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Contemporary Therapy for Small Node-Negative Triple-Negative Breast Cancer: A Retrospective Cohort Study

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Abstract

Multi-agent neoadjuvant therapy (NAT) with immune checkpoint blockade is standard for Stage II–III triple-negative breast cancer (TNBC), though its role in smaller node-negative tumors remains less clearly defined. We performed a retrospective multi-institutional cohort study evaluating demographics, treatment patterns, and outcomes in a contemporary “small TNBC” population (n = 215) comprising Stage I (n = 154) and Stage II, T < 3 cm TNBC (n = 61). Within the small TNBC cohort, Stage II, < 3 cm tumors demonstrated higher rates of grade 3 histology (93.4% vs 74.7%, p = 0.0013), NAT (85.2% vs 61.0%, p = 0.0006), adjuvant pembrolizumab (56.8% vs 24.7%, adjusted p = 0.0024), and neoadjuvant KEYNOTE-522 (75.0% vs 45.7%, adjusted p = 0.0052) compared with Stage I disease. Despite these treatment differences, recurrence and mortality rates were similar between groups. Among NAT-treated patients with small TNBC (n = 146), the overall pathologic complete response (pCR) rate was 51.3% (75/146), without significant difference between Stage I and Stage II, < 3 cm tumors (51.1% vs 51.9%, p = 0.92). There were no significant differences in regimen-specific pCR rates or event-free survival (EFS) when comparing NAT between Stage I and Stage II, < 3 cm tumors, or comparing NAT vs no NAT for the small TNBC cohort. Stage I and Stage II, < 3 cm TNBC demonstrated overlapping clinicopathologic features, pCR rates, and short-term survival outcomes despite substantially different treatment approaches. These findings support further prospective evaluation of risk-adapted and size-based treatment frameworks for small node-negative TNBC.

Intro

Breast cancer is the most common cancer and second leading cause of cancer-related death among women in the United States[1]. Triple-negative breast cancer (TNBC) comprises 10–15% of breast cancers and is defined by a lack of estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2) expression. TNBC demonstrates aggressive clinical behavior, limited targeted treatment options, and higher rates of early recurrence[2]. Surgery is the backbone of non-metastatic TNBC treatment, often paired with radiation and systemic therapies. Neoadjuvant therapy (NAT) is the standard approach for Stage II-III TNBC following the KEYNOTE-522 trial, which demonstrated improved pathologic complete response (pCR) rate, event-free survival (EFS), and overall survival (OS) with the addition of immunotherapy[3]. However, the role of NAT in Stage I disease remains less clearly defined.

Current NCCN Guidelines© (v.3.2026) recommend upfront surgery followed by adjuvant chemotherapy for node-negative tumors measuring 1–2 cm, reserving neoadjuvant approaches for higher-risk cases[4]. Despite this, the use of NAT in Stage I TNBC has increased in recent clinical practice. This shift is driven by several advantages, including in vivo assessment of chemosensitivity, clinical downstaging for breast-conserving surgery, and adjuvant therapy guidance by pathologic complete response (pCR), defined as the absence of residual invasive disease at surgery[5]. For example, patients who failed to achieve pCR with NAT demonstrated increased disease-free survival (DFS) and overall survival (OS) over standard of care when treated with adjuvant capecitabine in the CREATE-X trial, with similar findings for adjuvant olaparib in patients with germline BRCA mutations in the OlympiA trial[6, 7].

However, the clinical trials establishing NAT as standard of care excluded or did not analyze Stage I patients, limiting applicability to this population. For example, both the NeoPACT and NeoSTOP trials studied NAT outcomes in Stage I-III TNBC but did not specifically analyze Stage I cohorts[8, 9]. Similarly, the ongoing NeoTRACT trial did not analyze Stage I alone in preliminary results[10]. Stage I-specific retrospective studies have evaluated predictors of pCR or compared outcomes between NAT and adjuvant therapy, with limited data comparing specific neoadjuvant regimens[11–13]. This knowledge gap is clinically important because Stage I TNBC generally has a more favorable prognosis, making overtreatment and treatment-related toxicity particularly relevant considerations[14].

