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Perspective

Neoadjuvant Immunotherapy in Triple-Negative Breast Cancer: Striking Potential or Need for Caution?

Panni Li[1,2#], Xianan Guo[1,2#], Wenhui Ruan[3,4], Jing Guo[5], Wei Wu[6*], Yiding Chen[1,2*], Yunxiang Zhou[1,2*]

[1]Department of Breast Surgery and Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China. [2]Cancer Institute (Key Laboratory of Cancer Prevention and Intervention, China National Ministry of Education), The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China. [3]Department of Thyroid and Breast Surgery, People's Hospital of Anji, Huzhou, Zhejiang, China. [4]Department of Thyroid and Breast Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China. [5]Department of Microbiology and Immunology, Stanford University School Medicine, Stanford, CA, 94305, USA.[6]Department of Medical Oncology, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou, Zhejiang, China.

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ABSTRACT: Triple-negative breast cancer (TNBC) is an aggressive malignancy with limited targeted therapies and a substantial unmet clinical need. Immunotherapy has emerged as a transformative frontier in TNBC, with immune checkpoint inhibitors (ICIs) representing a major category of this approach. The KEYNOTE-522 trial established pembrolizumab, an ICI, combined with chemotherapy as a standard neoadjuvant regimen for TNBC. However, the clinical outcomes of neoadjuvant immunotherapy-containing regimens are influenced by multiple factors, including the specific immunotherapeutic agents employed, companion strategies (such as distinct chemotherapy backbones or antibody-drug conjugates), patient characteristics, and trial design. Therefore, the implementation of neoadjuvant immunotherapy in broader clinical practice should be approached with caution. Elderly patients (≥65 years, over one-quarter of all breast cancer cases) may experience reduced efficacy from immunotherapy due to immunosenescence and are more susceptible to treatment-associated toxicity. Leveraging the neoadjuvant setting for biomarker-driven risk stratification will be essential to guide age-tailored treatment optimization and minimize unnecessary toxicity. This perspective highlights the opportunities and challenges associated with neoadjuvant immunotherapy in TNBC and outlines future directions for optimizing its clinical application.

Keywords: triple-negative breast cancer, neoadjuvant immunotherapy, immune checkpoint inhibitor, elderly patient, antibody-drug conjugate, biomarker

Introduction

Breast cancer is the most frequently diagnosed malignancy worldwide and ranks as the fourth highest cause of cancer-related mortality [1]. Triple-negative breast cancer (TNBC), characterized by absent expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), accounts for 15–20% of all breast cancers but is disproportionately responsible for nearly 40% of breast cancer-related deaths [2]. Because of its aggressive biology and lack of effective targeted options, TNBC has long been considered the subtype of breast malignancy with the greatest unmet clinical need [3].

***Correspondence should be addressed to:** Dr. Yunxiang Zhou (Email: yxzhou@zju.edu.cn) and Dr. Yiding Chen (Email: ydchen@zju.edu.cn), The Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang, China. Dr. Wei Wu, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine, Chinese Academy of Sciences, Zhejiang, China. Email: onco_wuwei@zju.edu.cn.
#These authors contributed equally to this study.

Biologically, TNBC is characterized by distinctive immunological features, including higher levels of immune cell infiltration, elevated programmed death-ligand 1 (PD-L1) expression, pronounced genomic instability, and an increased mutational burden relative to other breast cancer subtypes [4-7]. As such, these features make immunotherapeutic approaches more favorable for treating TNBC. PD-1/PD-L1 immune checkpoint inhibitor (ICI)-based immunotherapy has demonstrated clinical efficacy in advanced TNBC, which has motivated further studies to investigate immunotherapy in TNBC patients at earlier disease stages [8].

To date, pembrolizumab plus neoadjuvant chemotherapy followed by pembrolizumab monotherapy as adjuvant therapy has achieved remarkable success in patients with high-risk early-stage TNBC and has become the standard of care (SoC). However, no other immunotherapy-containing neoadjuvant regimens have been able to replicate this success, underscoring that neoadjuvant immunotherapy in TNBC, while holding striking potential, still warrants cautious optimism.

From mechanistic rationale to clinical standard of care

The neoadjuvant setting may be an especially favorable clinical context for the application of immunotherapy, as the tumor microenvironment is immunologically active at this stage, and systemic immunity remains largely intact before the establishment of multiple immune escape mechanisms [9-11]. Consequently, clinical research on immunotherapy-containing neoadjuvant regimens in TNBC has expanded considerably in recent years, with key trials summarized in Table 1.

Table 1. Clinical trials with disclosed data on immunotherapy-containing neoadjuvant regimens in triple-negative breast cancer (TNBC).

