EJMI

DOI: 10.14744/ejmi.266171
EJMI 2026;10(2):171–178

Research Article

Real-World Outcomes of Neoadjuvant Pembrolizumab plus Chemotherapy in Early-Stage Triple-Negative Breast Cancer: A Multicenter Study from Türkiye

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Abstract

Objectives: Neoadjuvant pembrolizumab plus chemotherapy is the standard of care for high-risk early-stage triple-negative breast cancer (eTNBC), yet real-world data remain limited. We evaluated the effectiveness and safety of this regimen in Türkiye.

Methods: This multicenter retrospective cohort study included consecutive adults with stage I–III eTNBC treated with neoadjuvant pembrolizumab plus chemotherapy between 2022 and 2025 at four centers. Primary endpoints were pathological complete response (pCR) and event-free survival (EFS). Safety was assessed using CTCAE v5.0 criteria.

Results: Sixty-one women were included (median age 44 years); 37.7% had stage III disease and 62.3% had nodal involvement. Most tumors were grade 3 (78.7%) with high Ki-67 (>=40% in 85.2%). Planned neoadjuvant chemotherapy was completed in 91.8% of patients. The pCR rate was 62.3%. At a median follow-up of 12.2 months, five EFS events (8.2%) occurred. Estimated 12- and 18-month EFS rates were 91.4% and 86.8%. pCR was the only significant predictor of EFS (1-year EFS 100% vs. 75.5%, p = 0.001). Grade >=3 adverse events were mainly hematologic, while severe immune-related toxicity was rare.

Conclusion: Neoadjuvant pembrolizumab plus chemotherapy demonstrated high pCR rates and preliminary favorable early survival outcomes in real-world practice, confirming pathological response as a key driver of prognosis in eTNBC.

Keywords: Breast Cancer, Neoadjuvant Therapy, Pembrolizumab, Real-World Evidence, Triple-Negative

Cite This Article: *Ismayilov R, Oğuz A, Akyıldız A, Hendem E, Almuradova E, Altundağ E, Altundağ K. Real-World Outcomes of Neoadjuvant Pembrolizumab plus Chemotherapy in Early-Stage Triple-Negative Breast Cancer: A Multicenter Study from Türkiye. EJMI 2026;10(2):171–178.*

Triple-negative breast cancer (TNBC) represents a biologically aggressive disease entity associated with frequent relapse and an unfavorable long-term prognosis. Neoadjuvant systemic therapy is preferred in early-stage TNBC (eTNBC) because it facilitates tumor downstaging, enables breast-conserving surgery, and allows the assessment of treatment response through pathological complete response (pCR), which serves as a strong surrogate for long-term outcomes.[1]

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Submitted Date: March 9, 2026 **Revision Date:** June 30, 2026 **Accepted Date:** July 3, 2026

The therapeutic approach to eTNBC has undergone a major shift with the incorporation of immunotherapy. The rationale for using immune checkpoint inhibitors (ICIs) is based on the observation that TNBC often exhibits a robust immune microenvironment, making it a prime candidate for therapies that enhance the anti-tumor T-cell response.[2,3] This hypothesis was tested in the landmark phase 3 KEYNOTE-522 trial, which evaluated the addition of the anti-programmed cell death protein-1 (PD-1) antibody pembrolizumab to standard neoadjuvant chemotherapy (NAC) for patients with previously untreated stage II or III TNBC.

The initial results of the KEYNOTE-522 trial demonstrated a statistically significant improvement in pCR rates, with 64.8% of patients in the pembrolizumab-chemotherapy arm achieving pCR compared to 51.2% in the placebo-chemotherapy arm.[4] Subsequent analyses confirmed that this benefit translated into a significant improvement in event-free survival (EFS).[5] Most recently, long-term follow-up data established a significant overall survival (OS) benefit, cementing the regimen of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab as the standard of care for high-risk eTNBC.[6]

While the results of this pivotal randomized controlled trial are practice-changing, clinical trials operate under strict inclusion and exclusion criteria, which may not fully represent the broader patient population encountered in routine clinical practice.[7] There is a critical need to validate the effectiveness and safety of the KEYNOTE-522 regimen in a real-world setting, where patients may present with a wider range of performance statuses and demographic characteristics. Data from diverse ethnic and geographic populations are essential to confirm the generalizability of the trial's findings.

