International Journal of Biomedicine 16(3) (2026) 346-351
http://dx.doi.org/10.21103/Article16(3)_OA3

ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF BIOMEDICINE

Integrated Immunomorphological and Molecular Profiling Predicts Response to Neoadjuvant Therapy in Breast Cancer

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Abstract

Background: To investigate whether integrating assessment of the tumor immune microenvironment with molecular genetic alterations improves prediction of response to neoadjuvant systemic therapy in patients with invasive breast cancer.
Methods and Results: This retrospective study included 23 patients with invasive breast cancer treated at the Cancer Research Institute, Tomsk National Research Medical Center, from 2023 to 2025. All patients received neoadjuvant systemic therapy followed by surgery. Pathological response was assessed using the Residual Cancer Burden (RCB) system. Pretreatment tumor specimens were analyzed for stromal tumor-infiltrating lymphocytes, immune cell subsets and ratios, immune phenotype, immunosuppressive index, and copy number alterations in genes associated with chemotherapy response and drug resistance. Pathologic complete response (pCR; RCB-0) was achieved in 17 patients (73.9%), and a favorable pathological response (RCB-0/I) was observed in 19 patients (82.6%). Individual immune cell populations showed limited predictive value, whereas integrated immune parameters demonstrated stronger associations with treatment response. Patients with a favorable response had significantly higher CD8/FOXP3 ratios (4.07 vs. 1.72, p = 0.0002), lower FOXP3/CD8 ratios (0.25 vs. 0.58, p = 0.002), and lower CD68-positive macrophage infiltration (42 vs. 66.5 cells/HPF, p = 0.023). An inflamed immune phenotype and a low immunosuppressive index were associated with the highest probability of achieving pCR. Although no individual copy number alteration independently predicted treatment response, alterations involving TUBB3, ERBB2, and TOP2A were significantly associated with distinct tumor immune microenvironment characteristics.
Conclusions: Integrated assessment of the tumor immune microenvironment provides greater predictive value for neoadjuvant treatment response than evaluation of individual immune biomarkers alone. The observed associations between genomic alterations and immune microenvironment characteristics suggest that molecular alterations may influence therapeutic sensitivity through immune remodeling. Integrated immunomorphological and molecular profiling represents a promising strategy for predicting treatment response and personalizing neoadjuvant therapy in breast cancer. (**International Journal of Biomedicine. 2026;16(3):346-351.**)

Keywords: breast cancer • neoadjuvant therapy • pathological complete response • tumor immune microenvironment • immune profiling • copy number alterations • predictive biomarkers • personalized medicine

For citation: Vtorushin SV, Tarabanovskaya NA, Krakhmal NV, Naumov SS, Litviakov NV. Integrated Immunomorphological and Molecular Profiling Predicts Response to Neoadjuvant Therapy in Breast Cancer. International Journal of Biomedicine. 2026;16(3):346-351. doi:10.21103/Article16(3)_OA3

Abbrevations

BC, breast cancer; **pCR,** pathological complete response; **NAT,** neoadjuvant therapy; **TME,** tumor microenvironment; **TILs,** tumor-infiltrating lymphocytes; **sTILs,** stromal tumor-infiltrating lymphocytes; **CNA,** copy number alterations; **TNBC,** triple negative breast cancer; **IHC,** immunohistochemistry; **RCB,** residual cancer burden

Introduction

Breast cancer (BC) remains the most common malignant tumor in women worldwide and one of the leading causes of cancer-related mortality.[1] In recent years, neoadjuvant systemic therapy has become an essential component of treatment for patients with localized and locally advanced BC, particularly in triple-negative and HER2-positive subtypes. This approach not only reduces tumor burden and increases the feasibility of breast-conserving surgery but also provides

a unique opportunity to assess tumor sensitivity to systemic treatment in vivo.[2]

Pathologic complete response (pCR) is one of the key endpoints used to evaluate the efficacy of neoadjuvant therapy (NAT). Achievement of pCR is associated with improved disease-free and overall survival, especially in patients with biologically aggressive BC subtypes.[3,4] However, marked intratumoral heterogeneity leads to substantial variability in treatment response, even among tumors within the same molecular subtype. This highlights the need for additional biomarkers that can more accurately predict therapeutic sensitivity.

