (54.5)	65 (68.4)	1 (3.8)	
Chemotherapy regimen	Antracycline	18 (12.7)	15 (12.9)	3 (11.5)	1.000
	Antracycline + Taxane	124 (87.3)	101 (87.1)	23 (88.5)	

ER= Estrogen Receptor, PR= Progesterone Receptor, mPEPI= modified preoperative endocrine prognostic index (mPEPI)

Pathological complete response (pCR) was defined as no invasive tumor in breast and/or lymph nodes after neoadjuvant treatment. Disease free survival (DFS) was defined as the interval between initiation of treatment and relapse or death of any cause. Overall survival (OS) was defined as the interval between initiation of treatment and death of any cause.

Ethical Approval: This study protocol was reviewed and approved by ethics commitee (UHS, Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, 26.05.2021, 2021-05/1184) and has been performed in accordance with the ethical standards laid down in the 1964 Decleration of Helsinki.

Statistical Analyses

Kolomogorov Simonov test was used to assess normality distribution of variables. Continous variables were presented as median [range or interquartile range (IQR)]. Categorical variables were presented as frequency (percentage). Parametric continous variables were compared by independent sample t-test while nonparametric ones were compared by Mann-Whitney U test. Chi-square test or Fisher's exact test was used for comparison of categorical variables. Median follow-up and survival analysis was performed by Kaplan-Meier method with comparison of groups by log-rank test. Parameters with p< 0.100 in univariate analysis were included in Cox-regression models for determina-

tion of dependent prognostic factors. All tests were two-sided and p< 0.05 was accepted as statistically significant. Statistical analysis was performed by IBM SPSS Statistics for Windows software v.25.0 (IBM, NY, USA).

RESULTS

Between April 2011 & July 2020, 142 locally advanced stage ER (+) / HER2 (-) luminal-like breast cancer patients with available data were evaluated, retrospectively. All of them had neoadjuvant chemotherapy. Median age was 53 years (range: 29-76). More than half (54.9%) of the patients were premenopausal. Twenty-six (18.3%) patients had pCR. Clinical and pathological features of the patients in whole population and subgroups according to pathological response are summarized in Table 1. There were more patients with smaller tumor size (cT1-cT2) and higher tumor grade (grade 3) in pCR subgroup (p= 0.037, p: 0.035) (Table 1). Fourteen (9.9%) patients had lower ER (< 10%) positivity rate. Median value for both basal PR positivity rate and ki 67 level (basal & postoperative) was 40%, as well. Since median value of ki 67 level in our study was different from reported cut-off value in the literature, we evaluated the prognostic role of ki 67 according to both cut-off levels as 20 (i.e. literature) and 40 (i.e. median value), as mentioned before in Methods section. One hundred and twelve (78.9%) patients had higher ki 67 (> 20%). Median mPEPI score was 5.0 (IQR: 4.0-7.0) for all patients while pCR subgroup had a trend towards to lower mPEPI score as 3.5 (IQR:2.0-4.5) versus 5 (4.0-7.0) (p= 0.052). Additionally, more patients in pCR subgroup had significantly lower (< 5.0) mPEPI score when compared with non-pCR subgroup (96.2% versus 31.6%, p< 0.001).

Median follow-up was 38 (range: 7-128) months. Median DFS or OS could not have been reached, yet. 5-year DFS and 5-year OS rates were as 69.1% & 77.7%, respectively. The patients who had pCR with neoadjuvant chemotherapy had better survival outcomes. 5-year DFS was significantly higher for the patients with pCR (93.8% versus 63%, p=0.012) (Figure 1). Similarly, median OS was almost higher in pCR subgroup (100% versus 72.1%, p= 0.018) (Figure 2).

