Recent progress in the PD-1/PD-L1 axis in breast cancer: Biological mechanisms, clinical implications and future directions (Review)

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Abstract. Breast cancer exhibits substantial subtype- and stage-dependent immunological heterogeneity, resulting in unequal sensitivity to programmed cell death protein 1/programmed death-ligand 1 (PD-L1) blockade. In triple-negative breast cancer, pembrolizumab-based therapy has an established role in high-risk early disease and in PD-L1$^+$ advanced disease, whereas the evidence in HER2$^+$ and hormone receptor$^+$/HER2$^-$ breast cancer remains more context-dependent and is largely investigational. The present structured narrative review integrates breast cancer-specific evidence across four interrelated topics, which comprise the molecular regulation of PD-L1, subtype-specific clinical translation, the mechanisms underlying primary, adaptive and acquired resistance and the standardization of biomarkers and assays. It distinguishes mechanisms directly demonstrated in breast cancer from those extrapolated from other malignancies and organizes therapeutic strategies according to evidence maturity. Consideration is given to the fact that PD-L1 assays and scoring systems are not interchangeable, to the limitations of complementary biomarkers and to the emergence of antibody-drug conjugate-checkpoint inhibitor combinations. The literature is organized according to subtype, disease setting, biomarker and level of evidence to distinguish established clinical practice from investigational and preclinical approaches and to identify priorities for precision immunotherapy in breast cancer.

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1. Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide, with an estimated 2.3 million new cases and 670,000 associated deaths in 2022, and remains a key cause of cancer mortality, while its extensive clinical and molecular heterogeneity continues to challenge precision therapy (1,2). Tumor immunotherapy has emerged as a key therapeutic advancement in oncology (3). Although breast cancer has historically been regarded as relatively poorly immunogenic, accumulating evidence indicates that this characterization does not apply uniformly across molecular subtypes. Triple negative breast cancer (TNBC) frequently contains abundant tumor-infiltrating lymphocytes (TILs) and programmed death-ligand 1 (PD-L1) expression, features compatible with an inflamed tumor immune microenvironment. By contrast, numerous hormone receptor-positive (HR$^+$)/HER2$^-$ breast cancer cases exhibit sparse immune infiltration, consistent with immune-excluded or immune-desert phenotypes (4-6).

This intrinsic immune heterogeneity provides a biological basis for the marked differences in response to checkpoint blockade across breast cancer subtypes.

The programmed cell death protein-1 (PD-1)/PD-L1 pathway is a mechanism of adaptive immune suppression. PD-L1 expressed by tumor cells and immune cells (ICs) within the tumor microenvironment (TME) engages PD-1 on activated T cells and attenuates T cell receptor signaling, cytokine production, proliferation and cytotoxic function, and this functional suppression ultimately leads to T cell exhaustion and immune evasion, favoring tumor progression (7,8). Clinical translation of PD-1/PD-L1 blockade has been most successful in TNBC. KEYNOTE-355 established pembrolizumab plus chemotherapy for previously untreated locally recurrent inoperable or metastatic TNBC with a PD-L1 combined positive score (CPS) of ≥10 assessed using the 22C3 assay (9,10). In stage II-III early TNBC, KEYNOTE-522 demonstrated that neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab improved long-term outcomes without requiring PD-L1 positivity for treatment selection (10,11). More recently, ASCENT-04/KEYNOTE-D19 demonstrated a progression-free survival (PFS) benefit from sacituzumab govitecan plus pembrolizumab in first-line PD-L1$^+$ advanced TNBC and supported a new U.S. first-line option for CPS ≥10 disease (12,13).

Despite this progress, several challenges remain, including non-interchangeable PD-L1 assays and scoring systems, heterogeneous treatment response across subtypes, incompletely defined breast-cancer-specific resistance mechanisms and limited benefit in immunologically cold tumors (5,14,15). Recent reviews have addressed PD-1/PD-L1 biology, TNBC immunotherapy and biomarker development (4,6,8). To provide a more distinct synthesis, the present review organized the relevant evidence according to subtype, disease stage, biomarker context and level of evidence. The present review first examines multilevel PD-L1 regulation and immune escape, then compares clinical translation across TNBC, HER2$^+$ and HR$^+$/HER2$^-$ disease, classifies resistance as primary, adaptive or acquired, grades resistance-overcoming strategies by evidence maturity and finally addresses PD-L1 assay standardization and complementary biomarkers.

2. Literature search and evidence appraisal

The present article is a structured narrative review rather than a systematic review or meta-analysis. PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov/) was searched for English language literature published using combinations of the terms 'breast cancer', 'triple-negative breast cancer', 'HER2-positive', 'hormone receptor-positive', 'PD-1', 'PD-L1', 'pembrolizumab', 'atezolizumab', 'nivolumab', 'immune checkpoint inhibitor', 'resistance', 'biomarker', '22C3', 'SP142', 'CPS', 'TILs', 'TMB' and 'ctDNA'. Earlier landmark studies were retained when necessary to define key clinical evidence or standardized methodology. Targeted searches were additionally performed for antigen-presentation and IFN-signaling defects, T cell exclusion, myeloid suppression, alternative checkpoints, PD-L1 spatial-temporal heterogeneity, antibody-drug conjugate combinations and emerging delivery or microenvironment-directed strategies. ClinicalTrials.gov (https://clinicaltrials.gov/) and official U.S. Food and Drug Administration (FDA; https://www.fda.gov) and European Medicines Agency (EMA; https://www.ema.europa.eu) sources were consulted when trial status or regulatory context required clarification. Evidence was prioritized in the following order: Randomized phase III breast cancer trials, prospective breast cancer clinical studies, breast cancer specific translational or preclinical studies and mechanistic evidence from other tumor types. Pan-cancer mechanisms are explicitly identified when breast cancer specific validation is limited, and *in vitro* or preclinical strategies were not assigned the same evidentiary weight as clinical trials.

3. Biological mechanisms of the PD-1/PD-L1 axis

Regulation of PD-L1 expression. PD-L1 expression in breast cancer is governed by multiple regulatory mechanisms, including cytokine-driven transcription, oncogenic signaling, epigenetic modifications, translational control, protein trafficking and post-translational regulation (Fig. 1). Fig. 1 integrates these regulatory layers, illustrating the progression from transcriptional control in the nucleus to post-translational modifications and surface trafficking. These processes collectively determine the abundance and functional activity of PD-L1 at the tumor cell surface (5-7).

Transcriptional regulation. Inflammatory cytokine mediated transcriptional induction represents a key mechanism of adaptive immune resistance. IFN-γ is a potent inducer of PD-L1 expression. After binding to the IFN-γ receptor, IFN-γ activates Janus kinase (JAK)1/JAK2-STAT1 signaling, promoting IFN regulatory factor 1-dependent CD274 transcription and increases PD-L1 expression (7,8,16).