To date, there is limited published real-world evidence on the outcomes of this regimen, particularly in low- and middle-income countries. Therefore, the primary aim of this study was to evaluate the real-world effectiveness and safety of neoadjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab, in a cohort of patients with eTNBC treated in Türkiye.

Methods

Study Design

This multicenter retrospective cohort analysis comprised patients managed and followed at four centers across Türkiye. We identified all consecutive patients with a diagnosis of eTNBC who initiated the KEYNOTE-522 treatment regimen between January 2022 and December 2025. Inclusion criteria required patients to be adults (>=18 years of age) with histologically confirmed, previously untreated, non-metastatic (stage I–III) invasive breast carcinoma. Triple-negative status was defined according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.[8,9] as estrogen receptor (ER) <1%, progesterone receptor (PR) <1%, and negative for human epidermal growth factor receptor 2 (HER2). Tumors were classified as HER2-negative if they demonstrated immunohistochemical (IHC) scores of 0–1+, or IHC 2+ without evidence of HER2 amplification by in situ hybridization. Patients were excluded if they presented with stage IV or recurrent disease, had received prior systemic treatment for breast cancer, or had insufficient data in their medical records for the evaluation of primary endpoints.

Ethical Considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments. The study protocol was approved by the Institutional Review Board of Başkent Universty (Project No: KA25/352; Approval Date: 02.10.2025). Given the retrospective design of the study and the use of anonymized data, the requirement for individual informed consent was waived.

Data Collection

A comprehensive data review was performed by retrospectively collecting information from electronic medical records, pharmacy records, and pathology archives. We extracted baseline patient characteristics, including age at diagnosis, menopausal status, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status, and germline BRCA1/2 mutation status, where available. Tumor characteristics collected included clinical tumor (T), nodal (N), and overall disease stage according to the American Joint Committee on Cancer (AJCC) 8th edition staging manual.[10], histological subtype, tumor grade, Ki-67 proliferation index, and HER2 IHC score. Detailed treatment data were recorded, including the chemotherapy sequence, carboplatin schedule, completion of planned NAC, type of surgery, and the utilization of adjuvant therapies.

Treatment Regimen

All included patients had an intention to be treated with the KEYNOTE-522 regimen as the standard of care.[4] The neoadjuvant phase consisted of pembrolizumab 200 mg intravenously every 3 weeks, administered concurrently with chemotherapy. The chemotherapy backbone involved four cycles of paclitaxel and carboplatin, administered either before or after four cycles of an anthracycline-based regimen (doxorubicin or epirubicin) plus cyclophosphamide. Following the completion of neoadjuvant therapy, patients underwent definitive breast and axillary surgery. Radiation

therapy was provided in the adjuvant setting based on standard clinical indications. Based on the physician's discretion, adjuvant pembrolizumab was continued every 3 weeks for up to nine additional cycles. Patients with residual disease following surgery were additionally considered for adjuvant capecitabine. Treatment was terminated in cases of disease progression, recurrence, or unacceptable toxicity.

Endpoints and Definitions

The primary endpoints of the study were pCR and EFS. pCR was assigned when invasive carcinoma was not detected in the breast or assessed axillary lymph nodes (ypT0/is ypN0) on examination of the surgical specimen. EFS was determined from the date of diagnosis until the occurrence of progression precluding definitive surgery, local or distant recurrence, the emergence of a second primary malignancy, or death from any cause. The secondary endpoint was safety and tolerability. Treatment-related adverse events (TRAEs) were systematically captured and graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.[11]

Statistical Analysis

All statistical analyses were conducted using R software, version 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria), utilizing the survival and survminer packages for survival analysis. Continuous variables were reported as medians with interquartile ranges (IQR), while categorical variables are presented as frequencies and percentages. EFS was estimated by the Kaplan-Meier method, with subgroup comparisons performed using the log-rank test to evaluate prognostic associations. A two-sided p-value of less than 0.05 was considered to indicate statistical significance.