Growing evidence indicates that the tumor microenvironment (TME) plays a critical role in modulating the response to systemic therapy. Among its components, tumor-infiltrating lymphocytes (TILs) have been extensively investigated as predictive biomarkers in BC. Higher levels of stromal TILs are associated with an increased probability of achieving pCR, particularly in triple-negative BC (TNBC) and HER2-positive BC.[5,6]

Importantly, not only the density of immune infiltration but also its qualitative composition and spatial organization are of major biological and clinical relevance. A predominance of CD8-positive cytotoxic T lymphocytes reflects an active antitumor immune response, whereas accumulation of FOXP3-positive regulatory T cells and macrophage components contributes to the formation of an immunosuppressive microenvironment and may reduce the efficacy of systemic therapy.[7,8] Therefore, integral immune parameters that reflect the balance between effector and suppressive immune components may provide greater predictive value than individual immune markers alone.

In addition to immune microenvironmental features, molecular genetic alterations of tumor cells may also influence treatment response. Copy number alterations (CNA) in genes involved in DNA repair, drug transport, cell-cycle regulation, and microtubule dynamics may contribute to both direct sensitivity or resistance to cytotoxic therapy and tumor-immune microenvironment interactions.[9,10] However, the relationship between molecular genetic alterations and immune contexture in BC treated with NAT remains insufficiently characterized.

Despite the growing amount of data on immune and molecular predictors of treatment response, their integrated assessment remains an unresolved issue. The development of combined immunomorphological and molecular approaches may improve risk stratification and help identify patients with a higher probability of achieving a favorable response to NAT.

This study aimed to investigate the associations between immune TME parameters, molecular-genetic characteristics, and the efficacy of neoadjuvant systemic therapy in patients with BC.

Materials and Methods

Study Design and Patients

This retrospective study included 23 female patients with invasive BC who underwent examination and treatment at the Department of General Oncology, Cancer Research Institute, Tomsk National Research Medical Center (Tomsk, Russian Federation) between January 2023 and December 2025. All patients received neoadjuvant systemic therapy followed by surgical treatment. The median age at diagnosis was 46 years (range, 25-68 years). Before treatment initiation, all patients underwent a comprehensive clinical evaluation, including mammography, breast and regional lymph node ultrasonography, and histopathological confirmation of the diagnosis using ultrasound-guided core needle biopsy. Clinical staging was established according to the American Joint Committee on Cancer (AJCC) TNM Classification, 8th edition. The study cohort predominantly consisted of patients with cT2 tumors (69.6%) and clinically node-negative disease (cN0, 73.9%). Histological grading revealed grade 2 tumors in 65.2% of cases and grade 3 tumors in 34.8%. According to molecular subtype, the cohort included 9 cases (39.1%) of TNBC, 7 cases (30.4%) of triple-positive tumors, 5 cases (21.7%) of luminal B/HER2-negative tumors, and 2 cases (8.7%) of HER2-positive tumors.

Neoadjuvant Treatment and Response Assessment

Neoadjuvant treatment consisted of anthracycline-, taxane- and platinum-based chemotherapy regimens with anti-HER2 targeted therapy administered to patients with HER2-positive disease according to contemporary clinical guidelines. Depending on tumor subtype and treatment protocol, patients received four to eight treatment cycles. Following completion of NAT, all patients underwent surgical treatment. Breast-conserving surgery was performed in 8 patients (34.8%), whereas modified mastectomy was required in 15 (65.2%). Sentinel lymph node biopsy was performed in 6 patients (26.1%), while one patient underwent axillary lymph node dissection. Postoperative systemic treatment was administered according to molecular subtype, residual tumor burden, nodal status, and current clinical recommendations.

Pathological response was evaluated using the Residual Cancer Burden (RCB) classification; pCR was defined as the absence of residual invasive carcinoma in both the breast and regional lymph nodes (RCB-0). Favorable treatment response included RCB-0 and RCB-I, whereas RCB-II and RCB-III were classified as unfavorable responses.

Immunohistochemistry

Immunohistochemistry (IHC) analysis was performed on pretreatment core biopsy specimens. Tissue samples were fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin, and sectioned at a thickness of 3-4 μm. Immunohistochemical staining was performed on the Leica BOND-MAX automated staining platform (Leica Biosystems, Germany) using the Bond Polymer Refine Detection system. The following primary antibodies were used: CD4 (clone 4B12), CD8 (clone 4B11), FOXP3 (clone 236A/E7) and CD68 (clone KP1). PD-L1 expression was evaluated separately on the Ventana BenchMark platform (Roche Diagnostics, USA) using the SP142 assay.

