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Role of Ki-67, Tumor-Infiltrating Lymphocytes (TILs-CD4 and CD8), and PD-L1 in Predicting pCR After Neoadjuvant Chemotherapy for Breast Cancer

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Abstract

Neoadjuvant chemotherapy (NACT) has become a standard treatment approach in breast cancer management, enabling in-vivo assessment of tumour chemosensitivity and facilitating breast-conserving surgery. Pathological complete response (pCR) serves as a validated surrogate endpoint for survival, particularly in aggressive subtypes. This review examines the predictive and prognostic roles of three key biomarkers—Ki-67, tumor-infiltrating lymphocytes (TILs including CD4+ and CD8+ subsets), and PD-L1—in forecasting pCR following NACT. Ki-67, a nuclear proliferation marker, consistently associates with treatment responsiveness, though its predictive value varies by breast cancer subtype and cut-off threshold. TILs, reflecting the immune landscape of the tumour microenvironment, demonstrate subtype-dependent predictive significance, with the strongest correlations observed in triple-negative (TNBC) and HER2-positive cancers. PD-L1, a mediator of immune evasion, emerges as a prognostic marker, particularly in residual disease. Individually and collectively, these biomarkers offer clinically actionable information for treatment stratification, potentially reducing unnecessary chemotherapy exposure and guiding immunotherapy candidacy. Standardised scoring protocols and molecular profiling advances will be essential to embed these biomarkers reliably into routine clinical practice.

Keywords: *Ki-67; Neoadjuvant chemotherapy; PD-L1; Pathological complete response (pCR); Predictive biomarkers; Tumor-infiltrating lymphocytes (TILs)*

1. Introduction

Breast cancer remains the most prevalent malignant tumour among women globally, accounting for approximately 36% of all female cancer diagnoses. An estimated 2.09 million new cases were recorded in 2018, and over 276,000 new diagnoses along with more than 42,000 deaths were projected in the United States alone for 2020.[1,2] Advances in molecular biology have transformed breast cancer from a perceived homogeneous disease into a recognised heterogeneous entity characterised by distinct genetic profiles, tumour behaviours, and clinical outcomes.

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The identification of at least four molecular subtypes—Luminal A, Luminal B, HER2-enriched, and triple-negative—has fundamentally altered diagnostic and therapeutic paradigms. The expression status of estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor-2 (HER2), and the Ki-67 proliferation index are used to stratify these subtypes. Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, mandatory immunohistochemical evaluation of ER, PgR, and HER2 is required in all invasive breast cancer cases, as these established biomarkers guide therapeutic decision-making.[3,4,5]

Neoadjuvant chemotherapy (NACT), defined as systemic therapy administered prior to surgical resection, was initially devised to render inoperable tumours surgically accessible. Its role has expanded to include downstaging, facilitating breast-conservation surgery, and providing an early indicator of chemosensitivity. The pathological evaluation of breast tissue and lymph nodes after NACT the gold standard for assessing response—culminates in determination of pathological complete response (pCR), widely recognised as a surrogate marker for long-term survival outcomes. This review focuses on the roles of Ki-67, tumor-infiltrating lymphocytes (TILs), and PD-L1 as predictive biomarkers of pCR in patients receiving NACT for breast cancer.[7,8]

1.1 Review of Literature

The landscape of breast cancer research has been shaped by landmark investigations into molecular subtypes, treatment response determinants, and the tumour immune microenvironment. Goldhirsch et al. established the St Gallen consensus framework for personalising early breast cancer treatment based on biologic subtype, reinforcing the clinical relevance of receptor expression and proliferative indices.[3] Cortazar and Geyer demonstrated that pathological complete response after neoadjuvant chemotherapy is a reliable surrogate endpoint for event-free and overall survival, particularly in high-risk subtypes such as TNBC and HER2-positive disease, lending scientific validity to biomarker-guided response assessment.[8] Whitfield et al. provided a foundational molecular characterisation of common proliferation markers, situating Ki-67 within the broader context of cell-cycle regulators and clarifying its superiority as a routine immunohistochemical tool in clinical oncology.[12]