Results

Baseline Characteristics

A total of 61 women with a median age of 44 years (IQR: 38–55) were included in the study (Table 1). The majority of the cohort was aged <65 years (88.5%) and premenopausal (65.6%). Most patients (82.0%) demonstrated an ECOG performance status of 0. Clinically, 95.1% of patients presented with stage II or III disease. Nodal involvement (cN1–N3) was present in 62.3% of cases, and 21.3% had T3 or T4 tumors.

The majority of tumors were invasive ductal carcinoma (85.2%); 78.7% were histological grade 3, and 85.2% exhibited a high Ki-67 proliferation index (>=40%). Germline BRCA1/2 mutations were detected in 9.8% of the total population (comprising 5 patients with BRCA1 and 1 patient with BRCA2 mutations). Regarding the chemotherapy backbone, 54.1% of patients received the taxane-platinum combination prior to the anthracycline regimen. Weekly carboplatin administration was the preferred schedule (65.6%) compared to the every-3-week regimen (34.4%).

Treatment Delivery and Pathological Response

The majority of patients (91.8%) completed the full course of planned NAC. Following neoadjuvant therapy, breast-conserving surgery was performed in 40 patients (65.6%), while 21 (34.4%) underwent mastectomy. The pCR rate was 62.3% (38/61). In the adjuvant setting, 91.8% of patients received radiotherapy. Adjuvant pembrolizumab was administered to 36.1% of patients, and 18.0% received adjuvant capecitabine (Table 2).

Survival Analysis

At a median follow-up of 12.2 months (95% CI: 10.2–14.2), a total of 5 EFS events (8.2%) were observed, and one patient (1.6%) died. The estimated 12-month and 18-month EFS rates for the entire cohort were 91.4% (95% CI: 83.0–99.8) and 86.8% (95% CI: 75.0–98.6), respectively.

Univariate analysis of prognostic factors revealed that attainment of pCR was the only statistically significant predictor of EFS (p=0.001). Patients who achieved a pCR had a 1-year EFS rate of 100%, compared to 75.5% in patients with residual disease (Fig. 1). None of the other factors, including patient demographics, tumor burden, biological features, or treatment-related variables, were significantly associated with EFS outcomes (Table 3).

Safety

The most frequently reported TRAEs of any grade were alopecia (68.9%), nausea (65.6%), neutropenia (55.7%), and

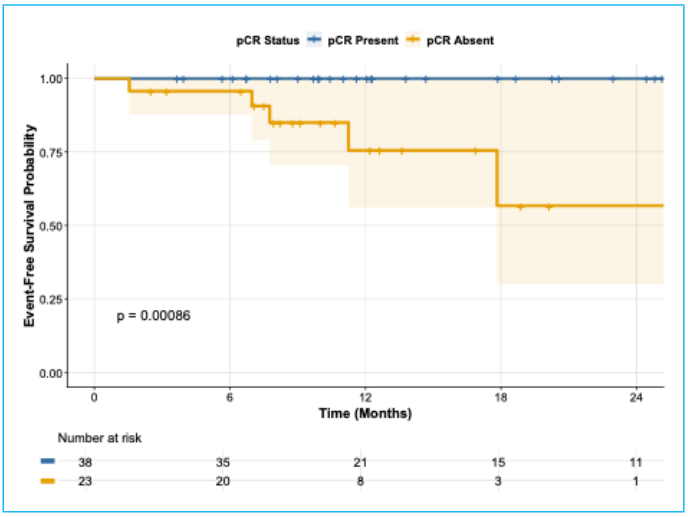

Figure 1. Kaplan-Meier estimates of event-free survival stratified by pathological complete response (pCR) status.