Stromal tumor-infiltrating lymphocytes (sTILs) were assessed on hematoxylin and eosin stained slides according to the recommendations of the International Immuno-

Oncology Biomarker Working Group (formerly International TILs Working Group). Only stromal lymphocytes within the borders of the invasive tumor were evaluated.

The numbers of CD4, CD8, FOXP3, and CD68-positive cells were assessed separately in the stromal and intratumoral compartments. Positive cells were counted in five representative high-power fields (HPFs; ×400 magnification), and the mean number of positive cells per HPF was calculated.

To characterize the immune microenvironment, the CD8/FOXP3, FOXP3/CD8 and CD4/CD8 ratios were additionally calculated. Furthermore, tumors were classified according to immune phenotype and an immunosuppressive index was determined as previously described.

Molecular Genetic Analysis

Molecular genetic analysis was performed using pretreatment tumor biopsy specimens. Genomic DNA was isolated using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. DNA quality and integrity were evaluated using the TapeStation System (Agilent Technologies, Santa Clara, CA, USA), whereas DNA purity was assessed spectrophotometrically using a NanoDrop 2000instrument (Thermo Fisher Scientific, Waltham, MA, USA).

Genome-wide CNAs were analyzed using the Affymetrix CytoScan HD Array (Affymetrix, Santa Clara, CA, USA). Sample preparation, hybridization, washing, staining, and scanning were performed according to the manufacturer's protocol using the GeneChip®Scanner 3000 7G system. Raw data were processed using Chromosome Analysis Suite (ChAS), version 4.0 (Affymetrix, USA). Copy number gains and losses were identified according to the manufacturer's analytical algorithms.

Genes associated with chemotherapy sensitivity, drug resistance, DNA repair, and cell-cycle regulation were evaluated, including *BRCA1, XRCC1, ERCC1, TYMS, ABCB1, ABCC1, ABCC5, ABCG2, ERBB2, TOP2A, CCND1, ESR1, CYP19A1, EGFR, TUBB3*, and *TAP2*. Copy number status was classified as gain, loss, or normal copy number. Molecular findings were subsequently correlated with clinicopathological parameters, immune microenvironment characteristics, and treatment response.

Statistical Analysis

Statistical analyses were performed using STATISTICA for Windows, version 10.0 (StatSoft Inc., Tulsa, OK, USA). The normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables are presented as median and interquartile range (IQR) and were compared using the Mann-Whitney U test. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test as appropriate. All statistical tests were two-sided, and a P value <0.05 was considered statistically significant.

The baseline clinicopathological characteristics of the study cohort are presented in Table 1. Most patients had cT2 tumors (69.6%) and clinically node-negative disease (73.9%). TNBC represented the largest molecular subtype (39.1%), followed by triple-positive (30.4%), Luminal B/HER2-negative (21.7%), and HER2-positive tumors (8.7%).

Table 1. Clinicopathological characteristics of the study cohort (n = 23)

Characteristic	Value
Age, years	
Median (range)	46 (25-68)
Histological type	
Invasive carcinoma of no special type (NST)	22 (95.7%)
Special histological subtype	1 (4.3%)
Histological grade	
Grade 1	-
Grade 2	15 (65.2%)
Grade 3	8 (34.8%)
Clinical tumor stage (cT)	
cT1	4 (17.4%)
cT2	16 (69.6%)
cT3	2 (8.7%)
Multicentric disease	1 (4.3%)
Clinical nodal status (cN)	
cN0	17 (73.9%)
cN1	5 (21.7%)
cN3	1 (4.3%)
Molecular subtype	
Triple-negative breast cancer	9 (39.1%)
Triple-positive breast cancer	7 (30.4%)
Luminal B/HER2-negative breast cancer	5 (21.7%)
HER2-positive breast cancer	2 (8.7%)
Ki-67 (%)	
Median (range)	60 (23–98)
Lymphovascular invasion	
Absent	10 (43.5%)
Present	13 (56.5%)
Response to neoadjuvant therapy (RCB)	
RCB-0 (pathologic complete response)	17 (73.9%)
RCB-I (minimal residual disease)	2 (8.7%)
RCB-II–III (moderate/extensive residual disease)	4 (17.4%)

Results

Response to Neoadjuvant Therapy

Among the 23 patients included in the study, pCR with RCB-0 was achieved in 17 (73.9%) patients. Minimal residual disease (RCB-I) was observed in 2 patients (8.7%), whereas 4 patients (17.4%) demonstrated moderate or extensive residual disease (RCB-II and RCB-III). Overall, a favorable pathological response (RCB-0/I) was achieved in 19 patients (82.6%).

