Expert consensus on the clinical application of immunotherapy in breast cancer: 2024

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Background: Significant progress has been made in immunotherapy of breast cancer (BC) with the approval of multiple immune checkpoint inhibitors (ICIs), particularly in early and metastatic triple-negative breast cancer (TNBC) settings. Most guidelines have recommended immune therapy as the important approach in BC, yet several critical aspects still require further clarification, including proper patient selection, treatment duration, optimized chemotherapy partner, predictive biomarkers, and specific considerations for Chinese patients.

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Methods: (I) Establishment of expert group: the expert group consists of 32 experts from departments such as medical oncology, breast surgery, and pathology; (II) literature search: mainly conducted in English databases (such as PubMed, Embase, and Cochrane Library) and Chinese databases (such as China National Knowledge Infrastructure, China Biology Medicine disc, and Wanfang Database), with a search cutoff date of April 23, 2024; (III) assessment of evidence quality and recommendation strength: evidence quality and recommendation opinions are graded based on the evidence category and recommendation level of the Chinese Society of Clinical Oncology (CSCO) guidelines; (IV) consensus formulation: on the March 2, 2024, through online consensus meeting, the consensus content is thoroughly discussed, and opinions from all experts are solicited.

Results: The consensus meeting has resulted in 15 detailed recommendations, providing clearer guidance on the clinical application of immunotherapy in BC management. The core suggestions are as follows: for early-stage II–III TNBC and metastatic TNBC (mTNBC) in the first-line setting, programmed cell death protein 1 (PD-1) inhibitors can be considered. However, for hormone receptor-positive/human epidermal growth factor receptor 2-negative BC ($HR^+/HER2^-$ BC), $HER2^+$ BC, and mTNBC in later lines of therapy, evidence is lacking to support the use of immunotherapy.

Conclusions: This consensus provides a comprehensive overview of BC immunotherapy, including immunotherapy for early-stage BC and late-stage BC, immune related adverse event (irAE) management, biomarkers of immunotherapy, and future directions. The consensus consolidates these deliberations into 15 evidence-based recommendations, serving as a practical guide for clinicians to more scientifically and systematically manage the clinical application of immunotherapy.

Keywords: Breast cancer (BC); immunotherapy; expert consensus

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Introduction

Breast cancer (BC) ranks to the most common malignant cancer exceeding lung cancer globally in 2020. And BC in China with 416,000 new cases diagnosed every year becomes the main female cancer related mortality accounting for 18.4% of global BC burden (1). In recent years, with significant improvement in diagnose and therapy and fast development of novel anti-tumor drugs, overall survival (OS) of BC has been largely extended. Immune checkpoint inhibitors (ICIs) as an excellent example of immunotherapy shows its promising efficacy and brought new survival hope to BC patients especially in triple-negative breast cancer (TNBC). Most guidelines have underscored the significance of immunotherapy in BC management (2-4), providing certain treatment regimens. However, in clinical practice, there remain several aspects where recommendations are less clear, such as proper patient selection, optimized chemotherapy partner, predictive biomarkers, the scientific management of side effect, etc.

Methods

Professor Zefei Jiang, Vice President and Secretary General of the Chinese Society of Clinical Oncology (CSCO), took the lead in formulating an expert consensus on the clinical application of immunotherapy in BC.

The steps for developing the consensus include (I) establishment of expert group: the expert group consists of 32 experts from departments such as medical oncology, breast surgery, and pathology; (II) literature search: mainly conducted in English databases (such as PubMed, Embase, and Cochrane Library) and Chinese databases (such as China National Knowledge Infrastructure, China Biology Medicine disc, and Wanfang Database), with a search cutoff date of April 23, 2024; (III) assessment of evidence quality and recommendation strength: evidence quality and recommendation opinions are graded based on the evidence category and recommendation level of the CSCO guidelines, CSCO evidence quality and recommendation grades are shown in Tables S1,S2; (IV) consensus

formulation: on the March 2, 2024, through online consensus meeting, the consensus content is thoroughly discussed, and opinions from all experts are solicited. The initial draft is compiled by the lead author, and other experts review and revise it collectively to finalize the manuscript, summary of expert recommendations refer to Table S3.