In the domain of tumour immunology, Denkert et al. conducted a pivotal pooled analysis of 3,771 patients across multiple NACT trials and demonstrated that tumour-infiltrating lymphocyte (TIL) density is a continuous, subtype-modulated predictor of treatment response and long-term survival, with the most pronounced effects observed in TNBC and HER2-positive breast cancer.[19] Mao et al. conducted a systematic review and meta-analysis confirming that elevated pre-treatment TILs significantly improve pCR odds in TNBC, underscoring TILs as a robust immune biomarker in the NACT setting.[20] Pruneri et al. validated the clinical utility of TIL assessment in triple-negative breast cancer across independent patient cohorts, affirming TILs as a standardisable prognostic parameter for routine pathological evaluation.[23]

Freeman et al. first characterised the PD-1/PD-L1 axis as a negative immunoregulatory checkpoint, establishing the mechanistic foundation for checkpoint inhibitor therapies now under active clinical investigation in breast cancer.[29] Wimberly et al. subsequently

demonstrated that PD-L1 expression in breast tumour epithelium and stroma independently predicts pCR, and that its co-expression with TILs defines a clinically distinct immunogenic subgroup with markedly improved response rates.[24] Ladoire et al. further showed that the in situ immune response following neoadjuvant chemotherapy quantified through TIL and immune marker scoring independently predicts survival in breast cancer patients, underscoring the translational value of immune profiling in the neoadjuvant setting.[30] Collectively, these seminal contributions from the evidential basis upon which the present review is constructed.

2. Breast Cancer and Neoadjuvant Chemotherapy

The TNM classification system, together with receptor expression status, determines tumour staging and available treatment modalities. Adjuvant polychemotherapy following primary surgery has demonstrated survival benefits in high-risk patients. Preoperative NACT offers several advantages: it can convert inoperable tumours to operable status, reduce tumour burden before surgery, increase eligibility for breast-conserving procedures, and provide prognostic information equivalent to adjuvant therapy.

NACT is currently a standard approach for locally advanced and inflammatory breast cancers, and its indications have expanded to include node-negative patients with unfavourable tumour biology when adjuvant systemic treatment would otherwise be warranted. Key advantages of NACT include early evaluation of therapeutic response, the ability to alter treatment regimens when response is inadequate, and the collection of tumour specimens at multiple time-points for translational research.[6,7] Evidence from a large randomised clinical trial encompassing 5,500 patients demonstrated that NACT prevented mastectomy in approximately 25% of cases; conversely, more than 5% of initially conservation-eligible patients required mastectomy due to disease progression during NACT.[7]

3. Biomarkers and Pathological Complete Response (pCR)

3.1 Defining pCR

Pathological complete response is defined as the total elimination of invasive cancer from the primary breast tumour following NACT, though the inclusion of ductal carcinoma in situ (DCIS) and axillary lymph node status in this definition remains debated. Table 1 summarises the major classification systems and their respective pCR definitions.

Table 1. Major Classification Systems and Definitions of pCR

Evaluation System	pCR Definition
JBCS / GEPARDO	No residual cancer in surgical specimen; DCIS excluded (ypT0).
NSABP B-18	DCIS and node-positive disease permitted; limited to clinical complete responders (ypT0/is ypN0/+).

BIG-NABCG	No invasive or in-situ cancer in breast and axillary nodes (ypT0/is ypN0).
Miller–Payne	No residual invasive carcinoma in breast tissue, irrespective of DCIS.
MD Anderson	No residual invasive cancer in breast or lymph nodes.

