Real-World Pathologic Complete Response Rates with Neoadjuvant Pembrolizumab in Stage II–III Triple-Negative Breast Cancer: Impact of Ki-67 Proliferation Index

Gokhan SAHIN, Oguzcan OZKAN, Caner ACAR, Haydar Cagatay YUKSEL, Sercan ON, Hasan Cagri YILDIRIM, Burcu CAKAR, Erhan GOKMEN

Ege University, Faculty of Medicine, Department of Medical Oncology

ABSTRACT

The addition of immunotherapy to neoadjuvant chemotherapy (NAC) has shown promising efficacy in early-stage triple-negative breast cancer (TNBC), particularly in achieving pathologic complete response (pCR). However, real-world data remain limited. This study aimed to evaluate pCR rates and potential predictive factors in a real-world cohort of patients with stage II–III TNBC receiving neoadjuvant pembrolizumab-based chemotherapy. We retrospectively analyzed 4 4 TNBC patients treated at Ege University between 2022–2024. All received pembrolizumab plus taxane- and anthracycline-based NAC. Clinical and pathological variables, including Ki-67 index, were analyzed for associations with pCR. The overall pCR rate was 56.8%, which is broadly comparable to real-world reports but slightly lower than clinical trials. No standard clinicopathologic variable, including age, stage, histology, or nodal status, significantly predicted pCR. While conventional Ki-67 cut-offs (≥ 30% or median) were not predictive, a ROC-derived threshold of ≥ 75% was significantly associated with higher pCR rates (OR 5.67; p= 0.042), although its discriminative ability was limited (AUC= 0.598). Neoadjuvant pembrolizumab yields pCR rates comparable to real-world reports but modestly lower than clinical trial outcomes. Extremely high Ki-67 proliferation index (≥ 75%) may help identify responders, though larger studies are warranted for validation.

Keywords: Triple-negative breast cancer, Neoadjuvant chemotherapy, Pembrolizumab, Pathologic complete response, Ki-67

INTRODUCTION

Triple-negative breast cancer (TNBC) is defined by the absence of estrogen and progesterone receptors and HER2, accounting for approximately 10-20% of all breast cancers and often affecting younger patients.[1,2] TNBC exhibits aggressive behavior with high histologic grade, early visceral metastasis, and a higher risk of recurrence compared to other subtypes.[3] Due to the lack of actionable targets, conventional cytotoxic chemotherapy has long been the backbone of systemic treatment for early TNBC.[4] Indeed, until recently, therapy for early-stage TNBC relied solely on surgery and chemotherapy, and outcomes were poorer than in other breast cancer subtypes.[5]

Neoadjuvant chemotherapy (NAC) is commonly used in TNBC to improve surgical options and assess treatment response pathologically.[6] Achieving a pathologic complete response (pCR) after NAC strongly correlates with improved long-term outcomes.[7] Despite the chemosensitivity of TNBC, standard anthracycline- and taxane-based regimens produce pCR in only 30-40% of patients. Incorporating platinum agents modestly increases this rate to approximately 50-55%. In the CALGB 40603 trial, adding carboplatin to standard NAC improved pCR from 41% to 54%.[8] Nevertheless, a substantial proportion of patients still have residual disease after NAC, underscoring the need for more effective systemic strategies in the neoadjuvant setting.

Immunotherapy has recently emerged as a transformative approach in TNBC. Early-phase studies combining immune checkpoint inhibitors with chemotherapy demonstrated encouraging efficacy in high-risk patients. The phase 1b KEYNOTE-173 trial of neoadjuvant pembrolizumab with various chemotherapy backbones showed manageable safety and pCR rates approaching 60% in early-stage TNBC.[9] Building on this, phase III trials such as IMpassion031[10] and KEYNOTE-522[11] confirmed that adding anti–PD-1/PD-L1 therapy to standard NAC significantly improves pCR. In KEYNOTE-522, pembrolizumab plus chemotherapy yielded a pCR rate of 64.8% compared to 51.2% with chemotherapy alone, translating into durable event-free and overall survival benefits at long-term follow-up.[11] These results established pembrolizumab-based chemo-immunotherapy as the standard of care for high-risk, early-stage TNBC, leading to FDA approval in 2021.