The prognostic significance of clinical and pathological features for the patients with postoperative residual disease (i.e. non-pCR) were evaluated. Median age was 52 years (range: 29-76) almost in non-pCR subgroup. In univariate analysis, ki67 level and mPEPI score were determined as prognostic factors (Table 2). 'Basal' ki67 level according to the cut-off level by literature (i.e. 20) had no prognostic significance in non-pCR subgroup (p: 0.585, p: 0.524). However, 5-year DFS (89.4% versus 39.4, p< 0.001) and 5-year OS (92.3% versus 58%, p< 0.001) were higher for the patients with lower 'postoperative' ki67 level (< 20% versus >20%). On the other hand, 'basal & postoperative' ki 67 level according to median value (i.e. 40) and mPEPI score had prognostic significance for both DFS and OS. According to basal ki67 cut-off level as 40, postoperative ki 67 cut-off level as 40 and mPEPI score, 5-year DFS rates were as 75.4% versus 51% (p: 0.01), 69.8% versus 38.4% (p<0.001) and 92.9% versus 46.2% (p< 0.001) while 5-year OS rates were as 85.5% versus 59.9% (p: 0.006), 78.4% versus 60.8% (p= 0.003) and 100% versus 60.7% (p: 0.001), respectively. In addition, the patients who had prominent ki67 decline with neoadjuvant chemotherapy had a better DFS and more likely to have better OS trend. For these patients, 5-year DFS was 75.3% versus 50.6% and 5-year OS was 85.6% versus 64.3% (p= 0.017, p= 0.059, respectively).

Basal ER positivity rate, ki67 level, ki67 decline & mPEPI score were found to be significant in univariate analysis. Therefore, these parameters were reevaluated in multivariate analysis. First of all, multivariate analysis was performed according to both ki 67 cut off values as 20 & 40 for relapse and death risks in Model 1 (Table 3). Basal ki 67 cut-off value as 40 & postoperative ki 67 cut-off value as 20 were defined as significant prognostic factors in Model 1. Basal ki 67 cut-off value as 20 had no prognostic significance. Therefore, we performed Model 2 by including median ki 67 cut-off value as 40 for both basal & postoperative ki 67 levels in order to evaluate their prognostic roles in these patients. Basal ki 67 level & mPEPI score were prognostic factors in multivariate analysis (Table 3). The patients with higher basal ki 67 level (> 40%) & mPEPI score (> 5) had higher risk of relapse or

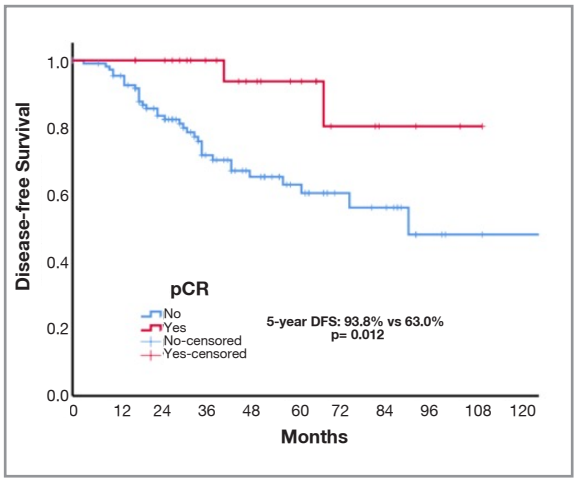

Figure 1. Disease free survival according to pCR

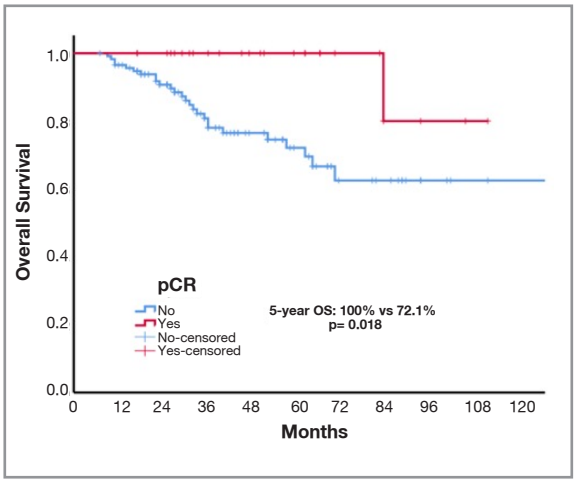

Figure 2. Overall survival according to pCR

death (p= 0.005, p= 0.014, p= 0.006, NA). None of the patients with higher mPEPI score has died at cut-off data date, Therefore, HR for OS could not have been estimated yet. However, postoperative ki 67 level had no prognostic significance. In addition, ki 67 decline with neoadjuvant chemotherapy did not differ for risk of relapse while the patients with prominent ki 67 decline had lower risk of death in Model 2 (p= 0.901, p= 0.022).

DISCUSSION

It is well-known that neoadjuvant treatment is a standard approach in locally advanced stage breast cancer. However, neoadjuvant treatment 'modality' (i.e. chemotherapy or endocrine treatment) is a dilemma in ER(+) / HER2(–) ones.

