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Abstract

Special histologic subtypes of triple-negative breast cancer (TNBC) are biologically distinct, yet their outcomes in the immunotherapy era remain undefined. We analyzed 823 patients with early-stage TNBC treated with pembrolizumab plus chemotherapy in the multicenter real-world Neo-Real/GBECAM-0123 cohort. Histologies included invasive carcinoma of no special type (NST; n=762, 92.6%), metaplastic carcinoma (n=26, 3.2%), triple-negative lobular carcinoma (n=17, 2.1%), and other rare variants (n=18, 2.2%). Metaplastic carcinoma demonstrated significantly lower pathological complete response (pCR) rates compared with NST (17.4% vs 65.4%; OR 0.14, 95% CI 0.04–0.44; p=0.001), suggesting relative resistance to chemo-immunotherapy, with a numerical trend toward worse event-free survival (EFS) (HR 2.07, 95% CI 0.88–4.88; p=0.094). Triple-negative lobular carcinoma achieved pCR rates comparable to NST (56.2%) but showed poorer 2-year EFS, with a significant association in the pre-surgical multivariable model (HR 4.25, 95% CI 1.50–12.06; p = 0.006), and a persistent trend after adjustment for pCR. This highlights the biological heterogeneity of TNBC and supports the investigation of histology-driven therapeutic strategies.

Keywords: Triple-Negative Breast Cancer; Special histologic subtypes; Early-stage; Immune Checkpoint Inhibitors.

Introduction

Triple-negative breast cancer (TNBC) accounts for approximately 10–20% of all breast cancers and is defined by the absence of estrogen receptor (ER), progesterone receptor (PR) expression and HER2 overexpression or amplification.^{1,2} Histopathologically, approximately 85–90% of TNBC cases correspond to invasive carcinoma of no special type (NST), representing the predominant morphologic substrate of receptor-defined triple-negative disease. In contrast, special histologic subtypes (SHT) collectively account for roughly 5–10% of TNBC and comprise a heterogeneous group of rare variants, including metaplastic and triple-negative lobular carcinoma.^{3–5} These tumors are biologically distinct from conventional NST TNBC, exhibiting unique morphologic features, genomic landscapes, immune microenvironments, and clinical trajectories.⁶

The prognostic landscape among these rare histologies is highly variable. While certain subtypes —such as adenoid cystic and secretory carcinomas— may exhibit relatively indolent behavior,^{7,8} others—particularly metaplastic carcinoma— are characterized by enrichment for mesenchymal and claudin-low transcriptional programs, intrinsic chemoresistance, early recurrence, and inferior survival despite aggressive multimodality

therapy.^{9,10} Triple-negative lobular carcinoma represents another distinct phenotype, often associated with lower proliferation indices yet paradoxically unfavorable long-term outcomes.¹¹

The incorporation of immune checkpoint inhibition into neoadjuvant chemotherapy has redefined the standard of care for stage II–III TNBC. In the phase III KEYNOTE-522 trial, the addition of pembrolizumab to multi-agent chemotherapy significantly improved pathological complete response (pCR), event-free survival (EFS) and overall survival (OS), establishing chemo-immunotherapy as the preferred regimen in high-risk early-stage disease.^{12,13} However, SHT of TNBC were underrepresented in KN522, and histology-specific outcomes were not reported.

Given the biological diversity and prognostic heterogeneity of rare TNBC subtypes, it cannot be assumed that the magnitude of benefit observed in NST applies uniformly across all morphologic variants. Real-world data are therefore essential to determine whether current chemo-immunotherapy strategies provide comparable benefit—or whether outcome disparities persist—in these uncommon but clinically challenging tumors.

In this context, we analyzed outcomes according to histologic subtype within the Neo-Real/GBECAM-0123 Cohort, a large multicenter real-world study of patients with early-stage TNBC treated with KEYNOTE-522 regimen in Brazil and Argentina. Our objective was to evaluate whether SHT demonstrates differential outcomes compared with TNBC NST in the contemporary immunotherapy era.

Results

Patient characteristics

Among 842 patients included in the registry, 823 were included in the analysis (97.7%). The 19 remaining had undifferentiated carcinoma (n=6), occult primary (n=2), or unavailable histology (n=11). The majority had invasive carcinoma NST (n=762, 92.6%), followed by metaplastic carcinoma (n=26, 3.2%), triple-negative lobular carcinoma (n=17, 2.1%), and other SHT variants (n=18, 2.2%). Among metaplastic carcinomas, mesenchymal and squamous differentiation were the most common subtypes (8 cases each, 30.8%), followed by spindle cell morphology (4 cases, 15.4%), while the specific subtype was not detailed in six cases (23.1%). In the group classified as other SHT, the histological types included apocrine (n=10), micropapillary (n=3), neuroendocrine (n=2), medullary (n=2), and papillary (n=1).

Baseline clinicopathologic characteristics according to histologic subtype are summarized in Table 1. Age differed significantly across subtypes ($p=0.005$), with triple-negative lobular carcinoma presenting in older patients (median 57 years) compared with NST (median 44 years) and metaplastic carcinoma (median 51 years).

Proliferation and grade varied across histologies. High Ki-67 ($\geq 50\%$) was more frequent in NST (77.4%) compared with metaplastic carcinoma (53.8%), triple-negative lobular carcinoma (56.2%) and other SHT variants (35.3%) ($p<0.001$). Grade 3 tumors predominated in NST (75.9%) and metaplastic carcinoma (84.0%), whereas it was less common in lobular (53.3%) and other SHT variants (50%) ($p=0.017$).