While randomized trials have proven the efficacy of pembrolizumab, real-world validation remains limited. Patients enrolled in clinical trials are often younger, have fewer comorbidities, and receive more standardized care than those encountered in routine oncology practice. Consequently, the generalizability of trial outcomes to broader patient populations remains uncertain. Real-world data are essential to determine whether the magnitude of benefit observed in trials translates into everyday practice, particularly in diverse healthcare settings.

In light of these considerations, we aimed to evaluate our institutional experience with neoadjuvant pembrolizumab-based chemotherapy in stage II–III TNBC. The primary objective was to assess real-world pCR rates and explore potential predictive factors in a contemporary cohort, contributing to the growing evidence base supporting immunotherapy in early-stage disease.

PATIENTS AND METHODS

Study Design and Patient Selection

This retrospective, single-center study included patients diagnosed with stage II–III triple-negative breast cancer (TNBC) who received neoadjuvant chemotherapy (NAC) with pembrolizumab at the Department of Medical Oncology, Ege University Faculty of Medicine between January 2022 and December 2024. Eligible patients were ≥ 18 years old, had histologically confirmed TNBC (ER < 1%, PR < 1%, and HER2-negative according to ASCO/CAP criteria), and completed at least one cycle of pembrolizumab-based NAC. Patients were excluded if they had metastatic disease at initial diagnosis, a history of prior systemic therapy for breast cancer, or lacked evaluable pathological response data.

Treatment Protocol

All patients received NAC consisting of pembrolizumab (200 mg every 3 weeks) combined with a taxane-based regimen, followed by anthracycline + cyclophosphamide, in line with the KEYNOTE-522 protocol. The sequence of taxane and anthracycline administration (i.e., whether anthracycline was given before or after taxane) varied among patients based on routine clinical practice. Surgery was performed within 4-6 weeks after the last chemotherapy cycle.

Pathological Assessment and Data Collection

Demographic, clinical, and pathological variables were extracted from electronic medical records, including age, menopausal status, clinical stage, nodal status, tumor histology, Ki-67 index, and sequencing of anthracycline administration. Ki-67 was analyzed both as a continuous variable and as categorical variables based on predefined cut-offs (30%, median value, and ROC-derived threshold).

Pathologic evaluations were performed by the institutional breast pathology team at Ege University, based on routine diagnostic reports. Ki-67 immunostaining was evaluated on formalin-fixed, paraffin-embedded tumor sections as part of routine diagnostic practice, and the percentage of tumor cells with nuclear staining was visually estimated as the Ki-67 proliferation index. Cases with missing clinicopathologic or outcome data were excluded from the corresponding analyses; no imputation was performed.

Pathological complete response (pCR) was defined as the absence of residual invasive cancer in the breast and axillary lymph nodes (ypT0/Tis, ypN0) according to the Residual Cancer Burden criteria. All pathological evaluations were conducted by experienced breast pathologists who were blinded to clinical data.

Table 1. Baseline characteristics of the study populatio

Characteristic	n (%)
Age	
Median (range), yr	50 (25-83)
< 65 yr	38 (86.4)
≥ 65 yr	6 (13.6)
Menopausal status	
Premenopausal	24 (54.5)
Postmenopausal	20 (45.5)
Histology	
IDC	24 (54.5)
Invaziv Carcinoma, NOS	6 (13.6)
Apocrine Differantie Carcinoma	3 (6.8))
Metaplastic Carcinoma	6 (13.6)
Other	5 (11.4)
Administration of anthracycline (AC)	
Before taxane	13 (31.7)
After taxane	28 (68.3)
Primary lesion type	
Unifocal	32 (72.7)
Multifocal / Multicentric	12 (27.3)
Primary tumor classification (T stage)	
T1–T2	35 (79.5)
T3–T4	9 (20.5)
Nodal involvement	
Negative	10 (22.7)
Positive	34 (77.3)
Overall disease stage	
Stage II	29 (65.9)
Stage III	15 (34.1)
Pembrolizumab cycle	
< 8	22 (50)
≥ 8	22 (50)

Abbreviations: *IDC= invasive ductal carcinoma; NOS= not otherwise specified; AC= anthracycline; T= tumor*

Ethical Approval: The study was approved by Ethical Review Board of Ege University Hospital; August 20, 2025 and No: 2025-5500 25-8T/44.