Based on retrospective analysis of 2,302 patients at MD Anderson Cancer Centre, comparable 5- and 10-year overall survival (OS) and disease-free survival (DFS) were found between patients achieving pCR and those with residual DCIS. A pooled meta-analysis of 12 trials (CTNeoBC) confirmed that isolated nodal micrometastases should not qualify as pCR. The BIG-NABCG consortium therefore defines pCR as the absence of invasive cancer in the breast and axillary lymph nodes regardless of DCIS, a definition that has achieved broad acceptance.[9]

3.2 Prognostic Significance of pCR

The NSABP B-18 and B-27 studies demonstrated significantly prolonged OS and DFS in patients achieving pCR compared to those with residual disease. However, pCR is not a universal prognostic surrogate. Its prognostic value is subtype-dependent: pCR strongly predicts improved survival in HER2-enriched and TNBC subtypes, whereas the correlation with luminal tumours is less consistent. Patients with HR-positive tumours tend to have better long-term outcomes even with lower pCR rates, indicating that pCR does not substitute for DFS and OS in this subtype. The CTNeoBC meta-analysis confirmed that pCR rates vary considerably across subtypes, and that its prognostic benefit is greatest in aggressive molecular phenotypes.[10] Factors potentially limiting pCR as a sole prognostic endpoint include additional patient-level risk factors, premenopausal status, and clinical stage IIIB–C disease. A minority of patients who achieve pCR still experience early recurrence or metastasis, underscoring the need for complementary biomarkers.

4. Ki-67 as a Predictive Biomarker

4.1 Biological Background

Ki-67 is a 359 kDa nuclear non-histone protein encoded by the MKI67 gene on chromosome 10q26.2, first characterised by Gerdes et al. in 1991 using monoclonal antibodies against the nuclei of Hodgkin's lymphoma cells.[11] The protein is expressed throughout the active phases of the cell cycle (G1, S, G2, and M) but is absent in quiescent (G0) cells, making it a reliable marker of cellular proliferation. Two isoforms (320 kDa and 359 kDa) arise from alternative splicing of the MKI67 mRNA.

Structurally, Ki-67 contains 16 tandem Ki-repeat domains in a 6842 bp exon, each harbouring a conserved 66 bp motif (the Ki-67 epitope targeted by antibodies such as MIB-1). Functionally, Ki-67 participates in nucleolar segregation, ribosomal RNA transcription,

perichromosomal layer formation during mitosis, and chromatin organisation through histone methylation complexes. Its short biological half-life (under one hour) reflects its role as a dynamic cell-cycle regulator. The Ki-67 labelling index (percentage of immunohistochemically positive nuclei) is the standard clinical measure and is inversely correlated with prognosis in many solid tumours: a high index typically signals aggressive disease and poor outcome.[12]

4.2 Predictive Value of Pre-treatment Ki-67

The theoretical basis for Ki-67 as a NACT predictor rests on the premise that highly proliferative tumours are more susceptible to cytotoxic agents. Table 2 summarises key studies evaluating pre-treatment Ki-67 across molecular subtypes.

Table 2. Predictive and Prognostic Value of Ki-67 Across Studies

Author (Year)	Sample / NACT	Subtypes	Cut-off	Key Finding
Botero et al. (2016)	n=357; CT±H	All	15%	Ki-67 decrease from >15% to ≤15% independently predicted lower LRR (p=0.03); improved DFS (p=0.0001) and OS (p=0.0016).
Sueta et al. (2014)	n=121; CT±H	Luminal, HER2+, TNBC	35%	High Ki-67 significantly associated with improved pCR in ER+/HER2− BC (OR 6.24; p=0.016); median Ki-67 43% vs. 29% in pCR vs. non-pCR groups.
Penault-Llorca et al. (2008)	n=710; CT only	HR+, HR−	1%	Positive Ki-67 correlated with clinical response (p=0.013) and higher pCR rates (p=0.02); pre-treatment Ki-67 not prognostic at cut-offs of 1%, 10%, or 20%.
Chen et al. (2018)	n=1,010; CT±H	All molecular subtypes	14%	Ki-67 ≥14% linked to better clinical and pathological response (p<0.001); optimal predictive cut-off 25.5% in luminal subtype by ROC analysis.

