

Article

Adding Neoadjuvant Immunotherapy to Chemotherapy in Non-Metastatic Triple-Negative Breast Cancer: A Propensity-Matched Cohort Study from a Tertiary Cancer Center

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Simple Summary: Triple-negative breast cancer is one of the most aggressive types of breast cancer, with limited treatment options and a high risk of recurrence. Recent studies have shown that adding pembrolizumab, a type of immunotherapy that helps the body's immune system attack cancer, to standard chemotherapy can improve patient outcomes. However, most of this evidence comes from clinical trials, and little is known about how this treatment works in everyday clinical practice. In this study, we looked at real-world patients treated at our center to see whether the addition of pembrolizumab to chemotherapy improved outcomes and how safe and feasible it was. We found that patients who received pembrolizumab had higher rates of tumor disappearance before surgery, tolerated treatment well, and experienced manageable side effects. These results suggest that incorporating immunotherapy into standard care may help improve survival and quality of life for patients with this challenging disease.

Abstract: Background: Triple-negative breast cancer (TNBC) is an aggressive subtype with limited targeted treatment options. Immunotherapy has recently emerged as a potential strategy. The addition of pembrolizumab to neoadjuvant chemotherapy, as established in the KEYNOTE-522 trial, represents a major advancement in targeted immunotherapy for TNBC. However, real-world data validating its feasibility and outcomes remain limited. This study aims to evaluate, in real-life settings, the impact of adding pembrolizumab to neoadjuvant chemotherapy on complete pathological response (pCR), recurrence-free survival (RFS), and overall survival (OS) in patients with non-metastatic TNBC. Methods: This retrospective cohort study included patients treated at King Hussein Cancer Center (KHCC) between 2015 and 2022. Among 8,523 breast cancer cases, 761 were TNBC. Eligible patients had non-metastatic TNBC, received neoadjuvant therapy, and underwent surgery. The immunotherapy group included patients treated with neoadjuvant pembrolizumab (2019–2022); the no-immunotherapy group received standard neoadjuvant chemotherapy (2015–2022). Propensity score matching (1:1, nearest neighbor) was performed based on pre-treatment covariates; including age, BMI, clinical stage, comorbidities, Smoking, and histopathology. Pathological response, complication rates, RFS, and OS were analyzed using logistic regression and Kaplan–Meier curves with log-

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rank testing. Results: The matched cohort included 130 patients (65 per group). The study groups baseline characteristics were well-balanced between the two groups. Postoperative complication rates were similar across groups, with no significant increase in adverse events observed in the immunotherapy group. The mean lymph node positivity ratio was significantly lower in the immunotherapy group (2.2 ± 7.7 vs. 24.3 ± 33.1 , $p < 0.001$), indicating reduced nodal burden. Pathologic complete response (pCR) was markedly higher with immunotherapy (66.2% vs. 9.2%, $p < 0.001$). However, survival outcomes were significantly improved with immunotherapy. At three years, RFS was markedly higher in the immunotherapy group (91.8%; 95% CI: 85.0–99.0%) compared to the control group (53.8%; 95% CI: 42.8–67.8%), with a log-rank $p < 0.001$. Overall survival also significantly favored the immunotherapy group, with three-year OS of 87.2% versus 67.8% in controls ($p = 0.0015$). Conclusion: Neoadjuvant pembrolizumab significantly enhances pathological response, reduces nodal involvement, and provides durable RFS and OS benefits in non-metastatic TNBC without increasing perioperative complications. This study supports incorporating immunotherapy into standard neoadjuvant regimens for TNBC patients and provides real-world evidence from a Middle Eastern tertiary cancer center.

Keywords: Triple-Negative Breast Cancer; Pembrolizumab; Neoadjuvant Chemotherapy; Pathological Complete Response; Immunotherapy; Surgical Outcomes; Immune-Related Adverse Events; Real-World Evidence; Survival

1. Introduction

Triple-negative breast cancer (TNBC) is a biologically aggressive subtype of breast malignancy, accounting for approximately 15–20% of all breast cancer diagnoses worldwide [1]. Defined by the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) amplification, TNBC is associated with an unfavorable clinical course, marked by high rates of early recurrence, visceral metastases, and poorer overall survival relative to other breast cancer subtypes [2–4]. It is intrinsic heterogeneity and lack of actionable molecular targets pose significant therapeutic challenges [5].

TNBC treatment traditionally relies on neoadjuvant chemotherapy (NACT) as the cornerstone approach for non-metastatic disease. NACT serves multiple purposes, including tumor downstaging in breast and axilla, facilitating breast-conserving surgery, and providing early systemic control of micrometastatic disease [6,7]. While standard NACT achieves relatively high rates of pathological complete response (pCR), which is associated with improved prognosis [8], a substantial subset of patients still experiences disease recurrence, particularly within the first few years post-treatment [9–11]. These suboptimal long-term outcomes underscore the limitations of chemotherapy alone in TNBC and highlight the urgent need for novel strategies to improve treatment efficacy and survival [5,12].

The immunogenic nature of TNBC has positioned it as a compelling candidate for immune-based therapies. This subtype is characterized by a higher prevalence of tumor-infiltrating lymphocytes (TILs), increased genomic instability, a higher tumor mutational burden (TMB), and elevated expression of programmed death-ligand 1 (PD-L1), all of which contribute to an active tumor immune microenvironment [13,14]. These features provide a strong rationale for the incorporation of immune checkpoint inhibitors (ICIs), such as pembrolizumab, into the neoadjuvant setting. Pivotal trials—most notably the KEYNOTE-522 study—have demonstrated that the addition of pembrolizumab to standard chemotherapy significantly enhances pCR rates and improves event-free survival (EFS) in early-stage TNBC, establishing a new therapeutic paradigm [15–17]. At the 5-year

follow-up, pembrolizumab plus chemotherapy was associated with a sustained event-free survival (EFS) benefit (81.2% vs. 72.2%) and an overall survival (OS) improvement (86.6% vs. 81.7%) compared to chemotherapy alone, thereby establishing a new therapeutic paradigm in early-stage TNBC [18].

However, despite these encouraging findings, several important gaps remain in the literature. Most available data are derived from randomized controlled trials (RCTs) that employ stringent inclusion criteria and exclude patients with common real-world complexities, such as comorbid conditions or poor performance status. Moreover, data on the real-world safety and surgical outcomes associated with neoadjuvant chemo-immunotherapy are limited [19,20]. Postoperative complications and immune-related adverse events in patients receiving combination regimens are particularly underreported, leaving an incomplete picture of the overall treatment burden [21,22].

Therefore, the present study aims to evaluate the real-world effectiveness of adding pembrolizumab to neoadjuvant chemotherapy in patients with non-metastatic TNBC. Specifically, we compare: (1) pathological response rates, including pCR; (2) postoperative complication profiles to assess the safety and surgical outcomes of treatment; and (3) overall survival outcomes between patients receiving standard chemotherapy alone and those treated with chemo-immunotherapy.

2. Materials and Methods

Study Design and Patient Population

This retrospective cohort study included breast cancer patients treated at King Hussein Cancer Center (KHCC) between January 2015 and December 2022. A total of 8,523 breast cancer cases were identified, of which 761 (8.93%) were triple-negative breast cancer (TNBC). From this subset, adult patients with non-metastatic TNBC who received neoadjuvant therapy and underwent definitive surgery were considered eligible for inclusion.