Immunotherapy for early-stage TNBC (eTNBC)

Treatment timing selection of immunotherapy in eTNBC

Immunotherapy, characterized by its unique antitumor mechanisms, it is more likely to offer prolonged survival benefits for BC patients. Compared to adjuvant immunotherapy, neoadjuvant immunotherapy maintains heightened immune activation post-surgery, effectively targeting residual tumor cells (5). In a preclinical mouse model of BC, neoadjuvant checkpoint inhibitor combination therapy with anti-programmed cell death protein 1 (PD-1) and anti-CD137 induces a stronger early expansion of tumor-specific cluster of differentiation 8 $(CD8)^+$ T cells than the same combination applied in the adjuvant setting and is directly associated with long-term survival (6).

Multiple studies showed efficacy of immunotherapy in neoadjuvant setting. KEYNOTE-522 (7-9) and IMpassion031 (10) showed higher pathological complete response (pCR) rates by 13.6% (64.8% *vs.* 51.2%, P<0.001) and 17% (58% *vs.* 41%, P=0.004) respectively in eTNBC. And 5-year event-free survival (EFS) benefit has also been seen in subsequent follow-up in KEYNOTE-522. Another phase II cTRIO study (11) focusing on Chinese patients confirmed the efficacy of immunotherapy in neoadjuvant of eTNBC (stages II–III) with 56.5% of pCR from chemotherapy and tislelizumab combination, which also showed good safety profile and well tolerance.

The ALEXANDRA/IMpassion030 trial is the first phase III study evaluating adjuvant chemo ± atezolizumab in eTNBC. This study enrolled 2,300 TNBC patients in stage II or III. After surgery, patients were randomized 1:1 into either receive chemotherapy plus atezolizumab or chemotherapy alone. The final analysis shows no improved disease-free survival (iDFS) improvement with the addition of atezolizumab to adjuvant chemotherapy [hazard ratio (HR) =1.11] (12).

For eTNBC candidates for neoadjuvant therapy, the CSCO guidelines (13) specify tumors >2 cm as the threshold for neoadjuvant consideration based solely on TNBC status. Concurrently, the Chinese Expert Consensus on Neoadjuvant Therapy for Breast Cancer (3) recommends neoadjuvant therapy for TNBC with substantial tumor burden (T2, N1+, or higher). Duration of immunotherapy is another important factor to be considered in neoadjuvant setting. The regimen choice and cycles of neoadjuvant chemotherapy mainly referred to the adjuvant therapy setting in last decades. Guidelines or consensus from China and Canada recommend patients to complete the standard duration of 6–8 cycles therapy before surgery (2-4). Pembrolizumab has been approved for the neoadjuvant therapy in eTNBC. KEYNOTE-522 study demonstrated a high rate of pathologic complete response (pCR) when pembrolizumab was combined with chemotherapy for 8 cycles in neoadjuvant setting, and there was an interim assessment at 4 cycles so as to determine continuation of treatment or transition to surgery for each patient (7-9).

Highlight box

Key recommendations

- For early-stage II–III triple-negative breast cancer and metastatic triple-negative breast cancer (mTNBC) in the first-line setting, programmed cell death protein 1 inhibitors can be considered. For $HR^+/HER2^-$ breast cancer (BC), $HER2^+$ BC, and mTNBC in later lines of therapy, evidence is lacking to support the use of immunotherapy.

What was recommended and what is new?

- Immunotherapy is widely endorsed in numerous guidelines as a pivotal treatment for breast cancer, with specified regimens provided for diverse subtypes and stages.
- Building upon existing frameworks, this consensus presents detailed, customized recommendations addressing crucial aspects of breast cancer immunotherapy: proper patient selection, treatment duration, optimized chemotherapy partner, predictive biomarkers, and specific considerations for Chinese patients. These refinements coalesce into a set of 15 key recommendations, aimed at enhancing the precision and practical application of immunotherapy in clinical practice.

What is the implication, and what should change now?

- The emergence of immune checkpoint inhibitors has transformed cancer treatment, significantly advancing the management of malignancies through pharmacology. However, the complexity of clinical scenarios hinders the broad application of immunotherapy in breast cancer. To address this, it is crucial to acknowledge and tackle these challenges, ultimately extending the benefits of immunotherapy to more breast cancer patients and promoting its wider use.

