Breast cancer in Western Pacific

Immunotherapy and its racial specificity for breast cancer treatment in Asia: a narrative review

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Summary

Immunotherapy, including immune checkpoint inhibitors, adoptive cell therapy, cancer vaccines, and other modalities, represents a significant advancement in cancer treatment. Breast cancer, traditionally considered less amenable to immunotherapy, has demonstrated responsiveness to immunotherapy when combined with conventional treatment options. These integrative strategies enhance the effectiveness of immunotherapy, bringing hope to patients. Furthermore, precision therapies guided by predictive biomarkers refine the scope of breast cancer immunotherapy and broaden its advantages. Notably, it is essential to recognise the differences in breast cancer epidemiology, clinical outcomes, and molecular signatures between Asian populations and those in Europe and North America. These include a higher proportion of premenopausal patients and variation in subtype distribution and gene mutation profiles, underscoring the importance of considering racial specificity in immunotherapy. Clinical efforts in Asia, supported by ethnicity-specific studies, indigenous immunotherapeutic agents, and precision medicine informed by predictive biomarkers, provide tailored treatment options. This review aims to present an overview of breast cancer immunotherapy while address the racial specificity to inform its application for Asian patients.

Keywords: Breast cancer; Immunotherapy; Immune checkpoint inhibitors; Racial specificity; Triple-negative breast cancer

Introduction

Breast cancer is a highly heterogenous malignancy ranking prominently in terms of incidence, morbidity, and mortality rates globally. This complex disease is categorised based on the expression profiles of key hormone receptors (HRs) –estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2), and was stratified into three main subtypes, including luminal-like, HER2-positive, and triple-negative breast cancer (TNBC). Current breast cancer treatment options encompass surgery, chemotherapy, and targeted therapies such as HER2 monoclonal antibodies, antibody–drug conjugates (ADCs), and Poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi) targeting *Breast Cancer Susceptibility Gene (BRCA)* mutations.[1] Furthermore, endocrine therapy impedes hormone-driven tumor activation and constitutes component management of breast cancer.

In contrast to conventional treatment options such as chemotherapy and radiotherapy, which exert direct cytotoxic effects, immunotherapy harnesses the host immune system to kill tumor cells. Immune checkpoint inhibitors (ICIs) represent a pivotal form of immunotherapy, revolutionising the management of various solid tumors such as melanoma.[2] In addition to ICIs, diverse immunotherapeutic strategies such as adoptive cell therapy (ACT) and cancer vaccines offer promising avenues. Immunotherapy holds particular promise for patients with breast cancer, particularly those diagnosed with TNBC, which accounts for 10%–20% of cases.[3] TNBC exhibits increased immunogenicity, tumor mutation burden (TMB), presence of tumor-infiltrating lymphocytes (TILs), and expression of programmed death ligand-1 (PD-L1),[4] thereby rendering it an exceptional candidate for immunotherapeutic interventions. The emergence of innovative approaches, such as combination regimens that integrate ICIs with conventional therapies and ACT, presents significant potential for improving outcomes in patients with breast cancer.

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This review delves into the breakthroughs and advancements in immunotherapy for breast cancer, with a particular focus on Asia. Given the escalating prevalence of breast cancer in this region and the notable disparities in terms of epidemiological patterns, clinical outcomes, and molecular characteristics between Asian population and White population, an exploration of immunotherapeutic strategies within this context is needed. These investigations can provide insights into tailored strategies that address these distinct differences, thereby advancing our capacity to effectively manage breast cancer across diverse populations.

Search strategy and selection criteria

For this review, we conducted searches on PubMed and Web of Science databases from January 1, 1990, to July 1, 2024. Only English-language papers were reviewed. The search aimed to identify articles focusing on immunotherapy in breast cancer and its racial specificity. We utilized a combination of relevant search terms, including "breast neoplasms," "breast cancer," "tripe-negative breast neoplasms," "triple-negative breast cancer," "immunotherapy," "immune checkpoint inhibitors," "immune checkpoint blockers," "PD-1," "PD-L1," "adoptive cell therapy," "tumor vaccine," "cancer vaccine," "Asian," and "Asia." We also searched ClinicalTrials.gov, using immunotherapy approaches or specific drug names in the interventions search box, and breast cancer in the conditions search box to identify relevant breast cancer immunotherapy trials from January 1, 2010, to July 1, 2024. The final reference list was compiled based on the originality and relevance of each paper to the comprehensive scope of this review. Additionally, we created a flow chart to illustrate the search and selection process (Fig. 1).

Current landscape of breast cancer immunotherapy

Immune checkpoint inhibitors (ICIs)

Immune checkpoints exhibit an immunosuppressive role in tumor immunity, aiding tumor evasion. ICIs counteract this by blocking receptors such as programmed death 1 (PD-1), PD-L1, and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Notably, PD-1/PD-L1 axis inhibition shows promise in breast cancer treatment.[5] Moreover, the combining of ICIs with chemotherapy demonstrates the potential to augment antitumor effects in TNBC.

Combine ICIs with chemotherapy

Chemotherapy acts as a promising adjunct to ICIs by enhancing tumor antigenicity and reshaping the immune microenvironment.[6] Clinical trials combining ICIs with chemotherapy have been conducted in both early- and advanced-stage breast cancer. In early-stage TNBC, the KEYNOTE-522 study established pembrolizumab's role in improving pathological complete response (pCR) and event-free survival (EFS) when added to neoadjuvant chemotherapy.[7,8] This study led to the Food and Drug Administration's (FDA) approval of pembrolizumab for neoadjuvant and adjuvant treatment in high-risk TNBC. Similarly, the IMpassion031 and I-SPY2 trials reinforced the benefit of combining ICIs with neoadjuvant chemotherapy for early-stage TNBC.[9,10]

In advanced TNBC, the KEYNOTE-355 trial established pembrolizumab plus chemotherapy as the standard first-line treatment for PD-L1 positive metastatic TNBC, exhibiting a significant progression-free survival (PFS) benefit.[11] Moreover, the IMpassion130 trial demonstrated a significant enhancement of overall survival (OS) and PFS among metastatic TNBC patients exhibiting high PD-L1 expression when treated with the combination of atezolizumab and chemotherapy,[12,13] which further underscores the efficacy of ICIs in tandem with chemotherapy for advanced TNBC.

However, not all combinations yield satisfactory outcomes. For instance, the IMpassion131 trial combining atezolizumab and paclitaxel did not significantly improve PFS or OS in advanced TNBC.[14] The varying chemotherapy dosage forms may explain disparate outcomes, as atezolizumab plus nab-paclitaxel showed positive results in the IMpassion 130 study.[12,13] The glucocorticoid premedication required for paclitaxel can diminish the efficacy of immunotherapy, whereas nab-paclitaxel does not necessitate this immunosuppressive factor.[14]

Collectively, the combined use of ICIs with chemotherapy has demonstrated considerable success in numerous clinical studies, advancing the application of immunotherapy in breast cancer. Nonetheless, there are still limitations and challenges to address, and additional research is needed to expand the population benefiting from this approach, reduce toxicities, and enhance overall antitumor efficacy.