In addition, current TNBC treatment paradigms are largely organized according to AJCC Stage definitions, yet node-negative tumors just below and above the 2 cm (T1c-T2a) threshold may demonstrate similar tumor biology and chemosensitivity. Consequently, a size-based framework for TNBC may help contextualize neoadjuvant treatment patterns and allow findings from early Stage II disease to inform the less well-studied Stage I setting. In this retrospective multi-institutional study, we investigated clinicopathologic characteristics and treatment outcomes in a “small TNBC” cohort, comprising Stage I and early Stage II node-negative disease.

Methods

This retrospective cohort study utilized real-world data from UT Southwestern Medical Center and Parkland Health. Clinical data were extracted from electronic health records and tumor registries. Eligible patients were aged ≥ 18 years with histologically confirmed TNBC, defined as breast carcinoma with ER and PR expression < 10% and HER2-negative status (IHC 0/1 + or IHC 2 + with negative FISH) diagnosed between July 2021 and December 2024. Patients with missing pathologic or treatment data, node-positive or metastatic disease, or other malignancy within five years of diagnosis that interfered with TNBC treatment were excluded. This study was approved by the institutional review boards of both institutions with waiver of informed consent.

“Small TNBC” was defined as node-negative TNBC with tumor size < 3cm, comprising T1N0 (Stage I) and T2N0 (Stage II, < 3 cm) groups. Initial screening captured all T1-2N0 patients meeting the TNBC criteria, although only the small TNBC cohort was included for subsequent analyses. Tumor size was determined by pre-biopsy measurement of the single largest focus, with MRI preferred when available, followed by diagnostic mammography and ultrasound. The primary outcome was pCR, defined as ypT0/Tis ypN0 on surgical pathology review by breast pathologists at each institution. Secondary outcomes included recurrence, death, and event-free survival (EFS). Events were defined as pathologically confirmed TNBC recurrence, death from any cause, or disease progression precluding surgery. Follow-up time was calculated from the date of initial diagnosis. Detailed demographic, comorbidity, surgical, radiation, and systemic treatment data were also collected.

All statistical analyses were performed using GraphPad Prism version 11.0.0. No formal sample size calculation was performed due to the retrospective exploratory study design. Continuous variables were

compared using Student's t-test for normally distributed data and Mann–Whitney U testing for nonparametric distributions. Categorical variables were analyzed through Pearson χ^2 tests or Fisher's exact tests when cell counts were < 5. Subgroup distributions were compared using 2×k contingency analyses, with significant omnibus tests followed by pairwise 2×2 post hoc comparisons using Bonferroni correction. The primary analysis compared pCR rates and EFS outcomes between various neoadjuvant treatments and between Stage I and Stage II, < 3 cm groups. EFS was estimated using the Kaplan–Meier method, with comparisons performed using log-rank (Mantel–Cox) testing with 95% confidence intervals reported. Statistical significance was defined as 2-sided $p < 0.05$.

Results

A total of 252 patients with T1-2N0M0 TNBC were identified across UT Southwestern Medical Center (n = 211) and Parkland Health (n = 41) (Fig. 1). The overall cohort comprised Stage I (n = 154), Stage II with tumor size < 3 cm (n = 61), and node-negative Stage II with tumor size > 3 cm disease (n = 37). Subsequent analyses focused on a predefined "small TNBC" cohort consisting of Stage I and Stage II, < 3 cm tumors (n = 215). The small TNBC cohort comprised 182 UTSW (84.7%) and 33 Parkland patients (15.3%). Baseline demographics and pathological variables were typical of TNBC (82.5% grade 3 histology; 89.3% ductal histology; Table 1). NAT was administered in 70.6% of patients, surgery in 98.8%, adjuvant therapy in 60.3%, and adjuvant radiation in 42.1%. KEYNOTE-522 was the most common NAT regimen overall (60.1% of NAT-treated patients). With a median follow-up of 2.6 years, recurrence occurred in 18 patients (7.1%) and death in 11 patients (4.4%). Collectively, this represented a contemporary, real-world TNBC cohort treated during the immunotherapy era.