Trial	Study Start	Phase	Population	Size	Neoadjuvant Regimen	Pcr Rate	Adjuvant Regimen	Survival/Safety	Ref
Anthracycline-Containing Neoadjuvant Immunochemotherapy									
I-SPY 2 (NCT01042379)	2015	II	Stage II-III HER2-negative breast cancer	114 TNBC	Arm A (n = 29): pembrolizumab + wP → AC; Arm B (n = 85): wP → AC	60% vs. 22%	TPC or SoC in both arms	EFS was not significantly improved	[12]
GeparNuevo (NCT02685059)	2016	II	Stage I-III TNBC	174	Arm A (n = 88): durvalumab + wnab-P → durvalumab + ddEC; Arm B (n = 86): placebo + wnab-P → placebo + ddEC	Overall: 53.4% vs. 44.2% (*P* = 0.287); Window cohort: 61.0% vs. 41.4% (***P* = 0.035**)	TPC without durvalumab in both arms	3-year iDFS: 85.6% vs. 77.2% (***P* = 0.036**); 3-year DDFS: 91.7% vs. 78.4% (***P* = 0.005**); 3-year OS: 95.2% vs. 83.5% (***P* = 0.006**); Comparable AEs	pCR [13], 3-year survival [14], biomarker [15, 16]
NCT02530489	2016	II	Stage I-III AC-resistant TNBC	37	Atezolizumab + nab-P	32.4%	Atezolizumab	NA	[17]
KEYNOTE-522 (NCT03036488)	2017	**III**	Stage II-III TNBC	1174	Arm A (n = 784): pembrolizumab + PCb → pembrolizumab + AC/EC; Arm B (n = 390): placebo + PCb → placebo + AC/EC	64.8% vs. 51.2% (***P* < 0.001**)	Arm A: pembrolizumab; Arm B: placebo	5-year EFS: 81.2% vs. 72.2% (***P* < 0.001**); 5-year OS: 86.6% vs. 81.7% (***P* = 0.002**); Grade ≥3 TRAEs: 78.0% vs. 73.0%	pCR [18], 3-year survival [19], 5-year survival [20]
GeparDouze (NCT03281954)	2017	**III**	Stage II-III TNBC	1550	Arm A (n = 773): atezolizumab + wPCb → atezolizumab + AC/EC; Arm B (n = 777): placebo + wPCb → placebo + AC/EC	63.3% vs. 57.0% (***P* = 0.009**)	Arm A: atezolizumab; Arm B: placebo	4-year EFS: 85.2% vs. 81.9% (*P* = 0.08); 4-year OS: 90.2% vs. 89.5%; Grade ≥3 TEAEs: 75.3% vs. 73.4%	[21]

IMpassion031 (NCT03197935)	2017	**III**	Stage II-III TNBC	333	Arm A (n = 165): atezolizumab + wnab-P → atezolizumab + ddAC; Arm B (n = 168): placebo + wnab-P → placebo + ddAC	58% vs. 41% (***P* = 0.0044**)	Arm A: atezolizumab + SoC; Arm B: SoC	2-year EFS and OS were not significantly improved; Grade ≥3 TRAEs: 56.7% vs. 53.3%	pCR [22], 2-year survival [23]
CamRelief (NCT04613674)	2020	**III**	Stage II-III TNBC	441	Arm A (n = 222): camrelizumab + nab-PCb → camrelizumab + EC; Arm B (n = 219): placebo + nab-PCb → placebo + EC	56.8% vs. 44.7% (***P* = 0.004**)	Arm A: camrelizumab + SoC; Arm B: SoC; camrelizumab prohibited	Grade ≥3 AEs: 89.2% vs. 83.1%	[24]
NCT04213898	2020	II	Stage II-III TNBC	39	Camrelizumab + nab-P + E	64.1%	TPC	Grade ≥3 TRAEs: 76.9%	[25]
TREND (CHICTR2000035262)	2020	II	Early-stage TNBC	44 EES	Tislelizumab + nab-P → tislelizumab + EC	68.2%	NA	Grade ≥3 TRAEs: 11.3%	[26]
Neotennis (NCT04418154)	2020	II	Stage II-III TNBC	70	ddEC → toripalimab + wnab-P	55.7%	SoC	Grade ≥3 AEs: 22.9%	[27]
NeoMono (NCT04770272)	2021	II	Stage I-III TNBC larger than 10 mm	359	Arm A (n = 180): 2-week atezolizumab → atezolizumab + wPCb → atezolizumab + EC; Arm B (n = 179): atezolizumab + wPCb → atezolizumab + EC	Overall: 65.7% vs. 69.0%; PD-L1^{+} subgroup : 91.5% vs. 82.2%	SoC in both arms	Comparable in both arms	[28]
Anthracycline-Free Neoadjuvant Immunochemotherapy									
NeoTRIP (NCT002620280)	2016	**III**	Early-stage TNBC	280	Arm A (n = 138): atezolizumab + nab-PCb; Arm B (n = 142): nab-PCb	48.6% vs. 44.4% (*P* = 0.48)	Anthracycline regimen in both arms	5-year EFS: 70.6% vs. 74.9% (*P* = 0.76)	pCR [29], 5-year survival [30], biomarker [31]
NCI 10013	2017	II	Stage II-III TNBC	67	Arm A (n = 45): atezolizumab + wPCb; Arm B (n = 22): wPCb	55.6% vs. 18.8% (***P* = 0.018**)	ddAC in both arms	Grade ≥3 TRAEs: 57.8% vs. 62.5%	[32]
NeoPACT (NCT03639948)	2018	II	Stage I-III TNBC	115	Pembrolizumab + TCb	57.7%	TPC	Estimated 3-year EFS: 86%; Estimated 3-year OS: 89%; Grade ≥3 TRAEs: 26.9%	[33]
cTRIO (CHICTR2100041675)	2021	II	Stage II-III TNBC	62	Tislelizumab + nab-PCb	62.0%	Tislelizumab	Grade ≥3 TRAEs: 54%	[34]
CABIN (CHICTR2200067005)	2023	II	Stage I-III TNBC	29	Cadonilimab + nab-PCb	65.5%	NA	Grade ≥3 TRAEs: 51.7%	[35]
Novel Immunotherapy-Containing Neoadjuvant Regimens									