Novel ICIs targeting new targets

Beyond conventional targets, ICIs targets lymphocyte-activated gene-3 (LAG3), T cell immunoglobulin domain and mucin domain-3 (TIM3), and T cell immune receptor with Ig and ITIM domain (TIGIT) are under investigation.[15–18] LAG3 inhibitors have shown promise, doubling remission rates in advanced breast cancer.[15] A trial found that LAG3 inhibitors did not improve survival in breast cancer. However, it demonstrated benefits in the subgroup with a high neutrophil-lymphocyte ratio, suggesting that LAG3 is a promising target and warranting further studies to validate its antitumor efficacy.[16] Combination therapies, such as TIGIT inhibitor tiragolumab with atezolizumab or anti-TIM3 antibody with chemotherapy, also improve antitumor responses.[17,18] Ongoing clinical trials continue to explore the potential of novel ICIs in breast cancer treatment (NCT03667716; NCT06175390).

ICIs represent the cornerstone of immunotherapy, whether through conventional targeting of the PD-1/

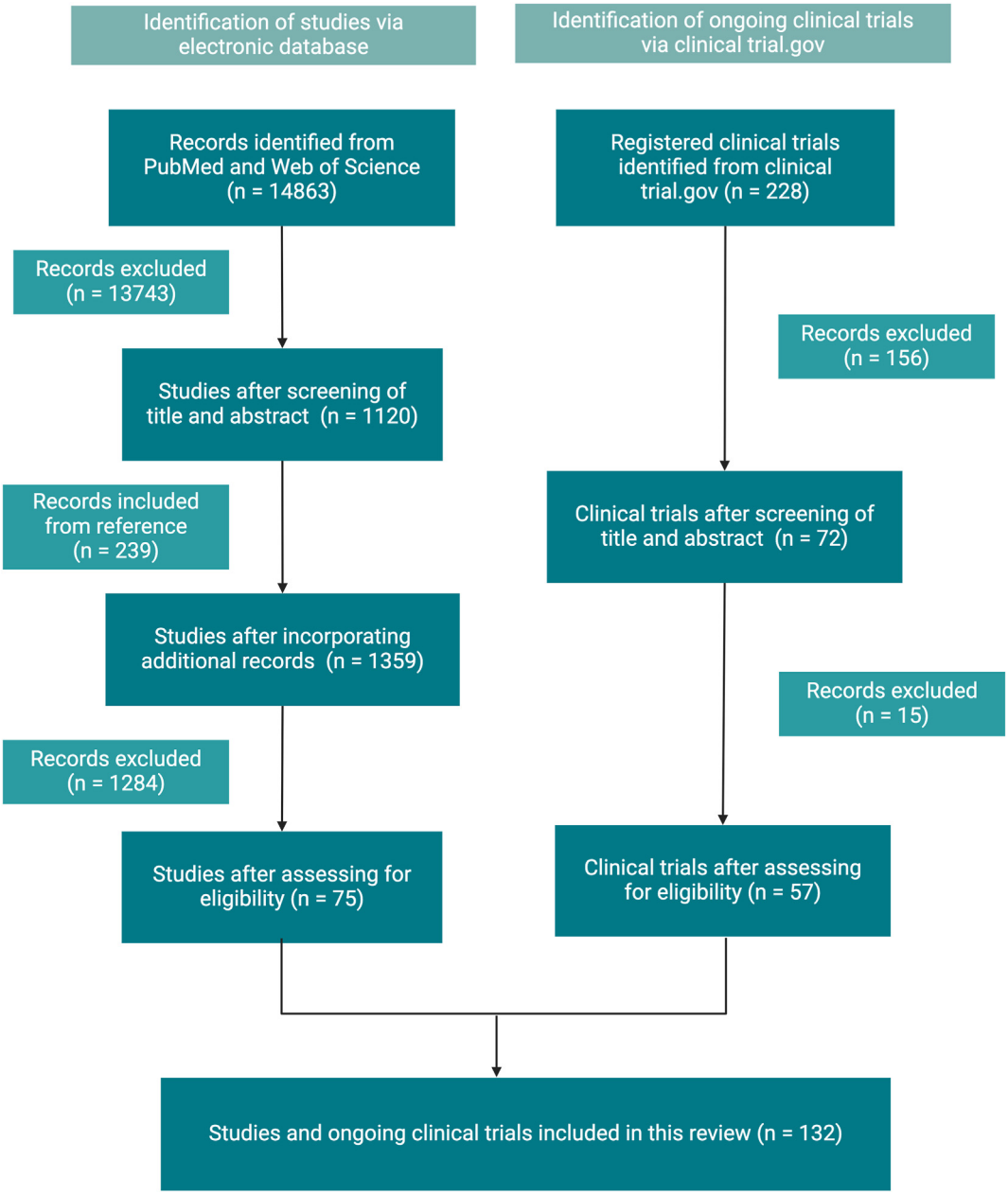

Fig. 1: Flow chart of references and ongoing trials selection.

PD-L1 axis or in conjunction with chemotherapy. Furthermore, the advent of novel ICIs continues to expand treatment options.

Beyond ICIs: diverse immunotherapeutic approaches

Adoptive cell therapy (ACT)

Beyond ICIs, ACT is a crucial aspect of immunotherapy, involving the ex vivo manipulation of patient-derived cells. These modified cells, categorized as chimeric antigen receptor T (CAR-T) cells, chimeric antigen receptor Natural Killer (CAR-NK) cells, T cell receptor-gene engineered T (TCR-T) cells, and TILs are subsequently reintroduced into the patient to combat tumors.

CAR-T therapy entails modifying the circulating T cells to target tumor-associated antigens. CAR-T targeting hepatocyte growth factor receptor (HGFR) has demonstrated promising antitumor efficacy and manageable safety profiles in animal models and clinical trials.[19] Ongoing clinical trials are exploring CAR-T

therapies targeting other antigens such as mesothelin, MUC1, and EpCAM (NCT02792114; NCT02915445; NCT04348643; NCT04025216; NCT02706392). Moreover, macrophages and NK cells can also be engineered into CAR-macrophages or CAR-NK cells to exert antitumor effects.[20,21]

Other ACT, such as TCR-T and TIL therapies, have shown potential antitumor effects in breast cancer.[22,23] Despite promising clinical trial results, ACT faces challenges including unsustainable cell expansion, treatment-associated toxicity, high costs, and immunosuppression within the tumor microenvironment.[24] Studies have also reported unsatisfactory clinical outcomes due to these challenges. CAR-T targeting ROR1 for the treatment of TNBC reported one death from respiratory failure (NCT05274451). Additionally, studies with acceptable safety profiles and positive results remain limited to small samples and advanced patients after multiple lines of therapy. Their efficacy requires validation in larger, more diverse cohorts and with further adjustments to the ACT protocols.