Recommendation 1: for stage II–III TNBC patients eligible for neoadjuvant chemotherapy, it can be considered for a combined immunochemotherapy regimen in the neoadjuvant treatment phase. It is recommended to do imaging-based efficacy evaluations every 2 cycles during the course of treatment. For patients who have good response (including complete or partial remission or stable disease (SD) without significant enlargement) to neoadjuvant therapy, it is recommended to full complete the proposed treatment course, while for those with disease progression should modify the therapeutic regimen timely (IA, Grade 1).

Patient selection of immunotherapy for eTNBC

Suitable population selection differs a little according to chemotherapy alone or combine with immune drugs in neoadjuvant setting. Multiple studies of immune combination with chemotherapy in neoadjuvant TNBC setting mainly enrolled patients of stages II–III and even with negative lymph nodes patients. KEYNOTE-522 was the only study approved by Food and Drug Administration (FDA) and National Medical Products Administration (NMPA), which recruited newly diagnosed, unpretreated eTNBC (T1c, N1–2 stage or T2–4, N0–2 stage) patients. The regimen of pembrolizumab with chemotherapy in KEYNOTE-522 showed enhanced pCR rates and EFS benefit independent of tumor size, lymph node status or staging. This combination regimen showed better 5-year EFS versus chemotherapy alone. The HR of 5-year EFS is more favorable in stage II than III patients (0.59 *vs.* 0.71), and more favorable in lymph node-negative versus positive patients (0.56 *vs.* 0.67) (7-9). Although there is no head-to-head evidence, we can still see the trend that patients with earlier stage can benefit more from immunotherapy and patient even with negative lymph node status can also choose immunotherapy in neoadjuvant setting. National Comprehensive Cancer Network (NCCN) Guidelines (2023, V5) recommend pembrolizumab in combination with chemotherapy as neoadjuvant regimen for high-risk, eTNBC (stage II–III), followed by adjuvant pembrolizumab alone as the preferred choice (14).

Recommendation 2: it is recommended that immunotherapy be considered for patients with eTNBC who are operable and in II–III stages; based on KEYNOTE-522 study, patients with low tumor burden (cT2N0) can also be considered to receive combined immunotherapy (IA, Grade 1).

Chemotherapy regimen selection of immunotherapy for eTNBC

There are many chemotherapy partners in TNBC neoadjuvant therapy including anthracyclines, taxanes, platinum agents, and cyclophosphamide. Anthracycline combining or followed by taxanes are still most preferred. In patients with heavy tumor burden, paclitaxel with platinum regimen can significantly increase pCR rate and improve prognosis. In KEYNOTE-522 study paclitaxel with platinum and then followed by anthracycline enhanced both pCR and EFS rates in TNBC patients (7-9). There is still controversy of whether need to combine anthracycline in TNBC therapy. phase II NeoPACT study (15) showed patients treated with preoperative anthracycline-free chemotherapy (carboplatin and docetaxel) with pembrolizumab achieved a pCR rate of 58% and a 3-year EFS of 86%. cTRIO study showed patients treated with 6 cycles of non-anthracycline (nab-paclitaxel + carboplatin + tislelizumab) achieved a pCR of 56.5% (11). All above data are in accordance with pCR benefit from other trials of anthracycline as immunotherapy partner. SWOG 2212 trial (SCARLET) (16) will evaluate EFS of patients who received anthracycline (KN522 regimen) versus non-anthracycline (NeoPACT regimen) chemotherapy backbone and this trial can provide more options to chemo-partner choose strategies in neoadjuvant immunotherapy.

Recommendation 3: based on KEYNOTE-522 study, when considering immunotherapy in the combination with chemotherapy, it is recommended to employ a chemotherapy regimen that begins with combination of taxanes and platinum agents followed by anthracyclines. Taxane and platinum drugs combination can also be considered as an optional choice (IB, Grade 2).