Constitutive oncogenic signaling can also influence PD-L1 expression and IC exclusion, with specific mechanisms including PTEN loss increasing PD-L1 protein through PI3K/AKT effectors such as eIF4E and S6K1, NF-κB activated by IFN-γ or PMA inducing PIPK1-γ to elevate PD-L1 transcription in TNBC cells, and MYC binding to the PD-L1 promoter to increase PD-L1 expression (8). RAS/MAPK/ERK signaling also contributes to immune exclusion, and ongoing combination studies with immune checkpoint blockade evaluate PI3K/AKT or RAS/MAPK/ERK inhibitors to address this resistance (15). The relative contribution of these pathways is context dependent and they should not be interpreted as equivalent direct transcriptional regulators in every breast cancer subtype.

Epigenetic regulation. Epigenetic mechanisms regulate PD-L1 without altering the underlying DNA sequence, primarily by changing chromatin accessibility and transcriptional competence (4,5). DNA methylation and histone modifications regulate CD274, which encodes PD-L1, and specific patterns of these epigenetic marks correlate with distinct changes in PD-L1 expression. CpG island methylation within the CD274 promoter generally represses PD-L1 transcription, whereas promoter hypomethylation correlates with increased PD-L1 expression in breast cancer cells and in tumor-associated macrophages in TNBC models. Among histone modifications, H3K4me3 enrichment and increased histone H3 acetylation at the CD274 promoter coincide with transcriptional activation, whereas EZH2-mediated H3K27me3 deposition tracks with transcriptional repression.

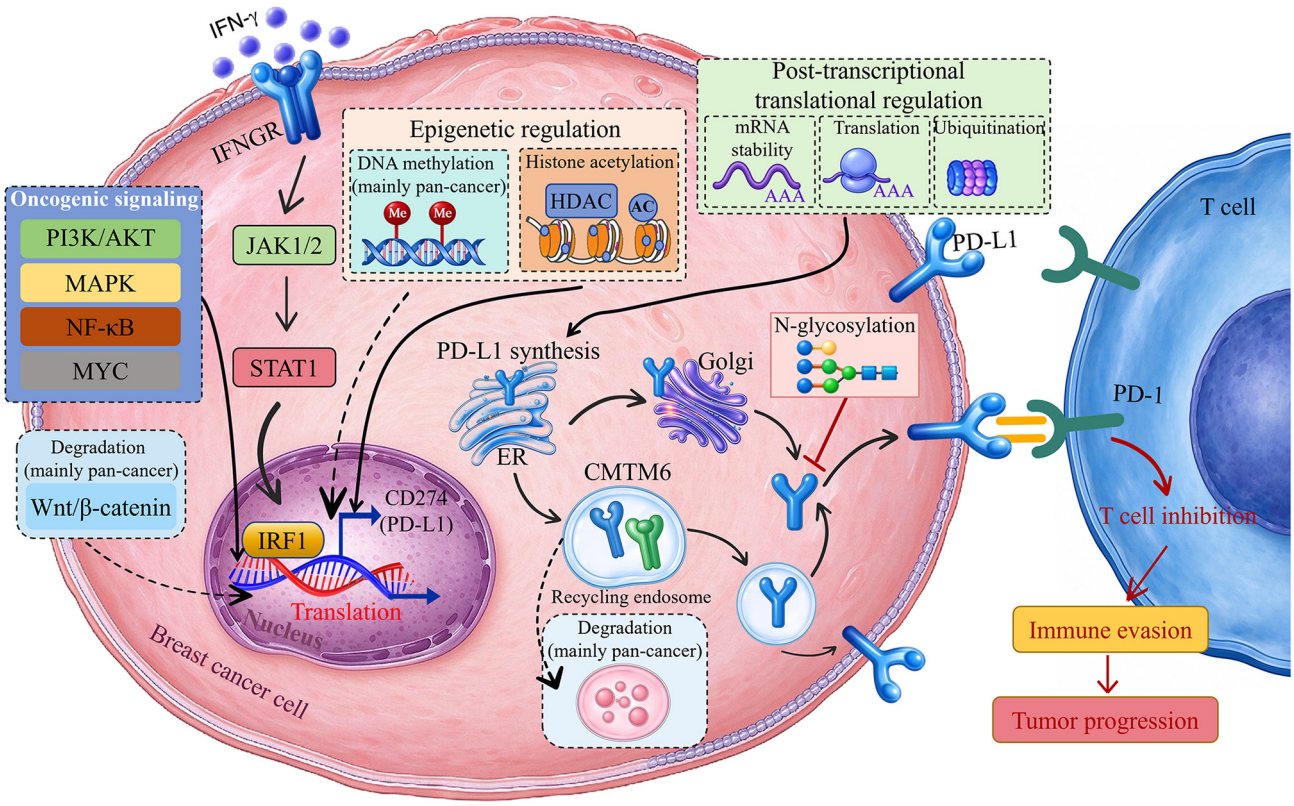


Figure 1. Multilevel regulation of PD-L1 expression and PD-1/PD-L1-mediated immune escape in breast cancer. HDAC, histone deacetylase; ER, endoplasmic reticulum; IRF1, interferon regulatory factor 1; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; CMTM6, CKLF-like MARVEL transmembrane domain-containing 6; IFNGR, IFN-γ receptor; JAK, Janus kinase; Me, methylation; Ac, acetylation.

Epigenetic modifications have been associated with variation in CD274 expression, representing reversible processes that can be therapeutically targeted (5,6,8). In TNBC models, histone deacetylase inhibition induces pyroptosis through the caspase 3-GSDME pathway, and pyroptotic TNBC cells release immunogenic substances that promote $CD8^+$ T cell and $CD11b^+$ myeloid cell infiltration and elevate intratumoral granzyme B, thereby shifting immunologically cold tumors toward an immune-infiltrated phenotype and providing a mechanistic rationale for combination strategies with immune checkpoint blockade (17). Such strategies remain investigational, and their net immune effect is context dependent.

Post-transcriptional and post-translational regulation. Beyond transcriptional and epigenetic control, PD-L1 is regulated at the translational and post-translational levels. Protein stabilization, ubiquitin-dependent degradation, endocytic recycling and glycosylation can alter the amount of functional PD-L1 at the cell surface, with higher surface PD-L1 enhancing PD-1-mediated T cell suppression and thereby promoting tumor immune evasion and contributing to resistance to PD-1/PD-L1 blockade (7,8,18). CKLF-like MARVEL transmembrane domain containing 6 has been implicated in PD-L1 stability and recycling across tumor models (8). N-linked glycosylation can further influence PD-L1 stability, trafficking and antibody recognition (18).