I-SPY 2 (NCT01042379)	2018	II	Stage II-III HER2-negative breast cancer	163 TNBC	Arm A (n = 21): durvalumab + olaparib + wP → AC; Arm B (n = 142): wP → AC	47% vs. 27%	TPC or SoC in both arms	Grade ≥3 AEs: 56.2% vs. 34.1%	[36]
CHARIOT (ACTRN12617000651381)	2018	II	Stage III anthracycline-resistant TNBC	34	Nivolumab + ipilimumab + wP	24.2%	Nivolumab	Estimated 1-year EFS: 85%; Estimated 1-year OS: 94%; Grade ≥3 AEs: 45.5%	[37]
BELLINI (NCT03815890)	2019	II	cT1c–2N0M0 TNBC with TILs ≥50%	15	Nivolumab + ipilimumab	33.3%	Chemotherapy in non-pCR pts	Grade ≥3 TRAEs: 40.0%	[38]
NeoSACT (NCT04877821)	2021	II	Stage II-III TNBC	29	Sintilimab + anlotinib + nab-PCb → sintilimab + anlotinib + EC	69.0%	Sintilimab + SoC	Estimated 2-year EFS: 92.4%; Grade ≥3 AEs: 31.0%	[39]
I-SPY2.2 (NCT01042379)	2022	II	Early HER2-negative breast cancer	64 TNBC	Durvalumab + Dato-DXd → P-based → AC	61.9%	TPC	2/5 pts discontinued Dato-DXd/ durvalumab	[40]
NeoSTAR (NCT04230109)	2023	II	Early-stage TNBC	50	Pembrolizumab + SG → TPC	32.0% → 50.0%	NA	Grade ≥3 AEs: 40.0%	[41]

Abbreviations: pCR: pathological complete response; Ref: reference; HER2: human epidermal growth factor receptor 2; wP: weekly paclitaxel; AC: doxorubicin and cyclophosphamide; TPC: treatment of physician's choice; SoC: standard of care; EFS: event-free survival; wnab-P: weekly nanoparticle albumin-bound paclitaxel; dd: dose-dense; EC: epirubicin and cyclophosphamide; iDFS: invasive disease-free survival; DDFS: distant disease-free survival; OS: overall survival; AEs: adverse events; NA: not available; PCb: paclitaxel and carboplatin; TRAEs: treatment-related adverse events; TEAEs: treatment-emergent adverse events; EES: efficacy evaluable set; PD-L1: programmed death-ligand 1; TCb: docetaxel and carboplatin; TILs: tumor-infiltrating lymphocytes; pts: patients; Dato-DXd: datopotamab deruxtecan; SG: sacituzumab govitecan

The practice-changing phase III randomized, double-blind KEYNOTE-522 trial investigated the addition of pembrolizumab to standard neoadjuvant chemotherapy in early-stage TNBC [18]. The combination treatment improved the rates of pathological complete response (pCR) [18] and significantly prolonged 3-year event-free survival (EFS) [19] compared with chemotherapy alone. Notably, the EFS benefit was independent of PD-L1 status [19]. In 2021, as a result of these findings, the U.S. Food and Drug Administration (FDA) approved pembrolizumab plus chemotherapy as a combination neoadjuvant therapy, followed by pembrolizumab monotherapy as adjuvant therapy for patients with high-risk early-stage TNBC. The recently reported final survival data from the KEYNOTE-522 trial further confirmed a sustained EFS benefit and demonstrated a significant improvement in overall survival (OS) [20].