Adjuvant therapy strategies after eTNBC neoadjuvant immunotherapy

Patients with pCR after neoadjuvant therapy have good prognosis. KEYNOTE-522 study showed if patients who received immunotherapy in neoadjuvant setting chose to continue immune therapy in subsequent adjuvant setting in TNBC could have improved prognosis regardless of pCR or not. After long term follow-up, 5-year absolute benefit of EFS (92.2% *vs.* 88.2%) was larger than 3-year absolute benefit of EFS (94.4% *vs.* 92.5%) in pCR patients (8,9). In order to confirm the value of pembrolizumab in adjuvant post neoadjuvant setting, an OptimICE-PCR (NCT05812807) study has been conducted in which the

patients achieving pCR in neoadjuvant with chemotherapy and immunotherapy were randomized to receive pembrolizumab or observation in adjuvant setting, and this trial will provide more hints or suggestions for pCR patients' adjuvant regimen choice.

For non-pCR eTNBC patients who have received neoadjuvant chemotherapy, CREATE-X study (17) showed that capecitabine as adjuvant regimen significantly iDFS and OS after anthracycline and paclitaxel combination regimen in neoadjuvant therapy. In OlympiA study (18), non-pCR TNBC patients with germline BRCA mutation (BRCAm) who received 1 year of olaparib as adjuvant therapy had higher 3-year iDFS rate (81.4% *vs.* 67.7%) versus placebo. With 3.5 years of median follow-up, OlympiA demonstrates statistically significant improvement in OS with adjuvant olaparib compared with placebo for gBRCA1/2pv-associated early breast cancer (EBC) (4-year OS rate 89.8% *vs.* 86.4%). Moreover, subgroup benefits were consistent with the overall population (19). In KEYNOTE-522 study, patients with residual lesions in pembrolizumab group had better survival versus placebo (5-year EFS: 62.6% *vs.* 52.3%). But subgroup analysis showed that patients with a residual cancer burden (RCB) score of 3 had worse outcomes (8,9), and maybe we need to find better treatment strategies for these non pCR population. There is no direct evidence for pembrolizumab combining with capecitabine or olaparib in adjuvant setting, but two trials of capecitabine with pembrolizumab in metastatic BC (mBC) are ongoing which showed manageable toxicity and safety profile, and the most common adverse events are consistent with that of capecitabine monotherapy (20,21). These data may suggest capecitabine and pembrolizumab regimen as suitable combination partner.

Recommendation 4: for pCR TNBC patients, if PD-1 inhibitor drugs have been used before surgery, it is recommended to continue PD-1 inhibitor drug therapy for 1 year after surgery (IA, Grade 1).

Recommendation 5: for non-pCR TNBC patients, if PD-1 inhibitors have been used before surgery, it can be considered to continue using PD-1 inhibitors for 1 year after surgery (IA, Grade 1).

Recommendation 6: for non-pCR TNBC patients, there is insufficient evidence of postoperative immunotherapy combining with capecitabine or olaparib, but clinical experts believe it can be considered to use based on previous data and clinical experience (IIB, Grade 3).

Immunotherapy for mBC

First-line immunotherapy for metastatic TNBC (mTNBC)

IMpassion130 study (22,23) showed atezolizumab + nab-paclitaxel significantly improves progression-free survival (PFS) compared to placebo + nab-paclitaxel in both programmed death-ligand 1 (PD-L1) positive and intention-to-treat (ITT) mTNBC population. Although no significant difference in OS benefit between atezolizumab and control arms in ITT population, there is a clinically significant 7.5 months extended benefits in PD-L1 positive patients' median OS (mOS). And the PD-L1 positive was defined as immune cells (ICs) ≥1% (SP142) in this trial. But regretfully the confirmatory study of IMpassion131 (24) with paclitaxel combining atezolizumab did not duplicate the above benefit trend.

In KEYNOTE-355 study (25,26), mTNBC patients with PD-L1-positive [combined positive score (CPS) ≥10] treated by pembrolizumab and chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine plus carboplatin) had significantly longer mPFS (9.7 *vs.* 5.6 months) and mOS (23.0 *vs.* 16.1 months) versus mono-chemotherapy, and pembrolizumab treatment arm showed both enhanced objective response rate (ORR) and median duration of response (DoR) regardless of chemotherapy partners. The phase III TORCHLIGHT study (27) from China showed toripalimab + nab-paclitaxel treatment group significantly prolonged PFS benefit of mTNBC patients in PD-L1-positive (CPS ≥1) and ITT populations, and there was also a significant trend of OS benefit. The application for the combination of toripalimab with chemotherapy as a treatment for advanced TNBC patients has been accepted for review, it may provide a new treatment option for mTNBC patients in China.