PD-1/PD-L1-mediated immune escape. Within the breast cancer TME, PD-L1 facilitates immune evasion through several interrelated mechanisms. These include direct suppression of effector T cell signaling, multicellular remodeling of an immunosuppressive microenvironment and tumor-intrinsic programs that alter immune recognition and the malignant phenotype (7,14,19). The relative contribution of each mechanism differs by subtype and disease setting, which helps explain why PD-L1 immunohistochemistry alone is an incomplete surrogate for immune responsiveness.

Direct T cell inhibition and microenvironmental suppression. PD-L1 expressed by tumor cells and ICs binds PD-1 on tumor-infiltrating effector T cells, attenuating downstream T cell receptor signaling, proliferation, cytokine secretion and cytotoxic function (7,8). In parallel, tumor-associated macrophages, regulatory T cells, suppressive myeloid populations, inhibitory cytokines, hypoxia, nutrient competition and stromal barriers can limit effective T-cell infiltration or function (14,15,19). Thus, PD-1/PD-L1 signaling acts within a broader suppressive ecosystem rather than as an isolated pathway.

Tumor-intrinsic immune-evasion programs. Preclinical breast cancer studies have associated PD-L1-related networks with stem-like states, epithelial-mesenchymal transition, invasion and therapy resistance (20-22). Oncogenic signaling and impaired antigen presentation can also reduce immune recognition despite detectable PD-L1 expression (8,14,15). These tumor-intrinsic processes are biologically relevant but should be distinguished from the more directly established inhibitory effect of PD-1/PD-L1 signaling on antitumor T cell responses.

Subtype-specific immune context. TNBC generally exhibits greater immune infiltration and more frequent PD-L1 positivity in clinically relevant assay contexts than

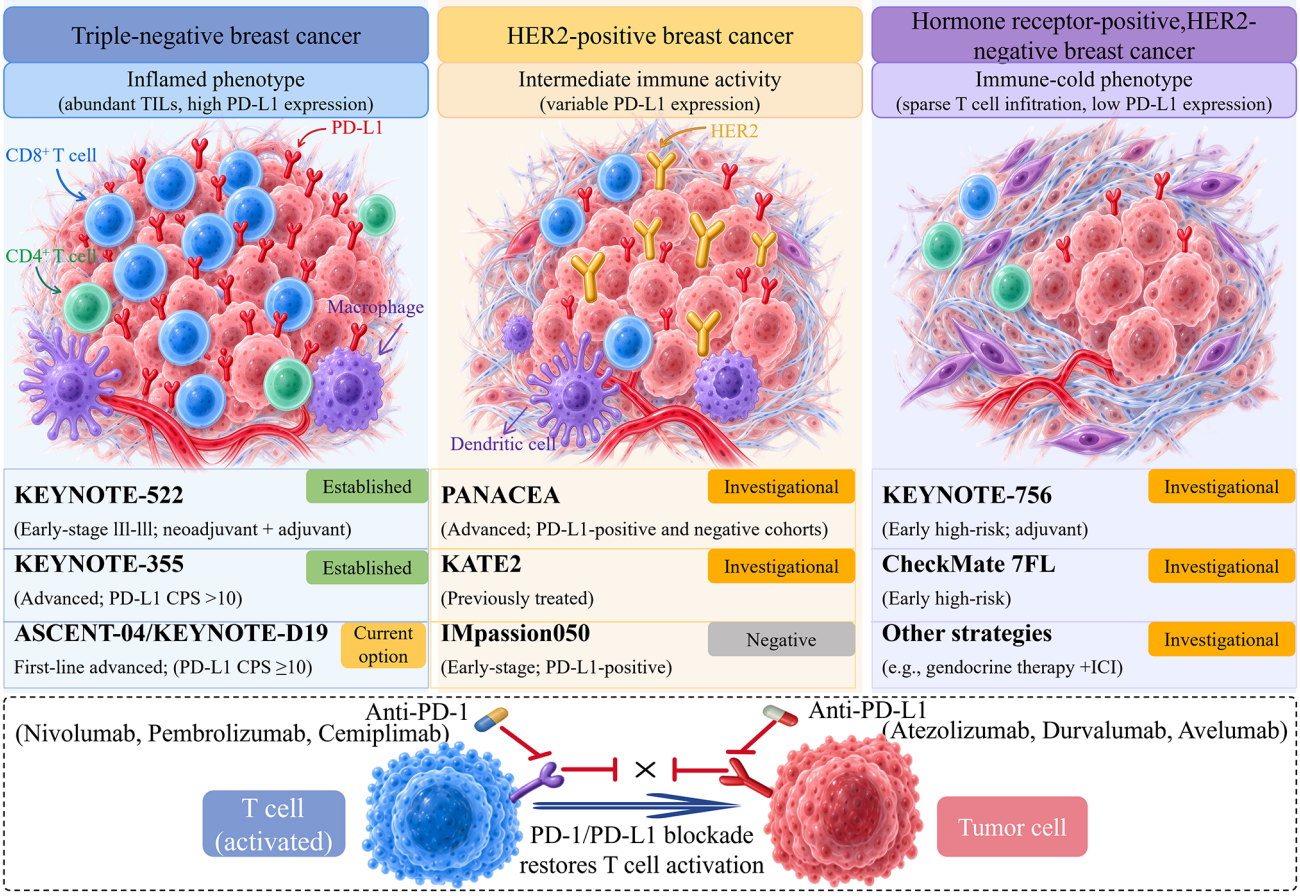


Figure 2. Subtype-specific immune ecosystems and clinical translation of PD-1/PD-L1 blockade in breast cancer. PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; ICI, immune checkpoint inhibitor; TILs, tumor-infiltrating lymphocytes; CPS, combined positive score.

other breast cancer subtypes, where these contexts refer to the 22C3 pharmDx assay with a CPS cutoff of 10 for pembrolizumab and the SP142 assay with an IC cutoff of 1% for atezolizumab (23-25). $HR^+/HER2^-$ breast cancer is more often immune-cold, although selected high-risk early tumors can be immunologically responsive, as demonstrated by recent neoadjuvant phase III trials (26,27). $HER2^+$ disease is immunologically heterogeneous whereby HER2-directed antibodies can themselves modify antitumor immunity through Fc-dependent effector functions and through immunogenic cell death associated with antibody drug conjugates (25,28). This subtype-specific context is clinically key since the strength and regulatory status of checkpoint inhibitor evidence differ substantially across breast cancer subtypes, with approved checkpoint inhibitor combinations in TNBC, whereas in $HER2^+$ and $HR^+/HER2^-$ disease, checkpoint inhibitor-based regimens remain under active clinical investigation and have not yet entered routine clinical practice

4. Subtype-specific clinical translation of the PD-1/PD-L1 blockade

The clinical value of PD-1/PD-L1 blockade varies according to molecular subtype, disease stage, treatment backbone, PD-L1 assay and regulatory context (Fig. 2). Fig. 2 visually maps this heterogeneity, contrasting the distinct immune microenvironments of TNBC, $HER2^+$ and $HR^+/HER2^-$ subtypes alongside the current evidence status of their respective key clinical trials. Table I summarizes major trials using an evidence hierarchy and separates established or regulatory supported regimens from investigational strategies.