Cancer vaccine

In addition to ICIs and ACTs, cancer vaccines activate the immune system by exposing tumor antigens, yielding antitumor responses. Vaccines targeted HER2-associated antigens demonstrate notable safety and potential antitumor immune response in breast cancer.[25] Further investigations are needed to confirm their efficacy. A vaccine targeting another HER2-associated antigen reported no significant differences in disease-free survival (DFS) in patients with breast cancer.[26] Adagloxad simolenin, targeting Globo H, showed promising results in a phase I trial, significantly increasing IgM antibody titers and disease-free survival in patients with metastatic breast cancer.[27]

In a word, cancer vaccines are generally well tolerated; however, their survival benefits are less pronounced than those of other immunotherapies. Nonetheless, further analysis has revealed antitumor immune response at the cellular level in vaccinated patients, and antibody titers may help identify populations that could benefit from vaccination. Future efforts toward identifying more effective antigenic targets, refining vaccine assembly, and developing strategies to select populations may improve the efficacy of cancer vaccines.

Future directions in immunotherapy

Expansion of population benefiting from immunotherapy

Research on immunotherapy for breast cancer has predominantly focused on TNBC, considered the subtype most likely to benefit from such treatments. However, with advancing insights into immunotherapy, its scope is expected to expand. Monotherapy trials employing ICIs demonstrated an ORR of 12% in PD-L1 positive HR-positive/HER2-negative breast cancer.[28] Additionally, studies investigating combination regimens further advocate for the use of ICIs in this subtype.[9,29]

In HR-positive/HER2-negative breast cancer, pairing immunotherapy with chemotherapy has yielded promising outcomes. The KEYNOTE-756 trial demonstrated the superiority of neoadjuvant pembrolizumab alongside chemotherapy, followed by adjuvant pembrolizumab with endocrine therapy, showing improved total pCR rate and reduced residual cancer burden in early-stage disease.[29] Similarly, findings from the CheckMate 7FL trial demonstrated a significant increase in total pCR rate upon adding nivolumab to neoadjuvant chemotherapy and adjuvant endocrine therapy.[30] These studies affirm that immunotherapy's applicability in breast cancer extends beyond the TNBC subtype. Given the variations in immune microenvironments across subtypes, the mechanisms underlying combination therapy in the luminal subtype warrant detailed analysis through high-throughput sequencing and other methodologies. Furthermore, the potential for large-scale clinical applications of this combination regimen in luminal breast cancer requires validation through extensive clinical trials.

Another promising agent for combination with immunotherapy is the CDK4/6 inhibitor. Preclinical evidence suggests that CDK4/6 inhibitors, alongside chemotherapy, can augment the antitumor effects of ICIs by suppressing Tregs and enhancing T-cell infiltration, activation, and antigen presentation.[31] Despite the promising antitumor activity demonstrated by combinations, concerns have arisen regarding their tolerability with reports of intolerable toxicity and treatment-related fatality,[32] limiting their recommendation for further investigation and clinical application. Hence, there is a pressing need for a more judicious selection of combination regimens and dosing strategies to mitigate treatment-related toxicity and broaden treatment options, thereby improving patient outcomes in the future.

The success of immunotherapy in TNBC has encouraged its application to other breast cancer subtypes. Agents like endocrine therapy and CDK4/6 inhibitors for luminal breast cancer and HER2-targeted drugs for HER2-positive breast cancer are anticipated to demonstrate synergistic antitumor effects when combined with ICIs. Ongoing clinical trials targeting different breast cancer subtypes show promise for extending the application of immunotherapy across the entire spectrum of the disease.

Combine immunotherapy with other approaches

Combine immunotherapy with radiotherapy

In addition to the chemotherapy introduced above, researchers have explored the integration of other modalities with immunotherapy. Radiotherapy holds

promise when combined with ICIs based on the preclinical evidence that radiotherapy can induce antigen release, promote T cell priming, and shift myeloid compartments toward an antigen-presenting phenotype.[33] However, clinical data on combined radiotherapy and immunotherapy in breast cancer are limited. The TONIC study results indicated that in TNBC, the group receiving radiotherapy combined with nivolumab achieved a lower ORR than the group receiving chemotherapy combined with nivolumab.[33] Several trials investigating the combination of radiotherapy and immunotherapy are currently underway (NCT02954874; NCT03051672; NCT03366844; NCT03789097; NCT03875573), which will offer valuable insights. Larger sample sizes are essential to confirm the clinical benefits.

Combine immunotherapy with molecularly targeted therapies

PARPi has shown promise in treating breast cancer with germline BRCA1/2 mutations. Preclinical studies indicate that PARPi can upregulate PD-L1 expression via inhibiting GSK3β and the combination of PARPi and ICI has demonstreated increased therapeutic efficacy in preclinical models.[34] Numerous clinical trials are investigating the synergy between ICIs and PARPi, for instance, the KEYNOTE-162 and MEDIOLA studies have demonstrated manageable safety profiles and encouraged antitumor efficacy in TNBC and HER2-negative breast cancer with germline-BRCA mutations.[35,36] Both preclinical and clinical data underscore the potential of combining PARPi with immunotherapy in breast cancer treatment. Advances in BRCA mutation detection and subtyping are expected to enhance the prediction of PARPi and immunotherapy efficacy, facilitating the identification of beneficiary populations.

ADCs have shown potential in augmenting immunotherapeutic efficacy through mechanisms that include increasing T-cell infiltration, upregulating PD-L1 expression, generating T-memory cells, and activating immune cells.[37] The BEGONIA study reported improved survival with the combination of durvalumab and trastuzumab deruxtecan (T-DXd) or datopotamab deruxtecan (Dato-DXd). The success of BEGONIA underscores the potential of ADCs in combination with immunotherapy for breast cancer. Conversely, the KATE2 study found that combining ADC with atezolizumab did not improve PFS, however, the PD-L1 positive subgroup showed potential benefits.[38] Further clinical studies are required to evaluate the toxicities and synergistic antitumor effects of ADCs with immunotherapy. Additionally, biomarker-based prediction systems are essential for identifying patients who are most likely to benefit from these combinations.

Moreover, the integration of immunotherapy with anti-angiogenic agents presents a promising approach to breast cancer management, with evidence suggesting immunotherapy's potential to normalize tumor vascular structure.[39] Lwin reported significant antitumor activity by combining Lenvatinib and pembrolizumab in previously treated TNBC,[40] while cohorts from China show promising effects with camrelizumab and anti-angiogenic agents in advanced TNBC.[39,41]

The diversity of therapeutic agents in breast cancer offers numerous combination options for immunotherapy beyond chemotherapy. These regimens have shown promise in preclinical models and early-phase clinical trials. However, they require further validation in advanced clinical studies to confirm their efficacy and safety.