Patients who received neoadjuvant immunotherapy with pembrolizumab as part of their treatment protocol from 2019 onward were identified as the immunotherapy group. A comparator group of patients treated with standard neoadjuvant chemotherapy alone was selected from earlier years (2015–2019) and overlapping years (2019–2022).

Observational data from tertiary cancer centers, where patient populations are heterogeneous and treatment decisions reflect routine practice, can provide critical insights into the effectiveness, safety, and feasibility of integrating immunotherapy into standard care. In this context, the use of propensity score matching offers a robust methodological approach to reduce selection bias and adjust for baseline differences, thereby enhancing the comparability of treatment groups and mimicking the balance achieved in RCTs. To minimize confounding and ensure balance between groups, propensity score matching (PSM) was performed using a 1:1 nearest neighbor approach without replacement. Matching variables included age, body mass index (BMI), clinical stage at diagnosis, smoking status, comorbidity status, and tumor histopathology. After matching, the final analytical sample consisted of 130 patients: 65 in the immunotherapy group and 65 in the chemotherapy group. (Figure 1)

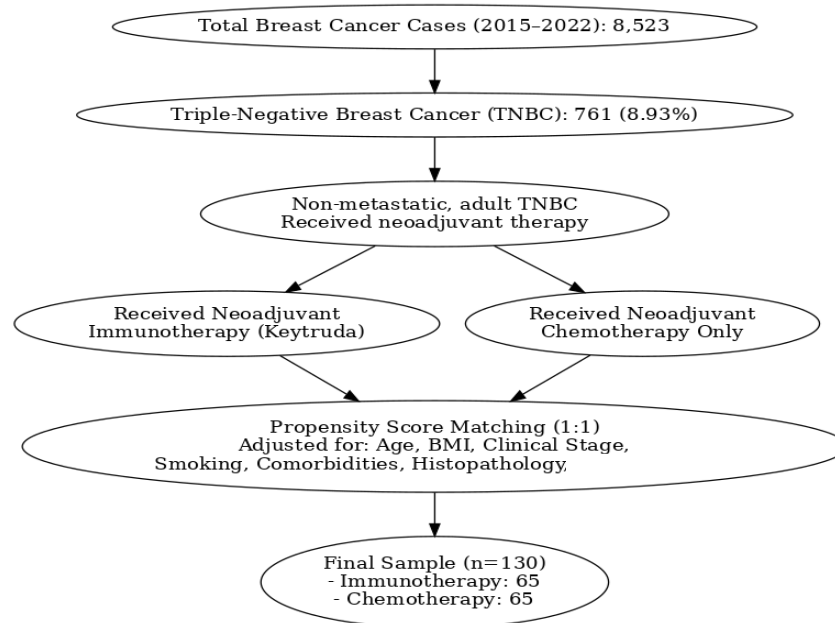


Figure 1. Study sample flowchart.

Treatment Protocols

Neoadjuvant chemotherapy backbones followed institutional (KHCC) guidelines and were tailored according to tumor receptor status. For TNBC, the historical standard regimen consisted of anthracycline-based therapy (doxorubicin and cyclophosphamide [AC]) followed by a taxane (paclitaxel or docetaxel). With the adoption of the KEYNOTE-522 protocol, the backbone shifted to carboplatin plus paclitaxel, followed by anthracycline-based therapy, with pembrolizumab administered across all phases of treatment. Beginning in 2019, pembrolizumab was approved per institutional policy for patients younger than 65 years and was delivered concurrently with chemotherapy. Axillary management adhered to internal guideline recommendations. Pathologic complete response (pCR) was defined as absence of invasive carcinoma in breast and axillary specimens (ypT0/is, ypN0).

In the adjuvant setting, patients were offered continuation of pembrolizumab if they had received it during neoadjuvant therapy, or adjuvant capecitabine, as supported by the CREATE-X trial [23].

Outcomes Definition

The primary outcome of this study was pathological complete response (pCR), defined as the absence of residual invasive carcinoma in both the breast and axillary lymph nodes at the time of surgery (ypT0/Tis, ypN0). Secondary outcomes included overall survival (OS), defined as the time from initiation of treatment to death from any cause, and recurrence-free survival (RFS), defined as the time from initiation of neoadjuvant therapy to the first documented disease progression, either local (LRFS) or distant recurrence (DRFS). Safety outcomes were evaluated by documenting and grading immune-related adverse events (irAEs), as well as postoperative complications in both groups. Postoperative complications were assessed within 30 days of surgery and included overall postoperative complications, surgical site infection (SSI), hematoma, and wound dehiscence. Simple seromas were not included in the composite measure of overall postoperative complications but were instead reported independently as a distinct postoperative outcome.

Propensity Score Matching and Statistical Analysis

Propensity score matching (PSM) was conducted using 1:1 nearest neighbor matching without replacement. The model included the following covariates: age at diagnosis, body mass index (BMI), clinical stage (IA–IIIC), smoking status, comorbidity (yes/no), histopathology (DCIS, IDC, ILC, IMC). Covariate balance was assessed using standardized mean differences (SMDs). As shown in the Love plot (see Appendix A [Figure A1]), the adjusted cohort demonstrated good balance across all covariates, with post-matching SMDs reduced to below 0.1 for all included variables. This indicates that the matching process effectively minimized baseline differences between treatment groups. Out of 208 eligible patients, 130 were matched (65 in each group). All patients in the immunotherapy arm were matched successfully, while 78 unmatched patients from the chemotherapy group were excluded. Post-matching analysis confirmed adequate covariate balance across groups.

Primary endpoints were pathologic outcomes (pCR rates, nodal status, lymph node ratio) and safety (30-day postoperative complications). Secondary endpoints were recurrence-free survival (RFS) and overall survival (OS), estimated by Kaplan–Meier analysis and compared using the log-rank test. Median follow-up time was estimated using the reverse Kaplan–Meier method. Odds ratios (ORs) for complications were calculated via univariable logistic regression. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Analyses were performed using R software version 4.2.0.

3. Results

Baseline Characteristics Before and After Matching

Post-matching comparisons demonstrated no statistically significant differences between groups across all covariates, including age ($p=0.9051$), BMI ($p=0.9131$), smoking status ($p=0.6842$), comorbidity ($p=0.8482$), clinical stage ($p=0.8992$), histopathology ($p=0.6982$). This indicates that the matching process effectively minimized baseline imbalances between the two treatment groups.

For surgical management, there was no significant difference in the distribution of surgery types between the two groups ($p = 0.6742$), nor in ASA scores ($p = 0.7932$). However, significant differences were observed in pathological outcomes between the immunotherapy and non-immunotherapy groups. Sentinel lymph node biopsy (SLNBx) was more frequently performed in the immunotherapy group compared to the standard chemotherapy group (66.1% vs. 35.9%, $p < 0.001$), while axillary dissection (AD) was more common in the non-immunotherapy group (64.1% vs. 33.9%, $p < 0.001$). (Table 1)

Table 1. Baseline demographic and clinical characteristics of patients receiving neoadjuvant chemotherapy versus chemoimmunotherapy before and after propensity score matching (PSM).