Table 1
Characteristics for Overall TNBC Cohort

Variable n (%)	Stage I n = 154	Stage II, < 3 cm n = 61	Stage II, > 3 cm n = 37	< 3 cm n = 215	Overall n = 252
Age at diagnosis, median (range) - yrs	57.3 (47.5–66.3)	53.8 (41.5–64.5)	47 (42–63)	57 (46–66)	57 (45–65)
BMI, median (range) – kg/m²	27.3 (23.5–31.1)	30.3 (25.4–34.5)	28.7 (24.8–36.3)	28.6 (23.5–33.5)	28.3 (23.8–33.3)
Postmenopausal	110 (71.4%)	36 (59.0%)	18 (48.6%)	146 (67.9%)	164 (65.1%)
HTN	82 (53.2%)	37 (60.7%)	18 (48.6%)	119 (55.3%)	137 (54.4%)
HLD	89 (57.8%)	36 (59.0%)	18 (48.6%)	125 (58.1%)	143 (56.7%)
DM	30 (19.5%)	18 (29.5%)	9 (24.3%)	48 (22.3%)	57 (22.6%)
BRCA+	17 (11.0%)	3 (4.9%)	5 (13.5%)	20 (9.3%)	25 (9.9%)
Histologic G3	115 (74.7%)	57 (93.4%)	36 (97.3%)	172 (80.0%)	208 (82.5%)
Ki-67, median (range) - %	65 (40–80)	70 (46.3–85.4)	85 (65–90)	69 (40–85)	70 (40.5–85)
IDC	132 (85.7%)	58 (95.1%)	35 (94.6%)	190 (88.4%)	225 (89.3%)
NAT	94 (61.0%)	52 (85.2%)	32 (86.5%)	146 (67.9%)	178 (70.6%)
AC/T	17 (18.1%)	3 (5.8%)	1 (3.1%)	20 (13.7%)	21 (11.8%)
CT + P	18 (19.1%)	6 (11.5%)	4 (12.5%)	24 (16.4%)	28 (15.7%)
KEYNOTE	43 (45.7%)	39 (75.0%)	25 (78.1%)	82 (56.2%)	107 (60.1%)
Other NAT	16 (17.0%)	4 (7.7%)	2 (6.3%)	20 (13.7%)	22 (12.4%)
No NAT	60 (39.0%)	9 (14.8%)	5 (13.5%)	69 (32.1%)	74 (29.4%)
Adj chemo +/- RT	36 (60.0%)	4 (44.4%)	1 (20.0%)	40 (58.0%)	41 (55.4%)
Adj RT only	10 (16.7%)	1 (11.1%)	0 (0.0%)	11 (15.9%)	11 (14.9%)
RT only	0 (0.0%)	1 (11.1%)	0 (0.0%)	1 (1.4%)	1 (1.4%)
Surgery only	14 (23.3%)	2 (22.2%)	4 (80.0%)	16 (23.2%)	19 (25.7%)

Variable n (%)	Stage I n = 154	Stage II, < 3 cm n = 61	Stage II, > 3 cm n = 37	< 3 cm n = 215	Overall n = 252
No treatment	0 (0.0%)	1 (11.1%)	0 (0.0%)	1 (1.4%)	2 (2.7%)
Surgery	154 (100.0%)	58 (95.1%)	37 (100.0%)	212 (98.6%)	249 (98.8%)
BL mast	64 (41.6%)	22 (37.9%)	13 (35.1%)	86 (40.6%)	99 (39.8%)
UL mast	18 (11.7%)	10 (17.2%)	8 (21.6%)	28 (13.2%)	36 (14.5%)
Lump	72 (46.8%)	26 (44.8%)	16 (43.2%)	98 (46.2%)	114 (45.8%)
Adj Therapy	89 (56.5%)	37 (59.0%)	26 (67.6%)	126 (58.6%)	152 (60.3%)
Pembro	22 (24.7%)	21 (56.8%)	16 (61.5%)	43 (34.1%)	59 (38.8%)
Pembro + Cape	16 (18.0%)	10 (27.0%)	7 (26.9%)	26 (20.6%)	33 (21.7%)
Cape	10 (11.2%)	2 (5.4%)	1 (3.8%)	12 (9.5%)	13 (8.6%)
Other	41 (46.1%)	4 (10.8%)	2 (7.7%)	45 (35.7%)	47 (30.9%)
Adj RT	67 (43.5%)	26 (42.6%)	13 (35.1%)	93 (43.3%)	106 (42.1%)
Deaths (anytime)	3 (1.9%)	4 (6.6%)	4 (10.8%)	7 (3.3%)	11 (4.4%)
Recurrence (anytime)	10 (6.5%)	2 (3.3%)	6 (16.2%)	12 (5.6%)	18 (7.1%)