Pathologic complete response

Overall pCR rates differed significantly by histologic subtype ($p<0.001$). NST achieved a pCR rate of 65.4%, compared with 56.2% in triple-negative lobular carcinoma, 50.0% in other SHT variants, and 17.4% in metaplastic carcinoma. (Figure 1) Among metaplastic carcinomas, pCR rates did not differ significantly according to metaplastic

subtype ($p=0.886$), with one pCR observed in each subgroup: mesenchymal (12.5%), spindle cell (33.3%), squamous cell (16.7%), and tumors without further subtype specification (16.7%).

In univariable analysis, metaplastic histology was associated with markedly lower odds of pCR compared with NST (OR 0.11, $p<0.001$), whereas triple-negative lobular carcinoma and other SHT were not significantly different. Grade 3 (OR 1.88, $p<0.001$) and high Ki-67 (OR 2.77, $p<0.001$) were associated with increased likelihood of pCR, while stage III disease (OR 0.56, $p=0.001$), receipt of fewer than 6 cycles of pembrolizumab (OR 0.49, $p<0.001$) were associated with reduced pCR. (Table 2)

In multivariable analysis, metaplastic histology remained independently associated with lower odds of pCR (OR 0.14, $p = 0.001$). Stage III disease (OR 0.51, $p < 0.001$) and receipt of fewer than six cycles of pembrolizumab (OR 0.51, $p = 0.007$) were also independently associated with reduced pCR. In contrast, grade 3 tumors (OR 1.72, $p = 0.008$), and high Ki-67 (OR 2.22, $p < 0.001$) were independently associated with increased odds of pCR. (Table 3)

Post-neoadjuvant systemic treatment according to histologic subtype was explored separately among patients with and without pCR (Supplementary Table 1), with no significant differences in treatment patterns across histologic subtypes in either group.

Event-free survival

After a median follow-up of 24 months, recurrence or death occurred in 83 patients with NST (10.9%), 6 triple-negative lobular carcinomas (35.3%), 6 metaplastic carcinomas (23.1%), and 3 other SHT variants (16.7%) ($p=0.006$). Two-year EFS was 87.9% (95% CI 84.8–90.3%) for NST, 58.3% (95% CI 29.0–79.0%) for triple-negative lobular carcinoma, 77.7% (95% CI 53.9–90.2%) for metaplastic carcinoma, and 81.6% (95% CI 53.0–93.7%) for other SHT variants. (Figure 2)

Among patients who achieved pCR, EFS events occurred in 15 of 472 NST tumors (3.2%) and in 2 of 9 triple-negative lobular carcinomas (22.2%), whereas no events were observed among metaplastic carcinomas ($n=4$) or other SHT variants ($n=9$) achieving pCR. (Table 4) EFS differed significantly according to histological subtype among patients who achieved pCR (log-rank $p=0.0024$). The EFS curves for NST, metaplastic carcinomas, and other SHT variants largely overlapped, whereas triple-negative lobular carcinomas showed poorer outcomes. In contrast, no significant differences in EFS were observed among patients with residual disease (log-rank $p=0.6338$). (Figures 3 and 4) Similar findings were observed when patients were stratified by residual cancer burden (RCB 0–1 vs. RCB 2–3) (Supplementary Table 2 and Supplementary Figures 1 and 2).

Most recurrence or death events occurred within 6 months after completion of systemic therapy across all histologic subtypes, with no significant differences in recurrence timing (Supplementary Table 3). Likewise, the distribution of recurrence sites did not differ significantly according to histologic subtype (Supplementary Table 4).

In univariable analyses, pCR was strongly associated with EFS (HR 0.13, $p < 0.001$). Grade 3 tumors were also associated with improved EFS (HR 0.62, $p = 0.032$). Conversely, receipt of fewer than six cycles of pembrolizumab (HR 3.13, $p < 0.001$), stage III disease (HR 3.66, $p < 0.001$), and lobular histology compared with NST (HR 3.89, $p = 0.001$) were associated with worse EFS. Metaplastic histology showed a non-significant trend toward poorer outcomes (HR 2.29, $p = 0.050$). (Table 5)

In the multivariable model, assessment of the proportional hazards assumption revealed that disease staging violated the assumption at the individual level ($\rho = -0.249$; $\chi^2 = 5.24$; $p = 0.022$), while the global test

remained borderline non-significant ($\chi^2 = 13.68$; $df = 7$; $p = 0.057$). To account for this violation, stage was modeled as a time-varying coefficient. In the final model, triple-negative lobular carcinoma was independently associated with worse EFS compared with NST (HR = 4.25; 95% CI: 1.50–12.06; $p = 0.006$), while metaplastic carcinoma showed a trend toward inferior EFS (HR = 2.07; 95% CI: 0.88–4.88; $p = 0.094$). Higher histological grade was associated with a reduced hazard (HR = 0.58; 95% CI: 0.37–0.93; $p = 0.022$), which may reflect its association with higher pCR rates. Regarding the time-varying effect of stage, the interaction between stage and $\ln(t)$ was positive and statistically significant (HR = 1.58; 95% CI, 1.35–1.86; $p < 0.001$), indicating that the relative effect of stage III disease on EFS increased over follow-up. Because stage was modeled as a time-varying covariate, this estimate should not be interpreted as a conventional constant hazard ratio (Table 6). When pCR was included in the model, it remained a strong independent prognostic factor (HR 0.15, $p < 0.001$), while lobular histology showed a persistent trend toward worse EFS that did not reach statistical significance (HR 2.95, $p = 0.079$) (Supplementary Table 5).

