Immunotherapy in the treatment of breast cancer

BORBÁLA SZÉKELY[1,2], LAJOS PUSZTAI[3]

[1]Department of Thoracic and Abdominal Tumors and Clinical Pharmacology, [2]National Tumor Biology Laboratory, National Institute of Oncology, Budapest, Hungary, [3]Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA

Levelezési cím:
Dr. Székely Borbála, Országos Onkológiai Intézet,
1122 Budapest, Ráth György u. 7–9, tel.: 06/1-224-8600/3761,
e-mail: szekely.borbala@oncol.hu

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Breast cancer is the most common malignancy in women worldwide, with triple-negative breast cancer (TNBC) posing the greatest therapeutic challenge due to limited treatment options and high recurrence rates. Immunotherapy, particularly immune checkpoint inhibitors (ICIs), has redefined management in TNBC, with pembrolizumab now a standard of care in both early-stage and metastatic settings. Emerging strategies, including cancer vaccines, adoptive cellular therapies, and combination immunotherapies are under investigation, and yet to demonstrate clinical benefit. Key unmet needs include biomarker development for better patient selection and prediction of risk for immune related adverse events, as well as rapid diagnosis, and management of immune-related toxicities. Despite these challenges, immunotherapy offers transformative potential to improve outcomes in breast cancer. Magy Onkol 69:427-433, 2025

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Az emlőrák a nők körében világszerte a leggyakoribb rosszindulatú daganat, a tripla-negatív altípus (TNBC) nagy terápiás kihívást jelent a korlátozott kezelési lehetőségek és a magas kiújulási arány miatt. Az immunterápia, különösen az immunellenőrzőpont-gátlók (ICI-k) használata újraértelmezte a TNBC kezelését, a pembrolizumab ma már a korai stádiumú és az áttétes esetekben is standard kezelésnek számít. Az új stratégiák, beleértve a rákvakcinákat, az adaptív sejtterápiákat és a kombinált immunterápiákat, még vizsgálat alatt állnak, klinikai hasznukat még nem igazolták. A legfontosabb kielégítetlen igények közé tartozik a betegkiválasztást és a mellékhatások kockázatának előrejelzését segítő biomarkerek fejlesztése, valamint a kezeléssel összefüggő toxicitások gyors diagnosztizálása és kezelése. Ezen kihívások ellenére az immunterápia áttörést jelenthet az emlőrák kimenetelének javításában.

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Kulcsszavak: emlőrák, immunterápia, immunellenőrzőpont-gátlók, tripla-negatív emlőrák

INTRODUCTION

Breast cancer remains the most common malignancy in women worldwide and represents a leading cause of cancer-related mortality. Traditional therapeutic approaches—such as surgery, radiotherapy, chemotherapy and targeted treatments—have improved survival, but treatment resistance and recurrence continue to pose significant challenges especially in the triple-negative subtype (TNBC) which lacks estrogen and progesterone receptor expression and has no human epidermal growth factor-2 (HER2) overexpression. Over the past decade, immunotherapy has emerged as a promising strategy to harness the body's immune system against tumor cells. While immunotherapy has quickly transformed the management of malignancies such as melanoma, non-small cell lung cancer, and renal cell carcinoma, its development in breast cancer has been less straightforward due to tumor heterogeneity, variable immunogenicity, and a generally more immunosuppressive tumor microenvironment (TME) (1).

THE IMMUNOLOGICAL LANDSCAPE OF BREAST CANCER

Breast cancer was traditionally regarded as a "cold tumor," characterized by low levels of tumor-infiltrating lymphocytes (TILs) and targetable immune checkpoint molecules. However, certain subtypes—particularly TNBC and HER2-positive breast cancers—exhibit higher immunogenicity compared to hormone receptor (HR)-positive disease. More recent studies also revealed that a minority of HR-positive cancers also have high immune infiltration and share many molecular and clinical features with TNBC (2, 3). Multiple large cohort studies show that patients with high TIL (defined >30-50% of stromal TILs) have a more favorable outcome compared to low TIL cases and its prognostic power is independent of other clinicopathologic factors such as patient's age, tumor size, nodal status or histologic grade (4). In stage I TNBC, 5-year overall survival (OS) with TILs≥50% is higher compared to TILs<30% patients (95% vs 82%), and a recent study showed that patients with pT1c tumors and TIL≥75% had a 10-year survival of 98% even without any adjuvant/neoadjuvant chemotherapy (5). These findings motivated TIL-guided de-escalation studies in early-stage TNBC. The frequent and abundant TIL presence in TNBC, and the known association between immune cell presence and greater benefit from ICI therapy in other cancer types, also made TNBC an attractive target for ICI therapy.