Table 1. Baseline characteristics (n=61)

Characteristic	Group	N (%)
Age	<65 years	54 (88.5)
	≥65 years	7 (11.5)
Menopausal status	Premenopausal	40 (65.6)
	Postmenopausal	21 (34.4)
Body mass index	<30 kg/m^2	41 (67.2)
	≥30 kg/m^2	20 (32.8)
ECOG-PS score	0	50 (82.0)
	1	11 (18.0)
Clinical T stage	T1 or T2	48 (78.7)
	T3 or T4	13 (21.3)
Clinical N stage	N0	23 (37.7)
	N1 to N3	38 (62.3)
Overall disease stage	I	3 (4.9)
	II	35 (57.4)
	III	23 (37.7)
Histological subtype	IDC	52 (85.2)
	Other	9 (14.8)
Grade	2	13 (21.3)
	3	48 (78.7)
Ki-67 index	<40%	9 (14.8)
	≥40%	52 (85.2)
HER2 status score	0-1	56 (91.8)
	2	5 (8.2)
BRCA1/2 mutation status	Positive	6 (9.8)
	Negative	37 (60.7)
	Unknown	18 (29.5)
Chemotherapy sequence	Prior PC	33 (54.1)
	Prior AC	28 (45.9)
Carboplatin schedule	Weekly	40 (65.6)
	Every 3 weeks	21 (34.4)

AC: Adriamycin (doxorubicin) and cyclophosphamide; BRCA1/2: Breast cancer gene 1/2; ECOG-PS: Eastern Cooperative Oncology Group performance status; HER2: Human epidermal growth factor receptor 2; IDC: Invasive ductal carcinoma; PC: Paclitaxel and carboplatin.

anemia (52.5%). Grade >=3 adverse events were predominantly hematological, with neutropenia (13.1%) and anemia (9.8%) being the most frequent.

Regarding potential immune-mediated adverse events, hypothyroidism occurred in 13.1% of patients and hyperthyroidism in 4.9%. Pneumonitis was rare, occurring in a single patient (1.6%) as a Grade >=3 event (Table 4). Treatment-related hospitalizations were required for 4 patients (6.5%), primarily managed for grade 3 neutropenia and pneumonitis. Pembrolizumab was permanently discontinued due to treatment-related adverse events in 3 patients (4.9%). No treatment-related deaths occurred during the study period.

Discussion

Table 2. Treatment delivery and pathological response (n=61)

Parameter	Group	N (%)
Completion of planned NAC	Yes	56 (91.8)
	No	5 (8.2)
Type of surgery	BCS	40 (65.6)
	Mastectomy	21 (34.4)
Pathological complete response	Present	38 (62.3)
	Absent	23 (37.7)
Adjuvant pembrolizumab	Yes	22 (36.1)
	No	39 (63.9)
Adjuvant capecitabine	Yes	11 (18.0)
	No	50 (82.0)
Adjuvant radiotherapy	Yes	56 (91.8)
	No	5 (8.2)

BCS: Breast-conserving surgery; NAC: Neoadjuvant chemotherapy.

This multicenter, retrospective cohort study provides real-world evidence on the implementation of neoadjuvant pembrolizumab combined with chemotherapy in patients with early-stage TNBC in Türkiye. Our analysis demonstrated a pCR rate of 62.3%, closely comparable to the 64.8% pCR rate reported in the KEYNOTE-522 trial.[4] Furthermore, our findings confirm the strong prognostic value of pCR and the manageable safety profile of the regimen, with no new or unexpected toxicity signals observed. Collectively, these results suggest that the efficacy and tolerability of the KEYNOTE-522 regimen are preserved when translated from controlled clinical trials into real-world oncology practice in this region.