Unfortunate failure to reproduce a landmark success

Following the encouraging results observed with pembrolizumab therapy, further investigations using other PD-1/PD-L1 inhibitors have been conducted, albeit with varying degrees of success. For example, atezolizumab [21, 22] and camrelizumab [24] have both shown encouraging clinical activity in phase III trials, with significant improvements in pCR rates when administered in addition to neoadjuvant chemotherapy. However, EFS and OS were not significantly improved with atezolizumab [21, 23], and survival data for camrelizumab have not yet been reported [24]. Conversely and unexpectedly, the findings of the phase II GeparNuevo trial demonstrated meaningful long-term survival gains with combination therapy, despite only a modest increase in pCR and even without continued adjuvant durvalumab therapy [13, 14].

Indeed, among patients with high-risk early-stage TNBC, only the KEYNOTE-522 trial has confirmed the efficacy of pembrolizumab when administered as neoadjuvant therapy followed by adjuvant therapy, significantly improving pCR, EFS, and OS; a success that has not been reproduced with other PD-1 or PD-L1 inhibitors to date.

Caution amid the complexity of neoadjuvant immunotherapy

While the above data seem to suggest differential effects among ICIs, the same ICI has also yielded variable outcomes across different clinical trials. For instance, phase III trials of atezolizumab combined with neoadjuvant chemotherapy (GeparDouze [21], IMpassion031 [22], and NeoTRIP [29]) have produced

inconsistent results in terms of pCR improvement, as NeoTRIP failed to show significant improvement while the other two trials did. One important reason for the inconsistent results may lie in differences in trial design, including the neoadjuvant chemotherapy regimens used in the immunochemotherapy combinations and the dosing schedules across studies. Specifically, NeoTRIP employed an anthracycline-free chemotherapy regimen consisting of paclitaxel plus carboplatin for eight cycles (24 weeks), with anthracyclines administered postoperatively as adjuvant therapy. In contrast, IMpassion031 and GeparDouze both incorporated taxane-based chemotherapy followed by anthracyclines and cyclophosphamide, although IMpassion031 omitted carboplatin and administered the drugs on a biweekly schedule. In addition, baseline patient characteristics may have contributed to the divergent results. Exploratory analyses of the NeoTRIP trial suggested that baseline imbalances in stromal and intratumoral tumor-infiltrating lymphocytes (TILs) between the two arms could have reduced the expected increase in pCR rates with immunotherapy [31].

Correspondingly, caution is warranted when considering the use of ICIs other than pembrolizumab in combination with neoadjuvant chemotherapy for TNBC. The complexity of neoadjuvant immunotherapy stems from the interplay of multiple factors, including the specific immunochemotherapy regimens, baseline patient characteristics, and trial designs, each of which can profoundly affect therapeutic outcomes. Accordingly, these factors require further clarification and standardization across studies.

Unresolved challenges of immunotherapy in elderly TNBC patients

Among the baseline patient characteristics, age is an especially important factor. Notably, over 26% of breast cancer patients are aged ≥65 years, and this proportion continues to rise [42]. Nevertheless, the efficacy of immunotherapies in elderly patients can be compromised by the age-related decline in immune function, namely immunosenescence [43, 44]. Immunosenescence fosters a tumor-promoting microenvironment and impairs immune surveillance, contributing to cancer progression and poorer therapeutic outcomes (Fig. 1) [43-45].

In the landmark KEYNOTE-522 trial, only a small subset of participants were aged ≥65 years (84 of 784) who received immunochemotherapy. Although the addition of pembrolizumab to polychemotherapy produced significant benefit in the overall population, exploratory subgroup analysis indicated virtually no benefit among elderly patients, with a hazard ratio for event or death of 0.99 (95% CI, 0.54–1.82) [20]. Consistently, real-world studies have included only about 10% of patients aged ≥65 years in both the neoadjuvant [46-48] and metastatic [49] TNBC settings, perhaps reflecting a clinical reluctance to administer intensive immunochemotherapy in this population. A real-world analysis involving 118 TNBC patients treated with neoadjuvant pembrolizumab plus chemotherapy further demonstrated that advanced age was associated with lower pCR rates [50].

Importantly, the KEYNOTE-522 regimen must be interpreted in light of its considerable toxicity: treatment-related adverse events of grade ≥3 occurred in 78.0% of patients [18]. Given that older patients are generally more vulnerable to treatment-related toxicity and may experience specific complications [51, 52], alternative and less toxic regimens should ideally be explored, particularly as the therapeutic benefit of pembrolizumab remains uncertain in this population. Taken together, these findings underscore a major unmet need for elderly TNBC patients, highlighting the necessity to develop therapeutic strategies that achieve toxicity de-escalation and efficacy enhancement, or biomarker-guided tailored approaches to optimize treatment and improve outcomes in this population.

