

[SYSTEMATIC REVIEW]

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PD-L1 Expression as a Predictor of Response to Neoadjuvant Immunotherapy in Triple-Negative Breast Cancer

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Abstract

Background: Immune checkpoint blockade has changed the treatment of high-risk early-stage triple-negative breast cancer (TNBC), yet the clinical role of programmed death-ligand 1 (PD-L1) expression in the neoadjuvant setting remains unsettled. PD-L1 may identify an immune-enriched tumor microenvironment and therefore correlate with pathologic complete response (pCR), but a predictive biomarker must also demonstrate differential treatment benefit according to biomarker status.

Methods: A structured systematic search of PubMed/MEDLINE and trial-specific publisher records was performed through 31 July 2026, supplemented by backward citation searching of major randomized trials, regulatory summaries, and contemporary meta-analyses. Prospective neoadjuvant PD-1/PD-L1 inhibitor studies in early TNBC were included when pretreatment PD-L1 was assessed and response data were reported. Owing to heterogeneity in PD-L1 assays, cutoffs, chemotherapy backbones, and study designs, findings were synthesized narratively rather than pooled quantitatively.

Results: Nine prospective primary studies were identified, including four pivotal randomized chemoimmunotherapy trials and five biomarker-rich early-phase or single-arm studies. Across KEYNOTE-173, KEYNOTE-522, GeparNuevo, NeoPACT, and camrelizumab studies, higher PD-L1 expression was generally associated with higher absolute pCR probability. However, randomized evidence did not show a reproducible PD-L1-by-treatment interaction. In KEYNOTE-522, pCR improved with pembrolizumab in both PD-L1-positive (68.9% vs 54.9%) and PD-L1-negative tumors (45.3% vs 30.3%). IMpassion031 similarly showed higher pCR with atezolizumab in PD-L1-positive (69% vs 49%) and PD-L1-negative disease (48% vs 34%). NeoTRIP identified PD-L1 as a strong correlate of pCR, yet atezolizumab did not significantly improve pCR overall. Assay discordance between 22C3, SP142, and SP263 and variable use of CPS versus immune-cell scoring further constrain interchangeability.

Conclusions: Pretreatment PD-L1 expression is best regarded as a response-enrichment and immune-context biomarker in early TNBC, not a validated stand-alone selector for neoadjuvant checkpoint blockade. Current evidence does not support withholding standard perioperative pembrolizumab solely because a tumor is PD-L1 negative. Composite biomarkers integrating PD-L1 with tumor-infiltrating lymphocytes, immune gene-expression signatures, spatial features, and early on-treatment dynamics are more promising for treatment personalization.

Keywords: triple-negative breast cancer; PD-L1; pembrolizumab; atezolizumab; durvalumab; camrelizumab; neoadjuvant immunotherapy; pathologic complete response; predictive biomarker

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1. Introduction

Triple-negative breast cancer (TNBC), conventionally defined by the absence of estrogen receptor and progesterone receptor expression and lack of human epidermal growth factor receptor 2 overexpression or amplification, is biologically heterogeneous and clinically aggressive. Compared with hormone receptor-positive breast cancer, TNBC is frequently characterized by higher

genomic instability, greater tumor-infiltrating lymphocyte (TIL) density, and more prominent interferon-driven immune signaling. These features make the immune microenvironment particularly relevant to treatment response. In pooled neoadjuvant cohorts, increasing TIL levels have been associated with higher pCR probability and with clinically meaningful prognostic information in TNBC [1].

Pathologic complete response after neoadjuvant therapy is an important individual-level prognostic marker in TNBC. The CTNeoBC pooled analysis demonstrated that the association between pCR and favorable long-term outcome is especially pronounced in aggressive breast cancer subtypes, including TNBC, although pCR is an imperfect trial-level surrogate for event-free or overall survival [2]. This distinction is important when interpreting immunotherapy trials: a biomarker may correlate with pCR without necessarily identifying the subgroup deriving the largest incremental survival benefit from immune checkpoint blockade.

The phase III KEYNOTE-522 program established perioperative pembrolizumab plus multi-agent chemotherapy as a major standard for high-risk stage II-III TNBC. Pembrolizumab increased pCR in the initial analysis [3], subsequently improved event-free survival [4], and, with longer follow-up, produced a statistically significant overall-survival advantage [5]. The US Food and Drug Administration approved pembrolizumab with neoadjuvant chemotherapy followed by adjuvant pembrolizumab in July 2021, with efficacy demonstrated irrespective of PD-L1 status [6]. ASCO similarly recommended the KEYNOTE-522 regimen for eligible high-risk early TNBC [7].

In metastatic TNBC, PD-L1 testing can function as a treatment-selection biomarker for specific checkpoint-inhibitor regimens. Extrapolating that paradigm to early TNBC, however, is problematic. PD-L1 expression in treatment-naïve early TNBC is closely related to immune-cell infiltration and may also associate with chemotherapy sensitivity. A systematic review of non-metastatic TNBC treated with neoadjuvant chemotherapy reported higher pCR among PD-L1-positive tumors even in the absence of checkpoint inhibition [8]. Therefore, a higher pCR rate in PD-L1-positive patients receiving chemoimmunotherapy does not by itself establish PD-L1 as a treatment-specific predictive biomarker.