Discussion

In this large multicenter real-world cohort of patients with early-stage TNBC treated with the KEYNOTE-522 regimen, we observed differences in clinicopathologic characteristics, treatment response, and survival patterns according to histologic subtype. While NST achieved high pCR rates and favorable short-term EFS, metaplastic carcinoma demonstrated a markedly reduced likelihood of achieving pCR and numerically lower EFS. In contrast, triple-negative lobular carcinoma achieved pCR rates approaching those observed in NST but showed less favorable EFS, highlighting a discordance between pathological response and survival outcomes. These findings suggest that histologic subtype continues to convey prognostic and predictive information even within the contemporary chemo-immunotherapy era.

TNBC is widely recognized as a heterogeneous disease at the molecular and clinical levels. Nevertheless, in routine clinical practice, patients are treated uniformly based on hormonal receptor and HER2 negativity, with limited consideration of histologic architecture. SHT are biologically distinct entities characterized by divergent genomic landscapes, transcriptional programs, differentiation states, and immune microenvironments.^{2,14,15} The persistence of outcome disparities in our cohort despite standardized neoadjuvant chemo-immunotherapy underscores that receptor-based classification alone does not fully capture the biological diversity within TNBC. In our cohort, baseline clinicopathologic features also differed across subtypes, including older age and lower proliferation indices among lobular tumors and marked high-grade predominance in metaplastic carcinoma. Although multivariable adjustment accounted for these variables, the persistence of survival disparities suggests that intrinsic biological differences beyond conventional prognostic factors contribute to the observed outcomes.

Among histologic subtypes, the most pronounced therapeutic divergence was observed in metaplastic carcinoma. In our cohort, metaplastic tumors achieved a substantially lower pCR rate than NST (17.4% vs 65.4%). Two-year EFS was also less favorable in this subtype (77.7%), although this association did not retain statistical significance after adjustment, likely reflecting limited sample size and event counts in this subgroup. In contrast, metaplastic histology remained strongly associated with reduced likelihood of achieving pCR in multivariable analysis (OR 0.14), reinforcing its relative resistance to systemic therapy. Biologically, metaplastic carcinomas are enriched for epithelial–mesenchymal transition programs, stem-like transcriptional signatures, genomic instability, and frequent PI3K/AKT/mTOR pathway alterations.^{16–18} Although subsets may express PD-L1 or exhibit tumor-infiltrating lymphocytes, immune landscapes are heterogeneous and may include immune-excluded or immunosuppressive phenotypes.¹⁹

These observations are consistent with broader evidence suggesting that metaplastic tumors are frequently chemotherapy resistant. In a National Cancer Database analysis of 5136 patients with stage I–III metaplastic breast cancer, a pCR rate of only 4.9%. Compared with patients treated with neoadjuvant chemotherapy, those who underwent upfront surgery followed by adjuvant chemotherapy had significantly better 5-year overall survival (HR 0.56, 95% CI 0.46–0.67; $p < 0.0001$), raising the possibility that standard neoadjuvant approaches may not confer the same benefit observed in conventional TNBC.²⁰ Notably, recent data similarly demonstrated persistently low pCR rates in metaplastic TNBC treated with neoadjuvant chemo-immunotherapy (22%), similar to those reported in real-world studies of metaplastic TNBC treated with neoadjuvant chemotherapy without immunotherapy.^{21,22} Together, these findings suggest that immune checkpoint inhibition, although transformative in unselected TNBC populations, may not fully overcome lineage-specific resistance programs embedded within certain morphologic subtypes, such as metaplastic carcinoma. Nevertheless, pCR in the same chemo-immunotherapy cohort was markedly higher among tumors with high stromal TILs (62% for sTILs $\geq 60\%$ vs. 9% for sTILs $< 60\%$), raising the possibility that immune biomarkers may identify a subset of metaplastic tumors with greater treatment sensitivity — a hypothesis that warrants prospective validation.²²

Triple-negative lobular carcinoma demonstrated a distinct but clinically relevant pattern, although this observation should be interpreted cautiously given the limited number of patients and events. Lobular tumors achieved pCR rates comparable to NST (56.2%) yet were associated with significantly worse event-free survival (HR 4.25, 95% CI 1.50–12.06; $p = 0.006$), with a 2-year EFS of 58.3%. This association remained significant in multivariable models excluding pCR and showed a persistent trend after adjustment for pCR. The dissociation between early pathological response and long-term outcomes raises the possibility that the prognostic significance of pCR may not be uniform across histological subtypes. These findings are corroborated by a National Cancer Database analysis of over 80000 patients with stage I–III TNBC, of whom 944 (1.2%) had triple-negative lobular carcinoma. Lobular histology was independently associated with increased mortality risk despite neoadjuvant treatment (aHR 1.34, 95% CI 1.05–1.70; $p = 0.02$). Notably, no survival difference was observed by pCR status among matched lobular patients (5-year OS: 66% with pCR vs. 69% without pCR; $p = 0.54$), even though the addition of immunotherapy showed a trend toward improved pCR rates (aOR 1.69, 95% CI 0.95–3.01; $p = 0.07$).²³