Recommendation 7: for PD-L1 positive mTNBC patients (same as mTNBC patients in China), based on current evidence, combination of chemotherapy and ICIs can be recommended. Pembrolizumab + chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine + carboplatin) (CPS ≥10) or toripalimab + nab-paclitaxel (CPS ≥1) can be considered as the first-line treatment (IA, Grade 1).

Maintenance therapy and treatment duration of first-line immunotherapy for mTNBC

In KEYNOTE-355 study (25,26), among patients who received pembrolizumab with chemotherapy and then

achieving complete response (CR), partial response (PR), or SD ≥24 weeks, the median duration of immunotherapy was 14 months for patients who early discontinued chemotherapy and the duration of chemotherapy in these patients was 6 months. These patients were proven to have similar final efficacy to that of ITT populations, the duration of immunotherapy they received would be longer if with higher CPS scores, and finally all could convert to PFS and OS benefit. Therefore, for patients who achieved CR/PR/SD after immunotherapy with chemotherapy, immune monotherapy as a maintenance regimen should be continued after chemotherapy discontinuation and could be used till disease progression or intolerable toxicity. The optimal maintenance therapeutic strategy for immunotherapy still needs further exploration.

Recommendation 8: for patients who achieve CR/PR/SD through immune and chemotherapy combination, it is recommended to maintain immunotherapy till disease progresses or intolerable toxicity. Simultaneously, regularly evaluation of the efficacy should be given during the treatment so as to adjusted treatment regimen timely once disease progress occurred (IIA, Grade 2).

Safety management of immunotherapy

Immunotherapy functions by reshaping T lymphocyte activity, counteracting tumor balance mechanisms, reversing immune escape, activating immune responses (28), and then activates the killing effect of ICs on tumor cells. But, because of the new antigens generated by tumor mutations may be highly homologous with the autoantigens expressed in normal tissues, ICIs may also cause damage to normal tissues (29). In addition, due to activation of immune response, factors such as increased levels of inflammatory cytokines and existing autoantibodies in the body may also lead to a wide range of inflammatory side effects, which are commonly referred to as immune related adverse events (irAEs) (30). Although irAEs have a broad toxicity spectrum, irAEs are most commonly seen in the gastrointestinal tract, endocrine glands, skin, and liver (31). It rarely involves the central nervous system, cardiovascular system, lungs, musculoskeletal system, and blood system (30). Different to chemotherapy side effect, irAEs mostly occur later and most of these irAEs are mild and reversible if detected early and specifically addressed (32-34).

Once irAEs occur, it is recommended to accurately assess the severity based on symptoms and signs, laboratory tests, and imaging examinations, and develop a treatment plan suitable for the patient hierarchically (35). The common irAEs in BC ICIs trials are infusion reaction, thyroid dysfunction and severe skin reaction (7,8). irAEs can be effectively managed by interrupting ICI treatment and using glucocorticoids or hormone replacement therapy. Therefore, early identification and intervention of irAEs is the key factor to ensure sustainable benefits for patients in immunotherapy combination therapy (34). Assessing the susceptibility of patients to irAEs before starting ICIs therapy, knowing irAEs spectrum beforehand, identifying irAEs as early as possible based on their clinical symptoms, and dynamically monitoring common irAEs related indicators during immunotherapy are all important measures to prevent the risk of irAEs (35). After occurrence of side effect, timely clinical management of irAEs should be carried out according to toxicity grading principle. If necessary, multidisciplinary teams consultations would be needed, and restart ICI treatment at an appropriate time after irAEs have resolved (36).

Recommendation 9: for BC patients undergoing ICIs therapy, we recommend proactive irAEs monitoring, patient education focused on prevention, and prompt identification of irAEs based on clinical signs. This underscores the necessity of thorough irAE management training for healthcare teams. The management principles can refer to the "management of immune checkpoint inhibitor-related toxicity" published by the CSCO (35) (IIA, Grade 1).