This review evaluates whether pretreatment PD-L1 expression predicts response to neoadjuvant immunotherapy in TNBC, with emphasis on the difference between prognostic/response-enrichment effects and true treatment-predictive effects. We synthesize trial-level pCR data, assay methodology, long-term outcomes, and emerging biomarker strategies, and we identify the implications for present-day clinical decision-making and future biomarker-driven trials.

2. Methods

2.1 Review design and reporting framework

This systematic narrative review was designed to synthesize prospective clinical evidence evaluating PD-L1 in the neoadjuvant immunotherapy setting for early TNBC. Reporting was informed by the PRISMA 2020 framework [9]. Because the principal aim was biomarker interpretation across heterogeneous prospective trials rather than estimation of a single pooled treatment effect, the review used structured study identification and qualitative synthesis. The review protocol was not prospectively registered.

2.2 Search strategy and information sources

PubMed/MEDLINE and trial-specific publisher records were searched from database inception through 31 July 2026. Search concepts combined terms for triple-negative breast cancer, neoadjuvant or preoperative treatment, PD-1/PD-L1 blockade, and PD-L1 expression, together with agent and trial names including pembrolizumab, atezolizumab, durvalumab, camrelizumab, KEYNOTE-173, KEYNOTE-522, GeparNuevo, Impassion031, NeoTRIPaPDL1, NeoPACT, and CamRelief. Reference lists of eligible trials, regulatory summaries, systematic reviews, and biomarker reports were screened to identify additional primary publications and mature follow-up reports.

2.3 Eligibility criteria

Eligible primary studies were prospective phase I-III neoadjuvant trials enrolling patients with non-metastatic TNBC and administering a PD-1 or PD-L1 inhibitor, alone or with systemic therapy, when pretreatment PD-L1 expression was measured and a pathological response endpoint was reported or analyzed in relation to PD-L1. Randomized trials were prioritized for assessment of treatment prediction because they permit comparison of immunotherapy and control effects within biomarker strata. Single-arm trials were retained for response-enrichment and biomarker-discovery evidence. Studies confined to metastatic disease, purely adjuvant therapy, retrospective cohorts without a prospective therapeutic trial, and reports without interpretable PD-L1-response information were excluded from the primary evidence table.

2.4 Outcomes and biomarker interpretation

The primary outcome was pCR, preferentially defined as ypT0/Tis ypN0. Secondary outcomes included event-free survival (EFS), invasive disease-free survival (iDFS), distant disease-free survival (DDFS), and overall survival (OS) when mature reports were available. PD-L1 findings were classified conceptually as: (1) response enrichment/prognostic association, when PD-L1-positive tumors had a higher response probability regardless of treatment; or (2) treatment-predictive association, when the incremental effect of checkpoint blockade differed meaningfully according to PD-L1 status. This distinction was central to interpretation.

2.5 Data synthesis and methodological considerations

Study design, sample size, regimen, PD-L1 clone/scoring algorithm, cutoff, overall pCR, and biomarker-specific response data were extracted from primary publications and mature trial updates. Quantitative pooling was not undertaken because PD-L1 was measured with non-equivalent antibody clones and scoring systems, cutoffs differed substantially, and several included cohorts were nonrandomized. The synthesis therefore emphasizes consistency, direction of association, randomized treatment contrasts, and biological plausibility rather than a pooled odds ratio.

3. Results

3.1 Included prospective evidence

Nine primary prospective studies met the prespecified clinical-biomarker criteria (Table 1). These comprised KEYNOTE-173 [10], GeparNuevo [11], a phase I/II durvalumab study by Foldi and colleagues [12], KEYNOTE-522 [3], IMpassion031 [13], NeoTRIPaPDL1 [14], NeoPACT [15], a single-arm phase II camrelizumab study [16], and the phase III CamRelief trial [17]. The evidence base spans anti-PD-1 and anti-PD-L1 agents, anthracycline-containing and anthracycline-free chemotherapy backbones, and several distinct PD-L1 assays. Four randomized studies - GeparNuevo, KEYNOTE-522, IMpassion031, and NeoTRIP - provide the most informative evidence for treatment interaction; CamRelief adds a more recent randomized anti-PD-1 dataset but its principal publication emphasizes consistency across PD-L1 strata rather than validating a single cutoff as a selector.

3.2 PD-L1 and pCR: consistent response enrichment

Across early-phase studies, PD-L1 expression generally enriched for pCR. In KEYNOTE-173, the overall pCR rate was 60%, and higher pretreatment PD-L1 combined positive score (CPS) was significantly associated with pCR ($P=0.0127$) [10]. In the single-arm durvalumab study, pCR was 55% in PD-L1-positive versus 32% in PD-L1-negative tumors, although the difference was not statistically significant ($P=0.15$) in a small cohort [12]. NeoPACT, an anthracycline-free phase II pembrolizumab regimen, demonstrated a marked association: among patients with centrally assessed 22C3 results, pCR was approximately 74% for CPS ≥ 10 versus 40% for CPS < 10 ; PD-L1 remained independently associated with pCR in multivariable modeling [15]. Similarly, the phase II camrelizumab study reported pCR in 91.7% of PD-L1-positive versus 40.9% of PD-L1-negative evaluable tumors using 22C3 CPS ≥ 1 [16]. These findings support PD-L1 as a biologically meaningful marker of an immune-responsive microenvironment.

The critical limitation is that single-arm studies cannot determine whether PD-L1 predicts sensitivity specifically to immunotherapy or instead reflects underlying sensitivity to chemotherapy and immune-mediated tumor clearance. This concern is not theoretical: PD-L1 positivity has also been associated with increased pCR after neoadjuvant chemotherapy without checkpoint blockade [8]. Consequently, randomized within-biomarker comparisons are necessary to establish clinical treatment prediction.