Predictive biomarkers to guide immunotherapy

PD-L1 expression

Immunotherapy does not benefit all patients and is associated with adverse effects, underscoring the urgent need for predictive biomarkers to optimize patient selection and treatment outcomes.

PD-L1 expression serves as a widely utilized biomarker, with clinical trials indicating significant improvements in outcomes among patients with high PD-L1 expression after immunotherapy treatment.[11,13] Nonetheless, the predictive efficacy of PD-L1 is constrained, notably influenced by the breast cancer stage. In the KEYNOTE-355 trial, metastatic TNBC patients with high PD-L1 expression benefited from pembrolizumab.[11] By contrast, the efficacy of pembrolizumab in early-stage TNBC was independent of PD-L1 expression.[8] Similar observations were made with atezolizumab.[10,13] This disparity could be attributed to the tumor immune microenvironment's impact on ICIs and chemotherapy efficacy, where a robust immune response in the early TNBC may render PD-L1 expression less decisive.[42]

Furthermore, variations in measurement criteria, including PD-L1 antibodies, and immunohistochemistry protocols, and the definition of PD-L1 positive, contribute to inconsistencies in predictive function.[43] Consequently, PD-L1 is not a perfect biomarker, additional biomarkers are imperative to enhance the efficacy of immunotherapy in patients with breast cancer.

Hereditary factors

Hereditary factors significantly influence breast cancer development and treatment, which also potentially serve as predictive markers for immunotherapy efficacy in this disease.

BRCA1/2 mutations inform immunotherapy response prediction due to changed tumor immune microenvironment,[44] with *BRCA2* deficiency correlating with enhanced immunogenicity and better ICI treatment outcomes, while *BRCA1* deficiency weakens response to ICIs. Beyond *BRCA1/2* mutations, human leukocyte antigen (HLA) genes, governing antigen presentation, also serve as biomarkers for immunotherapy efficacy prediction.[45]

Despite the exciting results of these results, the use of BRCA1/2 mutations and HLA as predictive biomarkers for breast cancer immunotherapy is not as extensive as that of PD-L1, but we are positive that improved testing protocols and predictive efficacy in this area will provide good biomarkers for breast cancer immunotherapy in the future.

Other biomarkers

Regarding additional predictive biomarkers, TMB and TILs emerge as significant indicators for immunotherapy efficacy. TMB reflects somatic mutation levels, where higher TMB signifies increased immunogenicity, theoretically enhancing immunotherapy response. Jaffee et al. illustrated a positive correlation between median TMB and ORR across 27 tumors treated with ICIs, including breast cancer.[46] It is approved by the FDA as the pan-cancer biomarker for pembrolizumab therapy, this designation is based on results from the KEYNOTE-158 trial.[47]

TILs, comprise various lymphocyte populations such as T cells, B cells, and NK cells. According to the distribution of TILs in the tumor microenvironment, they can be classified as intratumoral TILs and stromal TILs. Stromal TILs are more numerous and significant, and are used as a major indicator for both academic research and clinical application.[48] TILs are pivotal in TNBC immunotherapy, correlating with higher total pCR rates in clinical trials.[8,30] Despite their prognostic significance, devising tailored strategies to guide immunotherapy across breast cancer subtypes poses a challenge. The predictive effects of TILs in other subtypes such as HER2-overexpressing and luminal subtypes are unsatisfactory.[48] At the same time, different cells in TILs may also have different predictive effects, so further refinement of the predictive effects of the various components of TILs as well as in different subtypes of breast cancer based on high-throughput means is a future endeavor to refine the use of TILs as predictive biomarkers for breast cancer immunotherapy.

Current evidence underscores the inadequacy of singular biomarkers like PD-L1 in predicting immunotherapy efficacy. Instead, amalgamating multiple biomarkers, refining existing prediction systems, and innovating new markers represent the future trajectory of immunotherapy biomarkers research.

Racial specificity of breast cancer immunotherapy and precision therapy

Characteristics of breast cancer in Asia

Given the significant heterogeneity of breast cancer, variations in epidemiology across ethnic groups merit attention. Breast cancer incidence has risen in Asia, contrasting with declining trends in Europe and North America.[49] Additionally, breast cancer tends to occur at an earlier age in Asia, with peak onset observed between the ages of 45 and49 in China, Japan, and South Korea, compared to an average age of onset of 70 years in the United States.[50] Additionally, there is a higher prevalence of pre-menopausal, ER-negative, and HER2-positive breast cancer.[50–52] Higher breast density in this population necessitates the use of ultrasound over mammography for screening.[53,54] These epidemiological and clinical variations stem from underlying biological distinctions, including genomic profile and tumor microenvironment.[55,56]

Disparities in molecular pathology and mutation profile between Asian population and White population are noteworthy. A multi-omic analysis of 773 Chinese patients with breast cancer revealed a higher proportion of HER2-enriched subtype and more frequent somatic mutations in *V-Akt murine thymoma viral oncogene 1 (AKT1)* and *tumor protein 53 (TP53)*.[55] Consistently, other studies on Chinese patients also exhibit a higher incidence of somatic mutations in *TP53, AKT1, and phosphoinositide 3- kinase (PIK3)* pathway, potentially contributing to aggressiveness and metastatic propensity.[57–59] BRCA1/2 germline mutation rates are also higher in Chinese populations than in European and North American countries (except for the Jewish people).[60–62] Similarly, breast cancer cohorts from South Korea and Malaysia demonstrate elevated rates of HER2-positive and luminal B subtypes, along with increased frequencies of somatic *TP53* mutation and germline *BRCA1/2* mutations, accompanied by immune signatures enrichment compared to the cohort from The Cancer Genome Atlas Program (TCGA).[56,63] South Korean breast cancer cohorts demonstrate higher PD-L1 expression across all breast cancer subtypes compared to the United States cohorts.[56] However, direct comparisons of PD-L1 expression among patients with breast cancer from diverse ethnic backgrounds necessitate further research into this crucial molecular aspect of immunotherapy. Given these disparities (outlined in Table 1) and the growing breast cancer burden in Asia, it is essential to understand the regional and racial specificity in breast cancer immunotherapy. This is imperative for tailoring therapeutic approaches to meet the needs of diverse patient populations, which have predominantly been informed by data from European and North American countries.

Breast cancer immunotherapy in Asia

ICI treatment in Asia

The specificity of immunotherapy within Asia warrants scrutiny. Subgroup analyses from global clinical trials on ICIs, along with studies focusing exclusively on Asian ethnic groups and regionally developed therapeutics, can provide critical insights into the unique immunotherapeutic responses in this population.