In our study, pCR rate was 18.3%. We evaluated the prognostic and predictive roles of clinicopathological features on neoadjuvant 'chemotherapy' efficacy in nonmetastatic HER2(–) luminal-like breast cancer. In parallel to the literature, the patients with smaller tumor size and higher grade had better outcomes, in terms of pCR with neoadjuvant chemotherapy (p= 0.037, p= 0.035). Since there is no also well-established data for predictive role of molecular genomic assays for neoadjuvant chemotherapy in this subgroup, we were canalized to evaluate the roles of other factors including mPEPI score. mPEPI score is prognostic and predictive for neoadjuvant endocrine therapy efficacy.[12,13] However, we also apply neoadjuvant treatment as neoadjuvant chemotherapy in luminal-like breast cancer patients. Therefore, it seems to be rationale to evaluate the role of mPEPI score for neoadjuvant chemotherapy efficacy in this population. When we evaluate mPEPI score after neoadjuvant chemotherapy, we determined that median mPEPI score was slightly lower in pCR subgroup (3.5 versus 5, p= 0.052). Almost in non-pCR subgroup, the patients with mPEPI score (< 5) had better DFS (p< 0.001) and OS (p= 0.001), leading to the consideration of its possible predictive value for neoadjuvant chemotherapy efficacy, as if for neoadjuvant endocrine treatment. In ALTERNATE trial, the patients with mPEPI score as 0 (pT1-2, pN0, ki67 < 2.7 %) after neoadjuvant endocrine therapy were reported to have lower risk of recurrence without adjuvant chemotherapy 12.13. However, our study differed from ALTERNATE trial in terms of neoadjuvant treatment modality, such as chemotherapy, 'not' endocrine treatment in ER(+) / HER2(–) breast cancer. Our study also revealed similar outcomes with ALTERNATE trial, in terms of better outcomes with lower mPEPI score despite different neoadjuvant treatment approaches. However, it is an indirect inference since it is not a head-to-head prospective comparison of neoadjuvant chemotherapy and endocrine treatment for prognostic and predictive roles of mPEPI score. So, we need randomized controlled clinical trials for more clear

Table 2. Univariate analysis for disease free survival and overall survival in non-pCR group

		Non pCR			
		5-year DFS (%)	p	5-year OS (%)	p
All patients (n: 116)		63.0	–	72.1	
Age	< 52 y (n: 54)	62.9	0.678	80.8	0.302
	≥ 52 y (n: 62)	67.6		63.0	
Menoposal status	Premenoposal (n: 53)	66.2	0.904	76.2	0.412
	Postmenoposal (n: 63)	59.2		62.8	
T stage	T1-2 (n: 74)	66.6	0.684	73.8	0.414
	T3-4 (n: 42)	58.2		70.0	
N stage	N0 (n: 6)	75.0	0.548	100	0.772
	N1 (n: 43)	60.2		71.2	
	N2 (n: 67)	62.1		69.0	
ER (%) at diagnosis	< 10 (n: 12)	54.0	0.111	51.9	0.108
	> 10 (n: 104)	63.9		74.4	
PR (%) at diagnosis	< 20 (n: 38)	61.1	0.679	70.8	0.601
	≥ 20 (n: 78)	63.7		72.7	
PR (%) postoperative	< 20 (n: 34)	66.5	0.957	76.7	0.740
	≥ 20 (n: 58)	56.0		70.3	
Ki-67 (%) at diagnosis	< 20 (n: 17)	75.0	0.585	86.3	0.524
	≥ 20 (n: 92)	60.2		69.4	
Ki-67 (%) at diagnosis	< 40 (n: 52)	75.4	0.010	85.5	0.006
	≥ 40 (n: 57)	51.0		59.9	
Ki-67 (%) postoperative	< 20 (n: 40)	89.4	<0.001	92.3	<0.001
	≥ 20 (n: 53)	39.4		58.0	
Ki-67 (%) postoperative	< 40 (n: 69)	69.8	<0.001	78.4	0.003
	≥ 40 (n: 2)	38.4		60.8	
Ki-67 decline rate (%)	< 30% (n: 33)	50.6	0.017	64.3	0.059
	≥ 30% (n: 55)	75.3		85.6	
MPEPI score	< 5	92.9	<0.001	100	0.001
	≥ 5	46.2		60.7	

pCR= Pathological complete response, DFS= Disease-free survival, OS= Overall survival, ER= Estrogen receptor, PR= Progesterone receptor, mPEPI= modified preoperative endocrine prognostic index

data in this area. To best of our knowledge, the role of mPEPI score has not been clearly evaluated for outcomes of neoadjuvant chemotherapy in HER2(–) luminal-like breast cancer. Therefore, we consider that our study may contribute to the literature from this point of view, in spite of a small sample size in a retrospective design.