3.3 Randomized evidence: PD-L1 does not consistently select for checkpoint-inhibitor benefit

KEYNOTE-522 provides the strongest evidence against using PD-L1 as an exclusionary biomarker in high-risk early TNBC. In the first 602 randomized patients, pembrolizumab plus chemotherapy improved pCR overall from 51.2% to 64.8% [3]. Among PD-L1-positive tumors (22C3 CPS ≥ 1), pCR was 68.9% with pembrolizumab versus 54.9% with placebo; among PD-L1-negative tumors, pCR was 45.3% versus 30.3%, respectively. Thus, PD-L1 positivity identified a population with higher absolute response rates, but the raw absolute pCR

increment from adding pembrolizumab was similar in direction across biomarker strata. This pattern is inconsistent with PD-L1 negativity functioning as a reliable marker of no benefit.

IMpassion031 produced a comparable pattern. Atezolizumab increased overall pCR from 41% to 58% [13]. In PD-L1-positive tumors, defined by SP142 immune-cell staining $\geq 1\%$, pCR was 69% with atezolizumab versus 49% with placebo; in PD-L1-negative tumors, pCR was 48% versus 34%. The trial formally met its overall pCR endpoint, while the biomarker-stratified results again suggested response enrichment by PD-L1 but not confinement of treatment effect to PD-L1-positive disease.

GeparNuevo randomized 174 patients to durvalumab or placebo with nab-paclitaxel followed by dose-dense epirubicin/cyclophosphamide. Overall pCR was numerically higher with durvalumab (53.4% vs 44.2%) but the study did not meet its primary pCR objective [11]. PD-L1-positive tumors had higher pCR than PD-L1-negative tumors in both treatment groups. In the durvalumab arm, pCR was 58.0% in PD-L1-positive versus 44.4% in PD-L1-negative disease; in the placebo arm, pCR was 50.7% versus 18.2%. The larger apparent treatment increment in the PD-L1-negative subgroup was based on very small numbers and should not be overinterpreted. Collectively, the pattern supports PD-L1 as an immune-context marker rather than a durvalumab-specific selector.

NeoTRIPaPDL1 offers an additional caution. Atezolizumab added to carboplatin/nab-paclitaxel did not significantly improve pCR overall, while PD-L1 was the strongest factor associated with pCR in multivariable analysis [14]. Response increased with higher SP142 immune-cell categories, but the between-arm treatment increment was not monotonic across PD-L1 strata; in the PD-L1-negative IC0 subgroup, pCR was essentially similar between arms. A biomarker can therefore be strongly associated with response yet fail to predict incremental immunotherapy efficacy.

The phase III CamRelief trial subsequently showed that adding camrelizumab to neoadjuvant chemotherapy increased pCR from 44.7% to 56.8% in early or locally advanced TNBC [17]. Prespecified subgroup analyses were directionally consistent across PD-L1 CPS categories. The trial strengthens the broader observation that checkpoint-inhibitor activity in early TNBC is not restricted to a single PD-L1-positive subgroup, although differences in the E1L3N assay and scoring framework complicate direct comparison with 22C3 and SP142 studies.

3.4 Long-term outcomes weaken a pCR-only interpretation of PD-L1

Long-term outcome data reinforce the importance of separating pCR association from durable treatment benefit. KEYNOTE-522 demonstrated improved EFS with pembrolizumab [4], and the final overall-survival analysis reported a 5-year OS of 86.6% with pembrolizumab versus 81.7% with placebo [5]. Regulatory review concluded that EFS benefit was observed regardless of tumor PD-L1 status [6]. These findings underlie the

current clinical practice of treating eligible high-risk early TNBC without requiring PD-L1 positivity.

GeparNuevo is also instructive. Although the primary pCR comparison was not statistically significant, longer follow-up showed improved survival outcomes with neoadjuvant durvalumab. At an earlier survival analysis, durvalumab was associated with favorable iDFS, DDFS, and OS [18]. A 2026 update at a median follow-up of 86.4 months confirmed sustained improvements in iDFS (HR 0.56), DDFS (HR 0.41), and OS (HR 0.33) [19]. The dissociation between a modest pCR difference and durable outcome signals indicates that treatment efficacy may not be captured fully by baseline PD-L1 or by pCR alone.

Final IMpassion031 follow-up likewise reported long-term outcomes favoring perioperative atezolizumab, including numerically improved EFS, DFS, and OS, together with circulating tumor DNA analyses that emphasized the potential value of dynamic molecular response [20]. These data support a shift from static pretreatment biomarkers toward multitime-point models integrating baseline immunity with treatment-induced tumor clearance.

3.5 Assay heterogeneity limits cross-trial transportability

PD-L1 is not a single laboratory variable. KEYNOTE studies used the Dako 22C3 assay and CPS; IMpassion031 and NeoTRIP used Ventana SP142 with immune-cell scoring; GeparNuevo and the Foldi durvalumab study used SP263-based approaches; NeoPACT used a higher 22C3 threshold (CPS ≥ 10); and CamRelief used E1L3N with CPS categories. These assays differ in analytical sensitivity, cellular compartments counted, denominator definitions, and clinically chosen thresholds (Table 3).