Statistical analysis

Descriptive statistics were presented as median (range) for continuous variables and as frequency (percentage) for categorical variables. Comparisons between categorical variables were performed using the chi-square test or Fisher's exact test, as appropriate. Univariate logistic regression analysis was conducted to evaluate potential predictors of pCR, with results reported as odds ratios (ORs) and 95% confidence intervals (CIs). Variables with a p-value < 0.10 in the univariate analysis were entered into the multivariate logistic regression model. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value of Ki-67 for predicting pCR. All statistical analyses were performed using SPSS software, version 28.0.1.1 (IBM Corp., Armonk, NY, USA). A two-tailed p-value < 0.05 was considered statistically significant.

RESULT

Baseline Demographic and Clinical Characteristics

A total of 44 patients with stage II–III TNBC who received neoadjuvant pembrolizumab-based chemotherapy were included in the analysis. The median age was 50 years (range, 25-83), and the majority were younger than 65 years (86.4%). More than half of the patients were premenopausal (54.5%). The most common histological subtype was invasive ductal carcinoma (54.5%), followed by invasive carcinoma not otherwise specified (13.6%) and metaplastic carcinoma (13.6%). Anthracycline was administered before taxane in 31.7% of patients and after taxane in 68.3%.

Most patients had unifocal tumors (72.7%) and T1–T2 stage disease (79.5%). Nodal involvement was present in 77.3% of patients. Overall, 65.9% of patients had stage II disease, while 34.1% had stage III disease. Half of the patients (50%) received ≥ 8 cycles of pembrolizumab. Among those receiving < 8 cycles, one patient discontinued treatment after the 5th cycle due to grade 3 immune-related colitis, and another after the 7th cycle due to immune-related pancreatitis. In the remaining patients, treatment was discontinued before the 8th cycle due to reimbursement limitations and inability to obtain the drug. Baseline characteristics of the study cohort are summarized in Table 1.

Pathological Complete Response According to Clinicopathologic Subgroups

Overall, pCR was achieved in 25 patients (56.8%). Numerically higher pCR rates were observed in patients aged < 65 years compared to those ≥ 65 (60.5% vs. 33.3%, p= 0.211) and in premenopausal

Table 2. Pathological complete response (pCR) rates according to clinicopathologic subgroups

		Non-pCR n (%)	pCR n (%)	p
Age group	< 65	15 (78.9)	23 (92.0)	0.211
≥65		4 (21.1)	2 (8.0)	
Menopausal status	Premenopozal	8 (42.1)	16 (64.0)	0.149
	Postmenopozal	11 (57.9)	9 (36.0)	
Stage group	II	11 (57.9)	18 (72.0)	0.328
	III	8 (42.1)	7 (28.0)	
T_stage group	T1–2	13 (68.4)	22 (88.0)	0.111
	T2-3	6 (31.6)	3 (12.0)	
Nodal stage group	negative	3 (15.8)	7 (28.0)	0.338
	positive	16 (84.2)	18 (72.0)	
Histology group	IDC	9 (47.4)	15 (60.0)	0.405
	Non-IDC	10 (52.6)	10 (40.0)	
AC administration time	Before taxane	7 (43.8)	6 (24.0)	0.185
	After taxane	9 (56.3)	19 (76.0)	
Primary lesion	Single	13 (68.4)	19 (76.0)	0.576
	Multifocal or Multicentric	6 (31.6)	6 (24.0)	
Pembrolizumab cycle	< 8	12 (63.2)	10 (40.0)	0.128
	≥ 8	7 (36.8)	15 (60.0)	
Ki-67 median	< 57.5	10 (52.6)	12 (48.0)	0.761
	≥ 57.5	9 (47.4)	13 (52.0)	

Abbreviations: *IDC= invasive ductal carcinoma; AC= anthracycline; T= tumor; pCR= pathological complete response*
P values were calculated using the chi-square test.

versus postmenopausal patients (66.7% vs. 45.0%, p= 0.149), though neither reached statistical significance. Patients with stage II disease achieved pCR more often than those with stage III (62.1% vs. 46.7%), and pCR rates were higher in T1–T2 tumors compared with T3-T4 (62.9% vs. 33.3%, p= 0.111). Baseline nodal status showed no significant association (70.0% for node-negative vs. 52.9% for node-positive). No significant differences in pCR were observed across histological subtype, anthracycline sequencing, lesion focality, number of pembrolizumab cycles, or Ki-67 median value (Table 2).