The small TNBC cohort included 154 Stage I and 61 node-negative Stage II, < 3 cm patients. Demographic characteristics were largely similar between groups (Table 2). Median age did not significantly differ between Stage I and Stage II, < 3 cm disease, nor did menopausal status, hypertension, hyperlipidemia, diabetes, or BRCA mutation prevalence. Median BMI was higher in Stage II, < 3 cm patients (30.3 vs 27.3 kg/m², p = 0.016). Histopathologic features were also broadly similar between groups, although grade 3 histology was more common in Stage II, < 3 cm tumors (93.4% vs 74.7%, p = 0.0013).

Table 2
Characteristics for Small TNBC Cohort

Variable **n (%)**	**Stage I** **n = 154**	**Stage II, < 3 cm n = 61**	**p-value***
Age at diagnosis, median (range) - yrs	57.3 (47.5–66.3)	53.8 (41.5–64.5)	0.091
BMI, median (range) – kg/m²	27.3 (23.5–31.1)	30.3 (25.4–34.5)	**0.016**
Postmenopausal	110 (71.4%)	36 (59.0%)	0.079
HTN	82 (53.2%)	37 (60.7%)	0.32
HLD	89 (57.8%)	36 (59.0%)	0.87
DM	30 (19.5%)	18 (29.5%)	0.11
BRCA+	17 (11.0%)	3 (4.9%)	0.20
Histologic G3	115 (74.7%)	57 (93.4%)	**0.0013**
Ki-67, median (range) - %	65 (40–80)	70 (46.3–85.4)	0.28
IDC	132 (85.7%)	58 (95.1%)	0.06
NAT	94 (61.0%)	52 (85.2%)	**0.0006**
			0.0070†
AC/T	17 (18.1%)	3 (5.8%)	
CT + P	18 (19.1%)	6 (11.5%)	
KEYNOTE	43 (45.7%)	39 (75.0%)	**0.0052**
Other NAT	16 (17.0%)	4 (7.7%)	
No NAT	60 (39.0%)	9 (14.8%)	**0.0006**
			0.043†
Adj chemo +/- RT	36 (60.0%)	4 (44.4%)	
Adj RT only	10 (16.7%)	1 (11.1%)	
RT only	0 (0.0%)	1 (11.1%)	
Surgery only	14 (23.3%)	2 (22.2%)	

* p-value from comparing Stage I vs Stage II, <3cm groups. Continuous variables were compared with Mann–Whitney U test. Categorical variables were compared with Pearson chi-square test, with Fisher's exact test used when any cell count < 5.

† Global 2×k contingency test for subgroup distributions. Bonferroni correction applied to pairwise subgroup comparisons when global p < 0.05. Only significant post-hoc p-values were reported.

Variable n (%)	Stage I n = 154	Stage II, < 3 cm n = 61	p-value*
No treatment	0 (0.0%)	1 (11.1%)	
Surgery	154 (100.0%)	58 (95.1%)	**0.022**
			0.56†
BL mast	64 (41.6%)	22 (37.9%)	
UL mast	18 (11.7%)	10 (17.2%)	
Lump	72 (46.8%)	26 (44.8%)	
Adj Therapy	89 (56.5%)	37 (59.0%)	0.70
			0.0001†
Pembro	22 (24.7%)	21 (56.8%)	**0.0024**
Pembro + Cape	16 (18.0%)	10 (27.0%)	
Cape	10 (11.2%)	2 (5.4%)	
Other	41 (46.1%)	4 (10.8%)	**0.0008**
Adj RT	67 (43.5%)	26 (42.6%)	0.48
Deaths (anytime)	3 (1.9%)	4 (6.6%)	0.10
Recurrence (anytime)	10 (6.5%)	2 (3.3%)	0.52

* p-value from comparing Stage I vs Stage II, <3cm groups. Continuous variables were compared with Mann–Whitney U test. Categorical variables were compared with Pearson chi-square test, with Fisher's exact test used when any cell count < 5.

† Global 2×k contingency test for subgroup distributions. Bonferroni correction applied to pairwise subgroup comparisons when global p < 0.05. Only significant post-hoc p-values were reported.