Triple-negative lobular carcinomas frequently display lower prevalence of the basal-like intrinsic subtype and relative enrichment for luminal or HER2-enriched transcriptional programs despite receptor negativity.^{11,24} Importantly, triple-negative lobular carcinomas likely encompass molecularly heterogeneous tumors rather than a single biological entity, with reported enrichment for androgen receptor signaling, *Estrogen-Related Receptor Alpha (ESRRA)* gene alterations, and lower immune activation, which may further limit the predictive value of pCR in this subgroup. Loss of E-cadherin and alterations in cell adhesion and stromal interaction pathways could theoretically influence dissemination patterns and micrometastatic persistence, potentially contributing to inferior outcomes despite initial tumor eradication at surgery.^{24–27} These data raise the possibility that pCR may capture cytotoxic sensitivity but not necessarily eradicate micrometastatic niches in certain histologic contexts. Although speculative, these observations suggest that the prognostic value of pCR may not be uniform across biologically distinct TNBC subtypes, and that histologic architecture should be considered when interpreting response-based endpoints.^{28,29}

Regarding other findings from our multivariable analyses, pCR emerged as the strongest prognostic factor for EFS, reinforcing its central role as a marker of treatment sensitivity and long-term outcome in TNBC, particularly in NST disease. However, the discordant pattern observed in triple-negative lobular carcinoma underscores the limitations of pCR as a surrogate endpoint in certain histologic contexts. The association between grade 3 tumors and improved EFS further illustrates the complex interplay between tumor proliferation and therapeutic sensitivity within TNBC.

High-grade and highly proliferative tumors have demonstrated a greater likelihood of achieving pCR following neoadjuvant treatment. Therefore, the association observed in our cohort may reflect greater responsiveness to neoadjuvant therapy rather than a favorable biological behavior.³⁰⁻³² In contrast, advanced clinical stage remained an adverse prognostic factor in our cohort, underscoring that tumor burden continues to exert a relevant influence on outcome despite modern systemic therapy.³³ Receipt of fewer than six cycles of pembrolizumab in the neoadjuvant setting was also associated with lower pCR rates and worse EFS. However, this finding should be interpreted cautiously, as incomplete pembrolizumab exposure may reflect treatment interruption, toxicity, or more aggressive disease biology rather than a direct treatment effect. In addition, this association may also be affected by guarantee-time bias, as patients with early disease progression or treatment discontinuation are inherently more likely to receive fewer cycles.

From a broader perspective, our study provides contemporary real-world evidence addressing a major gap in the literature regarding the outcomes of TNBC special histologies in the modern immunotherapy era. Clinical trials have largely excluded or underrepresented these subtypes, resulting in limited guidance for clinicians managing these rare but biologically complex tumors. Our findings suggest that morphologic architecture is not merely descriptive but biologically instructive, with potential implications for therapeutic sensitivity and survival dynamics. The persistence of outcome disparities despite uniform chemo-immunotherapy challenges the assumption that TNBC behaves as a homogeneous entity defined solely by receptor status. These data highlight the need for innovative strategies, including histology-informed therapeutic development, translational efforts to define subtype-specific vulnerabilities, and biomarker-driven approaches that move beyond receptor negativity alone. Importantly, future clinical trial designs may need to intentionally include and stratify rare histologic variants rather than extrapolating outcomes from NST-dominant populations. Such approaches may enable more precise estimation of treatment benefit and avoid masking subtype-specific therapeutic vulnerabilities. Furthermore, the observed discordance between pathological response and long-term survival in certain subtypes raises critical questions regarding the histology-dependent validity of surrogate endpoints. Validation efforts for response-based endpoints may therefore require histology-specific calibration to ensure accurate interpretation of clinical benefit in the immunotherapy era.

Our findings must be interpreted considering some limitations. The limited number of events within rare histologic subtypes resulted in wide confidence intervals, and the study was not powered to detect moderate differences in survival across these groups. Although the median follow-up of 24 months limits long-term inferences, it provides a reasonable representation of early-stage TNBC outcomes, as most recurrences after neoadjuvant chemo-immunotherapy occur within 2 to 3 years after initial treatment, and in our cohort the majority of recurrence or death events occurred within 6 months after completion of systemic therapy. Nevertheless, the present analysis primarily reflects early recurrence dynamics, and longer follow-up will be required to characterize late recurrence patterns and determine whether the observed differences translate into overall survival outcomes.³⁴ Detailed data on adjuvant pembrolizumab completion rates, dose reductions, treatment delays, and chemotherapy dose intensity were not systematically captured, and treatment heterogeneity inherent to a retrospective multicenter cohort cannot be excluded. Comprehensive molecular profiling was also not uniformly available. Finally, no central pathology review was performed; however, participating centers are tertiary oncology institutions with breast pathology expertise. Despite these limitations, to our knowledge, this study represents one of the largest real-world analyses of TNBC SHT uniformly treated with KEYNOTE-522 regimen across multiple centers.

Overall, special histologic subtypes of TNBC demonstrated distinct clinical trajectories and therapeutic sensitivities in this real-world cohort, with poor outcomes observed in metaplastic and triple-negative lobular carcinoma despite standardized chemo-immunotherapy. The discordance observed between pCR and survival

outcomes in the lobular subtype raises the possibility that the prognostic significance of pathological response may differ across histological subtypes; however, these findings should be considered exploratory and hypothesis-generating given the limited number of patients and events. Rare histologic subtypes should be recognized as biologically distinct entities requiring dedicated translational investigation and subtype-specific therapeutic strategies. Integrating morphologic subtype into precision oncology frameworks may ultimately refine prognostic assessment and guide more rational therapeutic development in early-stage TNBC.