TNBC

Advanced disease. In previously untreated unresectable locally recurrent or metastatic TNBC, KEYNOTE-355 established pembrolizumab plus chemotherapy for tumors with PD-L1 CPS ≥10 measured using the 22C3 assay. In this subgroup, the median overall survival (OS) time was 23.0 months with pembrolizumab plus chemotherapy vs. 16.1 months with chemotherapy alone [hazard ratio (HR), 0.73] (9). The phase III ASCENT-04/KEYNOTE-D19 trial subsequently compared sacituzumab govitecan plus pembrolizumab with chemotherapy plus pembrolizumab in first-line $PD\text{-}L1^+$ (CPS ≥10) advanced TNBC. The median PFS time was 11.2 vs. 7.8 months (HR, 0.65), whereas OS data were immature at the initial report (12). In June 2026, the U.S. FDA approved sacituzumab govitecan plus pembrolizumab for first-line unresectable locally advanced or metastatic TNBC with PD-L1 CPS ≥10 by an FDA-authorized test (13).

IMpassion130 used a different biomarker framework; atezolizumab plus nab-paclitaxel was evaluated with the SP142 IC algorithm and PD-L1 positivity defined as IC ≥1% (29). The U.S. TNBC indication was subsequently withdrawn, a decision that followed the failure of the IMpassion131 confirmatory

Table I. Major clinical trials of PD-1/PD-L1-directed therapy in breast cancer by molecular subtype and disease setting.

Subtype/setting	Trial (phase)	Population/PD-L1 selection	Regimen	Key outcome	Evidence/clinical status	Main limitation/ interpretation	(Refs.)
TNBC, advanced 1L	KEYNOTE-355 (III)	Previously untreated locally recurrent inoperable/metastasis; 22C3 CPS ≥10 for validated benefit	Pembrolizumab + chemotherapy vs. placebo + chemotherapy	OS, 23.0 vs. 16.1 months; HR, 0.73	Established biomarker-defined regimen	Limited to the tested conditions; results cannot be extrapolated to other assays or agents.	(8,9)
TNBC, advanced 1L	IMpassion130 (III)	Metastatic; SP142 IC≥1% subgroup	Atezolizumab + nab-paclitaxel vs. placebo + nab-paclitaxel	PD-L1$^+$ subgroup: PFS, 7.5 vs. 5.0 months; HR, 0.62	Region-dependent	U.S. TNBC indication withdrawn; EMA indication remains under specified conditions	(26-28)
TNBC, advanced 1L	ASCENT-04/ KEYNOTE-D19 (III)	Unresectable locally advanced/metastatic; CPS ≥10	Sacituzumab govitecan + pembrolizumab vs. chemo-therapy + pembrolizumab	PFS, 11.2 vs. 7.8 months; HR, 0.65; OS immature initially	FDA-approved first-line option (June 2026)	Specific to CPS≥10 population and current U.S. regulatory context	(11,12)
TNBC, early	KEYNOTE-522 (III)	Previously untreated stage II-III; no PD-L1 selection requirement	Neoadjuvant pembrolizumab + chemotherapy, then adjuvant pembrolizumab	60-month OS rate 86.6 vs. 81.7%; P=0.002	Established perioperative regimen	PD-L1 testing is not required for treatment selection; immune-related adverse events require monitoring	(9,10)
HER2$^+$, advanced	PANACEA (Ib/II)	Trastuzumab-resistant; PD-L1-positive and PD-L1-negative cohorts	Pembrolizumab + trastuzumab	ORR, 15% (6/40) in PD-L1$^+$; 0/12 in PD-L1	Investigational proof-of-concept	Single-arm and small; no chemotherapy in regimen	(29)
HER2$^+$, advanced	KATE2 (II)	Previously treated advanced HER2$^+$	Atezolizumab + T-DM1 vs. placebo + T-DM1	PFS, 8.2 vs. 6.8 months; HR, 0.82; P=0.33	Investigational	No notable ITT PFS benefit	(30)
HER2$^+$, early	IMpassion050 (III)	High-risk earlyHER2$^+$; PD-L1 status evaluated	Atezolizumab vs. placebo added to neoadjuvant anti-HER2 therapy + chemotherapy	pCR, 62.4 vs. 62.7% (atezolizumab vs. placebo) in ITT; no improvement	Negative rando-mized phase III evidence	Did not improve pCR; argues against broad routine ICI use	(31)

Table I. Continued.

Subtype/setting	Trial (phase)	Population/PD-L1 selection	Regimen	Key outcome	Evidence/clinical status	Main limitation/ interpretation	(Refs.)
$ER^+/HER2^-$, high-risk early	KEYNOTE-756 (III)	Grade 3 high-risk early disease	Neoadjuvant pembrolizumab + chemotherapy vs. placebo + chemotherapy; after surgery, adjuvant pembrolizumab/placebo + endocrine therapy	pCR, 24.3% vs. 15.6%; EFS immature at publication	Randomized phase III; pCR-positive, EFS immature at publication	Current ASCO guidance still centers endocrine therapy in stage I-III HR^+/HER2 disease	(23,32)
$ER^+/HER2^-$, high-risk early	CheckMate 7FL (III)	High-risk grade 2/3 disease	Neoadjuvant nivolumab + chemotherapy vs. placebo + chemotherapy; adjuvant endocrine therapy, with nivolumab continued in the intervention arm per protocol amendment	pCR, 24.5 vs. 13.8%; larger pCR effect in $PD\text{-}L1^+$ tumors and with higher baseline TILs	Randomized phase III; pCR-positive, long-term efficacy not established	EFS became exploratory after protocol amendment; endocrine therapy remains the foundation of stage I-III $HR^+/HER2^-$ treatment	(24,32)

TNBC, triple-negative breast cancer; HR, hormone receptor; ER, estrogen receptor; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; pCR, pathological complete response; CPS, combined positive score; IC, immune cell; TILs, tumor-infiltrating lymphocytes; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; EMA, European Medicines Agency; ASCO, American Society of Clinical Oncology; ORR, overall response rate; 1L, first line; ITT, intention-to-treat; FDA, U.S. Food and Drug Administration.

trial to replicate the PFS and OS benefit of IMpassion130 when nab-paclitaxel was replaced by paclitaxel, rather than any new safety signal (30,31). By contrast, the EMA continues to list atezolizumab plus nab-paclitaxel for PD-L1$^+$ unresectable locally advanced or metastatic TNBC under specified conditions (32). These distinctions are clinically notable as 'PD-L1$^+$ advanced TNBC' does not represent a single interchangeable category across agents, assays, thresholds, lines of therapy and jurisdictions, a point illustrated by the divergence between IMpassion130 and IMpassion131 and the resulting split between U.S. and EMA regulatory status (29-32).