Proliferation indices, such as grade and ki 67 are well-known prognostic factors. Luminal A-like breast cancer patients have favorable prognosis with lower grade, lower ki 67 level, higher ER and PR rates. However, luminal B-like breast cancer subtype differs for PR rate, ki 67 level and HER2 positivity. HER2 (+) luminal B-like breast cancer patients are mainly treated by anti-HER2-based treatments. However, HER2(-) luminal B-like subtype is a heterogenous process, especially for PR positivity rate and/or ki 67 level. These pathological features have mainly role in decision of adjuvant/neoadjuvant chemotherapy in early stage, especially for those in whom molecular genomic tests are no feasible. In recent years, ki 67 has been focused as a dynamic predictive biomarker in ER(+) / HER2(-) early stage breast cancer.[14] In WSG-ADAPT trial, the predictive role of short term (i.e. 3 weeks) preoperative endocrine treatment response by ki 67 decrease and its correlation with Oncotype Dx recurrence score (RS) was evaluated in nonmetastatic ER(+) / HER2(-) breast cancer.[14] The patients without nodal involvement

Table 3. Cox regression model 1 and model 2 to determine the independent prognostic factors for DFS and OS

		DFS		OS	
Model 1		**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Ki 67 %	< 40	1.00	0.016	1.00	0.039
	≥ 40	3.256 (1.244-8.521)		3.394 (1.062-10.846)	
Ki 67 po %	< 20	1.00	0.004	1.00	0.025
	≥ 20	8.312 (1.941-35.585)		10.110 (1.329-76.919)	
Ki 67 decline %	≥ 30	1.00	0.731	1.00	0.752
	< 30	0.783 (0.194-3.154)		1.303 (0.252-6.745)	
mPEPIscore	≤ 4	1.00	0.175	NA	NA
	> 4	4.879 (0.495-48.123)		NA	
Model 2					
Ki 67 %	< 40	1.00	0.005	1.00	0.006
	≥ 40	3.967 (1.518-10.368)		5.445 (1.612-18.390)	
Ki67 po %	< 40	1.00	0.105	1.00	0.772
	≥ 40	2.159 (0.851-5.480)		1.213 (0.327-4.501)	
Ki 67 decline %	≥ 30	1.00	0.901	1.00	0.022
	< 30	1.090 (0.278-4.278)		4.579 (1.244-16.862)	
mPEPIscore	≤ 4	1.00	0.014	NA	NA
	> 4	12.541 (1.678-93.706)		NA	

or up to 3 lymph nodes involvement (i.e. N0-N1) with early endocrine response (ki 67 <10%) & intermediate risk recurrence scores (RS: 12-25) did well on adjuvant endocrine treatment, as if those with low risk subgroup (RS: 0-11).[14] So, ki 67 as a dynamic predictive factor has clinical significance. Optimal ki 67 cut-off value is not so clear, but 20% as a cut-off value for ki 67 has been more agreed in recent years.[2,4] Therefore, we evaluated our patients for both levels as 20 and median value (i.e. 40) in our study as cut-offs for ki 67, as we mentioned before. The patients with pCR had better survival, in paralel to the literature. The patients who had residual disease (i.e. non-pCR) had conflicting outcomes according to ki 67 cut-off values. In non-pCR group, the patients who had prominent ki 67 decline (ki 67 <%30) with neoadjuvant chemotherapy had better prognosis. Postoperative ki 67 cut-off value (i.e. 20 or 40) did not differ for prognosis in non-pCR group. Interestingly, basal cut-off value as 20 failed to have prognostic significance while 40 was shown to have significance. We consider that higher ki 67 cut-off value (40 versus 20) covers more tumors with more higher proliferation index leading to the possibility of achieveing lower residual tumor volume with neoadjuvant chemotherapy, almost in non-pCR group. Prominent ki 67 decline also supports this hypotheses. The more proliferative tumor with higher basal ki 67 level, the more tumor volume decrease with neoadjuvant chemotherapy, as well.