	Pre-PSM			Post-PSM		
	No-Immunotherapy (N=143)	Immunotherapy (N=65)	P	No-Immunotherapy (N=65)	Immunotherapy (N=65)	P
Age at diagnosis			0.027 ¹			0.905 ¹
Mean (SD)	48.9 (12.7)	44.9 (10.0)		45.2 (11.8)	44.9 (10.0)	
Range	19.0 - 84.0	22.0 - 68.0		19.0 - 65.0	22.0 - 65.0	
BMI			0.608 ¹			0.913 ¹
Mean (SD)	31.0 (6.5)	30.5 (6.6)		30.4 (6.0)	30.5 (6.6)	
Range	20.0 - 50.3	19.6 - 56.7		20.0 - 45.0	19.6 - 56.7	
Smoking Status			0.592 ²			0.684 ²
no	105.0 (73.4%)	50.0 (76.9%)		48.0 (73.8%)	50.0 (76.9%)	
yes	38.0 (26.6%)	15.0 (23.1%)		17.0 (26.2%)	15.0 (23.1%)	
Comorbidity			0.244 ²			0.848 ²

No	87.0 (60.8%)	45.0 (69.2%)	46.0 (70.8%)	45.0 (69.2%)
Yes	56.0 (39.2%)	20.0 (30.8%)	19.0 (29.2%)	20.0 (30.8%)
Clinical T	0.086 ²		0.349 ²	
1	19.0 (13.3%)	4.0 (4.6.1%)	7.0 (10.8%)	4.0 (6.2%)
2	76.0 (53.1%)	35.0 (53.8%)	27.0 (41.5%)	35.0 (53.8%)
3	43.0 (30.1%)	20.0 (30.8%)	27.0 (41.5%)	20.0 (30.8%)
4	5.0 (3.5%)	6.0 (9.2%)	4.0 (6.2%)	6.0 (9.2%)
Clinical N	0.516 ²		0.742 ²	
0	65.0 (45.5%)	26.0 (40.0%)	23.0 (35.4%)	26.0 (40.0%)
1	64.0 (44.8%)	35.0 (53.8%)	36.0 (55.4%)	35.0 (53.8%)
2	12.0 (8.4%)	4.0 (6.2%)	6.0 (9.2%)	4.0 (6.2%)
3	2.0 (1.4%)	0.0 (0.0%)	-	-
Clinical stage	0.302 ²		0.899 ²	
1A	14.0 (9.8%)	3.0 (4.6%)	4.0 (6.2%)	3.0 (4.6%)
2A	42.0 (29.4%)	16.0 (24.6%)	13.0 (20.0%)	16.0 (24.6%)
2B	48.0 (33.6%)	22.0 (33.8%)	25.0 (38.5%)	22.0 (33.8%)
3A	32.0 (22.4%)	18.0 (27.7%)	19.0 (29.2%)	18.0 (27.7%)
3B	5.0 (3.5%)	6.0 (9.2%)	4.0 (6.2%)	6.0 (9.2%)
3C	2.0 (1.4%)	0.0 (0.0%)	-	-
Grade	0.498 ²		0.329 ²	
1	3.0 (2.1%)	0.0 (0.0%)	1.0 (1.5%)	0.0 (0.0%)
2	25.0 (17.5%)	12.0 (18.5%)	17.0 (26.2%)	12.0 (18.5%)
3	115.0 (80.4%)	53.0 (81.5%)	47.0 (72.3%)	53.0 (81.5%)
Histopathology	0.602 ²		0.698 ²	
DCIS	2.0 (1.4%)	0.0 (0.0%)		
IDC	130.0 (90.9%)	61.0 (93.8%)	62.0 (95.4%)	61.0 (93.8%)
ILC	2.0 (1.4%)	0.0 (0.0%)		
IMC	9.0 (6.3%)	4.0 (6.2%)	3.0 (4.6%)	4.0 (6.2%)
Surgery	0.116 ²		0.674 ²	
BCS	65.0 (45.5%)	23.0 (35.4%)	20.0 (30.8%)	23.0 (35.4%)
Mastectomy with reconstruction	21.0 (14.7%)	17.0 (26.2%)	15.0 (23.1%)	17.0 (26.2%)
Mastectomy without reconstruction	57.0 (39.9%)	25.0 (38.5%)	30.0 (46.2%)	25.0 (38.5%)
Axillary surgery	<0.001 ²		<0.001 ²	
AD	86 (60.1%)	21 (33.9%)	41 (64.1%)	21 (33.9%)
SLNBx	57 (40.6%)	41 (66.1%)	23 (35.9%)	41 (66.1%)
ASA	0.475 ²		0.793 ²	
1	1 (0.7%)	0.0 (0.0%)		
2	134.0 (93.7%)	60.0 (92.3%)	61.0 (93.8%)	60.0 (92.3%)
3	7.0 (4.9%)	5.0 (7.7%)	4.0 (6.1%)	5.0 (7.7%)
4	1 (0.7%)	0.0 (0.0%)		

p-values were calculated using ¹Student's *t*-test for continuous variables and ²chi-square test or Fisher's exact test for categorical variables. PSM = Propensity Score Matching; SD = Standard Deviation; BMI = Body Mass Index; DCIS = Ductal Carcinoma in Situ; IDC = Invasive Ductal Carcinoma; ILC = Invasive Lobular Carcinoma; IMC = Invasive Mammary Carcinoma; BCS = Breast-Conserving Surgery; AD = Axillary Dissection; SLNBx = Sentinel Lymph Node Biopsy; ASA = American Society of Anesthesiologists.

Immunotherapy induced adverse events

Immune-related adverse events (irAEs) were noted in 50.8% of patients, with the most common being hypothyroidism (35.4%). Other reported complications included adrenal insufficiency (9.2%), pneumonitis (3.1%), colitis (1.5%), and skin toxicity (1.5%). (Table 2)

Table 2. Immune-related adverse events (N=65).

Immune-related Adverse event	N (%)
No	32 (49.2%)
Yes	33 (50.8%)
If yes, what is the type	
Hypothyroidism	23 (35.4%)
adrenal insufficiency	6 (9.2%)
colitis	1 (1.5%)
skin toxicity	1 (1.5%)
pneumonitis	2 (3.1%)

Postoperative Complications among The Study Groups

In the univariable logistic regression analysis comparing 30-day postoperative outcomes between patients who received neoadjuvant immunotherapy in addition to chemotherapy and those who received chemotherapy alone, a higher—though not statistically significant—odds of overall postoperative complications were observed in the immunotherapy group (OR = 1.41, 95% CI: 0.55–3.62, $p = 0.48$). There were no statistically significant differences between groups in terms of SSI (OR = 1.79, 95% CI: 0.61–5.25, $p = 0.29$), wound dehiscence (OR = 1.36, 95% CI: 0.29–7.12, $p = 0.690$), reoperation rate (OR = 1.00, 95% CI: 0.18–5.58, $p = 1.000$), or 30-day readmission (OR = 1.52, 95% CI: 0.24–11.87, $p = 0.650$). Similarly, the odds of seroma formation (OR = 0.72, 95% CI: 0.11–1.60, $p = 0.43$) and hematoma (OR = 1.00, 95% CI: 0.06–16.33, $p = 0.99$) did not differ significantly between the two groups. Collectively, these findings highlight that the overall postoperative complication profile was comparable. (Figure 2 & 3)

Forest Plot: Immunotherapy Arm vs Control

Odds Ratios and 95% Confidence Intervals (Postoperative Outcomes)