Univariate Analysis of Predictors of pCR

In the univariate logistic regression analysis (Table 3), none of the evaluated clinicopathologic

Table 3. Univariable logistic regression for predictors of pCR

Variable		OR	95% CI	p
Age group	≤ 65 vs > 65	3.07	0.50-18.88	0.227
Menopausal status	Pre vs Post	2.44	0.72-8.31	0.152
Histology	IDC vs non-IDC	1.67	0.50-5.56	0.406
AC administration time	Before taxane vs After taxane	0.41	0.11-1.56	0.190
Primary lesion type	Unifocal vs Multifocal/Multicentric	1.46	0.39-5.55	0.577
T stage group	T1-2 vs T3-4	3.39	0.72-15.89	0.122
Nodal involvement	Negative vs Positive	2.07	0.46-9.40	0.344
Clinical stage group	Stage II vs III	1.87	0.53-6.60	0.331
Pembrolizumab cycles	< 8 cycles vs ≥ 8 cycles	0.39	0.11-1.33	0.132

Abbreviations: *OR= odds ratio; CI= confidence interval; IDC= invasive ductal carcinoma; AC= anthracycline; pCR= pathological complete response.*
P-values were calculated using Wald chi-square test from logistic regression models.

Table 4. Logistic Regression for Ki-67 as Continuous and Categorical Variables

Variable		OR	95% CI	p
Ki67 (continuous)	—	1.012	0.985–1.040	0.384
Ki67 ≥ 30	≥ 30 vs < 30	1.462	0.385–5.545	0.577
Ki67 ≥ median	≥ median vs < median	1.204	0.365–3.974	0.761
Ki67 ≥75 (ROC cut-off)	≥ 75 vs <75	5.667	1.067–30.085	0.042

Abbreviations: *OR= odds ratio; CI= confidence interval; ROC= receiver operating characteristic. p-values were calculated using Wald chi-square test from logistic regression models.*

variables were significantly associated with pCR. Patients aged < 65 years had a higher, though non-significant, likelihood of achieving pCR (OR 3.07, 95% CI 0.50-18.88, p= 0.227), and premenopausal patients showed a similar trend (OR: 2.44, 95% CI 0.72-8.31, p= 0.152). Tumor stage (T1-2 vs T3-4; OR: 3.39, 95% CI: 0.72-15.89) and nodal status (negative vs positive; OR: 2.07, 95% CI: 0.46–9.40) did not demonstrate significant associations. Other variables including histological subtype, anthracycline sequencing, lesion focality, and number of pembrolizumab cycles were also non-predictive.

Ki-67 as a Predictor of pCR

Ki-67 was evaluated as both a continuous and categorical variable (Table 4). When analyzed continuously, Ki-67 expression did not show a statistically significant association with pCR (OR: 1.012, 95% CI: 0.985–1.040; p= 0.384). Likewise, categorization using conventional cut-offs ≥ 30% vs. <30% (OR: 1.462, 95% CI: 0.385–5.545; p= 0.577) and ≥ median vs. < median (OR: 1.204, 95% CI: 0.365–3.974; p= 0.761) did not reveal significant predictive value.

However, receiver operating characteristic (ROC) curve analysis identified a Ki-67 threshold of ≥ 75% as the optimal cut-off for predicting pCR (Figure 1). The AUC was 0.598 (95% CI: 0.43-0.77; p= 0.271), indicating modest discriminatory ability. Patients with Ki-67 ≥ 75% had a significantly higher likelihood of achieving pCR compared to those with Ki-67 < 75% (OR: 5.667, 95% CI: 1.067–30.085; p= 0.042). Despite the limited AUC, this high Ki-67 cut-off may help identify a subgroup with a more favorable response to pembrolizumab-based neoadjuvant chemotherapy.

DISCUSSION

Our real-world cohort of 44 stage II–III triple-negative breast cancer (TNBC) patients treated with neoadjuvant pembrolizumab plus chemotherapy achieved a pathologic complete response (pCR) rate of 56.8%. This outcome is notably lower than the 64.8% pCR reported in the pembrolizumab arm of the phase III KEYNOTE-522 trial, which established this combination as a new standard of care for early-stage TNBC.[11] Nonetheless, our findings remain within the expected response range, particularly when considering the complexities of real-world clinical practice.