The pCR rate observed in our cohort aligns not only with the registrational trial data but also with emerging real-world evidence from diverse geographic regions. A recent nationwide study from the Turkish Oncology Group reported a pCR rate of 63.9%.[12], while similar real-world analyses from the United States have reported rates ranging from 59.3% to 64.7%.[13-15] The consistency of these results across clinical trials and routine practice reinforces the robustness of the pembrolizumab-chemotherapy regimen, even when applied to unselected patient populations that may include comorbidities or performance statuses often excluded from randomized controlled trials.[7]

For instance, while the KEYNOTE-522 trial restricted enrollment to stage II–III disease, our cohort included a small number of patients (n=3) with clinical stage I disease. In routine practice, these patients with T1c tumors were selected for chemo-immunotherapy by multidisciplinary tumor boards due to highly aggressive tumor biology (e.g., very high Ki-67, grade 3 histology) and young age. Notably, our patient population was predominantly premenopausal (median age: 44 years) with high-grade tumors and high Ki-

Table 3. Univariate analysis of prognostic factors for 1-year event-free survival.

Factor	Group	N	1-year EFS, % (SE)	p*
Age	<65 years ≥65 years	54 7	90.2 (4.8) 100 (NA)	0.410
Menopausal status	Premenopausal Postmenopausal	40 21	90.8 (5.2) 93.8 (6.1)	0.645
Body mass index	<30 kg/m^2 ≥30 kg/m^2	41 20	90.4 (5.5) 93.8 (6.1)	0.663
ECOG-PS score	0 1	50 11	92.1 (4.6) 90.0 (9.5)	0.820
Clinical T stage	T1 or T2 T3 or T4	48 13	93.5 (4.5) 83.1 (11.0)	0.225
Clinical N stage	N0 N1 to N3	23 38	93.3 (6.4) 90.6 (5.2)	0.274
Overall disease stage	I II III	3 35 23	100 (NA) 90.9 (6.2) 90.6 (6.3)	0.855
Histological subtype	IDC Other	52 9	93.5 (3.6) 75.0 (21.7)	0.591
Grade	2 3	13 48	100 (NA) 88.7 (5.6)	0.208
Ki-67 index	<40% ≥40%	9 52	100 (NA) 89.7 (5.1)	0.306
HER2 status score	0-1 2	56 5	90.5 (4.7) 100 (NA)	0.503
BRCA1/2 mutation status	Positive Negative Unknown	6 37 18	100 (NA) 89.8 (5.7) 93.3 (6.4)	0.660
Chemotherapy sequence	Prior PC Prior AC	33 28	92.7 (5.0) 89.5 (7.4)	0.482
Carboplatin schedule	Weekly Every 3 weeks	40 21	91.4 (4.8) 92.3 (7.4)	0.883
Completion of planned NAC	Yes No	56 5	92.7 (4.3) 75.0 (21.7)	0.442
Type of surgery	BCS Mastectomy	40 21	92.7 (5.1) 90.2 (6.6)	0.181
Pathological complete response	Present Absent	38 23	100 (NA) 75.5 (11.4)	**0.001**
Adjuvant pembrolizumab	Yes No	22 39	90.9 (8.7) 91.3 (4.8)	0.809
Adjuvant capecitabine	Yes No	11 50	90.9 (8.7) 91.6 (4.8)	0.150
Adjuvant radiotherapy	Yes No	56 5	90.5 (4.7) 100 (NA)	0.466

AC: Adriamycin (doxorubicin) and cyclophosphamide; BRCA1/2: Breast cancer gene 1/2; ECOG-PS: Eastern Cooperative Oncology Group performance status; EFS: Event-free survival; HER2: Human epidermal growth factor receptor 2; IDC: Invasive ductal carcinoma; NA: Not applicable; PC: Paclitaxel and carboplatin; SE: Standard error. *Log-rank test. Bold text indicates statistical significance at p<0.05 level.

67 indices—features typically associated with aggressive biology but also high chemosensitivity.