Direct pathology comparisons demonstrate that assay substitution is unsafe. Huang and colleagues found the lowest PD-L1 positivity rate with SP142 relative to 22C3 and 28-8, with incomplete interchangeability across scoring methods [21]. In a four-assay interobserver/interassay study, Noske and colleagues observed good agreement for some pairs but materially lower concordance when SP263 was compared with other assays and when higher CPS thresholds were used [22]. A population-based early-TNBC comparison similarly showed different positivity rates for SP142 IC $\geq 1\%$, 22C3 CPS ≥ 1 , and 22C3 CPS ≥ 10 [23]. Consequently, a binary label of 'PD-L1 positive' can represent different biological and analytical populations across studies.

3.6 Emerging biomarkers beyond static PD-L1

The incomplete predictive performance of PD-L1 has accelerated evaluation of composite biomarkers. In NeoTRIP, the 27-gene immune-related DetermaIO signature identified tumors with greater sensitivity to atezolizumab-containing neoadjuvant therapy and provided information beyond conventional clinicopathologic variables [24]. A 2026 longitudinal transcriptomic analysis from NeoTRIP further showed that baseline proliferation, metabolic and stromal programs, together with early on-treatment immune activation and tumor-cell clearance, provided complementary response information; multifeature models outperformed reliance on a single static biomarker [25].

Other studies point to spatial and cellular immune architecture. The BELLINI trial demonstrated that short-course checkpoint blockade can induce marked immune activation in selected early TNBCs, with response associated with specific T-cell states and spatial immune features [26]. Across the neoadjuvant literature, stromal TILs, interferon-gamma-related signatures, antigen-presentation programs, tumor mutational and genomic features, and circulating tumor DNA kinetics have emerged as candidates. The most plausible future strategy is therefore a layered model: baseline PD-L1 as one component of immune context, combined with quantitative TIL assessment, gene-expression signatures, and early dynamic response markers.

4. Discussion

4.1 Principal finding

The central finding of this review is that pretreatment PD-L1 expression is clinically informative in early TNBC but is not sufficiently treatment-specific to function as a stand-alone selector for neoadjuvant immunotherapy. PD-L1-positive tumors repeatedly demonstrate higher absolute pCR rates, which is biologically coherent because PD-L1 often accompanies an inflamed, interferon-active, lymphocyte-rich microenvironment. Yet the defining test of a predictive biomarker is not whether biomarker-positive patients respond more often; it is whether the treatment effect differs according to biomarker status. In the most informative randomized trials, this interaction has not been reproducibly demonstrated.

The distinction explains an apparent paradox in the literature. KEYNOTE-173, NeoPACT, and the phase II camrelizumab trial show striking response enrichment among PD-L1-positive tumors [10,15,16]. At the same time, KEYNOTE-522 and IMpassion031 show meaningful ICI-associated pCR improvements in PD-L1-negative disease [3,13]. NeoTRIP shows that PD-L1 can be one of the strongest correlates of pCR even when the checkpoint inhibitor fails to improve pCR significantly overall [14]. The parsimonious interpretation is that PD-L1 captures pre-existing antitumor immunity and chemotherapy responsiveness to a substantial degree, whereas incremental ICI sensitivity depends on additional features not fully represented by baseline PD-L1 staining.

4.2 Clinical implications

For current practice, PD-L1 testing should not be used to deny an otherwise eligible patient the KEYNOTE-522 perioperative pembrolizumab regimen. This conclusion is supported by randomized pCR data, EFS and OS maturation, FDA review, and professional guidance [3-7]. The early-stage setting therefore differs materially from metastatic TNBC, where PD-L1 thresholds have been used to select patients for particular checkpoint-inhibitor combinations. Stage, curative intent, chemotherapy context, disease burden, and treatment duration all alter the biomarker-treatment relationship.

PD-L1 may nevertheless have value for research stratification and future de-escalation. A patient with a highly immune-enriched tumor, high TILs, strong immune gene-expression signals, and rapid early response might eventually be a candidate for less cytotoxic therapy,

whereas an immune-cold tumor might warrant intensification or alternative immunomodulatory strategies. Such approaches require prospective validation and should not be inferred from PD-L1 alone.

4.3 Why PD-L1 underperforms as a stand-alone predictive biomarker

Several mechanisms explain the limited discriminatory value of baseline PD-L1. First, PD-L1 is dynamic and inducible; chemotherapy and interferon signaling can increase expression after treatment begins. Second, spatial heterogeneity can lead to sampling error in a core biopsy. Third, tumor-cell and immune-cell PD-L1 may convey different biological information, yet assays count these compartments differently. Fourth, PD-L1 is correlated with TIL density and immune gene signatures, creating substantial biological redundancy. Fifth, checkpoint response depends on multiple steps - antigen release, presentation, T-cell priming, trafficking, cytotoxic capacity, and suppressive cell states - that cannot be summarized by one immunohistochemical stain (Figure 1).

Analytical heterogeneity compounds biological limitations. A tumor classified as negative by SP142 may be positive by 22C3 under another scoring algorithm, while CPS ≥ 1 and CPS ≥ 10 define substantially different populations [21-23]. This makes cross-trial threshold transfer scientifically unreliable. Harmonization of specimen timing, antibody clone, scoring system, digital pathology methods, and prespecified interaction testing is essential for future biomarker trials.