Toward less toxic and more effective immunochemotherapy

Despite the lack of benefit observed with the anthracycline-free immunochemotherapy regimen in NeoTRIP, subsequent studies (such as NeoPACT [33], NCI 10013 [32], and cTRIO [34]) have yielded encouraging pCR rates and promising early survival signals using similar anthracycline-free regimens with distinct ICIs. A retrospective study including 87 TNBC patients who received neoadjuvant immunochemotherapy suggested that anthracycline-free regimens may serve as an effective and safe alternative partner for immunotherapy, particularly in patients without lymph node involvement [53]. The ongoing phase III SWOG 2212 trial (NCT05929768) will directly compare an anthracycline-free immunochemotherapy regimen against the established KEYNOTE-522 protocol, which may provide crucial evidence that could potentially reshape the future SoC. Furthermore, as noted above, the IMpassion031 trial omitted carboplatin and failed to demonstrate a survival advantage [23]. By contrast, the GeparNuevo trial, also conducted without carboplatin, reported a significant improvement in survival outcomes [14]. At present, there is insufficient evidence to justify removing carboplatin from the KEYNOTE-522 regimen, but treatment decisions may still be individualized based on patient-specific toxicity considerations.

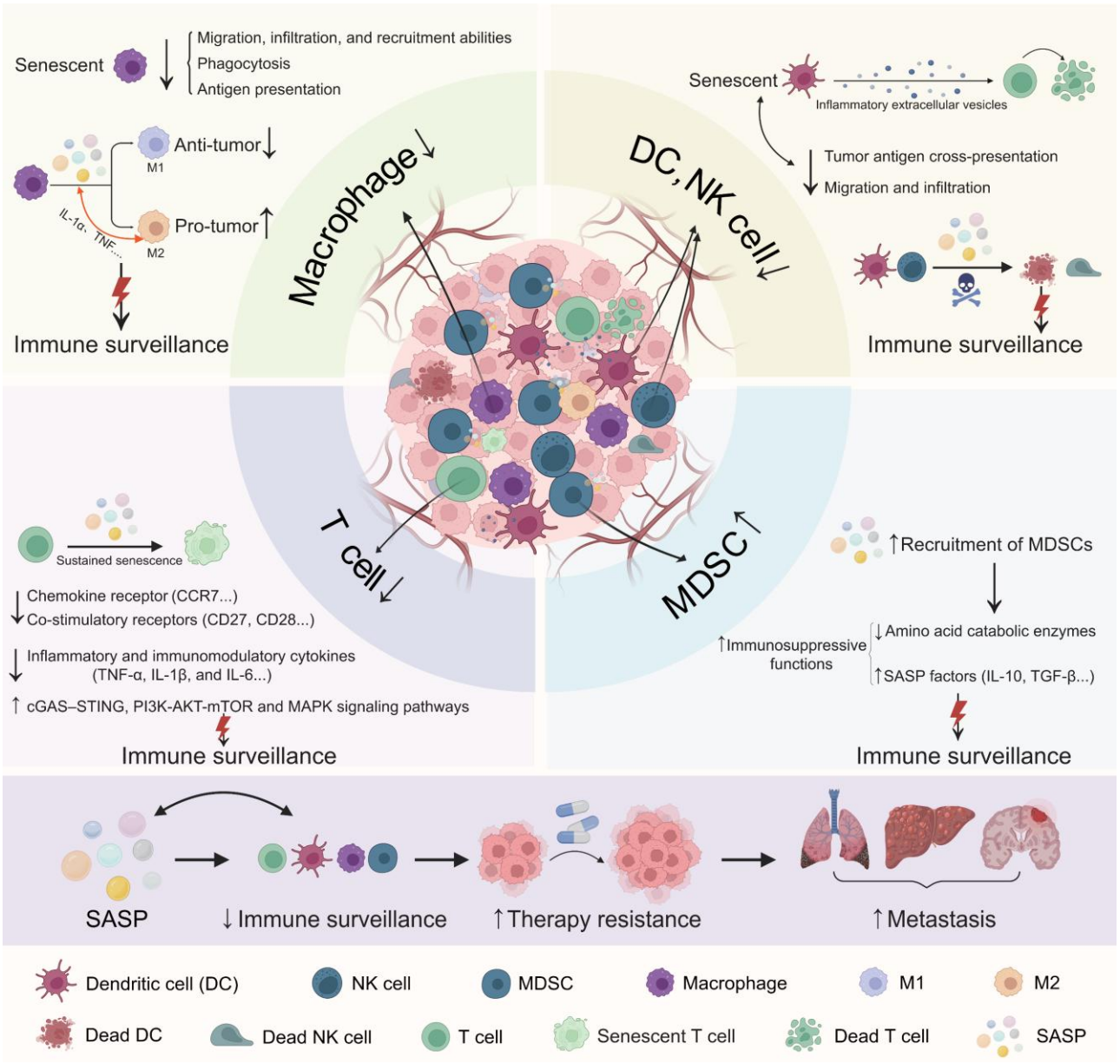

Figure 1. Immunosenescence-driven senescence-associated secretory phenotype (SASP) remodeling of the tumor microenvironment (TME) promotes immune evasion. Immune senescence amplifies SASP production, which promotes the recruitment of myeloid-derived suppressor cells (MDSCs), suppresses T-cell responses, impairs dendritic cell (DC) antigen cross-presentation and natural killer (NK) cell cytotoxicity, and skews macrophage polarization toward a pro-tumor phenotype (M2). These changes reduce immune surveillance and thereby favor tumorigenesis, therapeutic resistance, and metastasis. Arrows adjacent to the text indicate the direction of change (↑, increased; ↓, decreased). Icons at the bottom denote the cell types depicted in the panel. Created in BioRender. Zhou, Y. (2025) https://BioRender.com/h4l4ejv.

In parallel, local immunomodulatory approaches are under active investigation for their potential to enhance efficacy without increasing systemic toxicity. Preliminary data suggest that combining immunochemotherapy with radiotherapy can achieve pCR rates of up to 90%, with tolerable toxicity (grade ≥3 adverse events: 53.8%) [54]. Furthermore, a phase II study is evaluating perioperative immunotherapy combined with cryoablation in patients with early-stage TNBC who have residual operable disease following neoadjuvant chemotherapy [55].

Toward chemotherapy-free immunotherapy combinations

Antibody-drug conjugates (ADCs) targeting trophoblast cell surface antigen 2 (TROP2) have been shown to

enhance ICI activity through dendritic cell activation, PD-L1 upregulation, and increased neoantigen generation in some preclinical models (Fig. 2) [56, 57]. This observed synergy has been confirmed in the context of advanced TNBC based on findings from the phase III ASCENT-04/KEYNOTE-D19 trial [58]. In this study, sacituzumab govitecan combined with pembrolizumab significantly improved progression-free survival compared with chemotherapy plus pembrolizumab in treatment naïve, PD-L1-positive TNBC patients, while also demonstrating durable clinical responses and a favorable safety profile [58]. Following the ASCENT-04 trial, numerous phase III studies have been conducted to further explore the therapeutic potential of ADC–ICI combinations in TNBC (Fig. 3).