In conclusion, HER2(-) luminal B-like breast cancer is a heterogenous subtype. In our study, favorable prognostic factors were defined as lower basal ki 67 level (< 40%) & higher ki 67 decline (ki 67 <30%) for OS and lower basal ki 67 (< 40%), postoperative ki 67 (< 20%) & mPEPI score (< 4) for DFS. 'Basal' ki 67 cut-off level as 40, rather than 20 seems to have clinical significance whereas it does not matter for 'postoperative' ki 67 cut-off levels (i.e. 20 or 40). mPEPI score may also have prognostic and predictive significance for neoadjuvant 'chemotherapy'. mPEPI score was found to be a prognostic factor for those with pCR after NAK, leading to a possible contribution to the literature. We consider that basal and postoperative ki 67 levels, besides ki 67 decline & mPEPI score may contribute to the selection of best candidates for NAK in locally advanced ER(+) / HER2(-) breast cancer population. However, a more comprehensive randomized trial can be performed with a larger number of patients.

REFERENCES

1. Goldhirsch A, Ingle JN, Gelber RD, et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer. Ann Oncol 20: 319-329, 2009.
2. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer. Ann Oncol 22: 1736-1747, 2011.
3. Harbeck N, Thomssen C, Gnant M. St. Gallen 2013: brief preliminary summary of the consensus discussion. Breast Care (Basel) 8: 102-109, 2013.
4. Ono M, Tsuda H, Yoshida M, et al. Prognostic Significance of Progesterone Receptor Expression in Estrogen-Receptor Positive, HER2-Negative, Node-Negative Invasive Breast Cancer With a Low Ki-67 Labeling Index. Clin Breast Cancer 17: 41-47, 2017.
5. Sparano J, Gray RJ, Wood WJ, et al. TAILORx: Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor positive HER2 negative node negative breast cancer and an intermediate prognosis 21-gene recurrens score. J Clin Oncol 36: suppl LBA1, 2018.
6. Kalinsky K, Barlow WE, Meric-Bernstam F, et al. 21-Gene Assay to Inform Chemoteharpy Benefit in Node-positive Breast Cancer. N Engl J Med 385: 2336-2347, 2021.
7. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med 379: 111-121, 2018.
8. Albain KS, Barlow WE, Shak S, et al. Breast Cancer Intergroup of North America. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol 11: 55-65, 2010.
9. Cardoso F, van't Veer LJ, Bogaerts J, et al. MINDACT Investigators. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med 375: 717-729, 2016.
10. Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol 22: 476-488, 2021.
11. Ellis MJ, Tao Y, Luo J, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst. 100: 1380-1388, 2008.
12. Suman VJ, Ellis MJ, Ma CX. The ALTERNATE trial: assessing a biomarker driven strategy for the treatment of post-menopausal women with ER+/Her2- invasive breast cancer. Chin Clin Oncol 4: 34-40, 2015.
13. Ma CX, Suman V, Leitch AM, et al. ALTERNATE: Neoadjuvant endocrine treatment (NET) approaches for clinical stage II and III estrogen receptor-positive HER2-negative breast cancer (ER+ HER'- BC) in postmenopusal (PM) women: Alliance A011106. J Clin Oncol 38; 504, 2020.
14. Nitz UA, Gluz O, Kümmel S, et al. Endocrine Therapy Response and 21-Gene Expression Assay for Therapy Guidance in HR+/HER2- Early Breast Cancer. J Clin Oncol 40: 2557-2567. 2022.

Correspondence:

Dr. Mutlu DOGAN

Saglik Bilimleri Universitesi

Dr Abdurrahman Yurtaslan Ankara Oncoloji

Egitim ve Arastirma Hastanesi

Tibbi Onkoloji Bolumu, 06200, Yenimahalle

ANKARA / TURKIYE

Tel: (+90-505) 713 45 39

e-mail: mutludogan1@yahoo.com

ORCIDs:

Mutlu Dogan	0000-0001-9359-3770
Cengiz Karacin	0000-0002-7310-9328
Omur Kaman	000-0001-5489-8133
Zarife Melda Bulut	000-0000-0000-0000
Gamze Kiziltan	0000-0003-2637-592X
Berna Oksuzoglu	000-0000-0000-0001
Lutfi Dogan	0000-0002-3834-0911