The TME is composed of immune cells, stromal cells and various signaling molecules which play crucial roles in modulating response to immunotherapy. For example, PD-1 expression in breast cancer is more frequent on tissue resident macrophages and immune cells than on cancer cells, implying that PD-1 targeting therapies impact immune-cell to immune-cell communication (6). It has also been shown that breast cancers with high TIL that fail to respond well to immune checkpoint inhibitor (ICI) therapy have a different cytokine milieu than highly ICI sensitive cancers (7). The TME also changes during the progression of the disease. In a study we compared primary breast cancers and their corresponding distant metastases and learnt that the immune microenvironment of primary and metastatic lesions is different; TIL counts and PD-L1 expression are significantly lower at metastatic sites, and gene expression data also indicated that most immune effector cell types and anti-tumor immune functions were depleted in metastases (8). This is consistent with the hypothesis that metastatic lesions, which by definition have escaped immune surveillance at the primary tumor site, have lower 'immunogenicity' than the corresponding primary tumor (9).

IMMUNE CHECKPOINT INHIBITORS IN BREAST CANCER

ICIs target inhibitory pathways of maturing and activated T cells which tumors exploit to evade immune destruction. The most extensively studied pathways are the programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1), as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) mediated checkpoints. The PD-1 receptor on T cells binds to its ligands PD-L1 and PD-L2 which are expressed on cancer cells, antigen presenting cells, macrophages, and B cells and inhibit tissue resident T-cell activation. CTLA-4 is also expressed on T cells and binds to CD80 and CD86 which are mostly expressed on antigen presenting cells, B-cells, macrophages, but also some cancer cells. Among the currently US FDA-approved ICIs, ipilimumab and tremelimumab target CTLA-4, pembrolizumab, cemiplimab, toripalimab, and nivolumab target PD-1, and atezolizumab, avelumab, and durvalumab target PD-L1. Currently, only pembrolizumab is used routinely in the clinic to treat breast cancer.

Metastatic TNBC

The earliest ICI trials tested single agent PD-1/PD-L1 targeting drugs in heavily pretreated metastatic TNBC (mTNBC) patients. The results of these studies showed that single agent immunotherapy had only limited clinical benefit, but suggested greater benefit in patients who were less heavily pretreated (10–13). The KEYNOTE-119 trial which compared single agent

List of abbreviations:

ADCs: antibody drug conjugates, **CAR:** chimeric antigen receptor, **CPS:** combined positivity score, **CTLA-4:** cytotoxic T-lymphocyte-associated protein 4, **eTNBC:** early-stage TNBC, **FDA:** United States Food and Drug Administration, **HER2:** human epidermal growth factor-2, **HR:** hormone receptor, **ICIs:** immune checkpoint inhibitors, **irAEs:** immune-related adverse events, **mTNBC:** metastatic TNBC, **NK:** natural killer, **OS:** overall survival, **pCR:** pathologic complete response, **PD-1:** programmed death-1, **PD-L1:** programmed death-ligand 1, **PFS:** progression-free survival, **TCR:** T cell receptor, **T-DM1:** ado-trastuzumab emtansine, **TILs:** tumor-infiltrating lymphocytes, **TMB:** tumor mutational burden, **TME:** tumor microenvironment, **TNBC:** triple-negative breast cancer