Immune Microenvironment and Treatment Response

The composition of the immune TME differed between patients with favorable and unfavorable responses to NAT (Table 2).

Table 2. Immune tumor microenvironment parameters according to pathological response to neoadjuvant therapy

Parameter	RCB-0/I (n=19)	RCB-II/III (n=4)	p
CD8/FOXP3 ratio	4.07 (2.8-5.9)	1.72 (1.2–2.4)	0.0002
FOXP3/CD8 ratio	0.25 (0.16-0.36)	0.58 (0.42–0.81)	0.002
CD68+ cells, cells/HPF	42 (31-58)	66.5 (59–79)	0.023
Stromal TILs, %	24 (15-35)	13.5 (10–18)	0.18
CD8+ cells, cells/HPF	54 (38-71)	30 (22–38)	0.16
CD4+ cells, cells/HPF	44 (30-56)	31.5 (24–38)	0.19
FOXP3+ cells, cells/HPF	14 (9-18)	19.5 (16–24)	0.24
CD4/CD8 ratio	0.81 (0.65-1.02)	1.05 (0.91–1.22)	0.13

Representative immunohistochemical staining patterns of the evaluated immune cell populations are shown in Figure 1.

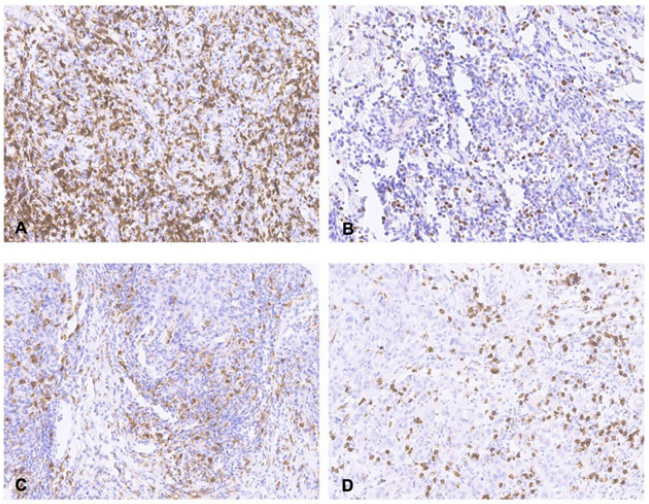

Fig. 1. *Representative immunohistochemical staining of immune cell populations in pretreatment breast cancer biopsy specimens. (A) CD8-positive cytotoxic T lymphocytes; (B) FOXP3-positive regulatory T lymphocytes; (C) CD68-positive macrophages; (D) CD4-positive T lymphocytes. Original magnification ×200.*

Patients achieving a favorable response exhibited higher levels of sTILs than those with residual disease (median, 24% vs. 13.5%; $p = 0.18$). Similarly, the numbers of CD8-positive cytotoxic T lymphocytes (54 vs. 30 cells/HPF; $p = 0.16$) and CD4-positive T lymphocytes (44 vs. 31.5 cells/HPF; $p = 0.19$) were higher in responders, whereas FOXP3-positive regulatory T cells were more abundant in non-responders (19.5 vs. 14 cells/HPF; $p = 0.24$).

The most pronounced difference was observed for CD68-positive macrophages. Patients with unfavorable treatment response demonstrated significantly higher numbers of CD68-positive cells than responders (66.5 vs. 42 cells/HPF; $p = 0.023$).

Analysis of immune cell ratios revealed marked differences between treatment response groups. The CD8/FOXP3 ratio was significantly higher in patients with favorable response (4.07 vs. 1.72; $p = 0.0002$), whereas the reciprocal FOXP3/CD8 ratio was significantly increased in patients with residual disease (0.58 vs. 0.25; $p = 0.002$). No significant difference was observed for the CD4/CD8 ratio ($p = 0.13$). PD-L1 expression assessed using the SP142 assay did not differ significantly between the two groups (median IC score, 1.2% vs. 0.7%; $p = 0.27$).