Biomarkers for immunotherapy of BC

Immunotherapy has made some progress, but some patients still have limited benefits. Some predictive biomarkers related to immune response can serve as important evidence to proper patients selection. Currently, emerging potential biomarkers include PD-L1 expression, tumor-infiltrating lymphocytes (TILs), tumor mutation burden (TMB), and microsatellite instability (MSI).

The role and value of PD-L1 in the treatment of BC

PD-L1 is widely expressed in activated T cells, B cells, and macrophages, and can bind to PD-1 to mediate immune escape. PD-L1 expressed in 40% to 60% of breast tumors, and its prognostic value differed in multiple studies (37,38). Previous clinical studies in mTNBC, including KEYNOTE-012, KEYNOTE-355, and IMpassion130, have shown that immunotherapy more effective for PD-L1 positive patients (9,39,40). Patients with PD-L1 positive

(CPS ≥1) in KEYNOTE-522 study and PD-L1 positive (TPS ≥1%) in IMpassion031 study confirmed the advantages of immune combination therapy, but the clinical benefit had no relation with PD-L1 expression status (9,41). Therefore, PD-L1 cannot be used as a full independent indicator to predict immunotherapy efficacy. This may be because of the heterogeneity of PD-L1 expression and different immune microenvironments in early and metastatic patients.

At present, PD-L1 detection mainly relies on immunohistochemical methods, with five types of test kits including 22C3, 28-8, SP263, JS311, and SP142. Among them, 22C3, 28-8, SP263, and JS311 have high consistency, while SP142 has poor consistency with the above four. There are different outcomes in PD-L1 expression level among different detection methods, with a positive overlap of ranging from 63% to 70% (42). In clinical practice, the approved indications and testing standards for PD-L1 testing vary by different ICIs drugs. Therefore, it is recommended to choose the corresponding PD-L1 antibody clone, testing platforms, and scoring methods based on different anti PD-1/PD-L1 agents.

Recommendation 10: clinical research shows that eTNBC can benefit regardless of the expression level of PD-L1, and the expression level of PD-L1 in advanced BC is related to the efficacy of PD-1/PD-L1 inhibitor. In clinical practice, the approved indications and testing standards for PD-L1 testing vary by different ICIs Therefore, it is recommended to choose the corresponding PD-L1 antibody clone, testing platforms, and scoring methods based on different anti PD-1/PD-L1 agents (Table S4) (IIA, Grade 2).

Selection of specimens for PD-L1 testing

PD-L1 detection should be first performed in paraffin embedded tumor tissue specimens, and surgical resection and biopsy specimens can also be used (43). Studies have demonstrated a high degree of consistency in PD-L1 expression rates among multiple tissue blocks from the same tumor (44). Cytological specimens, usually handled with methods such as ethanol fixation, direct smear, or liquid based sectioning, distinct from those used for tissue specimens, so it is not recommended to test them in cytological specimens now. Due to lack of experimental validation evidence, it is currently not recommended to perform PD-L1 immunohistochemistry (IHC) detection in decalcified bone metastasis specimens (43).

There is obvious inconsistency in expression of PD-L1 between primary and mBC lesions. The expression level of PD-L1 in lung, soft tissue or lymph node metastases is higher than that in the primary lesion, and the positive rate in liver, skin and bone metastases is lower than that in the primary lesion (42). Therefore, it is crucial to re-evaluate expression status of PD-L1 in biopsy samples with distant metastasis. Neoadjuvant therapy may cause some alteration in PD-L1 expression, but there is no clear evidence to verify the impact of these changes on treatment efficacy currently. Therefore, both tumor samples before and after treatment can be used to test PD-L1. Tumor tissues from new recurrences or metastatic lesions are the more accurate reflection of biomarker status, so PD-L1 testing should be prioritized for these tissues once available.

Recommendation 11: it is recommended to prioritize PD-L1 testing in paraffin embedded tissue. Surgical resection specimens and biopsy specimens can both be used for PD-L1 testing (IA, Grade 1).