TABLE 1. ICI+chemotherapy phase III studies – mTNBC

Name of study	Patients	Arms	n (ICI vs control)	PD-L1 pos. pts.	PFS (ICI vs control)	OS (ICI vs control)
IMpassion130	therapy-naive mTNBC	nab-paclitaxel +/- atezolizumab	451 vs 451	IC≥1%	7.5 vs 5 months, HR 0.62 (95% CI, 0.49 to 0.78; P<0.001)	25.4 vs 17.9 months, HR 0.67 (95% CI, 0.53 to 0.86)
IMpassion131	therapy-naive mTNBC	paclitaxel +/- atezolizumab	431 vs 220	IC≥1%	6.0 vs 5.7 months, HR 0.82 (95% CI, 0.60 to 1.12; P=0.20)	28.3 vs 22.1 months, HR 1.11 (95% CI, 0.76 to 1.64)
KEYNOTE-355	therapy-naive mTNBC	investigator's choice of chemotherapy +/- pembrolizumab	566 vs 281	CPS≥10	9.7 vs 5.6 months, HR 0.65 (95% CI, 0.49 to 0.86; P=0.0012)	23.0 vs 16.1 months, HR 0.73 (95% CI, 0.55 to 0.95; P=0.0185)
TORCHLIGHT	therapy-naive mTNBC	nab-paclitaxel +/- toripalimab	353 vs 178	CPS≥1	8.4 vs 5.6 months, HR 0.65 (95% CI, 0.470 to 0.906; P=0.0102)	32.8 vs 19.5 months, HR 0.62 (95% CI, 0.414 to 0.914; P=0.0148
IMpassion132	early relapse (<12 months)	carboplatin/ gemcitabin or capecitabin +/- atezolizumab	188 vs 192	IC≥1%	4.2 vs 3.6 months, HR 0.84 (95% CI, 0.67 to 1.06)	12.1 vs 11.2 months, HR 0.93 (95% CI, 0.73 to 1.20; P=0.59)

CI: confidence interval, CPS: combined positive score, HR: hazard ratio, IC: immune cells, ICI: immune checkpoint inhibitor, mTNBC: metastatic triple-negative breast cancer, OS: overall survival, PFS: progression-free survival

pembrolizumab with standard of care chemotherapy as 2nd or 3rd line therapy for mTNBC failed to demonstrate improved outcome. However, subset analysis showed increasing pembrolizumab benefit with increasing PD-L1 expression.

Due to limited single agent activity, multiple clinical trials started testing ICIs in combination with chemotherapy. The pivotal phase III trials are shown in *Table 1.* Based on the results of IMpassion130 trial (14) which showed improved progression-free survival (PFS) when atezolizumab was added to first line chemotherapy with nab-paclitaxel in PD-L1 positive mTNBC, the US Food and Drug Administration (FDA) approved this combination for 1st line treatment of PD-L1 positive mTNBC patients in 2019. However, subsequent confirmatory trials IMpassion131 (15) and -132 (16) failed to demonstrate improved survival and therefore the manufacturer voluntarily withdraw the indication. On the other hand, pembrolizumab in combination with chemotherapy (paclitaxel/gemcitabine, or paclitaxel/carboplatin) significantly improved PFS and also overall survival (OS) in a similar patient population in the KEYNOTE-355 trial which lead to its approval for 1st line treatment of PD-L1 positive (combined positivity score [CPS] ≥10) mTNBC by the FDA in November 2020, and has become standard of care in this population (17). The phase III TORCHLiGHT trial used toripalimab plus nab-paclitaxel in CPS≥1 mTNBC patients, and also demonstrated improved PFS (18), but it is not currently approved in that indication in the US or Europe. It is important to note that in each of these trials PD-L1 negative mTNBC showed no clear benefit from ICI therapy.

A new approach is the combination of ICI with antibody drug conjugates (ADCs) as there is still unmet need in the treatment of mTNBC patients. In the randomized phase III ASCENT-04/KEYNOTE-D19 study patients with previously untreated, PD-L1 positive metastatic or locally advanced breast cancer received pembrolizumab in combination with sacituzumab govitecan which resulted in a significantly longer median PFS (11.2 vs 7.8 months) and duration of response (16.5 vs 9.2 months) compared to the chemoterapy plus pembrolizumab arm (19).

Early TNBC

In parallel with the metastatic trials, ICIs were also tested as neoadjuvant therapy in combination with chemotherapy in early-stage TNBC (eTNBC) (20). Key early-stage ICI therapy trials are shown in *Table 2.*

The first studies of immunotherapy in eTNBC were part of the I-SPY2 platform trial which showed that pembrolizumab (and durvalumab), plus weekly paclitaxel neoadjuvant chemotherapy increased pathologic complete response (pCR) rates (21) in TNBC and in genomic ultrahigh risk HR+ cancers. The phase Ib KEYNOTE-173 which combined pembrolizumab with chemotherapy in the neoadjuvant setting also reported high (60%) pCR rates (22). The randomized phase II GeparNuevo trial using durvalumab with chemotherapy showed significantly improved survival and a numerical but not statistically significant increase in pCR rate (23). These results motivated the pivotal phase III KEYNOTE-522 trial which demonstrated improved pCR rates and improved PFS and OS when pembrolizumab was added to paclitaxel/carboplatin followed by doxorubicin or epirubicin and cyclophosphamide neoadjuvant chemotherapy. In this trial, single