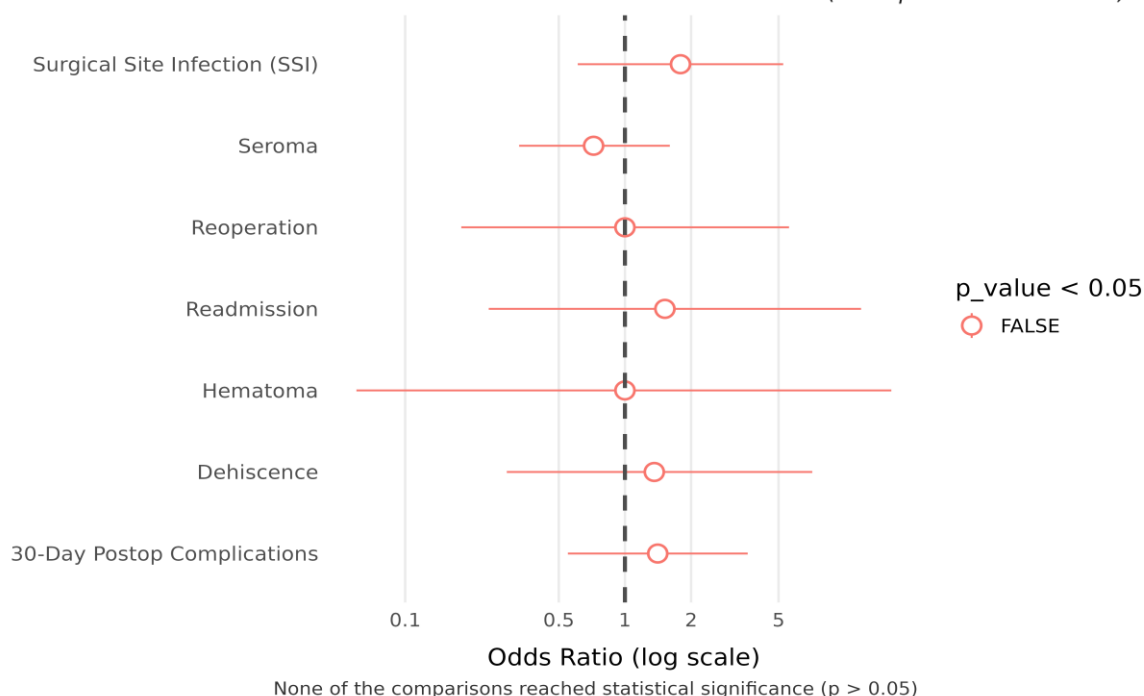


Figure 2. Forest Plot of Postoperative Outcomes: Immunotherapy vs. No-Immunotherapy.

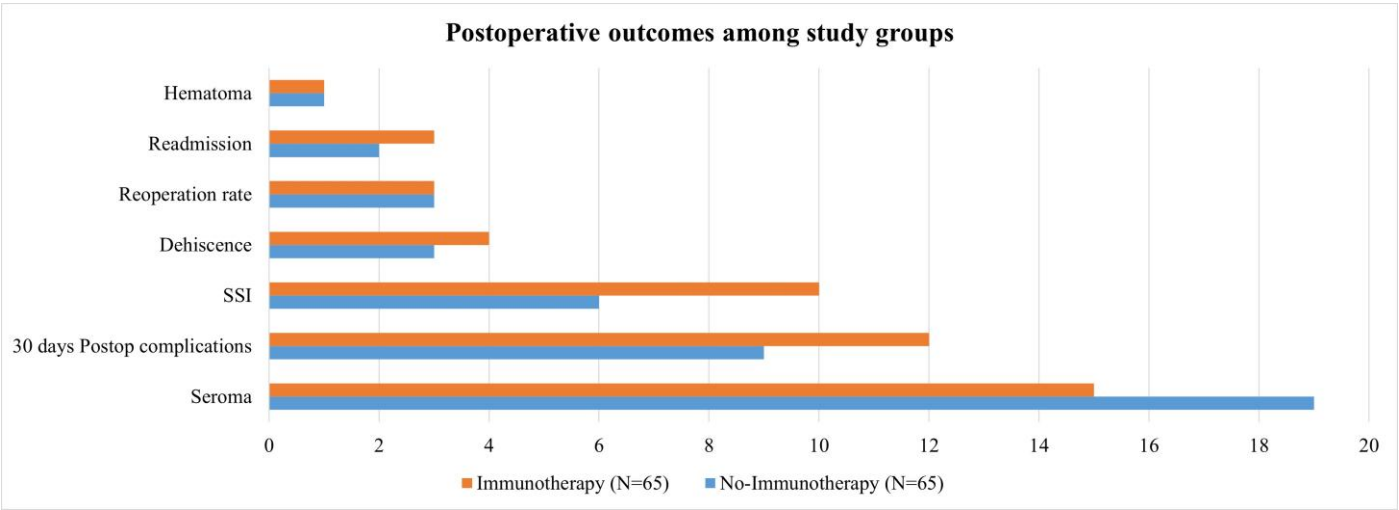


Figure 3. Distribution of Postoperative Complications by Treatment Group.

Pathological Outcomes:

Pathologic T staging also showed a marked difference, with a higher proportion of complete pathological response (ypT0) in the immunotherapy group (69.2%) versus 10.8% in the non-immunotherapy group ($p < 0.001$). Similarly, pathologic nodal staging (ypN0) was significantly more common in the immunotherapy group (88.7%) compared to the standard group (46.9%) ($p < 0.001$). (Figure 4)

Pathological complete response (pCR) rates differed significantly between the two groups ($p < 0.001$). In the non-immunotherapy group, 59 patients (90.8%) did not achieve pCR, while only 6 patients (9.2%) did. In contrast, in the immunotherapy group, 22 patients (33.8%) did not achieve pCR, whereas 43 patients (66.2%) achieved pCR. Moreover, the mean lymph node ratio (number of positive nodes to total examined) was significantly lower in the immunotherapy group (mean 2.2 ± 7.7) compared to the standard group (mean 24.3 ± 33.1 ; $p < 0.001$), reflecting a substantial reduction in nodal involvement. (Table 3)

These findings suggest that the addition of immunotherapy enhances pathologic response both at the primary tumor and nodal levels.