Methods

Study design and participants

The Neo-Real/GBECAM-0123 study is a multicenter, retrospective, real-world cohort study including patients with early-stage TNBC treated with neoadjuvant chemotherapy plus pembrolizumab since July 2020 across fourteen Brazilian and sixteen Argentine cancer centers. The cutoff date for this analysis was January 2026. Early-stage disease was defined according to the AJCC 8th edition as clinical stage I–III. Patients were eligible if they had histologically confirmed TNBC of any subtype and received at least one cycle of neoadjuvant chemo-immunotherapy consistent with the KEYNOTE-522 regimen. Histologic subtype classification (NST vs SHT) was based on local pathology reports. A tumor was classified as a special histologic subtype only if >90% of the tumor exhibited that subtype. Mixed tumors not meeting this criterion were classified according to the predominant histologic component. No central pathology review was performed; however, all participating institutions were specialized tertiary cancer centers with dedicated breast pathology expertise.

Objectives and endpoints

The objective of this analysis was to evaluate the effectiveness of the KEYNOTE-522 regimen in patients with TNBC according to histologic subtype, comparing NST with SHT. The endpoints of interest were pCR, defined as the absence of residual invasive disease in the breast and axillary lymph nodes (ypT0/Tis ypN0), and EFS, defined as the time from treatment initiation to disease progression precluding surgery, local or distant recurrence, second primary malignancy, or death from any cause. Associations between these outcomes and clinical variables—such as tumor stage, tumor grade, and Ki67 index—were also explored.

Data Collection

Clinical records were reviewed to extract demographic, clinical, pathological, and treatment-related variables, which were entered into a centralized REDCap database. This investigation was carried out within the framework of GBECAM (Grupo Brasileiro de Estudos em Câncer de Mama) and received approval from the Institutional Review Boards of all participating institutions. In Brazil, ethical approval was granted under protocol number 67950623.0.1001.0068, encompassing the following centers: Instituto D’Or de Pesquisa e Ensino, A.C. Camargo Cancer Center, Hospital Moinhos de Vento, Hospital Sírio-Libanês, Hospital Beneficência Portuguesa, Hospital 9 de Julho, Hospital Santa Paula, Clínica AMO, Instituto do Câncer do Ceará, Brasília Hospital, Centro Integrado de Pesquisa da Amazônia, Hospital São Domingos, Hospital Samaritano, and Instituto Américas. In Argentina, the study was approved by the CEMIC Institutional Review Board (protocol number 12805). The research adhered to the ethical standards established by the Declaration of Helsinki. Written informed consent was obtained from participants whenever feasible. For patients who were deceased or could not be reached, the requirement for consent was waived by the respective ethics committees, as analyses were conducted exclusively using de-identified

data. Data management and statistical analyses were coordinated by the Research Unit of Instituto D'Or de Pesquisa e Ensino (São Paulo, Brazil). The manuscript was prepared by the first and senior authors without industry-supported medical writing, and all co-authors critically reviewed and approved the final version, attesting to the accuracy and completeness of the reported data.

Statistical analysis

Baseline characteristics were described using median and range for continuous variables and absolute/relative frequencies for categorical variables. Distribution normality was assessed with the Shapiro–Wilk test. Continuous variables were compared using the Student's t-test (normally distributed) or the Mann–Whitney U test (non-normally distributed), while categorical variables were compared with Fisher's exact test.

EFS was estimated using the Kaplan–Meier method and compared using the log-rank test. Logistic regression analyses were performed to identify factors associated with pCR, and Cox proportional hazards models were used to evaluate factors associated with EFS. Because pCR may lie on the causal pathway between tumor biology and survival outcomes, two multivariable Cox models were performed: one excluding pCR to estimate total prognostic effects, and one including pCR to assess response-adjusted associations. The proportional hazards assumption was assessed for all covariates using the Schoenfeld residuals test. In the presence of a violation for a specific covariate, a time-varying coefficient approach was applied by incorporating an interaction term between the covariate and the natural logarithm of time $[\ln(t)]$, as recommended for Cox models in which the hazard ratio is not constant over the follow-up period.

Variables with $p < 0.1$ in univariate analysis or deemed clinically relevant were included in multivariable models. For both multivariable models (logistic regression for pathological response and Cox proportional hazards regression for survival analysis), multicollinearity was assessed using the Variance Inflation Factor (VIF) derived from a linear probability model with identical covariates. All VIF values were below 1.12, well within the acceptable threshold ($VIF < 5$), indicating no evidence of multicollinearity among the predictors included in either model. The analyses were performed according to the data availability; no method of data imputation was used. All analyses were conducted using Stata version 15.0 (StataCorp, College Station, TX, USA). P-values < 0.05 were considered statistically significant.

Data availability: The datasets generated and/or analyzed during the current study are not publicly available in order to protect patient privacy but are available from the corresponding author on reasonable request. Data analysis methods have been described thoroughly in the Methods section.

Code availability: No custom code was used for this study.

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Table 1. Baseline clinicopathologic characteristics according to histologic subtype

Characteristics	NST (N = 762)	Metaplastic (N = 26)	Lobular (N = 17)	Other SHT (N = 18)	p
	N (%)				
Median age	44.1	51.2	57.5	49.5	0.005
(range)	(21.5–91.3)	(22.5–74.9)	(38.2–83.0)	(38.3–83.7)	
Clinical stage					0.283
II	525/729	21/26	13/16	10/18	
	(72.0%)	(80.8%)	(81.2%)	(55.6%)	
III	204/729	5/26	3/16	8/18	
	(28.0%)	(19.2%)	(18.8%)	(44.4%)	
Histologic grade 3	532/701	21/25	8/15	8/16	0.017
	(75.9%)	(84.0%)	(53.3%)	(50.0%)	
Ki-67 ≥ 50%	561/725	14/26	9/16	6/17	< 0.001
	(77.4%)	(53.8%)	(56.2%)	(35.3%)	
TILs ≥ 30%	73/257	2/7	0/4	0/7	0.293
	(28.4%)	(28.6%)	(0.0%)	(0.0%)	