Consistent with the established literature, our analysis supported the concept that pathological response is the strongest surrogate for early survival outcomes. In the univariate analysis, the attainment of pCR was the only statistically significant predictor of EFS. We observed a stark separation in outcomes: patients achieving pCR had a 1-year EFS of 100%, compared to 75.5% in those with residual disease. This finding mirrors the results of the CTNeoBC pooled

Table 4. Treatment-related adverse events (n=61)

Adverse event	Any grade, n (%)	Grade ≥3, n (%)
Alopecia	42 (68.9)	1 (1.6)
Nausea	40 (65.6)	2 (3.3)
Neutropenia	34 (55.7)	8 (13.1)
Anemia	32 (52.5)	6 (9.8)
Fatigue	26 (42.6)	2 (3.3)
Diarrhea	17 (27.9)	1 (1.6)
Increased aminotransferase level	15 (24.6)	2 (3.3)
Rash	13 (21.3)	0 (0.0)
Peripheral neuropathy	12 (19.7)	1 (1.6)
Hypothyroidism	8 (13.1)	0 (0.0)
Hyperthyroidism	3 (4.9)	1 (1.6)
Pneumonitis	1 (1.6)	1 (1.6)

analysis, which established pCR as a valid surrogate for long-term EFS and overall survival in TNBC.[16], as well as exploratory analyses from KEYNOTE-522, which demonstrated reduced recurrence rates across lower residual cancer burden categories in pembrolizumab-treated patients.[17]

While other variables, such as baseline nodal involvement, tumor stage, or BRCA mutation status, did not reach statistical significance in our survival analysis, this is likely attributable to the limited number of events and the constraints on statistical power inherent to the sample size, rather than a lack of biological relevance. In larger cohorts, such as the pivotal KEYNOTE-522 trial and recent extensive real-world analyses, advanced clinical stage and node-positive disease are traditionally established as predictors of worse EFS, even though the addition of pembrolizumab provides proportional survival benefits across these subgroups.[5,12]

Similarly, while our study did not show a prognostic impact of BRCA status, this finding is actually consistent with emerging literature suggesting that the efficacy of neoadjuvant chemo-immunotherapy is largely independent of BRCA mutations.[7] Nevertheless, future real-world studies with larger sample sizes are needed to fully evaluate the interplay between these traditional clinicopathological factors and long-term EFS in the immunotherapy era.

The interpretation of survival outcomes in this study must be contextualized by the follow-up duration. With a median follow-up of 12.2 months, our EFS data represent early survival signals rather than long-term efficacy. Due to the low number of events, the observed EFS differences between subgroups are exploratory in nature and preclude definitive conclusions regarding long-term prognosis. However, given that recurrence in TNBC typically peaks within the first 2 to 3 years following diagnosis, short-term EFS remains clinically informative. Recent analyses indicate that recurrences within 24 months account for the majority of relapse events in patients treated with neoadjuvant chemo-immunotherapy.[18] Consequently, the early divergence of survival curves between pCR and non-pCR groups serves as a compelling indicator of the regimen's efficacy in preventing early relapses, which are common in TNBC.

Regarding treatment delivery, the feasibility of this intensive regimen in routine practice was demonstrated by the high completion rate of the neoadjuvant phase (91.8%). Furthermore, 65.6% of patients successfully underwent breast-conserving surgery, an outcome that serves as an indirect indicator of effective tumor downstaging. We observed some heterogeneity in the chemotherapy backbone, specifically regarding the scheduling of carboplatin and the sequencing of taxanes and anthracyclines. While these variations reflect institutional preferences and logistical considerations common in multicenter real-world studies, our sample size precluded a granular analysis of how specific chemotherapy modifications might impact pCR, an area that has shown conflicting results in other real-world comparisons.[19]

A notable divergence between our real-world practice and the KEYNOTE-522 trial protocol was observed in the adjuvant setting. Only 36.1% of patients in our cohort received adjuvant pembrolizumab, a rate significantly lower than the intended standard of care. This attrition likely reflects a combination of factors, including cumulative toxicity, logistical or reimbursement challenges specific to the healthcare environment, and evolving physician perspectives on de-escalation. There is an ongoing debate regarding the necessity of adjuvant immunotherapy for patients who achieve a pCR, with some experts questioning the risk-benefit ratio of continued therapy in excellent responders.[3,20] While the KEYNOTE-522 trial mandated adjuvant therapy regardless of pathological response, in the real-world setting, decision-making appears more nuanced, though the long-term survival implications of omitting the adjuvant phase remain uncertain.