TABLE 2. ICI+chemotherapy phase III studies – eTNBC

Name of study	Setting	Arms	n (ICI vs control)	Pt. population	pCR rate	Survival (ICI vs control)
KEYNOTE-522	neoadjuvant+ adjuvant	paclitaxel+carboplatin – EC +/– pembrolizumab	784 vs 390	ITT	64.8 vs 51.2%; P<0.001	5 yr EFS: 81.2 vs 72.2%, 5 yr OS: 86.6 vs 81.7%; P=0.002
NeoTRIPaPDL1	neoadjuvant	nab-paclitaxel+carboplatin +/– atezolizumab then AC/EC	138 vs 142	ITT	48.6 vs 44.4% p=0.48	5 yr EFS: 70.6 vs 74.9%; P=0.76
IMpassion031	neoadjuvant+ adjuvant	nab-paclitaxel then ddAC +/– atezolizumab	168 vs 165	ITT	58 vs 41%; P=0.0044	2 yr EFS: 85 vs 80%
IMpassion030	adjuvant	paclitaxel then ddAC +/– atezolizumab	1101 vs 1098	ITT	NA	OS events: 6.5 vs 5.3%
A-BRAVE	adjuvant – with residual disease after NACT	avelumab	238 vs 239	ITT	NA	3 yr OS: 84.8 vs 76.3%; P=0.035
GeparDouze	neoadjuvant	paclitaxel+carboplatin then AC/EC +/– atezolizumab	773 vs 77	ITT	63 vs 57%; P=0.091	4 yr OS: 90.2 vs 89.5%

AC: doxorubicin-cyclophosphamid, ddAC: dose-dense AC, EC: epirubicin-cyclophosphamid, EFS: event-free survival, eTNBC: early triple-negative breast cancer, ICI: immune checkpoint inhibitor, ITT: intention to treat, NA: not assessed, OS: overall survival, pCR: pathological complete response

agent pembrolizumab continued post-surgery to complete a total of 1 year of pembrolizumab therapy (24). Benefit was seen in all patients regardless of PD-L1 expression. Based on these results, the FDA approved pembrolizumab in stage II-III TNBC as neoadjuvant followed by adjuvant therapy. Interestingly, two smaller randomized neoadjuvant atezolizumab trials (IMpassion031, and NeoTRIP) in a similar patient population failed to demonstrate improved survival, and a large adjuvant trial which tested atezolizumab in combination with chemotherapy post-surgery (IMpassion030) was also negative. These results suggest that atezolizumab may be less effective than pembrolizumab, and that ICI therapy may be best used in the neoadjuvant rather than adjuvant setting in breast cancer.

However, in melanoma and lung cancer ICI therapy has demonstrated efficacy in both of these clinical settings. The smaller randomized A-BRAVE trial which evaluated the efficacy of 1-year of avelumab adjuvant treatment for high-risk eTNBC reported conflicting results (25). Avelumab did not significantly improve disease free survival, the primary endpoint of the trial, but in a descriptive analysis it showed improved OS and reduced incidence of distant metastases. This benefit was seen regardless of PD-L1 status. A large single agent adjuvant pembrolizumab trial in patients with residual TNBC after non-ICI containing neoadjuvant chemotherapy (SWOG S1418) is yet to report outcome.

It remains uncertain why PD-L1 expression is required for pembrolizumab efficacy in mTNBC, while it is not necessary in eTNBC. Several studies have shown that PD-L1 expression is rapidly induced by neoadjuvant chemotherapy in early-stage disease, and therefore PD-L1 negative tumors can quickly turn PD-L1 positive during treatment (26). Core needle biopsies of the breast which are the only baseline tissue available for neoadjuvant trials are also subject to sampling error, and sparse/low level PD-L1 positivity may be mistaken for PD-L1 negativity (27). We hypothesize that because of the greater immune fitness of the primary tumors, minimal immune presence could be sufficient to activate anti-tumor immunity in early-stage cancers. Whereas metastatic lesions in general have a more immune attenuated TME and high PD-L1 expression may simply identify metastatic lesions that possess residual immunogenicity, evidenced by the presence of PD-L1 positive immune cells.