<i>BRCA 1/2 status</i>					0.284
Mutated	112/762	2/26	2/17	0	
	(14.7%)	(7.7%)	(11.8%)	(0.0%)	
Wild-type/Unknown	650/762	24/26	15/17	18	
	(85.3%)	(92.3%)	(88.2%)	(100.0%)	
<i>AC regimen</i>					0.865
Dose-dense	384/724	14/24	7/15	7/15	
	(53.0%)	(58.3%)	(46.7%)	(46.7%)	
Every 3 weeks	340/724	10/24	8/15	8/15	
	(47.0%)	(41.7%)	(53.3%)	(53.3%)	
<i>Carboplatin regimen</i>					0.428
Weekly	582/653	20/23	10/13	15/17	
	(89.1%)	(87.0%)	(76.9%)	(88.2%)	
Every 3 weeks	71/653	3/23	3/13	2/17	
	(10.9%)	(13.0%)	(23.1%)	(11.8%)	
<i>Neoadjuvant pembrolizumab cycles</i>					0.001
≥ 6 cycles	630/745	14/25	14/16	10/16	
	(84.6%)	(56.0%)	(87.5%)	(62.5%)	
< 6 cycles	115/745	11/25	2/16	6/16	
	(15.4%)	(44.0%)	(12.5%)	(37.5%)	

Abbreviations: NST: No special type; SHT: Special histologic subtype; N: Number of patients; Ki-67: Ki-67 proliferation index; AC: doxorubicin and cyclophosphamide.

Note: Percentages were calculated based on available data for each variable; denominators may vary due to missing values.

Figure 1. pCR according to histology

Abbreviations: pCR: pathologic complete response; NST: No special type; SHT: Special histologic subtype.

Table 2. Univariate analyses of factors associated with pCR

Variable	OR	95% CI	p
AC regimen (dose-dense vs every 3 weeks)	1.11	0.83 - 1.50	0.479
Pembrolizumab <6 cycles (yes vs no)	0.49	0.33 - 0.72	<0.001

Variable	OR	95% CI	p
Age (≥ 65 vs < 65 years)	0.65	0.41 - 1.01	0.056
Stage III (vs II)	0.56	0.41 - 0.78	0.001
Lobular subtype (vs NST)	0.68	0.25 - 1.85	0.451
Metaplastic subtype (vs NST)	0.11	0.04 - 0.33	< 0.001
Other special subtype (vs NST)	0.53	0.21 - 1.35	0.184
Grade 3 (vs 1–2)	1.88	1.33 - 2.65	< 0.001
Ki67 $\geq 50\%$ (vs $< 50\%$)	2.77	1.97 - 3.89	< 0.001
TILs $\geq 30\%$ (vs $< 30\%$)	2.91	1.52 - 5.57	0.001
BRCA1/2 mutated (vs Wild-type/Unknown)	2.19	1.38 - 3.47	0.001

Abbreviations: pCR: pathologic complete response; OR: odds ratio; CI: confidence interval; NST: no special type; BRCA1/2 mutated: Breast cancer susceptibility genes 1 and 2 mutated.

Table 3. Multivariable analysis of factors associated with pCR among patients with complete data for all variables included in the model (n = 631).

Variables	OR	95% CI	p
AC regimen (dose-dense vs every 3 weeks)	0.94	0.66 – 1.33	0.707
Pembrolizumab < 6 cycles (yes vs no)	0.51	0.31 – 0.83	0.007
Age (≥ 65 vs < 65 years)	0.96	0.54 – 1.71	0.892
Stage III (vs II)	0.51	0.35 – 0.74	< 0.001
Lobular subtype (vs NST)	0.95	0.28 – 3.26	0.936
Metaplastic subtype (vs NST)	0.14	0.04 – 0.44	0.001
Other special subtype (vs NST)	0.54	0.14 – 2.02	0.358
Grade 3 (vs 1–2)	1.72	1.15 – 2.57	0.008
Ki67 $\geq 50\%$ (vs $< 50\%$)	2.22	1.47 – 3.34	< 0.001

Abbreviations: pCR: pathologic complete response; OR: odds ratio; CI: confidence interval; AC: doxorubicin and cyclophosphamide; NST: no special type;

Figure 2. Event-free survival according to histology

Legend: EFS events occurred in 83 NST cases, 6 triple-negative lobular carcinoma cases, 6 metaplastic carcinoma cases, and 3 other special histological subtype cases.

Table 4. Event occurrence (relapse/death) by histological subtype and pathological response

Histological Subtype	n (pCR)	Events pCR n (%)	n (no pCR)	Events no pCR n (%)
1 – NST	472	15 (3.2%)	250	60 (24.0%)
2 – Lobular	9	2 (22.2%)	7	3 (42.9%)
3 – Metaplastic	4	0 (0.0%)	19	4 (21.1%)
4 – Other SHT	9	0 (0.0%)	9	3 (33.3%)
Total	494	17 (3.4%)	285	70 (24.6%)

Abbreviations: n, number of patients; pCR, pathological complete response; NST, no special type; SHT, special histological type.

Footnote: This analysis includes only patients with available pathological response data (n = 779). Patients with missing pathological response data (n = 44) were excluded; therefore, event counts differ from those reported for the overall cohort.