For patients with residual disease, the management strategy in our cohort frequently incorporated adjuvant capecitabine (18.0%), aligning with the CREATE-X trial data which supports its use to improve survival in non-pCR TNBC.[21] The concurrent or sequential use of capecitabine with adjuvant pembrolizumab is not yet standardized, leading to heterogeneity in clinical practice. Although recent reviews suggest the combination is feasible, robust data on the optimal integration of additional adjuvant agents (including olaparib for BRCA carriers) with immunotherapy are still evolving.[22]

The safety profile observed in this study was consistent with previous reports, reassuring us of the regimen's tolerability. The most frequent Grade >=3 adverse events were hematological, specifically neutropenia and anemia, which were managed with standard supportive care. Immune-related adverse events were predominantly endocrine, with hypothyroidism occurring in 13.1% of patients, a rate comparable to that reported in large real-world analyses of pembrolizumab in eTNBC.[23] Severe immune-mediated toxicity was rare, with only one case of pneumonitis. These findings confirm that while the addition of immunotherapy introduces specific risks, they are manageable in routine clinical practice with appropriate monitoring.

Our study has several limitations inherent to its retrospective design. The sample size of 61 patients, while representative of a multicenter experience, limits the power of subgroup analyses regarding BRCA status or specific chemotherapy schedules and sequencing. Additionally, the median follow-up period is insufficient to draw definitive conclusions regarding overall survival or the long-term impact of the low adjuvant pembrolizumab utilization rate. Furthermore, pathological evaluations were performed locally by institutional pathologists without a centralized review process or the exclusive involvement of dedicated breast pathologists, which may introduce potential inter-observer variability in the assessment of residual disease. Despite these limitations, our data contribute valuable evidence from a middle-income country, addressing a gap in global real-world data availability.

Conclusion

In conclusion, our study confirms that neoadjuvant pembrolizumab plus chemotherapy is a highly effective and manageable standard of care for eTNBC in the Turkish population. The regimen yielded high pCR rates comparable to pivotal clinical trial data, with pCR serving as the primary driver of early event-free survival. Future research with larger cohorts and longer follow-up is essential to fully characterize the long-term survival benefits and to refine adjuvant treatment strategies for this high-risk population.

Disclosure

Ethics Committee Approval: The study was approved by the Institutional Review Board (or Ethics Committee) of Baskent University (Project no: KA25/11, Date: 14.01.2025).

Informed Consent: Due to the retrospective nature of the study and the use of anonymized, de-identified data, the requirement for individual patient informed consent was waived by the ethics committee.

Conflict of Interest: The authors declare no conflicts of interest.

Funding: This study received no specific grant or financial support from public, commercial, or not-for-profit funding agencies.

Use of AI for Writing Assistance: In preparing this manuscript, the authors utilized artificial intelligence (AI) tools to enhance language and readability. Specifically, ChatGPT 5.2 (OpenAI) was used exclusively for proofreading and refining the language of the author-generated text. All intellectual content, including the study's design, analysis, and conclusions, was developed solely by the authors, who are entirely responsible for the final manuscript.

Author Contributions: Concept – RI, KA; Design – RI, KA; Supervision – KA; Materials – AO, AA, EH, EA, OA, KA; Data Collection and/or Processing – RI, AO, AA, EH, EA, OA, KA; Analysis and/or Interpretation – RI, AO, KA; Literature Review – RI, AO, AA, EH, EA, OA, KA; Writing – RI; Critical Review – RI, AO, AA, EH, EA, OA, KA.

Peer-review: Externally peer reviewed.

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