Elevated baseline Ki-67 expression correlated consistently with increased pCR rates in multiple patient cohorts. In ER-positive/HER2-negative patients, the association is particularly

prominent; Kim et al. showed that a pre-treatment Ki-67 index above 25% was an independent pCR predictor in HER2+/ER− patients.[18] Alba et al. found that Ki-67 above 50% was associated with higher pCR rates specifically in ER−/HER2+ and ER−/HER2− subtypes.[17] The prognostic relevance of Ki-67 varies across studies, partly due to the absence of a universally validated cut-off threshold. The combination of baseline Ki-67 with other pretreatment biomarkers particularly on core needle biopsy may offer superior predictive information for patient selection. [13,14,15,16]

5. Tumor-Infiltrating Lymphocytes (TILs)

5.1 Composition and Tumour Microenvironment

TILs are mononuclear immune cells that migrate from the bloodstream into the tumour and surrounding stroma, forming a central component of the tumour microenvironment (TME). The TIL compartment comprises approximately 60% T cells (40% CD4+ helper and cytotoxic T cells; 20% CD8+ cytotoxic T lymphocytes), 20% B cells, 5% NK cells, 5% macrophages, and less than 1% dendritic cells. Clinically, TILs are characterised using T-cell markers (CD3, CD8, FOXP3), B-cell markers (CD20), and histiocytic markers (CD68). CD8+ cytotoxic T cells are associated with effective antitumour immunity and improved prognosis. CD4+ helper T cells regulate the antitumour immune response, with Th1 cells (interferon-γ producers) linked to favourable outcomes and Th2 cells associated with blunted antitumour responses. Regulatory T cells (CD4+/CD25+/FOXP3+) suppress immune activity and are associated with both favourable and unfavourable prognoses depending on context. Follicular helper T cells (Tfh) are positively correlated with prognosis in both adjuvant and neoadjuvant settings. Tumour-associated macrophages (TAMs), particularly the M2 phenotype, are associated with poor prognosis. The immunoediting framework describes three phases elimination, equilibrium, and escape that govern TIL function in tumour progression.

5.2 TILs and NACT Response

Pre-treatment TIL levels are positively associated with pCR rates, particularly in TNBC and HER2-positive subtypes. A meta-analysis involving 3,251 patients confirmed that higher pre-treatment TILs correlate with pCR in TNBC and HER2+ cancers but not in ER-positive tumours.[20] Tumours with TIL density above 50% are classified as lymphocyte-predominant breast cancer (LPBC); LPBC patients achieve pCR at significantly higher rates than non-LPBC patients ($p<0.001$) and produce lower residual cancer burden (RCB) scores.[19] Table 3 summarises key TIL studies.

Table 3. Key Studies Assessing TILs and Treatment Response in NACT

Study (Year)	n / Subtype	Biomarker	Key Finding
Miyashita et al. (2015)	n=131 TNBC with RD	CD8+ TIL; CD8/FOXP3 ratio	High CD8+ TIL group: 5-yr RFS 73% vs. 30% ($p<0.0001$); 5-yr BCSS 86% vs. 42% ($p<0.0001$). Higher CD8/FOXP3 ratio correlated with improved RFS and BCSS.

Denkert et al. (2018)	n=3,771 all subtypes	Continuous TIL level; low/intermediate/high groups	Each 10% rise in TILs improved prognosis in TNBC (DFS p=0.011) and HER2+ BC (DFS p=0.017); pCR rates: 6%/11%/28% (luminal), 32%/39%/48% (HER2+), 31%/31%/50% (TNBC). Elevated TILs correlated with adverse OS in luminal subtype.
Dieci et al. (2013)	TNBC without pCR	Continuous Str-TIL and It-TIL in residual disease	Higher post-NACT TILs: 5-yr OS 91% vs. 55% (p=0.0017); 5-yr MFS 81.5% vs. 46% (p=0.0019). Each 10% rise in Str-TIL reduced metastasis and death risk by 21%.