Despite largely similar demographic and pathological metrics, treatment patterns differed substantially between Stage groups (Table 2). NAT was more frequently utilized in node-negative Stage II, < 3 cm disease compared with Stage I disease (85.2% vs 61.0%, p = 0.0006). NAT regimen distributions also differed significantly (p = 0.0070), primarily driven by greater KEYNOTE-522 utilization in node-negative Stage II, < 3 cm patients (75.0% vs 45.7%, adjusted p = 0.0052). Surgical approach distributions were similar between groups (p = 0.56), although surgery rates were slightly lower in node-negative Stage II, < 3 cm disease due to disease progression precluding surgery (n = 2) and patient refusal (n = 1). Adjuvant treatment distributions also differed significantly (p = 0.0001), with node-negative Stage II, < 3 cm patients more frequently receiving adjuvant pembrolizumab, while Stage I patients more commonly received non-pembrolizumab adjuvant approaches. Adjuvant radiation utilization was similar between groups (43.5% vs 42.6%, p = 0.48). Despite greater neoadjuvant treatment intensity for node-negative

Stage II, < 3 cm disease, recurrence (6.5% vs 3.3%, p = 0.52) and mortality rates (1.9% vs 6.6%, p = 0.10) were not significantly different between groups (Stage II T<3cm, N0 vs Stage 1, respectively).

Among NAT-treated small TNBC patients (n = 146), KEYNOTE-522 was the predominant regimen (56.2%), followed by CT + P (16.4%), AC/T (13.7%), and other NAT regimens (13.7%) (Table 3). Overall pCR for the small TNBC NAT cohort was 51.3% (75/146), with similar pCR rates between Stage I and node-negative Stage II, < 3 cm tumors (51.1% vs 51.9%, p = 0.92). Regimen-specific pCR rates within the combined small TNBC cohort were 52.4% for KEYNOTE-522, 45.8% for CT + P, 50.0% for AC/T, and 55.0% for other NAT regimens. No NAT regimen demonstrated significantly different pCR rates within the small TNBC (p = 0.93), Stage I (p = 0.62), or node-negative Stage II, < 3 cm (p = 0.16) cohorts. No statistically significant differences in pCR between Stage I and Stage II, < 3 cm N0 disease were observed for any individual NAT regimen, including AC/T (47.1% vs 66.7%, p = 0.99), CT + P (55.6% vs 16.7%, p = 0.17), KEYNOTE-522 (51.2% vs 53.8%, p = 0.81), or other NAT regimens (50.0% vs 75.0%, p = 0.59). KEYNOTE-522 did not demonstrate significantly different pCR rates from AC/T (p = 0.84), CT + P (p = 0.57), or non-KEYNOTE-522 NAT (p = 0.77) within the small TNBC cohort. Similarly, no significant differences were observed within the Stage I group compared with AC/T (p = 0.77), CT + P (p = 0.75), or non-KEYNOTE-522 NAT (p = 0.99). While KEYNOTE-522 was the most frequently used regimen, substantial heterogeneity in NAT administration practice was observed. Beyond the four principal treatment groups, 10 additional NAT regimens were identified within the cohort (Supplementary Table 1).

Table 3
Small TNBC Neoadjuvant Treatments

Variable	Stage I n = 94	Stage II, < 3 cm n = 52	< 3 cm n = 146	p-value*
AC/T, n (%)	17 (18.1%)	3 (5.8%)	20 (13.7%)	
pCR, n	8	2	10	
pCR, %	47.1	66.7	50.0	0.99
CT + P, n (%)	18 (19.1%)	6 (11.5%)	24 (16.4%)	
pCR, n	10	1	11	
pCR, %	55.6	16.7	45.8	0.17
KEYNOTE, n (%)	43 (45.7%)	39 (75.0%)	82 (56.2%)	
pCR, n	22	21	43	
pCR, %	51.2	53.8	52.4	0.81
Other NAT, n (%)	16 (17.0%)	4 (7.7%)	20 (13.7%)	
pCR, n	8	3	11	
pCR, %	50	75	55.0	0.59
Any NAT, n (%)	94 (100%)	52 (100%)	146 (100%)	
pCR, n	48	27	75	
pCR, %	51.1	51.9	51.3 (43.2–59.6)	0.92

* p-value from comparing Stage I vs Stage II, < 3 cm groups. Combined < 3 cm group for descriptive purposes only. Categorical variables were compared with Pearson chi-square test, with Fisher's exact test used when any cell count < 5.