4.4 Relationship to previous evidence syntheses

Earlier meta-analysis of randomized neoadjuvant immunotherapy trials showed that adding PD-1/PD-L1 blockade increases pCR in TNBC, with a significant signal in PD-L1-positive disease [27]. More contemporary meta-analysis across early breast cancer has confirmed the efficacy of neoadjuvant checkpoint inhibition in TNBC while highlighting the importance of treatment timing and biomarker-defined heterogeneity [28]. The present review extends these analyses by focusing specifically on the conceptual status of PD-L1 as a predictor, incorporating mature OS data, 2025 IMpassion031 follow-up, and 2026 GeparNuevo and NeoTRIP translational updates. These newer data further weaken a binary PD-L1-positive/negative treatment-selection model.

4.5 Strengths and limitations

Strengths include emphasis on primary prospective trial data, explicit separation of response enrichment from treatment prediction, inclusion of assay methodology, and incorporation of mature long-term and translational evidence through July 2026. The review also avoids quantitative pooling across non-equivalent PD-L1 assays, a choice that reduces false precision.

Several limitations should be acknowledged. The search was centered on PubMed/MEDLINE and trial-specific publisher records rather than multiple bibliographic databases; therefore, the work is best interpreted as a systematic narrative synthesis rather than an exhaustive meta-analysis. PD-L1 subgroup analyses were not uniformly powered for formal interaction testing, and some subgroup estimates derive from exploratory

analyses with small denominators. Definitions of pCR, chemotherapy backbones, stage distributions, assay clones, scoring algorithms, and cutoff values varied. Finally, long-term outcome data by PD-L1 subgroup are less consistently reported than pCR data, limiting biomarker-specific survival conclusions.

5. Future Research Priorities

- Prospective biomarker interaction designs: Future randomized trials should prespecify treatment-by-biomarker interaction hypotheses rather than relying on within-arm response associations.
- Assay harmonization: Studies should standardize clone, platform, specimen timing, scoring algorithm, and clinically meaningful cutoffs, with centralized pathology and digital reproducibility studies.
- Composite immune biomarkers: PD-L1 should be integrated with quantitative TILs, immune gene-expression signatures, antigen-presentation markers, and spatial immune architecture.
- Dynamic response assessment: Early on-treatment biopsy, circulating tumor DNA clearance, and imaging response may identify immune-sensitive disease more accurately than baseline PD-L1 alone.
- De-escalation and escalation trials: Biomarker strategies should be tested for clinically actionable decisions, such as reducing chemotherapy intensity in highly immune-responsive tumors or introducing novel combinations in immune-cold/resistant disease.
- Long-term endpoints: Biomarker claims should be validated against EFS and OS, not pCR alone, because immunotherapy may confer durable effects not fully captured by surgical pathology.

6. Conclusion

PD-L1 expression in early TNBC is a reproducible marker of an immune-enriched tumor state and frequently identifies patients with a higher probability of pCR. Nevertheless, the totality of randomized evidence does not validate PD-L1 as a stand-alone predictor that can reliably separate patients who will versus will not benefit from neoadjuvant checkpoint inhibition. KEYNOTE-522 and IMpassion031 demonstrate treatment-associated pCR gains in both PD-L1-positive and PD-L1-negative disease, while NeoTRIP illustrates that strong PD-L1-response association can coexist with limited treatment-specific pCR discrimination. Current clinical use of perioperative pembrolizumab in eligible high-risk early TNBC should therefore remain independent of PD-L1 status. Future precision immunotherapy is more likely to emerge from composite, dynamic biomarkers that combine PD-L1 with TILs, transcriptomic immune signatures, spatial biology, and early treatment response.

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Registration

Not applicable.

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Table 1. Characteristics of all included prospective neoadjuvant immunotherapy studies with PD-L1 data in early TNBC.

Study (year)	Design / N	ICI	Chemotherapy backbone	PD-L1 assay and definition	Overall pCR	PD-L1-specific finding
KEYNOTE-173 (2020)	Phase Ib, multicohort; N=60	Pembrolizumab	Taxane +/- carboplatin followed by AC	22C3; CPS assessed (continuous and categorical)	60%	Higher pretreatment CPS significantly associated with pCR (P=0.0127).
GeparNuevo (2019)	Randomized phase II; N=174	Durvalumab	nab-paclitaxel -> dose-dense EC	SP263; tumor/immune-cell PD-L1 >=1% used for positivity	53.4% vs 44.2%	Higher pCR in PD-L1+ tumors in both arms; no convincing treatment-specific interaction.
Foldi et al. (2021)	Phase I/II, single-arm; 55 efficacy-evaluable	Durvalumab	nab-paclitaxel -> dose-dense AC	SP263; >=1% immune/tumor-cell staining	44%	pCR 55% PD-L1+ vs 32% PD-L1-; P=0.15.
KEYNOTE-522 (2020-2024)	Randomized phase III; N=1174	Pembrolizumab	Paclitaxel + carboplatin -> AC/EC; adjuvant pembrolizumab/placebo	22C3; CPS >=1	64.8% vs 51.2% (initial pCR cohort)	ICI-associated pCR improvement observed in both PD-L1+ and PD-L1- disease; EFS/OS benefit not restricted by PD-L1.
IMpassion031 (2020; final 2025)	Randomized phase III; N=333	Atezolizumab	nab-paclitaxel -> dose-dense AC; perioperative atezolizumab/placebo	SP142; IC >=1%	58% vs 41%	pCR improvement in both PD-L1+ and PD-L1- subgroups.
NeoTRIPaPDL1 (2022)	Randomized phase III; N=280	Atezolizumab	Carboplatin + nab-paclitaxel; anthracycline after surgery	SP142; IC0/1/2/3 categories	No statistically significant overall pCR improvement with atezolizumab	PD-L1 strongly associated with pCR, but overall atezolizumab pCR increment not significant and treatment effect not monotonic across PD-L1 strata.
NeoPACT (2024)	Phase II, single-arm; N=115	Pembrolizumab	Carboplatin + docetaxel (anthracycline-free)	22C3; CPS >=10	58%	pCR approximately 74% at CPS >=10 vs 40% at CPS <10; strong response enrichment.
Camrelizumab phase II (2023)	Phase II, single-arm; N=39	Camrelizumab	nab-paclitaxel + epirubicin	22C3; CPS >=1	64.1%	pCR 91.7% PD-L1+ vs 40.9% PD-L1- among evaluable tumors.
CamRelief (2025)	Randomized phase III; N=441	Camrelizumab	Taxane/platinum-based chemotherapy followed by anthracycline-containing therapy	E1L3N; CPS <1, 1-<10, >=10	56.8% vs 44.7%	Treatment effect directionally consistent across PD-L1 strata; no validated cutoff selected a nonbenefiting population.