Early-stage disease. In early-stage TNBC, KEYNOTE-522 established a different paradigm. Patients with previously untreated stage II-III TNBC received neoadjuvant pembrolizumab plus platinum-containing chemotherapy followed by surgery and adjuvant pembrolizumab. At ~5 years, the OS rate was 86.6% with the pembrolizumab regimen and 81.7% with placebo plus chemotherapy (P=0.002) (11). Notably, treatment selection in KEYNOTE-522 was not restricted to PD-L1$^+$ tumors (10,11). PD-L1 testing is mandated for treatment selection in advanced TNBC regimens, as recommended by the SITC guideline, whereas the perioperative KEYNOTE-522 strategy does not require PD-L1 assessment, as benefit is observed regardless of PD-L1 status (11,33).

HER2$^+$ breast cancer. The presence of PD-L1 expression and TILs in HER2$^+$ breast cancer has prompted clinical testing of checkpoint blockade combined with HER2-directed therapy, but the results have been inconsistent. In the PANACEA phase Ib/II trial, pembrolizumab plus trastuzumab was evaluated in trastuzumab-resistant advanced HER2$^+$ breast cancer; objective responses occurred in ~15% of patients who were PD-L1$^+$, whereas no objective response was observed in the PD-L1$^-$ cohort (34). In the randomized phase II KATE2 trial, atezolizumab plus trastuzumab emtansine did not significantly improve the PFS time in the intention-to-treat (ITT) population (8.2 vs. 6.8 months; HR, 0.82; P=0.33), although exploratory immune-enriched subgroups generated hypotheses for further study (35). Notably, the randomized phase III IMpassion050 trial on high-risk early HER2$^+$ breast cancer also did not observe an improved pathological complete response (pCR) when atezolizumab was added to neoadjuvant anti-HER2 therapy and chemotherapy (62.4 vs. 62.7% in the ITT population) (36). Collectively, these findings support continued biomarker-driven investigation rather than broad routine checkpoint inhibition across HER2$^+$ disease.

HR$^+$/HER2$^-$ breast cancer. HR$^+$/HER2$^-$ breast cancer generally exhibits lower immune infiltration and lower PD-L1 expression than TNBC, and single-agent checkpoint blockade with pembrolizumab or avelumab has demonstrated limited clinical activity in this subtype (37). However, recent randomized phase III neoadjuvant trials suggest that selected high-risk early HR$^+$/HER2$^-$ tumors may derive benefit from chemo-immunotherapy. In KEYNOTE-756, neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab plus endocrine therapy after surgery increased the pCR rate from 15.6 to 24.3% in patients with high-risk early HR$^+$/HER2$^-$ breast cancer; however, event free survival (EFS) data were immature at the time of the primary analysis, and longer follow-up is required to define the durability of clinical benefit (26). Similarly, CheckMate 7FL demonstrated an improvement in pCR with nivolumab-containing neoadjuvant chemo-immunotherapy, increasing pCR rates from 13.8 to 24.5%, with exploratory analyses suggesting greater benefit among PD-L1$^+$ tumors and tumors with higher baseline stromal TIL levels. However, due to protocol amendments and early termination, the EFS analysis was exploratory, and the study was not powered for a definitive assessment of EFS benefit (27). Current clinical guidelines continue to emphasize endocrine therapy as the backbone of systemic treatment for stage I-III HR$^+$/HER2$^-$ breast cancer and support individualized integration of emerging treatment strategies (38). Therefore, although these studies provide important evidence that immune-responsive subsets exist within HR$^+$/HER2$^-$ breast cancer, their findings should not yet be generalized to routine checkpoint inhibitor use across the entire HR$^+$/HER2$^-$ population.

5. Resistance biology and evidence-graded strategies to overcome resistance

Primary, adaptive and acquired resistance. Resistance to PD-1/PD-L1 blockade is not a single biological state and can be conceptualized as: i) Primary resistance, in which an effective antitumor immune response is not generated from treatment initiation; ii) adaptive resistance, in which compensatory suppressive mechanisms emerge during an active immune response; and iii) acquired resistance, in which disease progresses after an initial response or period of disease control (14,15). These categories overlap biologically but provide a clinically useful framework for organizing resistance mechanisms (Table II).

Primary resistance. Primary resistance may reflect insufficient tumor antigenicity, defective antigen presentation, low baseline T cell infiltration, oncogenic immune exclusion or physical exclusion by stromal and extracellular-matrix programs. Loss of major histocompatibility complex class I/β-2-microglobulin function and disruption of IFN-γ receptor/JAK signaling are mechanistically established routes to checkpoint resistance across different types of cancer. Their clinical prevalence in breast cancer remains undefined, although studies across cancer types have established these defects as routes to checkpoint resistance (39), and preclinical evidence from EMT6 murine mammary tumor models has shown that deletion of B2m, Jak1 or Psmb9 by CRISPR/Cas9, which respectively disable MHC class I surface expression, IFN-γ signal transduction and immunoproteasome-mediated antigen processing, renders EMT6 tumors that otherwise respond to checkpoint blockade refractory to both anti-PD-1 and anti-PD-L1 therapy (40). In breast cancer, immune-desert phenotypes, PI3K pathway activity, suppressive myeloid populations and stromal exclusion have more direct translational relevance (15,41).

Adaptive resistance. Adaptive resistance occurs when an ongoing immune response induces counter-regulatory programs. IFN-γ released by activated T cells can increase tumor PD-L1 expression, while tumors and ICs may upregulate alternative inhibitory pathways involving lymphocyte-activation gene 3, T cell immunoglobulin and

Table II. Resistance mechanisms to PD-1/PD-L1-directed therapy in breast cancer.