PD-1 inhibitors have demonstrated promising results in early and advanced TNBC as well as luminal breast cancer in Asian populations.[29,64,65] Subgroup

Characteristic	Asian patients	White patients
Incidence and Mortality of Breast Cancer[49]	Annual average percent changes in incidence and mortality from 2000 to 2012 in China and South Korea were recorded at 2.1–6.1% and 1.0–1.8% respectively	Annual average percent changes in incidence and mortality from 2000 to 2012 in the UK and the USA were recorded at −0.9 to −0.5% and ∼ −2.0% respectively
Peak Age of Breast Cancer Onset[29]	45–50 years	65–70 years
Percentage of Premenopausal Breast Cancer[51,52]	35–60%	15–25%
Breast Percent Density[53,54]	35–40%	25–30%
IHC-Based Subtypes[55,56]	ER + HER2- (Luminal-A/B): 55–60%;	ER + HER2- (Luminal-A/B): 64–67%;
	ER + HER2+ (Luminal-B): 13–15%;	ER + HER2+ (Luminal-B): 15–16%;
	ER- HER2+ (HER2-enriched): 8–10%;	ER- HER2+ (HER2-enriched): 3–5%;
	ER- HER- (TNBC)*: 15–20%;	ER- HER- (TNBC)*: 14–16%;
Frequency of Germline *BRCA1/2* Mutation[56,60–62]	6–11% in the overall group;	4–5% in the overall group (non-Jewish people);
		10–18% in the overall group (Jewish people);
	∼13% in the TNBC subtype	13–14% in the TNBC subtype (non-Jewish people);
		18–39% in the TNBC subtype (Jewish people)
Frequency of Somatic *TP53* Mutation[55,56,63]	40–48% in the overall group;	30–35% in the overall group;
	75–87% in the TNBC subtype	79–80% in the TNBC subtype
Frequency of Somatic *AKT1* Mutation[55,57]	6–8% in the overall group;	2–3% in the overall group;
	∼13% in the luminal A subtype;	∼4% in the luminal A subtype;
	∼6% in the luminal B subtype	∼2% in the luminal B subtype
Frequency of Somatic *PIK3CA* Mutation[55,58]	38–44% in the overall group;	34–36% in the overall group;
	49–50% in the luminal A subtype;	∼45% in the luminal A subtype;
	38–48% in the luminal B subtype	28–32% in the luminal B subtype
Immune Microenvironment[55,56]	Elevated TIL levels in the ER + subtype and HER2+ subtype, increased CD8A and PD-L1 expression, higher "hot" phenotype TME proportion across all subtypes	Increased TGF-β signaling in all subtypes, enriched TGF-β1 in ER+, ER+/HER2+ and TNBC subtypes

TNBC*: ER-negative, PR-negative, and HER2-negative. Abbreviations: UK, United Kingdom; USA, United States of America; IHC, immunohistochemistry; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; *BRCA 1/2, breast cancer susceptibility gene 1/2; TP53, tumor protein 53; AKT1, V-Akt murine thymoma viral oncogene 1; PIK3, phosphoinositide 3- kinase*; TIL, tumor-infiltrating lymphocyte; PD-L1, programmed death-ligand 1; TME, tumor microenvironment; TGF, transforming growth factor.

Table 1: **Racial specificity of breast cancer.**

analysis of global studies reveals that the benefits in Asian populations differed slightly from those in other racial groups. In the KEYNOTE-522 trial, the Asian subset (20% of the total population) showed greater numerical benefits in pCR progression and 3-year EFS rate compared to the overall cohort. (pCR: Δ18.7% vs Δ13.6%; 3-year EFS rate: Δ14.0% vs Δ7.7%), supporting the efficacy of pembrolizumab plus chemotherapy for early-stage TNBC in Asians.[64] Similarly, results from the Asian subgroup of the KEYNOTE-355 study, including Hong Kong, Japan, South Korea, Malaysia, and Taiwan demonstrated numerical improvements in OS and PFS than the overall data and other regional data irrespective of PD-L1 expression.[65] Subgroup analyses of TNBC studies indicate that Asian patients experienced numerically superior outcomes compared to the overall population. Notably, these results were not replicated in the HR-positive/HER2-negative subtype. The KEYNOTE-756 study explored immunotherapy combination regimens for HR-positive/HER2-negative breast cancer and showed diminished total pCR rates compared to Eastern Europe and all other countries in the Chinese subgroup (pCR: Δ2.6% vs Δ13.3% vs Δ8.4%).[29] Regional differences in treatment responses may stem from variations in mutational profiles across populations. The immune microenvironment of TNBC in Asian populations appears to be more active,[55,56] potentially explaining the better numerical benefit in the Asian subgroup. Conversely, HR-positive/HER2-negative breast cancer does not have an active immune microenvironment, suggesting that the mechanism of the combination regimen may differ from those in TNBC. Given the relatively small number of studies on immunotherapy in HR-positive/HER2-negative breast cancer, further investigation is warranted to explore its effect in this subtype within Asian populations.

Current research on PD-L1 inhibitors primarily focuses on TNBC. As previously noted, the use of PD-L1 inhibitors, such as atezolizumab, in TNBC has not been as successful as PD-1 inhibitors. Atezolizumab was withdrawn from FDA approval for TNBC, which has also hindered its application in other subtypes. Table 2 displays the results between the experimental