Figure 3. Event-free survival according to subtype among patients with pCR (log-rank p = 0.0024)**Figure 4. Event-free survival according to subtype among patients with residual disease (log-rank p = 0.6338)****Table 5. Univariate analyses of factors associated with EFS.**

Variable	HR	95% CI	p
pCR (yes vs no)	0.13	0.07 – 0.21	<0.001
AC regimen (dose-dense vs every 3 weeks)	1.20	0.78 – 1.83	0.404
Pembrolizumab <6 cycles (yes vs no)	3.13	2.06 – 4.75	<0.001
Age (≥65 vs <65 years)	1.66	0.97 – 2.84	0.063
Stage III (vs II)	3.66	2.45 – 5.48	<0.001
Lobular subtype (vs NST)	3.89	1.70 – 8.91	0.001
Metaplastic subtype (vs NST)	2.29	1.00 – 5.24	0.050
Other special subtype (vs NST)	1.73	0.55 – 5.47	0.351
Grade 3 (vs 1–2)	0.62	0.40 – 0.96	0.032
Ki67 ≥ 50% (vs < 50%)	0.85	0.53 – 1.34	0.476
TILs ≥ 30% (vs < 30%)	0.36	0.13-1.05	0.061
BRCA1/2 mutated (vs Wild-type/Unknown)	0.49	0.24 - 1.00	0.050

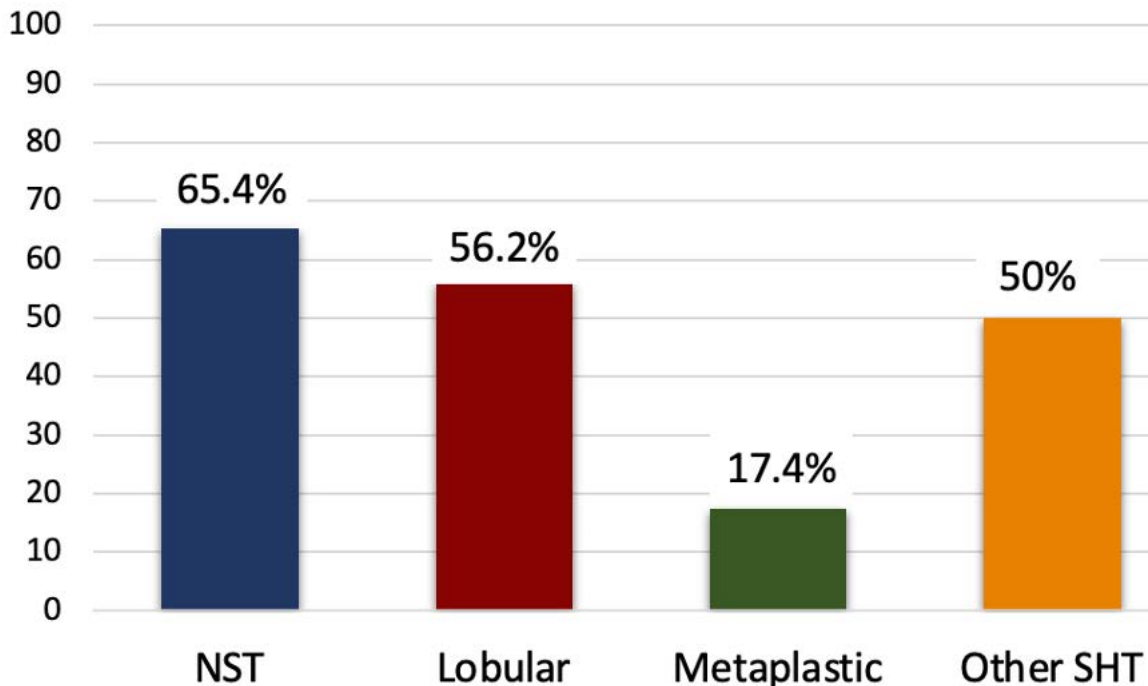
Abbreviations: EFS: event-free survival; HR: hazard ratio; CI: confidence interval; pCR: pathologic complete response; AC: doxorubicin and cyclophosphamide; NST: no special type; *BRCA1/2* mutated: Breast cancer susceptibility genes 1 and 2 mutated.

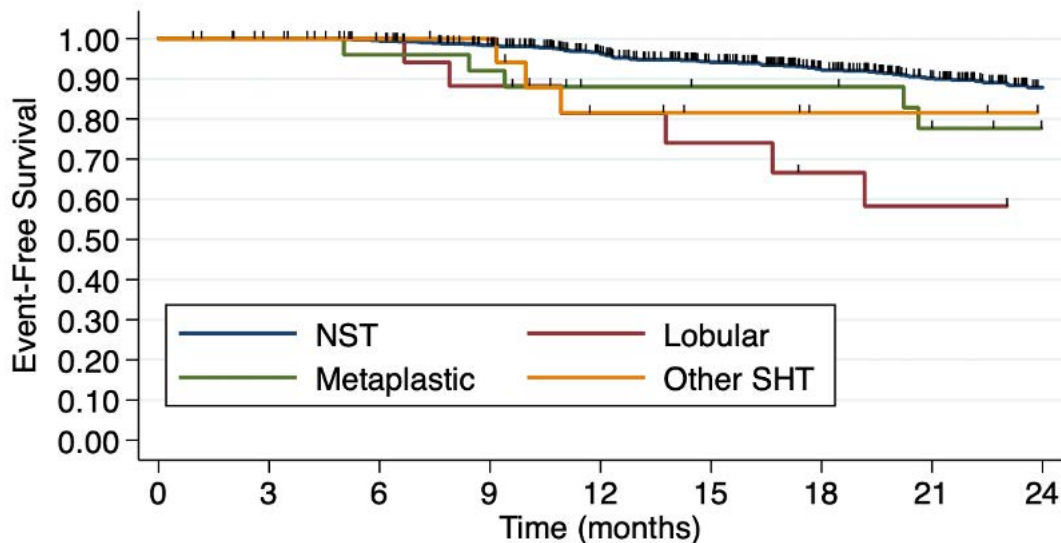
Table 6. Multivariable analysis of pre-surgical factors associated with EFS among patients with complete data for all variables included in the model (n = 732), excluding pCR