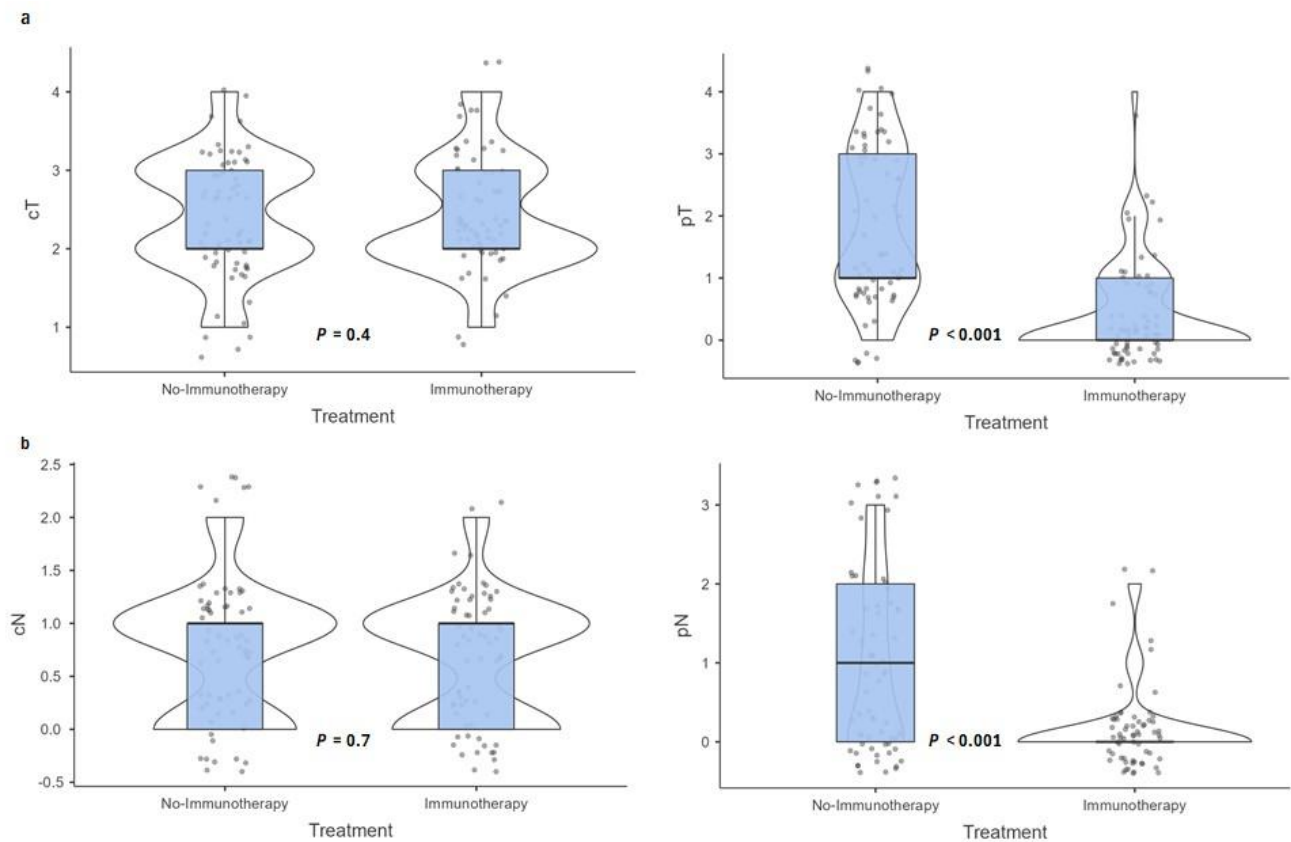


Figure 4. Comparison of Clinical and Pathological (a) T and (b) N Staging Between Immunotherapy and Non-Immunotherapy Groups.

Table 3. Pathological Outcomes by Treatment Group (Immunotherapy vs. Non-Immunotherapy).

Outcome	No-Immunotherapy (N=65)	Immunotherapy (N=65)	p-value
pCR			<0.001 ¹
No	59 (90.8%)	22 (33.8%)	
Yes	6 (9.2%)	43 (66.2%)	
Pathologic T Stage (pT)			<0.001 ¹
pT4	7 (10.8%)	1 (1.5%)	
pT3	18 (27.7%)	0 (0.0%)	
pT2	7 (10.8%)	5 (7.7%)	
pT1	26 (40.0%)	14 (21.5%)	
pT0	7 (10.8%)	45 (69.2%)	
Pathologic N Stage (pN)			<0.001 ¹
pN0	30 (46.9%)	55 (88.7%)	
pN1	13 (20.3%)	4 (6.5%)	
pN2	12 (18.8%)	3 (4.8%)	
pN3	9 (14.1%)	0 (0.0%)	
LN positivity ratio			<0.001 ²
Mean (SD)	24.3 (33.1)	2.2 (7.7)	
Range	0.0–100.0	0.0–41.2	

p-values were calculated using ¹ the chi-square test or Fisher's exact test for categorical variables and ² Student's *t*-test for continuous variables, as appropriate. SD = Standard Deviation; LN = Lymph Node; pCR = Pathologic Complete Response.

Among the 130 patients, the use of adjuvant radiotherapy did not significantly differ between groups (No-immunotherapy 75.4% vs. Immunotherapy 80.0%; $p = 0.527$). In contrast, the administration of adjuvant systemic therapy showed a marked difference, with only 24.6% of the No-immunotherapy group receiving systemic therapy compared to 83.1% in the Immunotherapy group ($p < 0.001$). When stratified by type of systemic therapy, immunotherapy was administered exclusively in the Immunotherapy group (78.5%), whereas chemotherapy was more common in the No-immunotherapy group (24.6% vs. 4.6%). (Table 4).

Table 4. Distribution of Radiotherapy and Systemic Therapy Between Study Groups.

	No-immunotherapy (N=65)	Immunotherapy (N=65)	Total (N=130)	p value
Adjuvant Radiotherapy				0.527 ¹
No	16.0 (24.6%)	13.0 (20.0%)	29.0 (22.3%)	
Yes	49.0 (75.4%)	52.0 (80.0%)	101.0 (77.7%)	
Adjuvant systemic therapy				< 0.001 ¹
No	49.0 (75.4%)	11.0 (16.9%)	60.0 (46.2%)	
Yes	16.0 (24.6%)	54.0 (83.1%)	70.0 (53.8%)	
Type of systemic therapy				-
Immunotherapy	0.0 (0.0%)	51.0 (78.5%)	51.0 (39.2%)	
Chemotherapy	16.0 (24.6%)	3.0 (4.6%)	19.0 (14.6%)	

¹Pearson's Chi-squared test

Survival outcomes – Overall survival outcomes

For the entire cohort, the median follow-up time was **36.15 months** (interquartile range [IQR], 31.91–49.67 months). The median overall survival was **not reached** during the follow-up period. The estimated 5-year overall survival rate was **65.0%** (95% confidence interval [CI], 55.0%–77.1%).

Following propensity score matching, Kaplan–Meier survival analysis demonstrated significantly improved overall survival in the immunotherapy group compared to the standard chemotherapy group (log-rank test, $p = 0.0015$). At 1 year, survival was identical in both groups at **98.5%** (95% CI: 95.5%–100.0%). However, divergence emerged at later time points: at 3 years, the immunotherapy group maintained a survival rate of **87.2%** (95% CI: 74.8%–100.0%), while the no-immunotherapy group declined to **67.8%** (95% CI: 57.2%–80.5%). At 5 years, survival remained stable at **87.2%** in the immunotherapy arm, in contrast to a further decrease to **55.5%** (95% CI: 44.2%–69.7%) in the control group. (Figure 5)

These findings highlight a sustained long-term survival advantage associated with the addition of checkpoint inhibitor immunotherapy