Study	Comparisons	Disease conditions	Overall results	Asian subpopulation	Results in Asian subpopulation	Other subpopulations	Results in other subpopulations
IMpassion031[10] (n = 333)	Atezo + chemo vs pbo + chemo	Early-stage TNBC, in neoadjuvant setting	pCR rate*: 58% vs 41%	Asian (n = 88)	pCR rate: 57% vs 34%	White (n = 210)	pCR rate: 58% vs 44%
						Black or African American (n = 24)	pCR rate: 44% vs 27%
IMpassion130[12,13] (n = 902)	Atezo + chemo vs pbo + chemo	Advanced or metastatic TNBC	ITT: mPFS: 7.2 ms vs 5.5 ms; mOS: 21.4 ms vs 18.7 ms	Asian (n = 161)	ITT: mPFS: 7.2 ms vs 5.5 ms; mOS: 27.9 ms vs 29.3 ms	White (n = 609)	ITT: mPFS: 7.2 ms vs 5.5 ms; mOS: 21.0 ms vs 17.6 ms
						Black or African American (n = 59)	ITT: mPFS: 6.8 ms vs 3.9 ms; mOS: 18.5 ms vs 15.7 ms
			PD-L1$^+$: mPFS: 7.5 ms vs 5.0 ms; mOS: 25.4 ms vs 17.9 ms	Asian (n = 66)	PD-L1$^+$: mPFS: 7.4 ms vs 5.3 ms; mOS: 23.7 ms vs 28.0 ms	White (n = 254)	PD-L1$^+$: mPFS: 7.5 ms vs 5.0 ms; mOS: 23.7 ms vs 16.0 ms
						Black or African American (n = 23)	PD-L1$^+$: mPFS: 11.1 ms vs 3.2 ms; mOS:/
IMpassion131[14] (n = 651)	Atezo + chemo vs pbo + chemo	Advanced or metastatic TNBC	PD-L1$^+$: mPFS: 6.0 ms vs 5.7 ms	Asian (n = 60)	PD-L1$^+$: mPFS: 7.3mons vs 7.2mons	White (n = 116)	PD-L1$^+$: mPFS: 5.9 ms vs 5.7 ms
						Black or African American (n = 8)	PD-L1$^+$: mPFS: 7.1 ms vs 3.6 ms
KEYNOTE-355[11,65] (n = 847)	Pembro + chemo vs pbo + chemo	Advanced or metastatic TNBC	ITT: mPFS: 7.5 ms vs 5.6 ms; mOS: 17.2 ms vs 15.5 ms	Asia (n = 160)	ITT: mPFS: 8.8 ms vs 6.7 ms; mOS: 24.1 ms vs 17.2 ms	North America-Europe-Australia and New Zealand (n = 536)	ITT: mPFS: 7.5 ms vs 5.7 ms; mOS: 16.8 ms vs 15.4 ms
						Rest of world (n = 151)	ITT: mPFS: 5.8 ms vs 5.4 ms; mOS: 12.4 ms vs 12.8 ms
			PD-L1 CPS≥10: mPFS: 9.7 ms vs 5.6 ms; mOS: 23.0 ms vs 16.1 ms	Asia (n = 56)	PD-L1 CPS≥10: mPFS: 17.3 ms vs 5.6 ms; mOS: 26.7 ms vs 17.4 ms	North America-Europe-Australia and New Zealand (n = 212)	PD-L1 CPS≥10: mPFS: 9.6 ms vs 5.7 ms; mOS: 23.5 ms vs 15.2 ms
						Rest of world (n = 55)	PD-L1 CPS≥10: mPFS: 7.6 ms vs 6.2 ms; mOS: 18.0 ms vs 22.0 ms
KEYNOTE-522[7,8,64] (n = 1174)	Pembro + chemo, followed by adjuvant pembro vs chemo + pbo, followed by pbo	Early-stage TNBC, in neoadjuvant setting	pCR rate: 51.2% vs 64.8%; 3 years EFS rate: 84.5% vs 76.8%	Asia (n = 216)	pCR rate: 58.7% vs 40.0%; 3 years EFS rate: 91.2% vs 77.2%	/	/
KEYNOTE-756[29] (n = 1278)	Pembro + chemo, followed by adjuvant pembro + ET vs pbo + chemo, followed by adjuvant pbo + ET	Early-stage ER+/HER2- breast cancer, in neoadjuvant setting	pCR rate: 24.3% vs 15.6%	China (n = 179)	pCR rate: 12.5% vs 9.9%	Eastern Europe (n = 269)	pCR rate: 29.5% vs 16.2%
						All Other Countries (n = 830)	pCR rate: 25.0% vs 16.6%

pCR rate*, pCR rate in this table are all total pCR rate. Abbreviations: atezo, atezolizumab; chemo, chemotherapy; pembro, pembrolizumab; pbo, placebo; TNBC, triple-negative breast cancer; pCR rate, pathologic complete response rate; ITT, intention-to-treat population; mPFS, median progression-free survival; mOS, median overall survival; CPS, combined positive score; EFS, event-free survival; PD-L1, programmed death ligand-1; ms, months; ET, endocrine therapy.

Table 2: **Analysis of the asian subgroup in global studies.**

and control arms in the Asian or Asia subgroups across the IMpassion031, IMpassion130, and IMpassion131 studies.[10,12–14] Notably, in the IMpassion130 study, the experimental group's median OS in the Asian subgroup was shorter than the placebo group, even among the PD-L1 positive population. This discrepancy challenges the conclusion drawn from the IMpassion130 study, emphasizing the imperative for more rigorous validation of atezolizumab plus nab-paclitaxel regimen for Asian patients with advanced TNBC.

Subgroup analyses of global studies and clinical trials within Asia have consistently shown the beneficial effects of combining immunotherapy with other approaches for breast cancer, suggesting that combination regimens from global studies are equally applicable to the Asian population. Notably, subtle differences in clinical benefit and tolerance have emerged. The Asian subgroup analysis of KEYNOTE-522 indicated slightly lower odds of grade 3 or 4 treatment-related adverse effects compared to the overall data in the experimental group.[64] These findings suggest that pharmacokinetic variations between racial groups should also be considered. Therefore, further optimization of therapeutic regimens based on these racial specificities could yield more effective treatment options for diverse ethnic groups.

Beyond global trial subgroups, research on ICIs in Asia has yielded valuable insights into breast cancer immunotherapy. The Japanese NEWFLAME trial evaluated the efficacy of nivolumab, abemaciclib, and endocrine therapy in advanced HR-positive/HER2-negative breast cancer, reporting notable antitumor activity but considerable toxicity.[32] Conversely, the South Korean KORNEILA trial demonstrated that combining nivolumab with eribulin yielded promising antitumor effects with manageable toxicity in patients with HER2-negative metastatic breast cancer.[66]

In addition to racial specificity, the high cost of imported ICIs limits patient access to immunotherapy. Conversely, domestically produced ICIs, particularly in China, enhance accessibility and affordability for the Asian population.

Toripalimab is a PD-1 inhibitor developed in China, which binds to the Fg loop of PD-1 via HCDR3, independent of glycosylation modifications.[67] The TORCHLIGHT trial assessed the efficacy and safety of first-line toripalimab plus nab-paclitaxel for metastatic or recurrent TNBC patients.[68] The results indicated a significant enhancement in PFS among PD-L1 positive patients in the experimental arm, along with markedly improved OS regardless of PD-L1 positive, accompanied by manageable adverse effects. The TORCHLIGHT validates the feasibility of employing ICIs alongside chemotherapy in the treatment of TNBC among Chinese patients. Camrelizumab, another Chinese-produced ICI targeting PD-1, has shown promising results in advanced TNBC when combined with angiogenesis inhibitors.[39,41] Beyond toripalimab and camrelizumab, other Chinese-developed ICIs, including the PD-1 inhibitor sintilimab and PD-L1 inhibitor adebrelimab, are undergoing clinical trials in breast cancer (Table 3). The encouraging outcomes with toripalimab and camrelizumab suggest these Chinese-made ICIs may offer cost-effective and potentially more targeted immunotherapy options for patients in China and across Asia. Ongoing and future clinical studies are crucial to establishing their safety and efficacy and advancing their clinical use. It is notable that ICIs independently developed in Asia and related clinical studies are predominantly based in China, reflecting regional imbalances in health economics and underscoring the need for joint efforts in drug development and international cooperation.