Variable	HR	95% CI	p
Pembrolizumab <6 cycles (yes vs no)	2.35	1.46–3.79	< 0.001
Age (≥65 vs <65 years)	1.17	0.63–2.18	0.618
Stage III (vs II) [†]	1.58	1.35–1.86	< 0.001
Lobular subtype (vs NST)	4.25	1.50–12.06	0.006
Metaplastic subtype (vs NST)	2.07	0.88–4.88	0.094
Other special subtype (vs NST)	1.35	0.42–4.35	0.615
Grade 3 (vs 1–2)	0.58	0.37–0.93	0.022

Abbreviations: EFS: event-free survival; HR: hazard ratio; CI: confidence interval; pCR: pathologic complete response; NST: no special type;

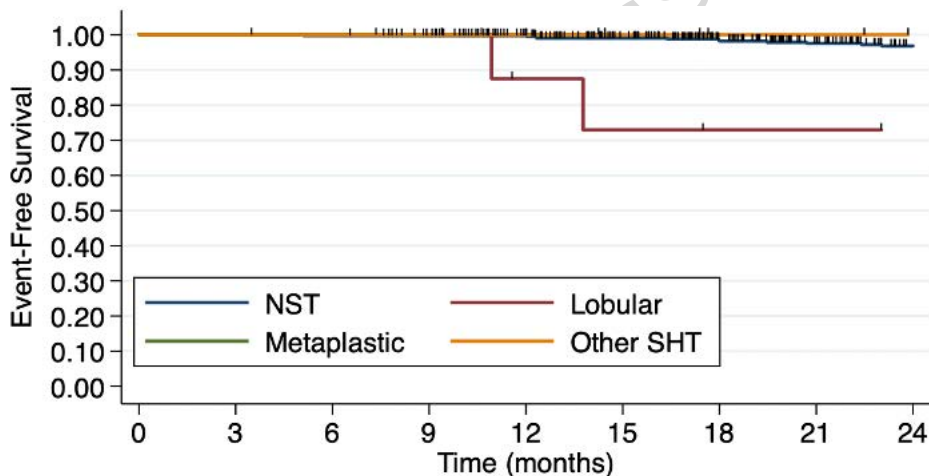
[†] Stage was modeled as a time-varying covariate through an interaction with $\ln(t)$ because it violated the proportional hazards assumption (Schoenfeld test: $p = -0.249$; $\chi^2 = 5.24$; $p = 0.022$). The reported HR represents the effect of the time-varying coefficient and should not be interpreted as a conventional constant hazard ratio.





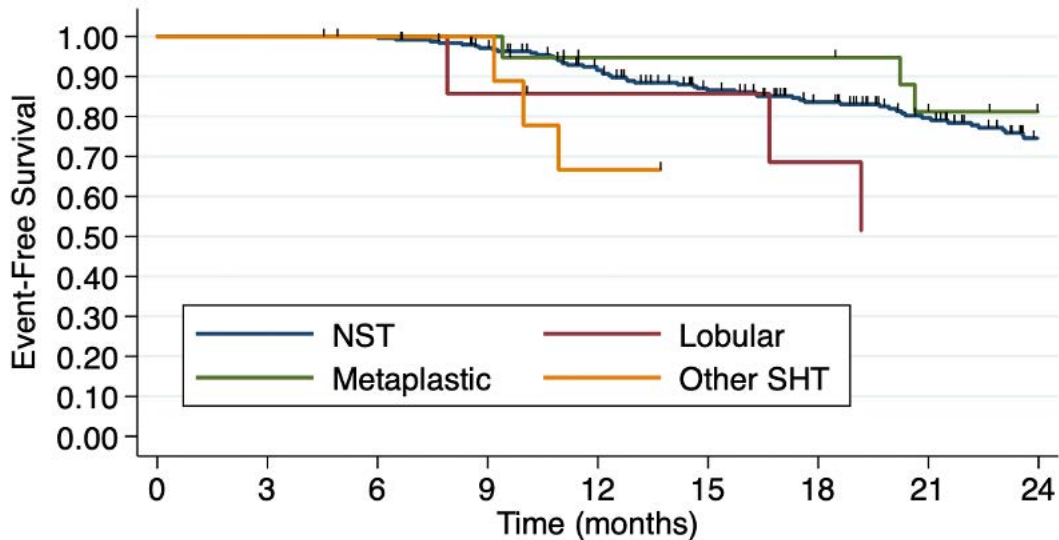
Number at risk

NST	759	753	740	704	640	574	496	423	358
Lobular	17	17	17	15	11	10	8	7	6
Metaplastic	26	26	24	23	19	18	18	15	11
Other SHT	18	18	18	17	13	11	9	9	7



Number at risk

NST	471	471	469	457	422	384	331	287	249
Lobular	9	9	9	9	6	5	4	4	3
Metaplastic	4	4	4	4	4	3	3	3	3
Other SHT	9	9	9	8	7	6	4	4	2



Number at risk

NST	249	249	247	233	209	182	163	136	109
Lobular	7	7	7	6	5	5	4	3	3
Metaplastic	19	19	19	19	15	15	15	12	8
Other SHT	9	9	9	9	6	5	5	5	5