Yam et al. demonstrated that a more clonal T-cell population in the TME, along with higher CD3+/CD68+ and CD3+CD8+/CD68+ ratios and physical proximity of T cells to malignant cells, are all predictive of pCR. Post-NACT TIL levels in residual disease also carry prognostic weight: stromal TIL levels above 25% in persistent disease were independently associated with outcome in HER2+ breast cancer, and every 10% rise in post-treatment TILs reduced the risk of metastasis and death by approximately 21–23%.[21,22]

5.3 Subtype-Specific Prognostic Value

The prognostic value of TILs is subtype-dependent. In TNBC and HER2-positive breast cancer, elevated TIL levels consistently associate with improved DFS, OS, and MFS. In contrast, luminal subtype patients with high TIL infiltration may paradoxically exhibit worse outcomes, possibly due to TIL-mediated resistance to endocrine therapy. This divergence underscores the importance of evaluating TILs within the molecular subtype context rather than applying uniform predictive frameworks across all breast cancer populations.[23]

6. PD-L1 as a Predictive and Prognostic Biomarker

6.1 Molecular Biology of PD-L1

PD-L1 (B7-H1) is a member of the B7 immunoregulatory ligand family, encoded on chromosome 9p24. It is a 33 kDa Type 1 transmembrane glycoprotein with 290 amino acids, carrying extracellular immunoglobulin (Ig) and IgC-like domains. PD-L1 is constitutively expressed on professional antigen-presenting cells (B cells, macrophages, dendritic cells) and inducibly expressed on non-haematopoietic cells including vascular endothelium, placental cells, and pancreatic islets. Its surface expression on peripheral tissues serves a protective function against autoimmune damage.[29]

PD-L1 expression on tumour cells is upregulated by interferon-gamma (IFN-γ) through the JAK1/JAK2–STAT1/STAT3–IRF1 signalling pathway. Additional regulators include cytokines (IL-4, IL-10, TNF-α, VEGF), EGFR signalling which stabilises PD-L1 by inactivating GSK3β—and N-linked glycosylation at residues N192, N200, and N219, which prevents β-TrCP-mediated proteasomal degradation. Engagement of PD-L1 with its receptor

PD-1 on T cells activates SHP-2 phosphatases, inhibiting TCR downstream signalling through the PI3K/Akt/mTOR and Ras/MEK/ERK pathways, ultimately driving T-cell exhaustion and immune escape.

6.2 PD-L1 in the Tumour Microenvironment

PD-L1 is broadly expressed on the surface of B and T lymphocytes, macrophages, and dendritic cells within the TME. High PD-L1 expression on tumour cells facilitates immune evasion by blunting cytotoxic T-lymphocyte (CTL) activation. Tumour-derived exosomes and cytokines within the TME further amplify the PD-L1/PD-1 signal, creating an immunosuppressive milieu. IFN-γ secreted by CD8+ T cells in ovarian and breast tumour models promotes PD-L1 overexpression, a mechanism that connects immune activation with immune escape a phenomenon termed adaptive immune resistance.[30]

6.3 PD-L1 and pCR Prediction

Multiple studies have established correlations between PD-L1 expression and NACT response. Table 4 summarises key findings.

Table 4. Key Studies Evaluating PD-L1 Expression and NACT Outcomes

Study (Year)	n / Subtype	Biomarker	Key Finding
Wimberly et al. (2015)	n=94; All BC	PD-L1 in epithelium and stroma (continuous score)	Stromal and epithelial PD-L1 correlated with pCR (p=0.0050 and p=0.0189, respectively), especially in HR+ and HER2-amplified BCs; positively correlated with TIL levels.
Cerbelli et al. (2017)	n=54; TNBC	PD-L1 expression ≥25%	PD-L1 ≥25% significantly predicted pCR (p=0.02). All LPBC patients (TILs >50%) with high PD-L1 achieved pCR (100%).
Chen et al. (2017)	n=309; All (with RD)	PD-L1 in residual tumor; PD-L1-high/CD8-low subgroup	PD-L1-high expression in residual disease: 5-yr RFS 45% vs. 89%; 5-yr OS 51% vs. 91% in TNBC. Worst outcomes in PD-L1-high/CD8-low patients (5-yr RFS 54%, OS 67%).