Mechanism	Resistance class	BC context	Evidence type	Evidence strength[a]	Biological implication	Key limitation	(Refs.)
Low antigenicity/ impaired antigen presentation (MHC-I/B2M)	Primary	Potentially all subtypes; clinical frequency incompletely defined	Strong pan-cancer mechanistic evidence + BC preclinical evidence (EMT6 B2m knockout)	Moderate	Failure of effective T cell recognition	Clinical prevalence and contribution in BC remain uncertain	(49,50)
IFN-γ receptor/ JAK1/2 signaling defects	Primary	Potentially all subtypes	Strong pan-cancer mechanistic evidence + BC preclinical evidence (EMT6 JAK1 knockout)	Moderate	Can blunt IFN-driven antigen presentation and immune recognition	BC clinical prevalence and contribution remain uncertain	(49,50)
PI3K/AKT-associated oncogenic immune suppression/ exclusion	Primary	Most studied in TNBC; HER2-linked signaling also relevant	BC preclinical/ translational + review evidence	Moderate	Reduces immune infiltration or promotes suppressive phenotype	Not a validated clinical resistance biomarker	(7,14)
Stromal and extracellular-matrix barriers/ T cell exclusion	Primary/ adaptive	Across subtypes; prominent in immune-cold tumors	Translational/preclinical	Moderate	Restricts effector-cell access to tumor	No standardized clinical assay	(13,33)
Suppressive myeloid cells (TAMs/MDSCs)	Primary/ adaptive	Strong rationale in TNBC	Translational + phase II pharmacodynamic evidence	Moderate	Macrophage programs can suppress T cell function	Randomized efficacy contribution not isolated	(33)
Tregs, inhibitory cytokines and metabolic constraints	Adaptive	Across subtypes	Preclinical/translational	Moderate-low	Maintains suppression despite T cell recruitment	Subtype specificity and actionable thresholds unresolved	(13,14)
Alternative checkpoints (LAG-3, TIM-3 and TIGIT-associated programs)	Adaptive	Potentially all; especially inflamed tumors under immune pressure	Preclinical/translational	Moderate-low	Compensatory inhibitory signaling	Limited prospective breast-specific validation	(13,14)
Antigen loss, altered presentation/ IFN signaling and clonal evolution	Acquired	Potentially all subtypes	Pan-cancer strong; breast longitudinal data sparse	Moderate-low for BC	Progression after initial response	Requires paired pretreatment/ progression sampling; BC longitudinal data remain sparse	(13,14, 49)

Table II. Continued.

Mechanism	Resistance class	BC context	Evidence type	Evidence strength[a]	Biological implication	Key limitation	(Refs.)
Spatial-temporal PD-L1 and immune heterogeneity	Acquired/measurement-related	Demonstrated in BC/TNBC	Breast pathology/translational	Moderate	Single biopsy may misclassify immune state	Assay, site and timing dependent	(34,35)

[a]Evidence strength was graded as moderate (pan-cancer mechanistic plus breast cancer-specific preclinical/translational data, or early-phase clinical evidence) and moderate-low (predominantly preclinical or lacking breast cancer-specific longitudinal validation). BC, breast cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; MHC-I, major histocompatibility complex class I; B2M, β2-microglobulin; JAK, Janus kinase; TAMs, tumor-associated macrophages; MDSCs, myeloid-derived suppressor cells; Tregs, regulatory T cells; TNBC, triple-negative BC; TIM-3, T cell immunoglobulin and mucin-domain containing-3; TIGIT, T cell immunoreceptor with Ig and ITIM domains; LAG-3, lymphocyte activating 3.

mucin-domain containing-3 or T cell immunoreceptor with Ig and ITIM domains associated programs (14,15). Expansion of tumor-associated macrophages, regulatory T cells and metabolic constraints can further suppress effector-cell function (42). These mechanisms are particularly relevant to tumors that remain T cell infiltrated but fail to sustain cytotoxic activity.

Acquired resistance. Acquired resistance can arise through clonal selection and evolution after an initial response to treatment. Potential acquired resistance mechanisms include antigen loss, impaired antigen presentation, altered IFN signaling, T cell dysfunction and compensatory immune suppression (14,15,39,40). Separately, breast-cancer studies demonstrate spatial and temporal heterogeneity in PD-L1 expression and discordance between primary and metastatic lesions (43,44). These observations are relevant to acquired resistance because PD-L1 status determined from a single biopsy at one site and one time point does not necessarily represent the tumor cell population that survives checkpoint blockade, and discordance among lesions reflects dynamic changes in PD-L1 expression during disease progression that can favor the emergence of subpopulations with reduced reliance on PD-L1-mediated immune suppression. Longitudinal breast-cancer tissue sampling remains limited, so mechanisms proven in other malignancies should not be assumed to occur at the same frequency in each breast cancer subtype.

Clinically prioritized resistance overcoming strategies. Therapeutic strategies should be interpreted based on the evidence summarized in Table III. Among the strategies reviewed in the present article, phase III randomized evidence is available from ASCENT-04/KEYNOTE-D19, in which sacituzumab govitecan plus pembrolizumab improved PFS vs. chemotherapy plus pembrolizumab in first-line PD-L1^{+} advanced TNBC (12). This result supports an antibody-drug conjugate checkpoint strategy in a biomarker-defined population and has already changed U.S. regulatory options (13).

Several mechanistically rational approaches have earlier phase breast cancer evidence. In the phase II MARIO-3 study, the PI3K-γ inhibitor eganelisib combined with atezolizumab and nab-paclitaxel was associated with macrophage reprogramming, immune activation and extracellular matrix remodeling in frontline metastatic TNBC (41). Camrelizumab plus the VEGFR2 inhibitor apatinib demonstrated clinical activity in an open-label phase II TNBC study (42). In MEDIOLA, olaparib plus durvalumab achieved a 12-week disease control rate of 80% (24/30 activity evaluable patients), although the non-randomized design does not isolate the contribution of durvalumab (43). More recently, a phase II study in anti-PD-1-refractory metastatic TNBC reported a confirmed objective response rate of 50% for cromolyn plus an anti-PD-1 backbone, providing proof-of-concept for an antigen-presenting mast-cell-directed resistance strategy (44).

Exploratory and preclinical approaches. Exploratory approaches should be clearly separated from clinically validated strategies. Nanomedicine platforms have been developed to improve tumor targeting, co-deliver chemotherapy and checkpoint blockade or remodel the TME in breast cancer models (45-48). These studies provide useful mechanistic

Table III. Strategies to overcome resistance to PD-1/PD-L1-directed therapy in breast cancer.