Abbreviations: AC, doxorubicin/cyclophosphamide; CPS, combined positive score; EC, epirubicin/cyclophosphamide; IC, immune-cell score; ICI, immune checkpoint inhibitor; pCR, pathologic complete response; TNBC, triple-negative breast cancer.

Table 2. PD-L1-stratified pathologic complete response findings in key neoadjuvant studies.

Study	PD-L1 definition	ICI + chemotherapy pCR	Control pCR	Absolute pattern	Interpretation
KEYNOTE-173	22C3 CPS; continuous association	Single-arm	Not applicable	Higher CPS associated with pCR (P=0.0127)	Response enrichment only; no control arm.
GeparNuevo	SP263 PD-L1+ vs PD-L1-	PD-L1+: 58.0%; PD-L1-: 44.4%	PD-L1+: 50.7%; PD-L1-: 18.2%	Raw ICI increment: +7.3 pp in PD-L1+; +26.2 pp in PD-L1-	PD-L1 associated with response, but not durvalumab-specific selection; small PD-L1-subgroup.

Study	PD-L1 definition	ICI + chemotherapy pCR	Control pCR	Absolute pattern	Interpretation
KEYNOTE-522	22C3 CPS ≥ 1 vs < 1	PD-L1+: 68.9%; PD-L1-: 45.3%	PD-L1+: 54.9%; PD-L1-: 30.3%	Raw ICI increment: +14.0 pp in PD-L1+; +15.0 pp in PD-L1-	Strong evidence against using PD-L1 negativity to exclude pembrolizumab.
IMpassion031	SP142 IC $\geq 1\%$ vs $< 1\%$	PD-L1+: 69%; PD-L1-: 48%	PD-L1+: 49%; PD-L1-: 34%	Raw ICI increment: +20 pp in PD-L1+; +14 pp in PD-L1-	Benefit not restricted to PD-L1-positive disease.
NeoTRIPaPDL1	SP142 IC categories	IC2/3: 87%; IC1: 56.2%; IC0: 35.1%	IC2/3: 72%; IC1: 44%; IC0: 41.1%	Higher PD-L1 correlates with pCR; no monotonic treatment interaction	Strong prognostic/response association; weak treatment-selection evidence.
Foldi et al.	SP263 $\geq 1\%$	PD-L1+: 55%; PD-L1-: 32%	Not applicable	23-pp within-arm difference; P=0.15	Suggestive enrichment; underpowered and nonrandomized.
NeoPACT	22C3 CPS ≥ 10	PD-L1+: 74%; PD-L1-: 40%	Not applicable	34-pp within-arm difference; OR 4.32; P<0.001	Strong enrichment but cannot isolate ICI-specific prediction.
Camrelizumab phase II	22C3 CPS ≥ 1	PD-L1+: 91.7%; PD-L1-: 40.9%	Not applicable	50.8-pp within-arm difference	Marked enrichment; small single-arm study.
CamRelief	E1L3N CPS strata	Overall pCR 56.8%; benefit directionally consistent across CPS subgroups	Overall pCR 44.7%	No validated discriminatory PD-L1 cutoff	Supports broad activity rather than binary PD-L1 selection.

Note: Percentages are reproduced from published trial reports and biomarker analyses. Cross-trial comparison should be qualitative because assays, cutoffs, patient populations, and chemotherapy backbones differ. pp = percentage points.

Table 3. PD-L1 assays, scoring systems, and interpretive implications in early TNBC neoadjuvant immunotherapy studies.

Assay / clone	Scoring approach	Representative cutoff(s)	Representative studies	Key interpretive issue
Dako 22C3	Combined positive score (CPS): PD-L1-positive tumor cells, lymphocytes and macrophages relative to viable tumor cells	CPS ≥ 1 ; CPS ≥ 10	KEYNOTE-173, KEYNOTE-522, NeoPACT, camrelizumab phase II	CPS ≥ 1 and CPS ≥ 10 classify materially different proportions of tumors; threshold is context-specific.
Ventana SP142	Immune-cell (IC) area-based scoring	IC $\geq 1\%$; IC0/1/2/3	IMpassion031, NeoTRIPaPDL1	Analytically less sensitive in some head-to-head comparisons; immune-cell scoring is not equivalent to CPS.
Ventana SP263	Tumor-cell and/or immune-cell staining approaches	Commonly $\geq 1\%$ in study-specific algorithms	GeparNuevo, Foldi et al.	Higher analytical sensitivity in some series; study-specific definitions complicate transferability.
E1L3N	CPS-based research/clinical scoring	CPS < 1 , 1- < 10 , ≥ 10	CamRelief	Not directly interchangeable with 22C3 without assay-bridging validation.
Cross-assay issue	Different clones, platforms, cell compartments and denominators	No universal threshold	Pathology concordance studies	A single label of "PD-L1 positive" does not represent an identical biological population across trials.