Recommendation 12: both primary and recurrent/metastatic lesions can be used for PD-L1 testing. It is recommended to prioritize PD-L1 testing in tumor tissue from recurrent/metastatic lesions (IIA, Grade 2).

Other biomarkers in immunotherapy of BC

TILs refer to a heterogeneous population of lymphocytes mainly present in tumor nest and stroma, playing an immune response and regulatory role in tumor immune mechanism. TILs are more common in TNBC and HER2 positive BC, and high levels of TILs are related to good prognosis of TNBC and HER2 positive BC, but the prognostic relationship between TILs and luminal BC is unclear (45,46). In GeparNuevo study, the pCR rate of eTNBC treated with Durvalumab and chemotherapy in neoadjuvant setting was significantly correlated with the increased interstitial TILs ($P<0.01$). eTNBC patients with medium/high TILs expression had a better trend of survival benefits compared to patients with low TILs expression (47). The IMpassion130 study classified TILs in PD-L1 positive advanced TNBC patients into immune-inflamed, immune-excluded, and immune desert types. Among them, ICIs are more likely to exert anti-tumor effects in immune-inflamed types. Among PD-L1 positive patients, CD8 positive and matrix TILs positive patients have better immunotherapy efficacy (48).

MSI refers to the phenomenon of short, repetitive DNA sequence length changes caused by insertion or

deletion mutations during DNA replication, often caused by mismatch repair (MMR) functional defects. MSI high (MSI-H) tumors have characteristic high mutations and abundant peptide expression, which can act as new antigens to trigger rapid immune responses. Due to its unstable and highly mutated nature, some malignant tumors express high-level checkpoint proteins, including PD-1 and PD-L1, which also makes MSI-H tumors more sensitive to PD-L1/PD-1 inhibitor immunotherapy. In 2017, US FDA approved pembrolizumab in MSI-H or deficient MMR (dMMR) solid tumor patients who had progressed after previous treatment based on five single arm studies (KEYNOTE-016/164/012/028/158). MSI-H is the first pan solid tumor immunotherapy biomarker. However, the prevalence of MSI-H in BC is extremely low (0–1.5%), so there is lack of clinical efficacy data of MSI-H BC population (49).

TMB refers to the number of somatic non synonymous mutations per Mb base in the exon region. Tumors with high TMB may produce more new antigens, which can activate more T cells within the tumor and generate a stronger immune response. TMB of BC is related to molecular typing, and counting of the average total mutation in TNBC is highest, then sequentially followed by HER2$^+$, luminal B, luminal A subtypes (50). KEYNOTE-119 study (51) also showed a positive correlation between TMB and clinical benefits of pembrolizumab treatment in mTNBC patients, but no correlation with chemotherapy efficacy.

Recommendation 13: there is lack of evidence that these biomarkers such as TILs, TMB, and MSI are prognostic or predictive, large-sample studies are needed to validate their clinical utility (IIB, Grade 3).

Prospects for immunotherapy in the future

Combination of immunotherapy with novel targeted drugs as first-line (1L) therapy and immunotherapy as second (2L) or later lines of therapy in mTNBC

The phase II FUTURE-C-PLUS study (52) showed that the combination of camrelizumab, famitinib, and nab-paclitaxel had promising anti-tumor efficacy in first-line treatment of immunomodulatory type (IM) (CD8 ≥10%) mTNBC patients with ORR 81.3%, PFS 13.6 months, OS 29.4 months, and disease control rate (DCR) 95.8%, and the side effects were manageable. Subsequently, the FUTURE-SUPER umbrella study (53) based on the "Fudan subtype" found that the IM group with the same combination regimen was with the greatest PFS benefit during which the absolute benefit was up to 8.6 months (15.1 *vs.* 6.5 months). The TOPACIO and MEDIOLA studies (54,55) have shown that immunotherapy combining with poly ADP-ribose polymerase (PARP) inhibitors could provide clinical benefits for mTNBC with BRCA mutations. The KEYLYNK-009 study (56) showed that in first-line maintenance treatment of mTNBC patients, pembrolizumab + olaparib did not significantly improve PFS and OS in ITT population compared to pembrolizumab + chemotherapy, but prolong PFS in patients with somatic BRCA mutations. Pembrolizumab + olaparib group had a lower incidence of treatment-related adverse events (TRAEs). The BEGONIA study cohort 7 (57) and COLET study (58) both showed that the combination of Dato-DXd and MEK inhibitor (cobimetinib) with immunotherapy had certain anti-tumor activity in first-line treatment of mTNBC patients. The above studies indicate that novel targeted drugs combining with ICIs has potential value for mTNBC patients, but lack of large phase III randomized controlled studies to validate the efficacy.