Strategy	Representative evidence	Subtype/setting	Evidence stage	Key observation	Evidence weight	Limitation/ interpretation	(Refs.)
ADC + PD-1 blockade	Sacituzumab govitecan + pembrolizumab (ASCENT-04/ KEYNOTE-D19)	PD-L1^{+} advanced TNBC, first-line	Phase III randomized	PFS, 11.2 vs. 7.8 months vs. chemotherapy + pembrolizumab	High	Biomarker- and setting-specific; OS initially immature	(11,12)
Myeloid/ PI3K-γ modulation	Eganelisib + atezolizumab + nab-paclitaxel (MARIO-3)	Frontline metastatic TNBC	Phase II clinical/ translational	Macrophage reprogramming, immune activation and ECM remodeling	Moderate-early	No randomized comparator; cross-trial comparisons are hypothesis-generating	(33)
Anti-angiogenic + PD-1 blockade	Camrelizumab + apatinib	Advanced TNBC	Open-label phase II	Clinical activity reported	Moderate-early	Small nonrandomized study; regimen not equivalent to pembrolizumab-based standards	(36)
PARP + PD-L1 blockade	Olaparib + durvalumab (MEDIOLA)	gBRCA-mutated HER2^{-} metastatic BC	Phase I/II basket cohort	12-week disease-control rate 80% (24/30 activity-evaluable patients)	Moderate-early	No randomized comparator to isolate durvalumab contribution	(37)
Mast-cell-directed strategy	Cromolyn + anti-PD-1 backbone	Anti-PD-1-refractory metastatic TNBC	Phase II	Confirmed ORR 50% in reported cromolyn arm	Moderate-early	Needs external validation and larger randomized testing	(38)
Nanomedicine/ local delivery	Anti-PD-L1-functionalized liposomes, hydrogel/ nanocapsules and responsive nanoplatforms	Mostly TNBC/ breast tumor models	Preclinical	Improved local delivery and/or TME reprogramming in models	Low/ exploratory	No established clinical efficacy; heterogeneous platforms	(39-42)
Natural compounds	Natural-compound approaches targeting PD-L1-related signaling or stemness/immune-evasion networks	Not clinically established	*In vitro*/ preclinical	*In vitro*/preclinical modulation of PD-L1-related pathways reported	Low/ exploratory	Review-level preclinical evidence; should not be described as a clinically validated sensitization strategy	(7,19)

ADC, antibody-drug conjugate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PARP, poly(ADP-ribose) polymerase; gBRCA, germline BRCA mutation; ECM, extracellular matrix; TME, tumor microenvironment; TNBC, triple-negative breast cancer; PFS, progression free survival; OS, overall survival; ORR, overall response rate.

Table IV. PD-L1 assays and complementary biomarkers for PD-1/PD-L1-directed therapy in breast cancer.

Biomarker/ score	Definition/assay concept	Current BC role	Evidence strength	Main limitations	(Refs.)
PD-L1 22C3 CPS	(PD-L1$^+$ tumor cells + lymphocytes + macrophages)/viable tumor cells x100 (score capped at 100)	Validated selection for pembrolizumab + chemotherapy in advanced TNBC at CPS≥10; current U.S. SG + pembrolizumab selection	Clinical companion-diagnostic context	Preanalytic and sampling variability; site/time heterogeneity; not interchangeable with IC/TPS	(8,9,12,43)
PD-L1 SP142 IC	% tumor area occupied by PD-L1$^+$ tumor-infiltrating immune cells	Used in IMpassion130; current clinical relevance depends on atezolizumab regulatory context	Clinical evidence in atezolizumab program	Different positive prevalence vs. 22C3; jurisdiction-specific regimen status	(26,28,43)
PD-L1 TPS	% viable tumor cells with membranous PD-L1 staining	Common in other malignancies; not principal selection algorithm for established TNBC ICI regimens	Standardized concept	May underrepresent immune-cell PD-L1; no established breast-specific treatment threshold	(44)
Stromal TILs	% stromal area occupied by mononuclear inflammatory cells on H&E	Prognostic and biologically informative, especially TNBC/HER2$^+$	Breast-specific standardized methodology	No universal ICI-selection cut-off; sampling/observer variation	(13,45)
TMB	Somatic mutations per megabase; platform dependent	Potential response-enrichment biomarker; limited BC-specific prospective data	Biological rationale + phase II basket signal	High TMB uncommon; platform/ cut-off heterogeneity; small BC cohort	(13,46)
ctDNA	Tumor-derived DNA detected in plasma	Dynamic response/MRD monitoring research	Prospective MRD-monitoring evidence; clinical utility remains investigational	Timing, assay sensitivity and actionability not standardized; c-TRAK TN demonstrated implementation challenges	(13,47)
Exosomal PD-L1	PD-L1 protein/RNA associated with extracellular vesicles	Investigational complementary biomarker	Early translational/ predominantly pan-cancer evidence	Isolation/detection heterogeneity; clinically validated thresholds and prospective BC-specific validation lacking	(48)

BC, breast cancer; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; CPS, combined positive score; IC, immune cell; TPS, tumor proportion score; TILs, tumor-infiltrating lymphocytes; TMB, tumor mutational burden; ctDNA, circulating tumor DNA; MRD, minimal residual disease; ICI, immune checkpoint inhibitor; TNBC, triple-negative breast cancer.