Human Epidermal Growth Factor Receptor-2 (HER2) positive breast cancer

Despite relatively high immune infiltration in many HER2-positive breast cancers, ICI therapy has not yet shown benefit in randomized trials in this cancer type (28). The reason behind it can be that the efficacy of standard neoadjuvant regimens combining dual HER2 blockade with chemotherapy is already very high (60-70%), leaving little room for further improvement with the addition of immunotherapy, and also the TME in HER2-positive breast cancers is characterized by immunosuppressive features.

In the IMpassion050 trial atezolizumab in combination with neoadjuvant chemotherapy did not increase pCR rates compared to chemotherapy and placebo (29). The ongoing ASTEFANIA trial evaluates the combination of ado-trastuzumab emtansine (T-DM1) and atezolizumab compared to

T-DM1 alone in patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant therapy, results have not been reported (30).

The small single arm phase Ib/II PANACEA study showed that pembrolizumab plus trastuzumab was safe and tumor responses were seen including durable clinical benefit in patients with PD-L1-positive, trastuzumab-resistant, metastatic HER2-positive breast cancer (31). However, a larger trial is yet to confirm this observation. The randomized phase II KATE2 trial compared T-DM1 plus atezolizumab with T-DM1 and placebo in metastatic disease and showed that atezolizumab did not improve PFS in the intent to treat population, but subset analysis suggested benefit in PD-L1 positive cancers (32).

ICIs in combination with other HER2-targeted ADCs (e.g., trastuzumab deruxtecan) are also under investigation in metastatic HER2-positive and HER2-low cancers (33).

HR-positive HER2-negative breast cancer

While most HR-positive breast cancers are immunologically cold, a substantial minority have high TIL and molecular features similar to TNBC (34). Two large phase III randomized trials KEYNOTE-756 (35) and CheckMate 7FL (36) showed that adding ICI to chemotherapy can increase pCR rates in grade III HR-positive cancers. The phase II randomized platform trial, I-SPY2 (37) also identified molecular predictive markers (MammaPrint-high 2 status) to select HR-positive patients to neoadjuvant ICI therapy. However, no long-term survival outcome has been reported so far from these trials and therefore ICI therapy remains investigational in early-stage HR-positive breast cancers (38, 39).

In the metastatic setting, the phase II NCT03051659 study used pembrolizumab in combination with eribulin, OS was not improved but further analysis is ongoing to identify molecular characteristics that might predict response to treatment (40). Another phase I/II trial used a CDK4/6 inhibitor with aromatase inhibitor (palbociclib and letrozole) with pembrolizumab and reported a 31% complete response rate in the front-line setting (41). While this is promising, the contribution of pembrolizumab is unclear, and larger randomized trials will be needed to establish benefit from ICI therapy.

CANCER VACCINES

Cancer vaccines are stimulating the patient's immune system to recognize and attack cancer cells through the presentation of cancer specific antigens (e.g. HER2, MUC1, MAM-A/mammaglobin, NY-ESO-1), resulting in a strong CD8-positive cytotoxic T-cell and CD4-positive helper T-cell response. Despite their promise, traditional peptide vaccines (e.g. Theratope) showed limited efficacy in breast cancer so far. More recent studies use them in combination with ICIs and explore tumor-specific mRNA vaccines (e.g. Allovax, GEN-009, PGV001). Another emerging approach is engineered cancer cell vaccines. The most advanced among these is Bria-IMT which uses an allogeneic human breast cancer cell line engineered to stimulate immune responses and is being evaluated in a phase III trial in metastatic breast cancer. Almost all other vaccine trials in breast cancer are phase I or phase II and therefore the clinical benefit of cancer vaccines still remains unproven, thus their use is restricted to clinical trials (42).

ADOPTIVE CELLULAR THERAPY

During adoptive cellular therapy autologous or allogeneic immune cells are collected, expanded or engineered ex vivo and then reinfused into the patient to target cancer cells. The most studied methods are TIL therapy (lymphocytes are isolated from the tumor, expanded in vitro then reinfused to the patient after lymphodepletion), chimeric antigen receptor (CAR) T cell therapy, T cell receptor (TCR)-engineered T cell therapy, natural killer (NK) cell therapy, and other approaches (43). A major limitation of this technology is the substantial toxicity and cytokine storm that these therapies cause in over 70% of patients. CAR T cells showed remarkable efficay in hematological cancers but their utility in solid tumors is yet to be established, their use is also restricted to clinical trials.