Table 4. Evidence appraisal: does each study support PD-L1 as a response marker or an immunotherapy-specific treatment selector?

Study	Design strength for prediction	PD-L1 response enrichment	Evidence for ICI-specific selection	Principal limitation / conclusion
KEYNOTE-522	High: large randomized phase III	Yes	No clear differential interaction; benefit in PD-L1+ and PD-L1-	Most clinically decisive evidence; PD-L1 should not gate therapy.
IMpassion031	High: randomized phase III	Yes	No; pCR gain in both biomarker groups	Supports immune enrichment but not exclusion of PD-L1-negative patients.
GeparNuevo	Moderate: randomized phase II	Yes	No consistent positive interaction	Small biomarker-negative subgroup and non-significant primary pCR comparison.
NeoTRIPaPDL1	High/moderate: randomized phase III with biomarker analyses	Strong	Not established	PD-L1 predicts pCR probability more clearly than atezolizumab-specific pCR benefit.
CamRelief	High: randomized phase III	Suggestive across strata	No validated discriminatory cutoff	Different assay and newer dataset; subgroup findings not a companion diagnostic.
KEYNOTE-173	Low for treatment interaction: single-arm phase Ib	Yes	Cannot assess	Useful hypothesis-generating evidence.
Foldi et al.	Low for treatment interaction: small single-arm phase I/II	Suggestive	Cannot assess	Underpowered biomarker comparison.
NeoPACT	Low for treatment interaction: single-arm phase II	Strong	Cannot assess	High-quality biomarker work but no chemotherapy-only comparator.
Camrelizumab phase II	Low for treatment interaction: small single-arm phase II	Strong	Cannot assess	Large within-arm difference but small sample and no comparator.

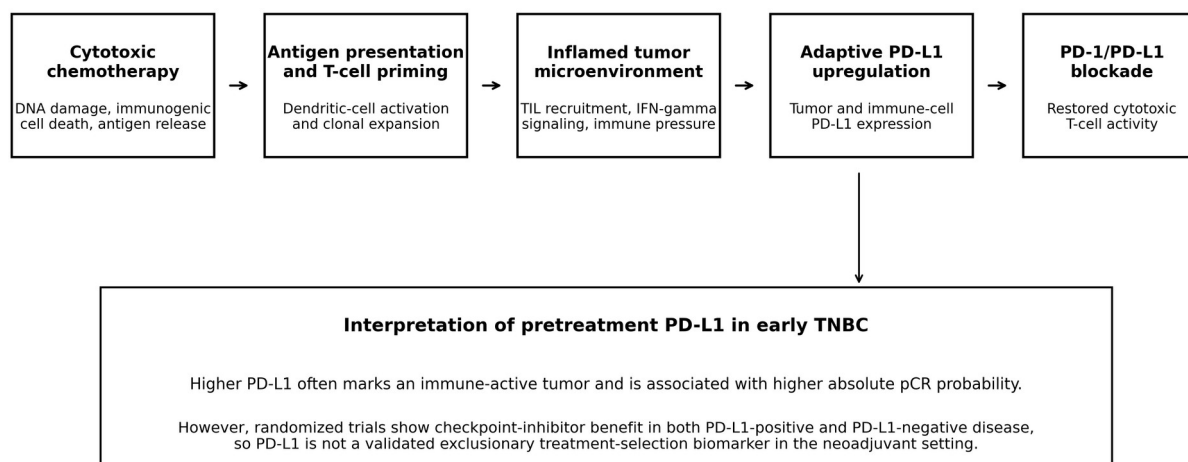


Figure 1. Mechanistic basis for PD-L1 expression and checkpoint-inhibitor response in early TNBC. Cytotoxic therapy can promote antigen release and immune priming, while interferon-driven immune pressure induces adaptive PD-L1 expression. PD-L1 therefore often marks an inflamed tumor microenvironment, but its dynamic and heterogeneous nature limits its ability to function as a stand-alone treatment-selection biomarker. Original schematic created for this review.