Wimberly et al. found that both stromal and epithelial PD-L1 expression served as independent predictors of pCR across all breast cancer subtypes, with the strongest correlations in HR+ and HER2-amplified tumours. Asano et al. reported that lower PD-1/PD-L1 expression predicted longer OS and DFS in TNBC, while high expression was associated with greater non-pCR rates.[25] Importantly, PD-L1-high/CD8-low patients demonstrated the poorest RFS and OS

among all subgroups, indicating that checkpoint inhibitors may be particularly necessary in this cohort.[27] Zhu et al. further showed that elevated PD-L1 expression can attenuate the survival benefit otherwise conferred by high TIL levels after NACT, emphasising the need for joint TIL and PD-L1 evaluation in treatment planning.[24,26,28]

7. Clinical Implications and Integrated Biomarker Strategy

Each of the three biomarkers reviewed here contributes distinct, partially complementary clinical information. Ki-67, the most operationally accessible, offers a pragmatic measure of proliferative activity obtainable from core needle biopsy specimens at diagnosis. Its predictive utility is most robust in luminal and HER2-positive subtypes when evaluated at subtype-specific validated cut-off thresholds. Serial Ki-67 measurement during NACT—comparing baseline to mid-treatment values—provides an early window into tumour response and offers a basis for early treatment modification.

TILs represent an increasingly standardised parameter in clinical trials, with the International TIL Working Group providing methodology for stromal TIL scoring. High pre-treatment TILs in TNBC and HER2+ cancers are now recognised as a favourable predictor of pCR and improved long-term outcomes. TIL assessment in residual disease after NACT yields additional prognostic information and may identify patients likely to benefit from post-NACT immunotherapy. CD8+/FOXP3+ ratio is an emerging sub-parameter with prognostic relevance in HER2-positive disease.

PD-L1 screening, while promising, requires standardised assay platforms and cut-off values before broad clinical implementation. Current evidence supports its utility as a prognostic marker in residual TNBC and as a potential guide for checkpoint inhibitor therapy in PD-L1-high/CD8-low patients. Integrating PD-L1 with TIL data may refine prognosis prediction more accurately than either marker alone.

An integrated biomarker approach combining Ki-67, TIL density, and PD-L1 expression—stratified by molecular subtype—represents the most clinically informative framework for treatment personalisation. This multi-marker strategy has the potential to reduce overtreatment in patients unlikely to achieve pCR, spare patients from unnecessary toxicity, identify candidates for immunotherapy, and enrich clinical trial populations for targeted interventions.

8. Conclusion

Ki-67, TILs, and PD-L1 have each emerged as clinically meaningful biomarkers for predicting pCR in breast cancer patients receiving NACT. Ki-67, as a marker of tumour proliferative activity, provides pre-treatment stratification information that is most predictive in luminal and HER2-enriched subtypes. TILs, reflecting immune engagement within the tumour microenvironment, demonstrate the strongest pCR predictive value in TNBC and HER2-positive disease, while their role in luminal tumours requires cautious interpretation. PD-L1 expression signals immune evasion and carries prognostic significance particularly in residual TNBC; its co-evaluation with CD8+ TIL density identifies a high-risk patient subset requiring checkpoint inhibitor therapy.

Collectively, these biomarkers have the capacity to transform the clinical management of breast cancer by enabling individualised treatment plans, minimising unnecessary surgical and

systemic interventions, and guiding the selection of patients most likely to benefit from emerging immunotherapeutic strategies. Their reliable incorporation into routine clinical practice requires standardised scoring methodologies, validated subtype-specific cut-off thresholds, and prospective validation in diverse patient populations. Advances in molecular profiling technologies and artificial intelligence-assisted pathological scoring are expected to enhance the precision and reproducibility of these predictive tools in the coming years.

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