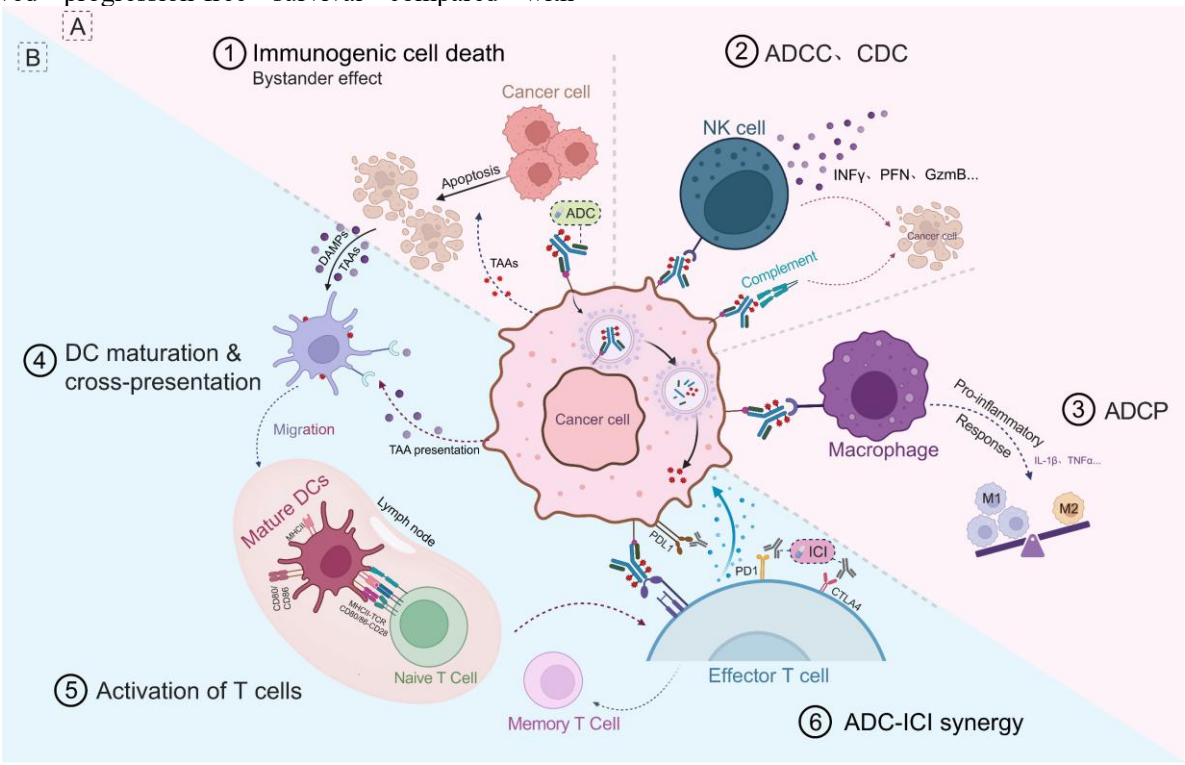

Figure 2. Synergistic anti-tumor immunity of antibody-drug conjugate (ADC) and immune checkpoint inhibitor (ICI) combination therapy. (A) ADC primes the immune response. ADC induces immunogenic cell death, releasing tumor antigens and danger signals (1). This, along with Fc-mediated recruitment of innate immune cells (2-3), promotes dendritic cell maturation to initiate T-cell immunity (4). **(B)** ICI unleashes and amplifies the response. Mature dendritic cells activate tumor-specific T cells (5). ICIs block inhibitory signals, reversing T-cell exhaustion and unleashing these cells to eradicate tumors. The resulting tumor destruction releases further antigens, establishing a self-reinforcing synergistic loop (6). Abbreviations: TAAs, tumor-associated antigens; ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; NK, natural killer; ADCP, antibody-dependent cellular phagocytosis; DCs, dendritic cells; DAMPs, damage-associated molecular patterns; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4. Created in BioRender. Zhou, Y. (2025) https://BioRender.com/ug1aqrq.

In the neoadjuvant setting, the I-SPY 2.2 trial reported high estimated pCR rates in HER2-negative patients treated with only four cycles of datopotamab deruxtecan plus durvalumab, reaching 65% in the immune-positive subtype and 43% in the TNBC cohort [40]. Accordingly, the ongoing phase III TROPION-Breast04 (NCT06112379) trial is evaluating neoadjuvant datopotamab deruxtecan plus durvalumab in comparison to the standard KEYNOTE-522 regimen, while the phase III TroFuse-032 (NCT06966700) trial assesses sacituzumab tirumotecan plus pembrolizumab as neoadjuvant therapy for TNBC. Several ongoing trials are specifically evaluating sacituzumab govitecan plus pembrolizumab in early-stage TNBC, either in comparison with sacituzumab govitecan monotherapy or standard-of-care chemotherapy, including the phase II studies NeoSTAR [41] and trial NCT05675579, as well as the phase III trials ADAPT-TN-III (NCT06081244) and ADAPT-TN-IV (NCT07178730). We speculate that TROP2-directed ADCs plus ICIs may emerge as a superior alternative approach to conventional immunochemotherapy in the neoadjuvant treatment of TNBC, given their potentially greater efficacy and manageable toxicity.

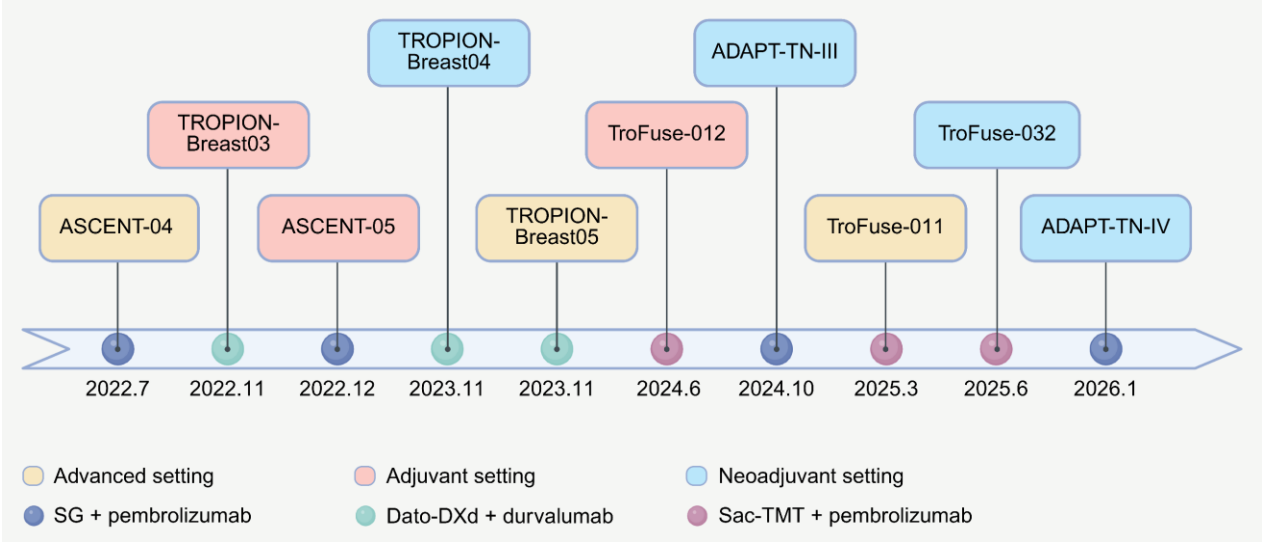

Figure 3. Phase III studies evaluating antibody-drug conjugate (ADC) and immune checkpoint inhibitor (ICI) combinations in early- and advanced-stage triple-negative breast cancer (TNBC). The timeline indicates the actual trial start time. Abbreviations: SG, sacituzumab govitecan; Dato-DXd, datopotamab deruxtecan; Sac-TMT, sacituzumab tirumotecan. Created in BioRender. Zhou, Y. (2025) https://BioRender.com/2n9nz0d.