Kaplan-Meier (KM) curves of event-free survival (EFS) of the small TNBC cohort (Stage I and Stage II, tumor < 3 cm). EFS calculated from date of diagnosis and compared via log-rank testing. **A)** KM curve comparing EFS for the most common neoadjuvant therapies (NAT). **B)** KM curve comparing EFS between any NAT and "No NAT", which comprised adjuvant only, surgery only, radiation only, or no treatment. **C)** KM curve comparing EFS for any NAT between Stage groups. **D)** KM curve comparing EFS for KEYNOTE-522 between Stage groups

Median follow-up for the overall small TNBC cohort was 2.6 years (range 1.8–3.5) without significant difference between Stage groups. Kaplan–Meier analyses demonstrated significant differences in EFS and RFS across NAT regimens (EFS p = 0.0025; RFS p = 0.0066), primarily driven by poorer outcomes in the CT + P subgroup (Fig. 2A). However, these findings should be interpreted cautiously as EFS did not significantly differ between NAT and non-NAT approaches within the small TNBC cohort (p = 0.16; Fig. 2B) and as NAT-treated Stage I versus Stage II T < 3 cm N0 patients demonstrated similar EFS (p = 0.86; Fig. 2C). Within KEYNOTE-treated patients, EFS also did not significantly differ by Stage subgroup

(p = 0.057; Fig. 2D). Taken together, small TNBCs had overall similar survival outcomes despite varying treatment strategies.

Discussion

In this contemporary TNBC cohort, Stage I and Stage II, < 3 cm node-negative tumors demonstrated broadly similar clinicopathologic characteristics, pCR rates, and short-term survival outcomes but substantially different treatment patterns. In line with NCCN guidelines, Stage II, T < 3 cm N0 patients were significantly more likely to receive NAT and adjuvant pembrolizumab, as KEYNOTE-522 represented the most frequent NAT approach. Similar clinical outcomes and demographic distributions across node-negative tumors < 3 cm despite Stage-guided treatment differences support further exploration of a size-based approach to small TNBC.

Historically, anthracycline-taxane chemotherapy regimens such as AC/T were the preferred treatment approach for higher-risk TNBC. Management of non-metastatic TNBC has evolved substantially following the publication and widespread clinical adoption of KEYNOTE-522[3]. Greater emphasis has been placed on NAT for assessment of pCR-guided adjuvant strategies and enabling breast-conserving surgery. However, NAT intensification must be balanced against risks of overtreatment, including NAT-associated toxicities, treatment delays, and financial burden[9]. Immune checkpoint inhibitors may produce durable endocrinopathies such as adrenal insufficiency or insulin-dependent diabetes mellitus, which are particularly burdensome in patients with otherwise favorable prognoses[15]. In this study, no individual NAT regimen demonstrated significantly superior pCR outcomes, while overall recurrence and mortality rates remained low. Despite being the most common NAT in our small TNBC cohort, KEYNOTE-522 did not demonstrate significantly superior pCR rates compared to other NAT approaches. These findings suggest that literature guiding NAT selection in Stage II-III TNBC may not easily translate to Stage I or node-negative Stage II disease.

Similar EFS between NAT and non-NAT approaches raises questions regarding potential overtreatment and optimal systemic therapy sequencing in small TNBC. Several retrospective studies have similarly reported limited differences in survival outcomes between neoadjuvant and adjuvant approaches among selected Stage I TNBC populations, although interpretation remains limited by selection bias and treatment heterogeneity[11, 12, 14]. These survival analyses should not be interpreted as evidence against NAT, particularly given the established prognostic value of pCR and the benefits of residual disease-directed adjuvant therapies. Rather, these data emphasize the need for improved patient selection strategies capable of identifying which small TNBC tumors derive meaningful benefit from intensified neoadjuvant approaches. To this end, our center is conducting a phase 2 prospective, randomized pilot study examining the efficacy of three neoadjuvant regimens for Stage 1 TNBC: a) carboplatin + paclitaxel; b) carboplatin + paclitaxel + pembrolizumab; c) pembrolizumab monotherapy (DETENTE-1). This feasibility study may help pave the way for larger studies to more carefully define optimal therapies for this understudied patient population.