Immunotherapy beyond ICIs in Asia

In addition to ICIs, research on ACT and cancer vaccines in Asia has yielded notable insights. Reports on ACT in Asian breast cancer are limited, likely due to its less prevalent use. A retrospective study from Japan indicated that αβ T cell therapy combined with systemic therapies comparable or superior OS and DFS in patients with solid tumors, including 41 with breast cancer.[69] However, due to the retrospective nature of this study, further trials with larger breast cancer cohorts are needed to validate the effectiveness of this cell therapy.

Cancer vaccines in Asia mirrored findings from European and North American countries, indicating good safety and detectable immune response. A Japanese study reported a median OS of 24.4 months in the refractory TNBC population following 6 vaccinations, accompanied by corresponding immune responses.[70] Larger studies are needed for efficacy confirmation. A Singapore phase I trial evaluated an adenovirus vector delivering MUC1 antigen in 21 advanced cancer patients, including 13 with breast cancer. While achieving its primary tolerability endpoint and shifting the cancer immunome, it did not confirm partial or complete responses.[71] Further investigations focusing on racial and ethnic variations in tumor antigens could enhance the efficacy and personalization of vaccine-based immunotherapies.

Precision therapy for breast cancer in Asia

The significant heterogeneity of breast cancer underscores the need for precision therapy. Fudan University Shanghai Cancer Center (FUSCC) spearheads research into precision therapy for Chinese patients with breast cancer. TNBC subtyping facilitates precision treatment and Lehmann et al. initially classified TNBC into six subtypes. Subsequent refinement yielded four subtypes: basal-like 1, basal-like 2, mesenchymal, and mesenchymal stem-like (MSL).[72] Jiang et al., delineated four subtypes including luminal androgen receptor (LAR), immunomodulatory (IM), basal-like immune-

NCT number	Status	Phase	ICI	Targeted immune checkpoint	Conditions	Trial design
NCT06178159	Recruiting	II	Toripalimab	PD-1	HER2+ BC	Toripalimab + Disitamab Vedotin + Pertuzumab vs placebo + Disitamab Vedotin + Pertuzumab
NCT05749575	Recruiting	II	Toripalimab	PD-1	HR+/HER2- BC	Single arm: Toripaliman + Chidamide + Paclitaxel
NCT06105008	Not yet recruiting	II	Toripalimab	PD-1	HR+/HER2 Low BC	Toripalimab + Disitamab Vedotin vs Disitamab Vedotin
NCT05291910	Not yet recruiting	IV	Toripalimab	PD-1	HR + BC	Single arm: Toripalimab + Nab-paclitaxel + Inetetamab
NCT05955105	Active, not recruiting	Ib/IIa	Toripalimab	PD-1	TNBC	Single arm: Toripalimab + ILB-2109
NCT05491694	Not yet recruiting	II	Toripalimab	PD-1	TNBC	Single arm: High Intensity Focused Ultrasound, followed by Toripalimab + Chemotherapy
NCT04418154	Active, not recruiting	II	Toripalimab	PD-1	TNBC	Single arm: Epirubicin hydrochloride + Cyclophosphamide, followed by Toripalimab + Nab-paclitaxel
NCT06227117	Recruiting	II	Toripalimab	PD-1	HR-/HER2 Low BC	Toripalimab + Disitamab Vedotin vs Toripalimab + Disitamab Vedotin + Carboplatin vs Toripalimab + Disitamab Vedotin + sequential Epirubicin + Cyclophosphamide + Toripalimab
NCT06078670	Not yet recruiting	Ib/IIa	Toripalimab, Sintilimab	PD-1	TNBC	Toripalimab + CVL218 + Paclitaxel vs Sintilimab + Paclitaxel vs CVL218 + Sintilimab + Fruquintnib
NCT05088057	Recruiting	II	Camrelizumab	PD-1	TNBC	Single arm: Camrelizumab + Doxorubicin + Cyclophosphamide + Docetaxel
NCT05576389	Enrolling by invitation	II	Camrelizumab	PD-1	g*BRCA*-mut HER2- BC	Single arm: Camrelizumab + Fluzoparib
NCT05085626	Recruiting	II	Camrelizumab	PD-1	HRD + HER2- BC	Camrelizumab + Fluzoparib vs Chidamide + Fluzoparib
NCT05656131	Recruiting	II	Camrelizumab	PD-1	HRD- BC	Camrelizumab + Fluzoparib vs Fluzoparib
NCT05447702	Recruiting	II	Camrelizumab	PD-1	TNBC	Single arm: Camrelizumab + Apatinib + Chemotherapy
NCT05438706	Not yet recruiting	II	Camrelizumab	PD-1	TNBC	Camrelizumab + Chidamide + Capecitabine vs Camrelizumab + Chidamide + Carboplatin
NCT04907344	Not yet recruiting	II/III	Camrelizumab	PD-1	TNBC	Camrelizumab + Nab-paclitaxel + Carboplatin vs Nab-paclitaxel + Carboplatin
NCT05761470	Recruiting	II	Camrelizumab	PD-1	HRRmut BC	Camrelizumab + Fluzoparib + Nab-paclitaxel
NCT05097248	Not yet recruiting	II	Camrelizumab	PD-1	TNBC	Camrelizumab + Liposomal doxorubicin + Losartan
NCT05670925	Recruiting	II	Camrelizumab	PD-1	TNBC	Single arm: Camrelizumab + Famitinib with/without Nab-palitaxel
NCT05475678	Recruiting	II	Camrelizumab	PD-1	TNBC	Camrelizumab + Docetaxel + Carbolplatin vs Docetaxel + Carboplatin
NCT04481763	Recruiting	Ib/II	Camrelizumab	PD-1	TNBC	Camrelizumab + Radiotherapy
NCT05760378	Recruiting	III	Camrelizumab	PD-1	IM TNBC	Camrelizumab + Famitinib + Nab-palitaxel + Capecitabine + Eribulin Mesylate + Carboplatin vs Camrelizumab + Nab-palitaxel + Capecitabine + Eribulin Mesylate + Carboplatin
NCT05999149	Recruiting	III	Camrelizumab	PD-1	TNBC	Camrelizumab + Nab-paclitaxel + Carbioplatin + Famitinib vs Camrelizumab + Nab-paclitaxel + Carbioplatin
NCT06308939	Not yet recruiting	II	Sintilimab	PD-1	HER2- BC	Single arm: Sintilimab + Erilulin
NCT05843292	Not yet recruiting	IV	Sintilimab	PD-1	TNBC	Single arm: Sintilimab + Taxane + Carboplatin
NCT05386524	Recruiting	II	Sintilimab	PD-1	TNBC	Single arm: Sintilimab + Bevacizumab biosimilar + Pegylated liposomal doxorubicin
NCT04877821	Recruiting	II	Sintilimab	PD-1	TNBC	Single arm: Sintilimab + Anlotinib + Nab-paclitaxel + Carboplatin + Epirubicin + Cyclophosphamide
NCT04734262	Active, not recruiting	II	Tislelizumab	PD-1	TNBC	Tislelizumab + Sitravatinib vs Tislelizumab + Sitravatinib + Nab-paclitaxel
NCT05746728	Not yet recruiting	Ib/II	Tislelizumab	PD-1	TNBC	Singel arm: Tislelizumab + Surufatinib
NCT04914390	Recruiting	II	Tislelizumab	PD-1	TNBC	Single arm: Tislelizumab + Anlotinib + Doxorubin + Epirubicin + Nab-paclitaxel
NCT05861635	Recruiting	IV	Tislelizumab	PD-1	HER2- Low BC	Single arm: Tislelizumab + Disitamab Vedotin