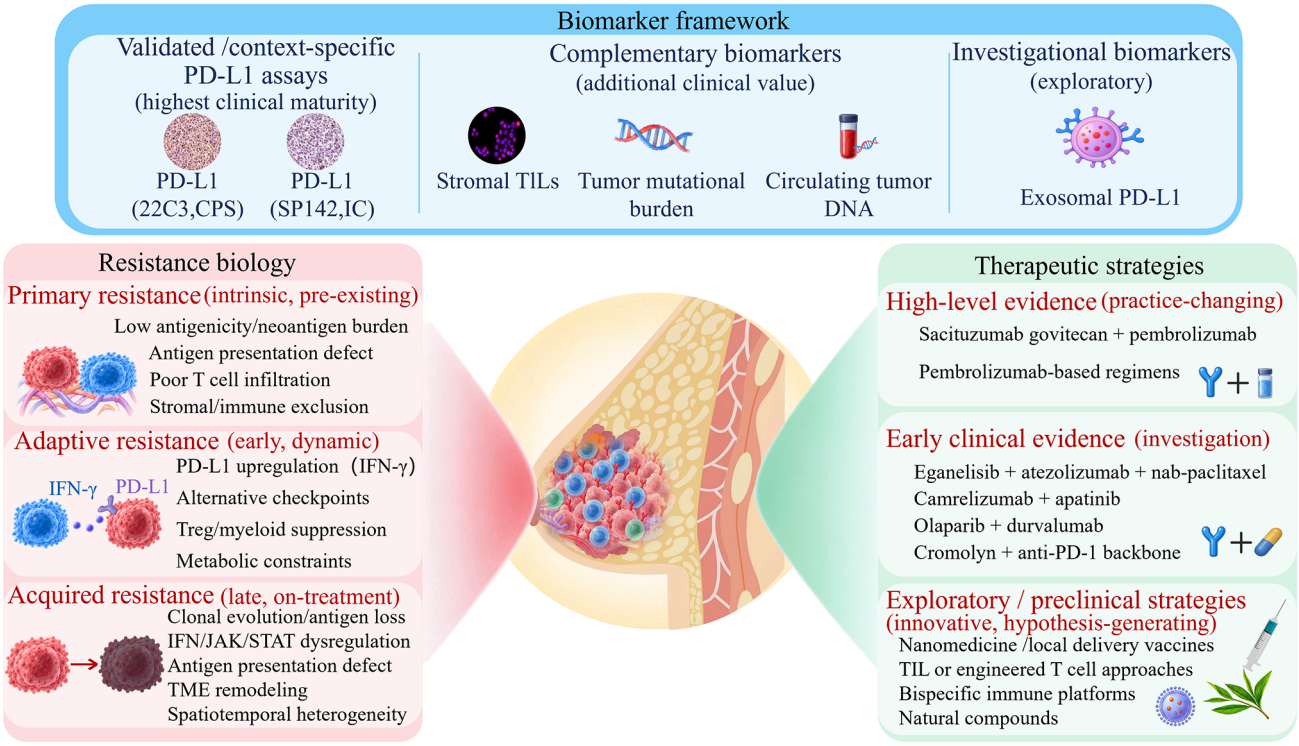


Figure 3. Integrated resistance, biomarker and evidence-graded strategy framework for PD-1/PD-L1-directed therapy in breast cancer. PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; TME, tumor microenvironment; CPS, combined positive score; Treg, regulatory T cells; JAK, Janus kinase.

concepts but remain preclinical. Vaccines, TIL-based approaches, engineered T cell strategies and bispecific immune platforms are also being explored in breast cancer, but their development is notably lower than that of approved checkpoint-based TNBC regimens and they should be discussed as emerging modalities rather than established sensitization strategies (3,4,19). Likewise, natural compounds reported to interfere with PD-1/PD-L1-related signaling or interaction should be regarded as hypothesis-generating *in vitro* evidence rather than clinical sensitizers (8,20). Maintaining this distinction prevents experimental innovations from being assigned the same weight as randomized clinical trials.

6. PD-L1 testing and complementary biomarkers

With the clinical success of immune checkpoint inhibitors (ICIs) in breast cancer, patient selection, efficacy prediction and resistance monitoring have become central translational challenges. PD-L1 is an established biomarker in specific advanced TNBC settings, and its clinical meaning depends on the assay, scoring algorithm, disease setting and treatment regimen (5,14). Table IV summarizes the principal PD-L1 scoring systems and complementary biomarkers discussed in the present section.

PD-L1 assays and scoring systems. The 22C3 CPS is calculated as (the number of PD-L1-stained tumor cells, lymphocytes and macrophages/the total number of viable tumor cells) x100, with the reported CPS capped at 100. CPS ≥10 is the validated selection threshold for pembrolizumab plus chemotherapy in advanced TNBC and for the current U.S. sacituzumab govitecan plus pembrolizumab indication (9,10,13). The SP142 IC score instead estimates the percentage tumor area occupied by PD-L1$^+$ tumor-infiltrating ICs and was used with an IC≥1% threshold in IMpassion130 (29,32). The tumor proportion score measures the percentage of viable tumor cells with membranous PD-L1 staining and is widely used in other tumor types, but it is not the principal validated selection algorithm for established breast cancer ICI regimens. Direct comparison studies demonstrate that assay/scoring combinations are not analytically interchangeable (49,50).

Spatial-temporal heterogeneity and sampling. Spatial and temporal heterogeneity further complicate PD-L1 assessment. PD-L1 expression can differ across regions of the same tumor and between primary and metastatic lesions (43,44). For instance, paired TNBC analyses using 22C3 and SP142 have demonstrated discordance between primary and metastatic samples, with assay-dependent agreement and a subset of PD-L1-negative primary tumors corresponding to PD-L1-positive metastases (44). Consequently, specimen site, biopsy timing, prior therapy, tissue adequacy, antibody clone, platform and scoring algorithm should all be reported when PD-L1 status is interpreted.

Complementary biomarkers. Complementary biomarkers provide additional biological information but also have limitations. Stromal TILs can be assessed using standardized histopathological methods and have established prognostic relevance, particularly in TNBC and HER2$^+$ disease (14,51), but there is no universal TIL cut-off validated to select patients for PD-1/PD-L1 blockade. High tumor mutational

burden (TMB) may enrich for response in a subset of metastatic breast cancer, as suggested by the TAPUR cohort, but high TMB is uncommon and platform/cut-off heterogeneity limits broad application (14,52). Circulating tumor DNA is being investigated for molecular-residual-disease monitoring; the c-TRAK TN trial highlighted challenges related to rapid relapse, timing of detection and the actionability of a positive result (53). Exosomal PD-L1 is biologically appealing as a non-invasive biomarker; however, current evidence is predominantly pan-cancer, and isolation/detection methods and clinically validated thresholds remain heterogeneous (54). Prospective breast cancer-specific validation is still required. These limitations support development of multiparametric biomarker models rather than substitution of one unvalidated marker for regimen-specific PD-L1 testing. An integrated framework linking resistance states, biomarker interpretation and evidence-graded resistance overcoming strategies is summarized in Fig. 3.

7. Conclusions and future directions

PD-1/PD-L1 blockade has become a key component of breast cancer therapy, but its clinical maturity is highly uneven across subtypes. In advanced TNBC, pembrolizumab-based treatment is linked to the 22C3 CPS ≥10 biomarker context, and sacituzumab govitecan plus pembrolizumab now has phase III evidence and a U.S. first-line indication for CPS ≥10 disease (8,9,11,12). In high-risk early TNBC, perioperative pembrolizumab improves long-term outcomes without requiring PD-L1 positivity for treatment selection (10). By contrast, $HER2^+$ and $HR^+/HER2^-$ breast cancer types contain immunologically responsive subsets but currently have less mature and more context-dependent checkpoint inhibitor evidence (23,24,29-32).

Future progress will depend on four linked priorities: i) Defining resistance mechanisms with longitudinal breast cancer-specific samples rather than relying predominantly on pan-cancer inference; ii) standardizing the interpretation of PD-L1 assays while integrating complementary immune, genomic and liquid-biopsy biomarkers; iii) testing mechanistically rational combinations in biomarker-enriched randomized trials; and iv) determining whether emerging delivery, cellular or vaccine-based platforms add clinically meaningful benefit beyond contemporary systemic therapy. Therefore, a subty pe-stage-biomarker-evidence framework provides a more clinically useful way to interpret the rapidly expanding PD-1/PD-L1 literature while preserving a clear distinction between established practice, investigational clinical strategies and preclinical concepts.

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Authors' contributions

WZha and JL conceived and designed the review, performed the literature search and screening, analyzed and interpreted the relevant literature, drafted the original manuscript and revised the manuscript. HZ, LL, XG, WZhu and HL contributed to the literature collection, data extraction, reference checking and manuscript revision. LY contributed to the conceptualization and supervision of the project and critically revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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