This retrospective analysis has several limitations. The observational design introduces potential selection bias and confounding by indication, particularly regarding NAT selection. Subgroups were relatively small, especially for regimen-specific analyses, limiting statistical power and precluding robust multivariable modeling. In addition, the cohort has limited follow-up and relatively few survival events to date. Consequently, survival analyses should be considered exploratory. Finally, substantial treatment heterogeneity complicated direct regimen comparisons, although this also reflects contemporary clinical practice.

Despite these limitations, this study provides a real-world evaluation of NAT utilization and outcomes in small node-negative TNBC in the immunotherapy era. Small TNBC tumors demonstrated overlapping characteristics and outcomes across the conventional Stage boundary, despite differing treatment approaches. Future prospective studies comparing NAT strategies in Stage I and early Stage II TNBC are needed, particularly around Stage cutoffs frequently used for treatment escalation. Development of integrated risk-stratification models incorporating demographic features, tumor size, genomic data, immune biomarkers, toxicity risk, and cost considerations may help guide more individualized NAT selection in small TNBC.

Declarations

Competing Interests

J. Gruber reports non-financial support from Hummingbird Bioscience and employment and stock ownership (immediate family member) from Guardant Health outside the submitted work. No other authors report competing interests.

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Ethics Declaration

This retrospective observational study involving human participants was conducted in accordance with the ethical standards of the 1964 Helsinki Declaration and was approved by the UT Southwestern Institutional Review Board (IRB number: STU-2023-0308). All medical data were presented in aggregate; no personally identifiable information was included in the manuscript. Consent to participate declaration: not applicable. Clinical trial number: not applicable.

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Declaration

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Author Contribution

Conceptualization: BL, BS, HM, JG; Data curation: BL, BS, AL, AK; Formal analysis: BL, SZ; Visualization: BL; Writing - original draft: BL; Writing - review & editing: all authors.

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Data Availability

All tables supporting the findings of this study are available within the paper and its Supplementary Information. Raw data were derived from institutional electronic medical records and are not publicly available. De-identified data may be available from the corresponding author upon reasonable request and with appropriate institutional approvals.