(Table 3 continues on next page)

NCT number	Status	Phase	ICI	Targeted immune checkpoint	Conditions	Trial design
(Continued from previous page)						
NCT04276493	Active, not recruiting	Ib/II	Tislelizumab	PD-1	BC	Tislelizumab + ZW25 + Capecitabine + Oxaliplatin vs ZW25 + Docetaxel
NCT04802876	Recruiting	II	Tislelizumab	PD-1	TNBC	Tislelizumab vs Spartalizumab
NCT04577963	Active, not recruiting	Ib/II	Tislelizumab	PD-1	TNBC	Tislelizumab + Fruquintinib
NCT05726175	Not yet recruiting	II	Penpulimab	PD-1	HER2-Low BC	Single arm: Penpulimab + Disitamab Vedotin
NCT05244993	Not yet recruiting	II	Penpulimab	PD-1	TNBC	Single arm: Penpulimab + Anlotinib hydrochloride + Nab-paclitaxel
NCT05632848	Recruiting	II	Zimberelimab	PD-1	TNBC	Single arm: Zimberelimab + Chidamide
NCT06238921	Not yet recruiting	I/II	Zimberelimab	PD-1	TNBC	Single arm: Zimberelimab + Stereotactic Radiation + Sacituzumab govitecan
NCT06149130	Recruiting	II	Adebrelimab	PD-L1	HR+/HER2- BC	Single arm: Adebrelimab + Dalpiciclib + Standard Endocrine Therapy
NCT06254066	Not yet recruiting	II	Adebrelimab	PD-L1	HRD+ HR+/HER2- BC	Single arm: Adebrelimab + Fluzoparib
NCT05353361	Recruiting	Ib/II	Adebrelimab	PD-L1	BC	Adebrelimab + SHR-A1811 vs Pyrotinib + SHR-A1811 vs Pertuzumab + SHR-A1811 vs Albumin-bound paclitaxel + SHR-A1811
NCT06229067	Not yet recruiting	II	Adebrelimab	PD-L1	TNBC	Adebrelimab + Vinorelbine + Cyclophosphamide + Capecitabine vs Vinorelbine + Cyclophosphamide + Capecitabine
NCT06165900	Recruiting	II	Adebrelimab	PD-L1	TNBC	Adebrelimab + Stereotactic Radiotherapy + Nab-paclitaxel + Carboplatin vs Adebrelimab + Nab-paclitaxel + Carboplatin

Abbreviations: PD-1, programmed death-1; PD-L1, programmed death ligand-1; BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TNBC, triple-negative breast cancer; g*BRCA*-mut, germline-breast cancer susceptibility gene mutation; HRD, homologous recombination deficiency; HRRmut, homologous recombination repair gene mutation; IM, immunomodulatory.

Table 3: **Ongoing clinical trials of Chinese-developed ICIs in breast cancer.**

suppressed (BLIS), and mesenchymal-like (MES), which is called Fudan Subtype.[59] To be specific, HER2-low TNBC was also classified into receptor tyrosine kinase-relevant (TKR) subtype, basal-like (BSL) subtype, and MSL subtype to guide the treatment of it.[73] Subsequent trials, including FUTURE and FUTURE-SUPER, have implemented precision treatments based on the Fudan Subtype, yielding promising outcomes, and validating that immunotherapy can be beneficial for the IM subtype.[74,75]

In contrast to the prevailing subtyping of TNBC in European and North American countries, the Fudan Subtype preserves the IM subtype, comprising about 20% of TNBC cases. Notably, patient selection for immunotherapy based on the IM subtype may inadvertently exclude beneficiaries. Approximately half of TNBC patients derive benefit from immunotherapy in clinical trials,[11] particularly those with high PD-L1 expression, with the IM subtype identified by CD8 expression.[75] Moreover, shifts in subtype distribution and genomic profiles in Asia have influenced precision treatment.[55] For instance, a higher prevalence of HER2-enriched subtype suggests a larger population may respond favorably to anti-HER2-targeted therapy. Similarly, the increased frequency of *AKT1* mutations indicates a greater likelihood of benefiting from protein kinase B (AKT) inhibitors.

Precision therapy based on refined molecular typing offers increased hope for patients with breast cancer, particularly those with TNBC. FUSCC's comprehensive studies exemplify precision therapy advancements in Asia. Future studies and clinical research are needed to deepen our understanding of breast cancer and address clinical challenges.

Conclusion

The advent of immunotherapy represents a significant stride in cancer treatment. Our review delineates the current landscape and future directions of immunotherapy in breast cancer, with a particular focus on its application in Asian patients. Combining ICIs with conventional therapies shows promise, while alternative approaches like ACT and cancer vaccines offer additional opportunities. Most studies currently focus on TNBC subtypes, but recent explorations into luminal subtypes, traditionally considered to have inactive immune microenvironments, have expanded the potential patient population for immunotherapy. The identification and development of biomarkers are also enhancing patient screening for these treatments.

We discuss subgroup data from global studies, immunotherapeutic drugs, and trials conducted

independently in Asia, highlighting the racial specificity of immunotherapy and confirming its feasibility for Asian populations. Ethnic differences between Asian and Western populations highlight the need for tailored immunotherapy protocols and agents aligned with local pharmacokinetics and pharmacodynamics. Future advancements in personalized precision therapy, informed predictive biomarkers and multidisciplinary models, along with an emphasize on racial specificity, are anticipated to advance the application of immunotherapy in breast cancer treatment.

Contributors

Ke-Da Yu and Rui-Chen Xu initiated the concepts. Rui-Chen Xu conceived and drafted the manuscript and drew the tables. Ke-Da Yu, Cui-Cui Liu, Yan-Wu Zhang, Ying-Ying Xu, and Zhi-Ming Shao discussed the concepts, provided valuable suggestions, and revised the manuscript. All authors revised the manuscript critically and approved the submission of the manuscript in its current form.

Declaration of interests

The authors declare no conflict of interest.

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