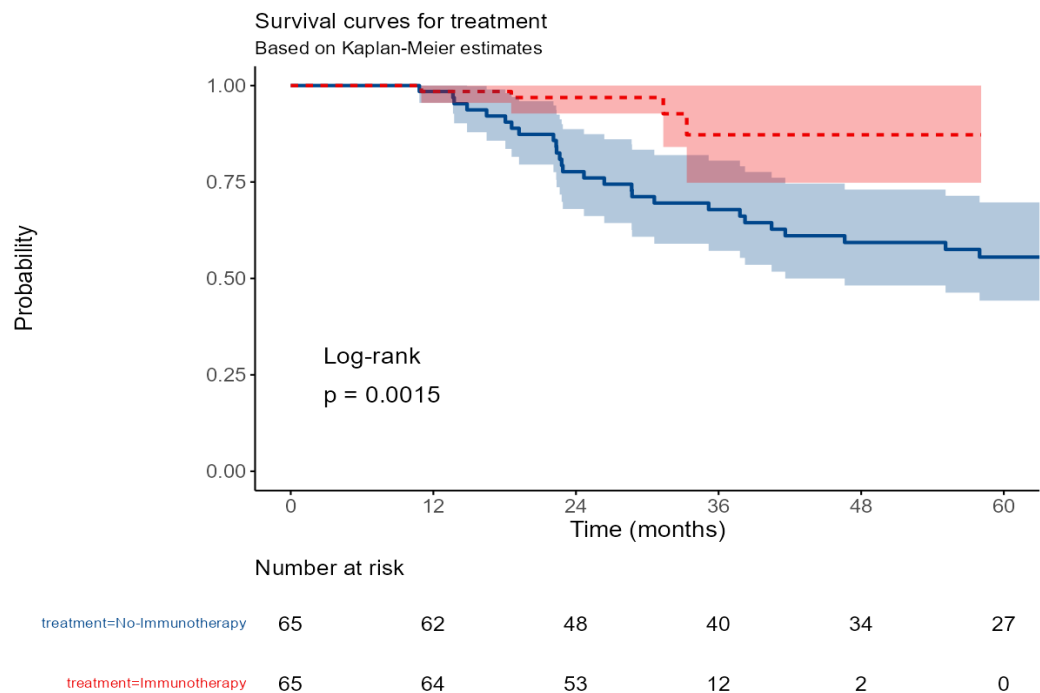


Figure 5. Kaplan–Meier curves for overall survival in patients receiving immunotherapy versus no immunotherapy.

Recurrence-Free Survival (RFS)

The Kaplan–Meier analysis showed a statistically significant improvement in recurrence-free survival among patients who received immunotherapy compared to those who received standard chemotherapy (log-rank test, $p < 0.001$). At 1 year, the RFS was 98.5% (95% CI: 95.5%–100.0%) in the immunotherapy group versus 89.2% (95% CI: 82.0%–97.1%) in the non-immunotherapy group. By 3 years, RFS remained high in the immunotherapy group at 91.8% (95% CI: 85.0%–99.0%), while it dropped to 53.8% (95% CI: 42.8%–67.8%) in the non-immunotherapy group. At 4 years, RFS was 81.6% (95% CI: 64.0%–100.0%) for the immunotherapy group compared to 50.5% (95% CI: 39.4%–64.6%) for the control group. These findings suggest a clear benefit of adding immunotherapy in reducing disease recurrence over time. (Figure 6)

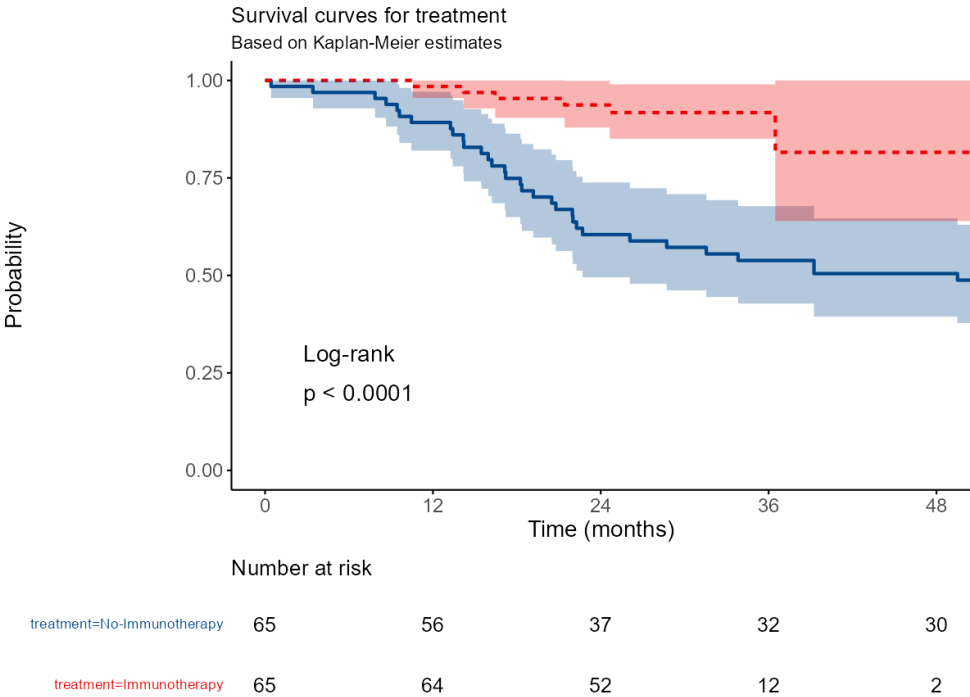


Figure 6. Kaplan–Meier curves for recurrence-free survival in patients receiving immunotherapy versus no immunotherapy.

In term of distant recurrence-free survival (DRFS) was significantly improved in the immunotherapy group compared to the no-immunotherapy group ($p = 0.0018$). At 3 years, DRFS in the immunotherapy group was 91.8% (95% CI: 85.0%–99.0%) compared to 60.8% (95% CI: 49.4%–74.9%) in the no-immunotherapy group. This difference persisted at 5 years, with DRFS rates of 81.6% versus 55.1%, respectively. These findings suggest that the addition of immunotherapy is associated with reduced risk of distant metastasis (Figure 7a).

The locoregional recurrence (Figure 7b), the immunotherapy group showed significantly improved locoregional recurrence-free survival compared to the no-immunotherapy group. At 3 years, the immunotherapy group had an LRFS of 96.9% (95% CI: 92.8%–100%) versus 85.6% (95% CI: 76.7%–95.4%) in the no-immunotherapy group ($p = 0.029$). This trend remained consistent through 5 years of follow-up, suggesting that adding immunotherapy may enhance locoregional disease control in this patient population.

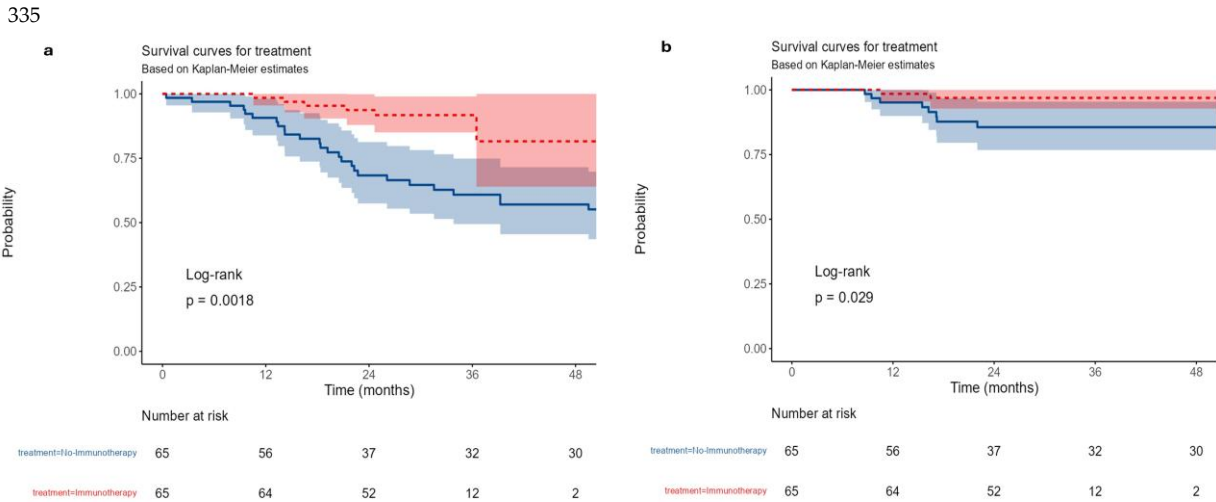


Figure 7. Kaplan–Meier curves for recurrence-free survival following propensity score matching. (a) Locoregional recurrence. (b) Distant recurrence.