Toward a biomarker-guided strategy

It is also critical to identify predictive biomarkers and implement patient-tailored strategies, particularly for subgroups prone to reduced immunotherapy responsiveness (e.g., elderly patients), to define responsive individuals rather than exclude them from therapy. In advanced TNBC, several FDA-approved biomarkers have been established, such as a PD-L1 combined positive score (CPS) ≥10, which serves as a definitive marker guiding first-line pembrolizumab use [59]. By contrast, reliable biomarkers for neoadjuvant immunotherapy remain under investigation, reflecting the complex and dynamic tumor-immune interplay and the biological differences in immune microenvironments between early- and advanced-stage disease [8, 32].

In the neoadjuvant setting, PD-L1 remains a putative biomarker with insufficient clinical evidence. Across trials, some have reported increased ICI efficacy irrespective of PD-L1 status [19, 22, 24], whereas others [29, 32, 33] have shown PD-L1-dependent benefit. Such inconsistencies may stem from heterogeneity in PD-L1 expression, assay methodologies, and positivity thresholds, as well as inter-observer variability [3]. Current consensus holds that neoadjuvant immunotherapy decisions should not rely solely on CPS [60]. TILs correlate with chemotherapy response and prognosis in early-stage TNBC [61-63] and are also positively associated with pCR rates following neoadjuvant immunochemotherapy in both prospective trials (e.g., NeoPACT [33] and GeparNuevo [13]) and real-world data [64], making it a promising biomarker.

Other emerging biomarkers, including high tumor mutational burden (TMB-H), microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) status, and immune-related gene expression profiles, show potential but with more limited evidence. TMB-H and MSI-H/dMMR may elevate neoantigen load and enhance tumor immunogenicity, supporting ICI efficacy [8, 65], and have been recognized by the FDA as predictive biomarkers in advanced cancers [59, 66, 67]. However, their prevalence in early-stage breast cancer is extremely low [68, 69]. Strikingly, in the GeparNuevo trial, early-stage TNBC patients with low TMB unexpectedly derived greater survival benefit from neoadjuvant immunochemotherapy compared with chemotherapy alone, whereas those with TMB-H did not experience additional benefit [16]. Similarly, immune gene signatures have shown evidence of correlation with immunochemotherapy response [15, 33], but their clinical implementation remains limited by availability and reproducibility. Overall, these genomic and molecular biomarkers require further validation. Multi-parameter models integrating PD-L1, TILs, and these immunogenomic biomarkers may provide a more robust framework for predicting immunotherapy response in early-stage TNBC.

Future perspectives

The approval of neoadjuvant pembrolizumab combined with polychemotherapy has transformed the treatment landscape for patients with early-stage TNBC. However, the landmark success of the KEYNOTE-522 trial has yet to be replicated with other PD-1 or PD-L1 inhibitors.

Clinicians must therefore exercise careful judgment when prescribing immunochemotherapy, as therapeutic outcomes are profoundly influenced by multiple factors, including the specific immunochemotherapy backbone, baseline patient characteristics, and trial design heterogeneity. Future research should focus on defining optimal immunotherapy partners, refining biomarkers for accurate patient selection, and elucidating resistance mechanisms to inform rational treatment strategies.

Age-related immunosenescence may compromise therapeutic benefit. Although clinical evidence on the efficacy and safety of immunotherapy in elderly TNBC patients remains limited, analyses of small cohorts suggest that older patients derive less benefit from neoadjuvant pembrolizumab. Moreover, older adults are more vulnerable to treatment-related toxicity. Several considerations may guide management and future trial design in this population. First, forthcoming studies should incorporate comprehensive geriatric and immunologic assessment tools to evaluate patient fitness and immune competence, thereby facilitating risk-adapted, biomarker-informed treatment decisions. Second, careful deliberation is warranted before de-escalating the KEYNOTE-522 regimen in elderly patients; ideally, novel regimens achieving both toxicity reduction and efficacy preservation should be developed. Finally, future research should aim to balance treatment intensity, life expectancy, and quality-of-life outcomes, ensuring that studies addressing elderly TNBC are both scientifically rigorous and ethically sound.

Author Contributions

YXZ and PNL conceived and designed the study. PNL and XNG drafted the manuscript. PNL and WHR prepared the figures. YXZ, XNG, WW, and JG critically revised the manuscript and figures. YXZ, YDC, and WW supervised the study and provided guidance for the discussion. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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