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Figures

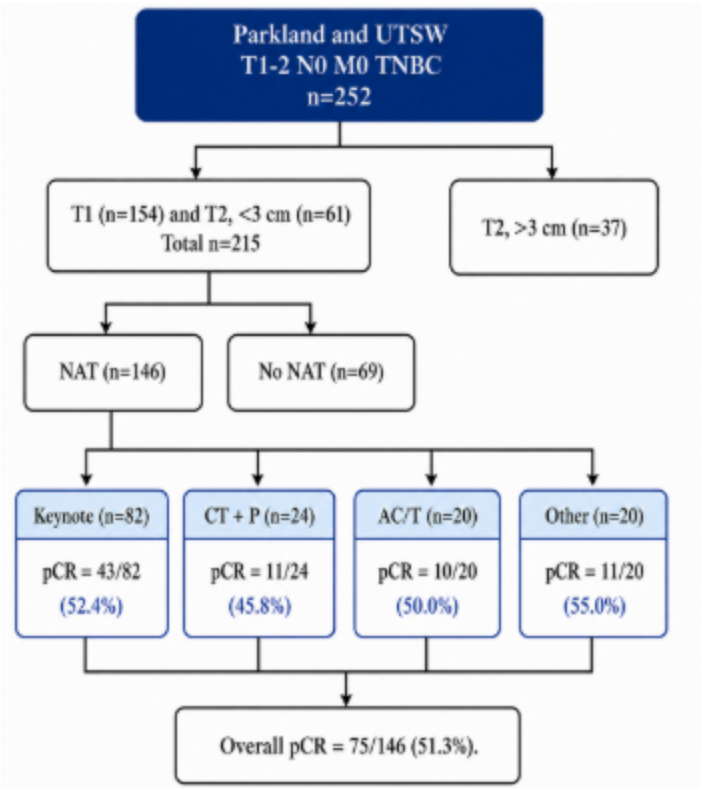


Figure 1

Study Cohort Diagram

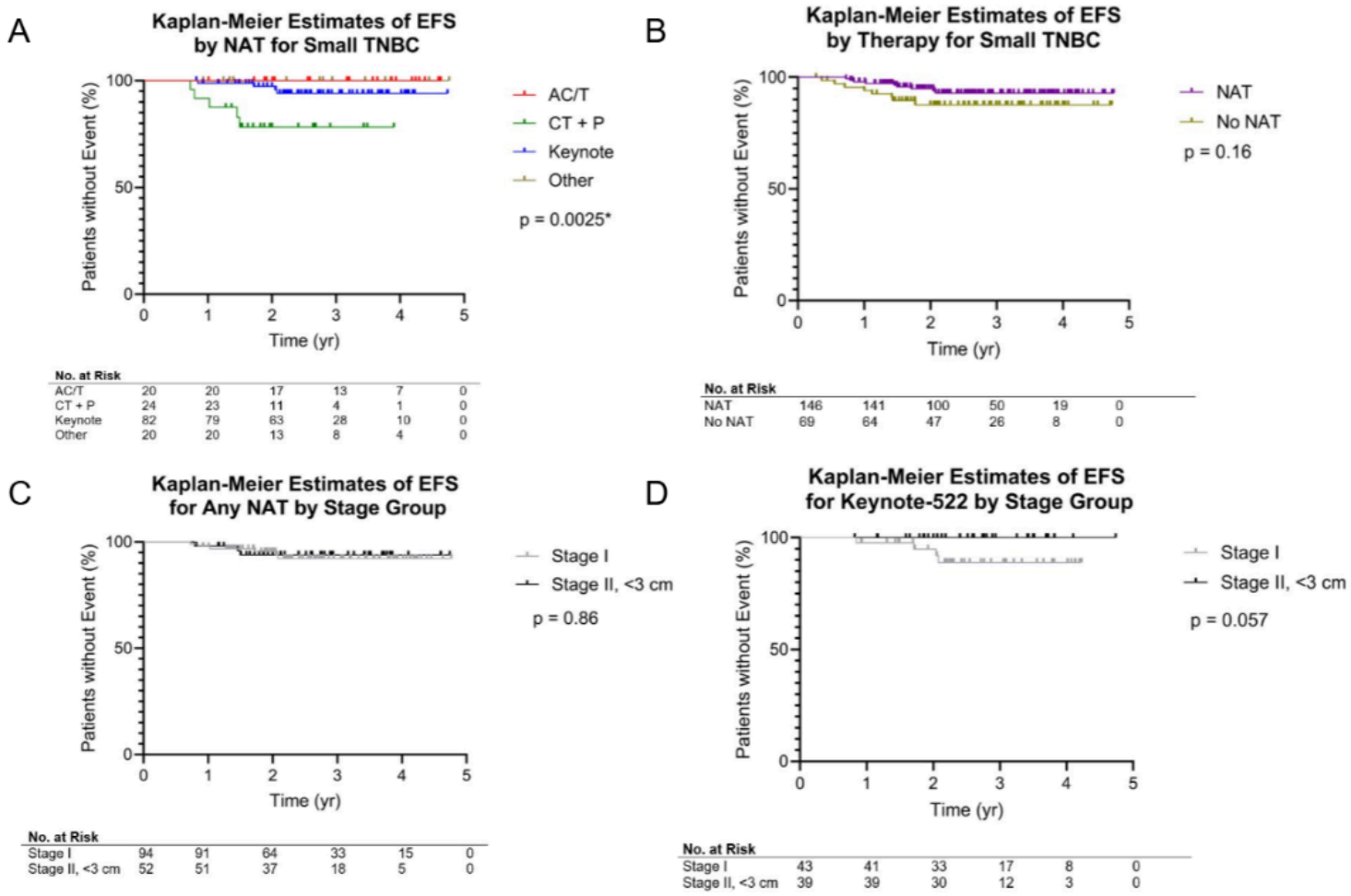


Figure 2

Survival of Small TNBC Cohort

Kaplan-Meier (KM) curves of event-free survival (EFS) of the small TNBC cohort (Stage I and Stage II, tumor <3 cm). EFS calculated from date of diagnosis and compared via log-rank testing. **A)** KM curve comparing EFS for the most common neoadjuvant therapies (NAT). **B)** KM curve comparing EFS between any NAT and “No NAT”, which comprised adjuvant only, surgery only, radiation only, or no treatment. **C)** KM curve comparing EFS for any NAT between Stage groups. **D)** KM curve comparing EFS for KEYNOTE-522 between Stage groups

Supplementary Files

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