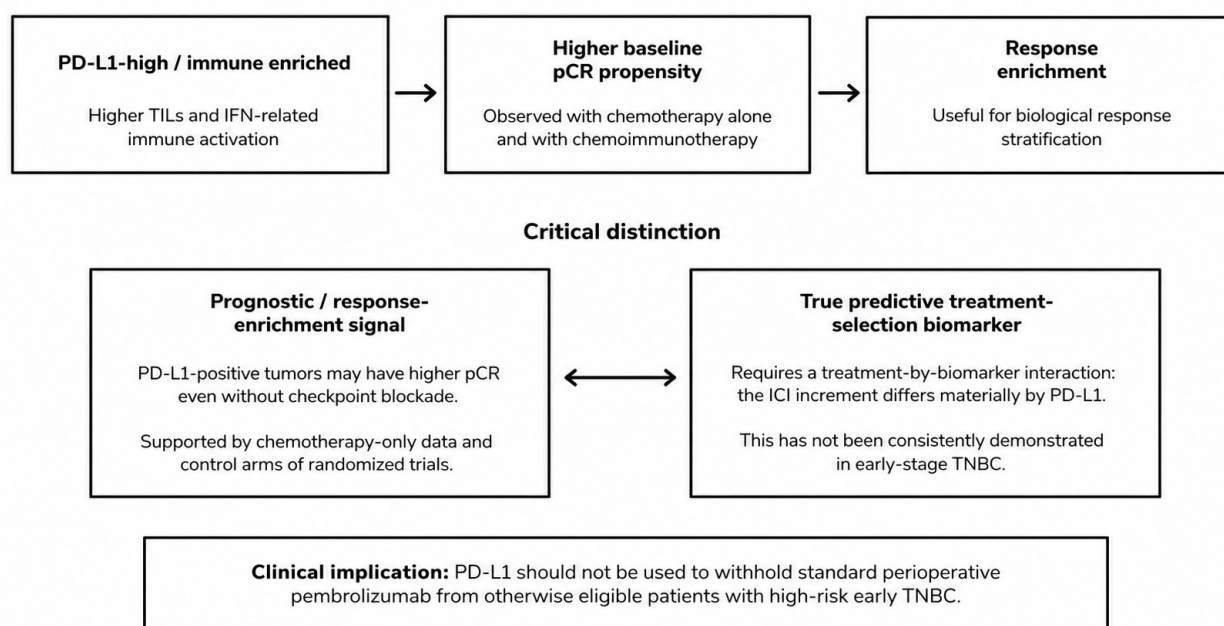


Figure 2. Distinguishing response enrichment from treatment prediction. A biomarker can be associated with higher pCR in both experimental and control groups and still fail to identify differential benefit from immunotherapy. A clinically predictive treatment-selection biomarker requires a treatment-by-biomarker interaction, not merely a higher response rate in the biomarker-positive subgroup. Original schematic created for this review.

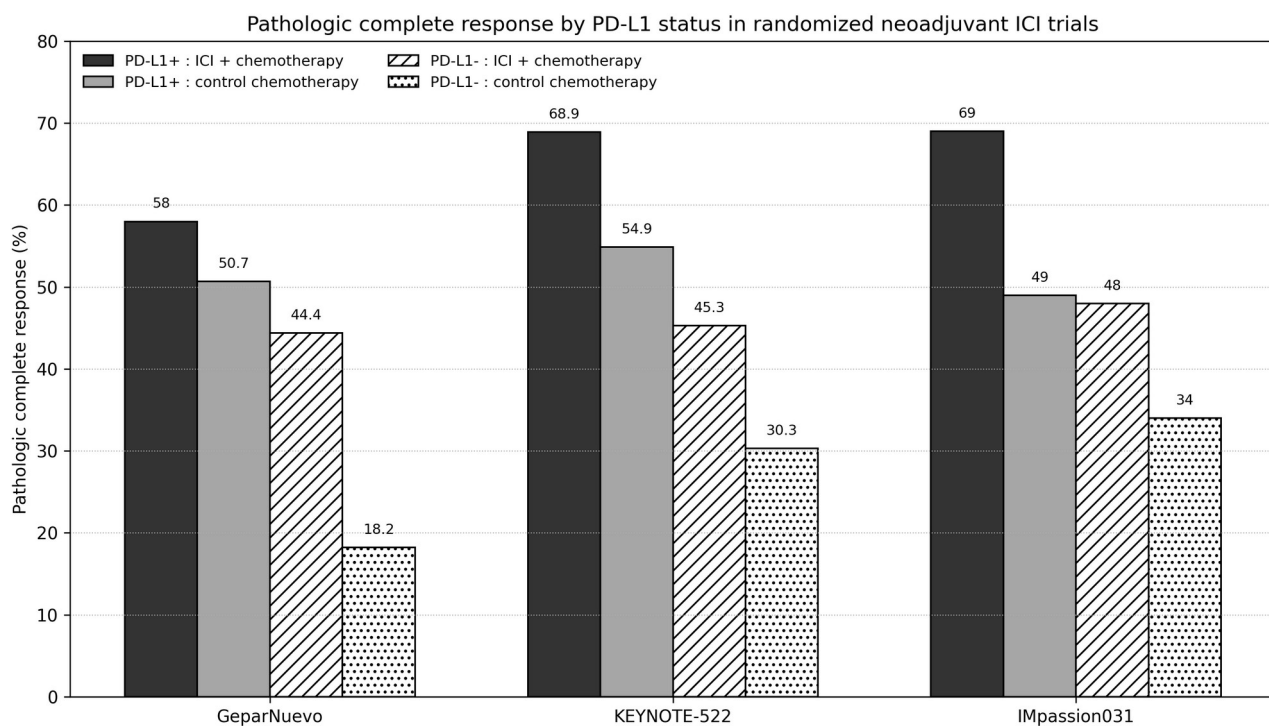


Figure 3. PD-L1-stratified pCR rates in representative randomized neoadjuvant checkpoint-inhibitor trials. PD-L1-positive tumors generally have higher absolute pCR rates, but checkpoint-inhibitor-associated pCR gains are also observed in PD-L1-negative tumors. Values are from GeparNuevo [11], KEYNOTE-522 [3], and IMpassion031 [13]. Definitions of PD-L1 positivity differ among trials; direct numerical comparisons should therefore be interpreted cautiously.