Real-world data from other retrospective cohorts have likewise reported modestly lower pCR rates compared to KEYNOTE-522. For instance, a Portuguese cohort of 70 patients reported a pCR rate of 52.6%, while another multicenter study noted 59.3% pCR in routine settings.[12,13] Several factors may explain this consistent pCR gap between trial and real-world outcomes. Clinical trials tend to involve younger, healthier, and more closely monitored patients, whereas routine care must account for a broader range of patient comorbidities, treatment toxicities, and logistical constraints. In our own cohort, only 50% of patients were able to complete all eight planned cycles of neoadjuvant pembrolizumab. This was primarily due to immune-related adverse events or insurance reimbursement issues limitations rarely encountered in a tightly regulated trial environment. Despite these barriers, more than half of our patients still achieved pCR, underscoring the robust efficacy of chemo-immunotherapy even in less-than-ideal conditions.

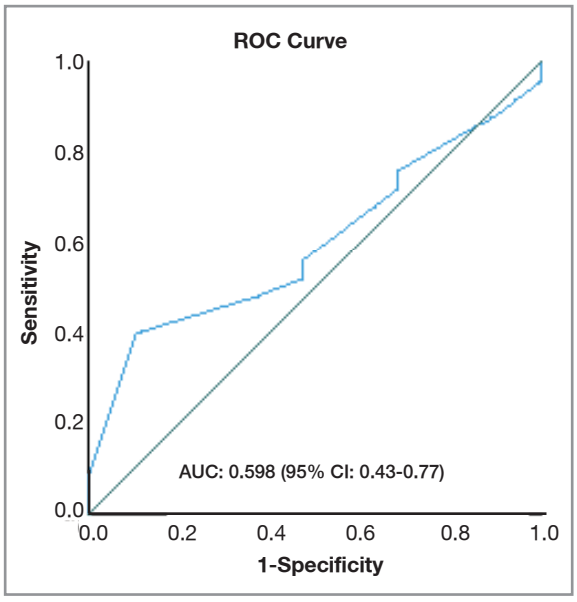

Figure 1. Receiver operating characteristic (ROC) curve for Ki-67 in predicting pathological complete response (pCR) in patients receiving neoadjuvant pembrolizumab-based chemotherapy

A key objective of our study was to identify predictive biomarkers of response, with a focus on the proliferation marker Ki-67. In our analysis, Ki-67 (whether treated as a continuous variable or using conventional cut-offs like 30% or the cohort median ~57%) was not significantly associated with pCR. However, an exploratory ROC curve identified an unusually high Ki-67 threshold (≥ 75%) as optimal for distinguishing responders. Patients with Ki-67 ≥ 75% had a markedly higher pCR rate than those with lower Ki-67 (OR ~5.67, p= 0.042). Although based on a small sample, this exploratory signal should be interpreted cautiously as a hypothesis-generating observation, suggesting that extremely proliferative tumors may be especially sensitive to neoadjuvant therapy, consistent with the general notion that highly proliferative cancers are more chemosensitive.[14] Indeed, abundant evidence links high Ki-67 to increased pCR rates. For example, a meta-analysis of 36 studies (~6,800 patients) found that breast cancers with high Ki-67 had nearly a four-fold greater odds of achieving pCR compared to those with low Ki-67.[15] In TNBC specifically, many studies have shown that elevated Ki-67 correlates with better response to neoadjuvant chemotherapy.[16,17] Wang et al. reported that in a cohort of 280 TNBC patients (treated with weekly paclitaxel plus carboplatin), both continuous Ki-67 and high Ki-67 status were independent predictors of pCR (p< 0.001) 16. Similarly, a recent prospective series from Institut Curie found that TNBC tumors with Ki-67 ≥ 30% had far higher pCR rates – with Ki-67 ≥ 30% emerging as a strong independent predictor of pCR (OR~5.2) in multivariate analysis alongside other factors such as abundant tumor-infiltrating lymphocytes.[18] Despite the observed associations, the predictive value of Ki-67 should be interpreted with caution. In our cohort, the ROC-derived cut-off of 75% although statistically significant emerged from a relatively small sample and showed only modest discriminative capacity (AUC ≈ 0.60). Moreover, Ki-67 thresholds reported in the literature vary considerably, with proposed cut-offs ranging from 20% to above 50%.[19-21] This variability largely stems from a lack of assay standardization and significant inter-observer differences in scoring, particularly in tumors with focal "hot spot" proliferation.[14] Such inconsistencies continue to limit the clinical applicability of Ki-67 as a stand-alone biomarker.