Immune Phenotype and Immunosuppressive Index

Based on the integrated assessment of immune cell distribution, 12 tumors (52.2%) were classified as inflamed whereas the remaining 11 tumors (47.8%) exhibited non-inflamed immune phenotypes, including immune-excluded, desert/excluded, immune-desert and excluded/inflamed patterns (Table 3).

Patients with an inflamed immune phenotype demonstrated a markedly higher frequency of pCR than those with non-inflamed tumors (91.7% vs. 54.5%). Although this difference did not reach statistical significance, a strong trend toward improved pathological response was observed (Fisher's exact test, $p = 0.069$).

Table 3. Association between tumor immune phenotype and pathological response to neoadjuvant therapy

Tumor immune phenotype	pCR (n = 17)	Residual disease (n = 6)	Total (n = 23)
Inflamed	11 (91.7%)	1 (8.3%)	12
Non-inflamed*	6 (54.5%)	5 (45.5%)	11

Fisher's exact test: P = 0.069
**Non-inflamed tumors included the immune-excluded, desert/excluded, immune-desert and excluded/inflamed phenotypes.*

The immunosuppressive index showed a significant association with treatment efficacy. A low immunosuppressive index (scores 0-1) was observed in 15 of 17 patients (88.2%) achieving pCR, whereas a high immunosuppressive index (scores 2-3) predominated among patients with residual disease (4 of 6; 66.7%) (Fisher's exact test, $p = 0.027$) (Table 4).

Table 4. Immunosuppressive index according to pathological response

Immunosuppressive index	pCR (n = 17)	Residual disease (n = 6)	Total (n = 23)
Low (scores 0-1)	15 (88.2%)	2 (11.8%)	17
High (scores 2-3)	2 (33.3%)	4 (66.7%)	6

Fisher's exact test: P = 0.027

The distribution of immune phenotypes also differed across molecular subtypes. HER2-positive and triple-positive tumors were predominantly characterized by an inflamed immune phenotype, whereas Luminal B/HER2-negative tumors more frequently exhibited non-inflamed immune phenotypes.

Copy Number Alterations and their Association with the Immune Microenvironment

Genome-wide copy number analysis identified recurrent alterations involving *TOP2A*(48%), *ABCC5*(43%), *ERBB2*(39%), *BRCA1* (39%) and *TUBB3* (35%). No individual CNA was significantly associated with pathological response to NAT. Because no direct associations with treatment response were identified, additional analyses were performed to evaluate relationships between genomic alterations and the immune microenvironment. Tumors harboring *TUBB3* CNA exhibited significantly lower sTILs levels than tumors without these alterations (10% vs. 25%; $p = 0.038$). Likewise, CD8-positive T cell density was significantly reduced in the presence of *TUBB3* alterations (23 vs. 59.5 cells/HPF; $p = 0.030$). Conversely, CNAs involving *ERBB2* and *TOP2A* were associated with increased numbers of FOXP3-positive regulatory T cells (17 vs. 10.5 cells/HPF; $p = 0.047$ and 19 vs. 12 cells/HPF; $p = 0.039$, respectively).

Discussion

The present study demonstrates that the immune TME plays a central role in determining the response to neoadjuvant systemic therapy in BC. Although a pCR was achieved in 73.9% of patients, treatment efficacy was associated not with individual immune cell populations but with the overall

functional organization of the immune microenvironment. This observation supports the concept that the balance between antitumor immune activation and local immunosuppression is a more informative predictor of therapeutic response than the absolute density of individual immune cell subsets.[5-8]

Among the evaluated immune parameters, sTILs tended to be more abundant in patients achieving a favorable pathological response, which is consistent with numerous studies demonstrating the predictive value of TILs in patients receiving NAT, particularly in TNBC and HER2-positive cases of BC.[5,6,11] However, the lack of statistical significance in the present study is most likely attributable to the limited sample size rather than the absence of a biological association.