CHALLENGES AND FUTURE DIRECTIONS

The clinically validated biomarkers to immunotherapy in breast cancer are PD-L1 expression in metastatic TNBC, TIL density primarily as a prognostic marker, and high tumor mutational burden (TMB; derived from next generation sequencing assays) as predictor of pembrolizumab benefit in metastatic cancers regardless of histology. In HR-positive breast cancer MammaPrint ultrahigh status, and less accurately histologic grade, are emerging as predictors of ICI sensitivity. However, no single biomarker reliably predicts response, therefore investigation to new markers is still ongoing. The efficacy of ICI therapies could also be improved and finding novel immunotherapy combinations remains an important goal (44).

A very important clinical challenge is to predict, diagnose, and mitigate immune-related adverse events (irAEs) which affect up to 30-60% of patients to various extent. It is crucial to recognize the early signs of irAEs and start the appropriate treatment on time. However, currently the diagnosis of irAEs is mostly based on excluding other etiologies behind the symptoms. Distinguishing between infection, disease progression, chemotherapy-related toxicity and irAE are often difficult, and more than one of these processes may occur simultaneously. As TNBC is more common in younger women compared to other breast cancer subtypes, and a vast majority of these patients are treated with ICI in the neoadjuvant setting, we need to be prepared for irAEs in the clinic as those events can have major and lasting impact on the patient's quality of life even if their TNBC is cured. Currently only nonspecific risk factors exist that predict increased probability of irAEs very imprecisely. History of an autoimmune disease is a well-established risk factor, about

30-50% of patients with history of well controlled autoimmune disease experience disease flare with ICI therapy. Antibiotic use, female gender, poor performance status, detection of asymptomatic autoantibodies in the blood, various HLA and PD-L1/CTLA-4 polymorphisms, high neutrophil/lymphocyte ratio, elevated baseline serum inflammatory markers, and particular gut microbiome have all been linked to irAEs in some studies (45, 46).

CONCLUSIONS

Immunotherapy represents a paradigm shift in the management of breast cancer, offering new therapeutic possibilities in a disease historically characterized as immunologically inert. Although breast cancer has long been regarded as a "cold" tumor, accumulating evidence has identified immunologically active subgroups, within TNBC and HR-positive cancers. The prognostic and predictive value of TILs and the evolving understanding of the TME underscore the importance of host–tumor immune interactions in shaping clinical outcomes. Studies demonstrating that metastatic lesions frequently exhibit diminished immune activity compared with primary tumors further highlight the rationale for deploying immunotherapeutic approaches at earlier stages of disease, when immune modulation may be most effective.

Among the most impactful advances has been the incorporation of pembrolizumab, into both early-stage and metastatic TNBC treatment paradigms. The clinical benefit of ICIs in HER2-positive and HR-positive breast cancers remains less well established. Preliminary trials suggest that only molecularly or immunologically enriched subsets derive meaningful benefit, emphasizing the urgent need for validated predictive biomarkers to optimize patient selection in these disease subtypes.

Beyond checkpoint inhibition, novel immunotherapeutic modalities such as cancer vaccines and adoptive cellular therapies represent promising avenues of investigation. Cancer vaccines designed to stimulate antigen-specific immune responses, and adoptive cell-based strategies, including TIL therapy and CAR T-cell approaches, offer potential to enhance tumor immunogenicity and circumvent immune evasion, however, these remain largely investigational.

Despite these advances, significant challenges remain. The absence of a reliable biomarker of response limits the precision of patient selection, while irAEs pose a substantial risk, particularly as immunotherapy becomes increasingly used in large patient populations. This is especially pertinent when these drugs are used in the early-stage curative setting as in stage II-III TNBC, which disproportionately affects younger women whose long-term quality of life may be impacted by treatment-related toxicity. Consequently, the development of predictive markers of both efficacy and toxicity, as well as improved strategies for early recognition and management of irAEs, is essential to ensure safe and durable benefit.

In conclusion, immunotherapy has already altered the therapeutic landscape of TNBC and holds considerable promise for broader application across other breast cancer subtypes. Future progress will depend on deepening the understanding of tumor–immune dynamics, refining biomarker-driven patient stratification, and designing rational therapeutic combinations that balance efficacy with safety. While challenges persist, the trajectory of current evidence indicates that immunotherapy will assume an increasingly central role in breast cancer care, with the potential not only to extend survival but also to achieve curative outcomes. Its integration marks a critical step toward a more precise, individualized, and effective approach to breast cancer treatment.

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