Beyond technical limitations, the biological role of Ki-67 is also complex. While tumors with high proliferation indices generally demonstrate better response to cytotoxic therapy, they often exhibit more aggressive behavior and worse outcomes if residual disease persists. In a meta-analysis by Tao et al., high Ki-67 tumors were significantly more likely to achieve pCR, yet among those who did not, relapse risk was nearly twice as high compared to their low Ki-67 counterparts.[15] Similar findings have been echoed in TNBC-specific studies, suggesting that Ki-67 may carry both predictive and adverse prognostic implications.[22-24] Taken together, these data suggest that while a high Ki-67 index may help identify patients more likely to respond to neoadjuvant chemo-immunotherapy, it should not be used in isolation. While our findings suggest that tumors with very high proliferation are more likely to respond to neoadjuvant chemo-immunotherapy, Ki-67 should be interpreted alongside other clinical and pathological features. Variability in scoring and the lack of standardization remain major limitations. Larger, prospective studies using harmonized methods are needed to better define how Ki-67 can be integrated into routine clinical practice.

Consistent with other reports, we found that no standard clinicopathologic features (e.g. age, stage, histologic subtype) significantly predicted pCR in our TNBC patients.[25] This highlights a persistent gap in our ability to stratify patients based on traditional factors, and underscores the need for robust, biomarker-driven approaches to guide immunotherapy use. Real-world studies play a crucial role in this context by verifying trial findings in broader patient populations and by generating hypotheses for biomarker discovery.

At the same time, they come with important limitations. Our study is limited by its retrospective nature, single-center design, and relatively small sample size, which restrict statistical power and the generalizability of the findings. The lack of a validation cohort further limits external confirmation of our results. Additionally, the follow-up duration was insufficient to evaluate long-term outcomes such as event-free or overall survival, precluding survival analyses. Without a randomized control arm, comparisons with historical controls must be interpreted cautiously. A recent institutional series, for example, reported no significant difference in short-term (2.4-year) survival outcomes between patients who received the KEYNOTE-522 regimen and those who received chemotherapy alone[13], whereas the 5-year results of KEYNOTE-522 have confirmed durable event-free and overall survival gains with pembrolizumab.[26] Finally, potential confounders inherent to real-world settings such as variability in treatment access, insurance coverage, and socioeconomic factors may also have influenced treatment delivery and outcomes. This disparity likely reflects the limited follow-up and sample size in real-world audits rather than an absence of long-term benefit. It underscores the importance of longer follow-up in real-world cohorts to capture the true survival benefit of neoadjuvant immunotherapy.

In summary, our real-world experience adds to the growing body of evidence supporting the clinical efficacy of neoadjuvant pembrolizumab in early-stage TNBC. It also highlights the need for improved patient selection strategies potentially involving biomarkers such as Ki-67 as well as practical considerations such as toxicity management and drug accessibility. To address the current limitations and validate potential predictive factors, prospective, multicenter studies with larger sample sizes and longer follow-up are warranted.

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Correspondence:

Dr. Burcu CAKAR

Ege Universitesi Tip Fakultesi

Tibbi Onkoloji Bolumu

35100 Bornova

IZMIR / TURKIYE

Tel: (+90-505 765 67 78)

e-mail: burcu.cakar@ege.edu.tr

ORCIDs:

Gokhan Sahin	0000-0003-1478-9383
Oguzcan Ozkan	0000-0002-4075-7775
Caner Acar	0000-0002-9782-6807
Haydar Cagatay Yüksel	0000-0001-8857-2983
Sercan On	0000-0003-1461-7485
Hasan Cagri Yildirim	0000-0003-3060-377X
Burcu Cakar	0000-0003-3790-791X
Erhan Gokmen	0000-0003-4596-2986