Importantly, immune cell ratios demonstrated substantially greater discriminatory ability than individual immune cell populations. The CD8/FOXP3 ratio was significantly higher in responders, whereas the reciprocal FOXP3/CD8 ratio was increased in tumors with residual disease. These findings indicate that the functional balance between cytotoxic and immunosuppressive immune compartments provides a more robust estimate of antitumor immune competence than isolated quantification of CD8-positive or FOXP3-positive cells. This observation is consistent with the current understanding that coordinated interactions between immune cell populations, rather than individual immune subsets, determine the effectiveness of antitumor immunity and therapeutic response.[7,8,11]

Another important finding was the association between increased CD68-positive macrophage infiltration and an unfavorable response to NAT. Tumor-associated macrophages are recognized as major regulators of tumor progression, immune evasion, angiogenesis, and resistance to systemic therapy. Previous studies have demonstrated that macrophage-rich TME promote immunosuppressive signaling, inhibit cytotoxic T cell activity, and contribute to resistance to chemotherapy and immunotherapy.[8] Our findings further support the clinical relevance of macrophage-associated immune suppression in BC.

An integrated assessment of the immune TME provided additional prognostic information beyond individual immune biomarkers. Patients with an inflamed immune phenotype demonstrated the highest frequency of pCR, whereas non-inflamed tumors were substantially more likely to exhibit residual disease after neoadjuvant treatment. Similarly, a low immunosuppressive index was significantly associated with pCR. Collectively, these observations emphasize that the spatial organization and functional architecture of the immune TME represent clinically relevant determinants of therapeutic sensitivity rather than merely descriptive histopathological features.

One of the most interesting observations of the present study was the relationship between CNA and immune microenvironment characteristics. Although none of the investigated genomic alterations demonstrated an independent association with pathological response, several alterations were significantly associated with immune composition. In particular, *TUBB3* copy number alterations were associated with reduced sTILs density and decreased CD8-positive T cell infiltration, whereas alterations involving *ERBB2* and *TOP2A* were associated with increased FOXP3-positive regulatory T cell infiltration. These findings suggest that genomic alterations may influence treatment response indirectly through remodeling of the immune microenvironment rather than solely through modulation of intrinsic tumor sensitivity to cytotoxic agents. Such an interpretation is consistent with the emerging concept that genomic and immune tumor characteristics should be considered complementary components of an integrated predictive model rather than independent biomarkers.[9,10]

The present study has several limitations. First, the relatively small sample size limited the statistical power of subgroup analyses. Second, the cohort included different molecular subtypes of BC treated with subtype-specific neoadjuvant regimens, which may have influenced immune composition and treatment response. Finally, the retrospective design precludes definitive conclusions regarding causal relationships between genomic alterations, immune remodeling, and therapeutic efficacy. Nevertheless, the present findings support the concept that integrated immunomorphological and molecular profiling provides a more comprehensive characterization of tumor biology than evaluation of isolated biomarkers. Future prospective studies involving larger and molecularly homogeneous patient cohorts are warranted to validate these observations and to establish clinically applicable predictive models incorporating both immune TME characteristics and genomic alterations.

Conclusion

The present study demonstrates that the tumor immune microenvironment is a major determinant of response to neoadjuvant systemic therapy in BC. Among the evaluated biomarkers, integrated immune parameters - including the CD8/FOXP3 ratio, immune phenotype and immunosuppressive index - provided greater predictive value than the absolute density of individual immune cell populations, highlighting the importance of the functional organization of the antitumor immune response. Although individual CNAs were not independently associated with pathological response, significant associations between alterations involving *TUBB3*, *ERBB2,* and *TOP2A* and distinct immune microenvironment characteristics suggest that genomic alterations may contribute to therapeutic sensitivity through modulation of the immune landscape. These findings support the concept that genomic and immune characteristics represent complementary rather than independent determinants of treatment response.

Collectively, our results indicate that integrated immunomorphological and molecular profiling may improve prediction of neoadjuvant treatment efficacy and provide a biologically meaningful framework for patient stratification and personalized therapeutic decision-making in BC. Further prospective studies in larger, molecularly homogeneous cohorts are warranted to validate these findings and establish clinically applicable predictive models.

Ethical Considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Local Ethics Committee of the Cancer Research Institute (Protocol No. 16, December 2023). Due to the retrospective study design and the use of anonymized archival tissue samples and clinical data, the requirement for informed consent was waived.

Competing Interests

The authors declare that they have no competing interests.

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