4. Discussion

In this propensity score-matched cohort study, we evaluated the impact of adding neoadjuvant immunotherapy to standard chemotherapy on pathological outcomes, postoperative complications, and survival in a TNBC. Matching effectively balanced baseline characteristics, minimizing confounding. Immune-related adverse events were observed in approximately half of patients, predominantly hypothyroidism, highlighting the need for vigilant monitoring. Postoperative outcomes were comparable between groups, with no significant differences in surgical complications, reoperation, or 30-day readmission. Pathologically, the immunotherapy group demonstrated markedly improved responses, including higher rates of complete pathological response (ypT0), nodal clearance (ypN0), and lower lymph node ratios, reflecting enhanced tumor response. Adjuvant systemic therapy patterns differed substantially, with immunotherapy administered almost exclusively in the experimental arm. Survival analyses revealed a sustained long-term benefit, with significantly improved overall survival, recurrence-free survival, locoregional recurrence-free survival, and distant metastasis-free survival in the immunotherapy group, suggesting that the addition of checkpoint inhibition enhances both local and systemic disease control while maintaining an acceptable safety profile.

In our study, we found no significant differences in 30-day postoperative complications, including surgical site infections, wound dehiscence, reoperations, or readmissions, between patients who received neoadjuvant chemoimmunotherapy and those treated with chemotherapy alone. These findings are consistent with those reported by Myers et al., who compared 139 patients treated with the KEYNOTE-522 regimen to 287 patients who received chemotherapy alone. They observed postoperative complications in 7.9% of the chemoimmunotherapy group versus 9.1% of the chemotherapy group ($P=0.6$), with no significant differences in the need for reoperation (1.4% vs 2.1%, respectively). While the most common complication in their chemotherapy cohort was surgical site infection and abscess, ischemia of mastectomy flaps was more frequent in the chemoimmunotherapy cohort, though still uncommon [24]. Taken together, these results reinforce that the addition of immunotherapy to standard chemotherapy does not increase short-term surgical morbidity, supporting the safety of integrating immune checkpoint inhibitors into neoadjuvant treatment for triple-negative breast cancer.

In addition to evaluating surgical outcomes, Myers et al. also reported on the frequency and type of immune-related adverse events (irAEs) among patients treated with the KEYNOTE-522 regimen. In the KN-522 trial, 43% of patients experienced immune-related adverse events (irAEs), with hypothyroidism (15.9%), hepatitis (14.6%), adrenal insufficiency (9.8%), dermatitis (9.8%), and pneumonitis (8.5%) being the most common toxicities. In contrast, our study demonstrated a higher overall incidence of irAEs (50.8%), with endocrine toxicities—particularly hypothyroidism—being disproportionately more frequent (35.4% vs. 15.9% in KN-522). Other complications such as adrenal insufficiency (9.2% vs. 9.8%) and colitis (1.5% vs. 4.9%) were comparable or slightly lower, while pneumonitis (3.1% vs. 8.5%) and dermatologic toxicity (1.5% vs. 9.8%) were less frequent in our cohort [24]. These differences may reflect variations in baseline patient characteristics, disease stage, genetic or ethnic predispositions, as well as differences in detection and reporting practices. Importantly, the higher burden of endocrine toxicities in our cohort underscores the need for vigilant long-term monitoring and tailored supportive care in patients receiving chemoimmunotherapy.

In term of treatment response, our findings parallel and extend the results reported by Helal et al., who recently investigated predictors of pathological complete response (pCR) in patients with stage II–III triple-negative breast cancer (TNBC) treated with neo-adjuvant chemoimmunotherapy (NACi) at Institut Curie hospitals. In their cohort of 208 patients, the overall pCR rate was 70%, consistent with other reports of NACi efficacy in TNBC. Similarly, in our study, the addition of immunotherapy to neoadjuvant chemotherapy yielded a pCR rate of 66.2%, closely mirroring the outcomes reported by Helal et al. and confirming the reproducibility of this benefit across independent populations [25].

Notably, however, our chemotherapy-only group achieved a markedly lower pCR rate of 9%. The relatively low pathological complete response (pCR) rate observed in our chemotherapy-only group is lower than the rates commonly reported in the literature, which typically range from 15% to 50% in TNBC cohorts [26–28]. Several factors may explain this discrepancy. First, our cohort included a clinically advanced population with higher baseline tumor burden and nodal involvement, which are known to negatively impact response to chemotherapy [29]. Second, differences in chemotherapy regimens, dose intensity, and treatment adherence could have contributed to suboptimal responses [30]. Third, biological heterogeneity, including variations in tumor-infiltrating lymphocytes (TILs), PD-L1 expression, and tumor mutational burden, may have influenced chemosensitivity [28,31]. Lastly, the relatively small sample size of our chemotherapy group ($n = 65$) increases the impact of individual patient outcomes on overall pCR rates, potentially amplifying apparent differences compared to larger clinical trials. These considerations highlight the importance of patient selection and underscore the potential benefit of adding immunotherapy to enhance response rates in TNBC populations.

Our findings are consistent with the KEYNOTE-522 trial, which showed that adding pembrolizumab to neoadjuvant chemotherapy significantly improved pathological complete response (pCR) rates and event-free survival in triple-negative breast cancer (TNBC). In KEYNOTE-522, 1,174 patients were randomized, with a median follow-up of 39.1 months, and the 36-month event-free survival was 84.5% in the pembrolizumab–chemotherapy group versus 76.8% in the placebo–chemotherapy group (hazard ratio, 0.63; $P < 0.001$), with adverse events primarily occurring during the neoadjuvant phase and consistent with known safety profiles [32]. In our cohort, the addition of immunotherapy similarly resulted in markedly improved pathological responses, with higher rates of complete tumor response (ypT0, 69.2% vs. 10.8%) and nodal clearance (ypN0, 88.7% vs. 46.9%) compared to chemotherapy alone. Long-term survival was also substantially better, with a 5-year overall survival of 87.2% in the immunotherapy group versus 55.5% in the chemotherapy-only group, highlighting a durable survival benefit that aligns with and extends the trends observed in KEYNOTE-522. Immune-related adverse events in our population were common (50.8%) but largely endocrine in nature and manageable which is higher than what reported in KEYNOTE-522 (35%), further supporting the tolerability of neoadjuvant PD-1 blockade [32]. Overall, these results reinforce both the efficacy and safety of incorporating immunotherapy into neoadjuvant regimens for TNBC in clinical practice.

Our findings are also consistent with the results of the phase II NeoPACT trial, which evaluated an anthracycline-free neoadjuvant regimen of pembrolizumab plus carboplatin and docetaxel. In that study, a pCR rate of 58% and a 3-year event-free survival (EFS) of 86% were reported, demonstrating that effective tumor clearance and durable survival benefits can be achieved even in the absence of anthracyclines. While the NeoPACT trial highlights the feasibility of a less cardiotoxic, anthracycline-sparing approach, our cohort—treated predominantly with anthracycline-based chemoimmunotherapy—achieved even higher rates of ypT0 (69.2%) and nodal clearance (88.7%), as well as a 5-year overall survival of 87.2% [33]. Together, these results reinforce that pembrolizumab is a key driver of therapeutic efficacy in TNBC, with flexibility in chemotherapy backbone

selection, while also underscoring the potential for regimen tailoring to optimize both efficacy and long-term safety.

Strengths and Limitations

The major strengths of this study include its real-world matched cohort design, which allowed for a robust comparison between patients receiving standard chemotherapy and those treated with chemoimmunotherapy. Propensity score matching ensured balanced groups and minimized baseline differences, while the relatively long follow-up period enabled the evaluation of multiple survival endpoints. Nonetheless, several limitations must be acknowledged. This was a single-institution dataset with a modest sample size of 130 patients, which may reduce the generalizability of the findings and limit statistical power in subgroup analyses. Furthermore, the absence of biomarker stratification—such as PD-L1 expression, tumor mutational burden (TMB), or tumor-infiltrating lymphocytes (TILs)—restricts the ability to identify subgroups that may derive differential benefit from immunotherapy.

5. Conclusions

Adding immunotherapy to neoadjuvant chemotherapy in this cohort significantly enhanced pathological responses, with higher rates of complete tumor and nodal clearance and a reduced need for axillary interventions. These improvements translated into substantial long-term survival benefits, including superior overall, recurrence-free, locoregional recurrence-free, and distant metastasis-free survival compared to chemotherapy alone. Importantly, the addition of immunotherapy did not increase postoperative complication rates, supporting its safety in the perioperative setting. Immune-related adverse events were observed in a notable proportion of patients but were generally manageable, predominantly affecting endocrine function.

Future research should focus on validating these findings in larger, prospective datasets to determine whether the observed trend toward surgical de-escalation—specifically the increased feasibility of sentinel lymph node biopsy over axillary dissection—can be consistently reproduced. Incorporating biomarker analysis, including PD-L1 status, tumor mutational burden (TMB), and BRCA mutations, will be essential to refine patient selection and optimize therapeutic benefit. Moreover, survivorship strategies must extend beyond oncologic outcomes to address long-term immune-related adverse effects, particularly endocrine toxicities such as thyroid and adrenal dysfunction, which may impact quality of life long after treatment completion.

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Informed Consent Statement: Patient consent was waived due to the retrospective design of the study, which involved the use of anonymized data collected from medical records and posed no more than minimal risk to participants.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to the retrospective nature of the study and the use of anonymized patient records, data are not publicly available to protect patient privacy and comply with ethical restrictions.

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

Abbreviations

The following abbreviations are used in this manuscript:

AC	Doxorubicin and Cyclophosphamide
AD	Axillary Dissection
CI	Confidence Interval
DCIS	Ductal Carcinoma in Situ
DRFS	Distant Recurrence-Free Survival
EFS	Event-Free Survival
ER	Estrogen Receptors
HER2	Human Epidermal Growth Factor Receptor 2
ICIs	Immune Checkpoint Inhibitors
IDC	Invasive Ductal Carcinoma
ILC	Invasive Lobular Carcinoma
IMC	Invasive Mammary Carcinoma
iRAEs	Immune-Related Adverse Events
KHCC	King Hussein Cancer Center
LN	Lymph Node
LRFS	Locoregional Recurrence-Free Survival
NACi	Neoadjuvant Chemotherapy with Immunotherapy
NACT	Neoadjuvant Chemotherapy
OR	Odds Ratio
OS	Overall Survival
pCR	Pathological Complete Response
PD-L1	Programmed Death-Ligand 1
PR	Progesterone Receptors
PSM	Propensity Score Matching
RFS	Recurrence-Free Survival
SD	Standard Deviation
SMDs	Standardized Mean Differences
SSI	Surgical Site Infection
TMB	Tumor Mutational Burden
TNBC	Triple-Negative Breast Cancer

Appendix A

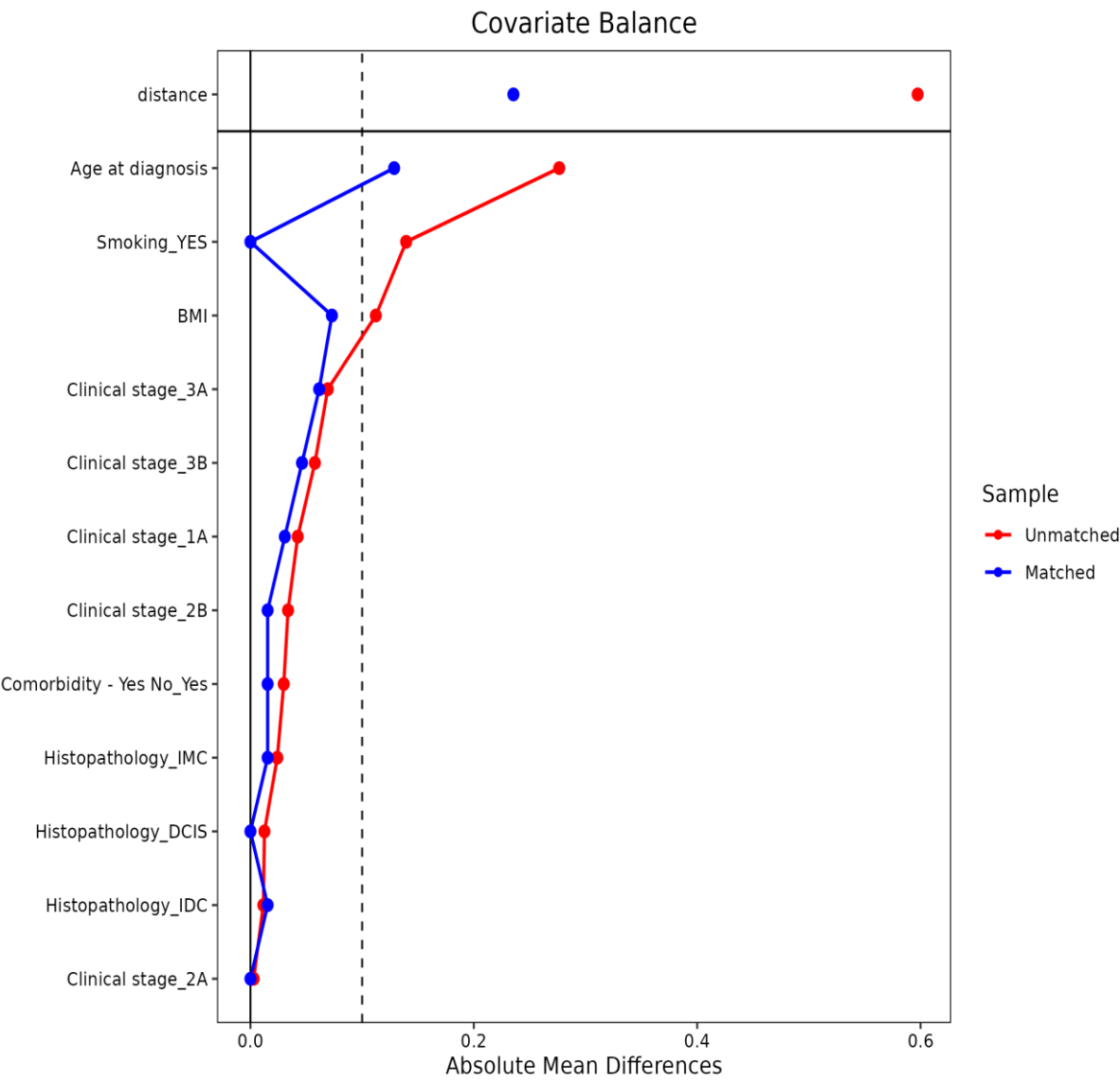


Figure A1. Covariate balance before and after propensity score matching (PSM) using standardized mean differences (SMDs).

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