For mTNBC patients previously treated by systemic therapy, KEYNOTE-119 study (51) showed pembrolizumab did not improve OS for patients, but there was benefit trend in patients with PD-L1 CPS ≥20. In a phase II study (59), toripalimab with VEX (vinorelbine + cyclophosphamide + capecitabine) metronomic group showed better DCR and PFS benefit for ≤1 line previous chemotherapy in HER2 negative mBC. In a phase II single-arm study, the triple combination of camrelizumab, apatinib, and eribulin showed good efficacy and manageable safety profile in mTNBC patients treated by multiple lines of therapy (60). Some phase I to II trials are focusing on ≥2 lines treatment of mTNBC, but none can be recommended as strong evidence. In clinical practice, the treatment decision can be considered based on level of immune enrichment in patient's tumor tissues (including MSI, TMB, etc.).

Exploration of immunotherapy in other subtypes of BC

Immunotherapy for HR$^+$/HER2$^-$ BC

In HR$^+$/HER2$^-$ EBC patients, phase II I-SPY2 study (61) showed immunotherapy combination in neoadjuvant chemotherapy could improve pCR rate (30% *vs.* 13%) of HR$^+$HER2$^-$ patients. KEYNOTE-756 study (62) showed in high-risk ER$^+$/HER2$^-$ EBC patients, pCR rate in chemotherapy and pembrolizumab group was significantly

improved (24.3% *vs.* 15.6%, P<0.001). CheckMate 7FL study (63) shows that nivolumab with chemotherapy can improve pCR rate of ITT population in high-risk HR$^+$/HER2$^-$ EBC patients (24.5% *vs.* 13.8%, P=0.002). No guidelines clearly recommended ICIs to be used in neoadjuvant setting of HR$^+$ BC. Both KEYNOTE-756 and CheckMate 7FL enrolled high-risk ER$^+$/HER2$^-$ BC patients with mainly Luminal B type. The pCR rates of ITT population after neoadjuvant immunotherapy with chemotherapy are similar. Subgroup analysis showed more benefit with higher expression of PD-L1 and lower expression of ER, which may suggest this tumor type might be sensitive to immunotherapy, and this may provide us a new option for neoadjuvant immunotherapy in HR$^+$/HER2$^-$ EBC patients.

In HR$^+$/HER2$^-$ mBC patients, KEYNOTE-028 study (64) showed pembrolizumab was safe and effective in PD-L1$^+$ (CPS ≥1) ER$^+$/HER2$^-$ mBC patients with ORR 12%, clinical benefit rate (CBR) 20%, and DoR 12 months. The KELLY study (65) found pembrolizumab with eribulin regimen had good efficacy in pretreated HR$^+$/HER2$^-$ mBC patients. However, NCT03051659 study (66) showed no significant difference in PFS and ORR benefit between pembrolizumab + eribulin versus eribulin alone in HR$^+$/HER2$^-$ mBC patients. NCT02779751 study (67) showed abemaciclib with pembrolizumab exhibited antitumor activity in HR$^+$/HER2$^-$ mBC patients with no previously treated by cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, but had a higher incidence of side effects as interstitial lung disease/pneumonia and severe transaminase elevation, with 58% of patients discontinuing the study treatment due to adverse events.

Recommendation 14: no strong evidence supports ICI use in HR$^+$/HER2$^-$ BC (IIA, Grade N/A).

Immunotherapy for HER2$^+$ BC

In HER2$^+$ mBC patients, PANACEA study (68) showed in PD-L1 positive (CPS ≥1) BC patients who were resistant to trastuzumab, immune therapy brought efficacy of ORR 15% and mPFS of 2.7 months and no response observed in PD-L1 negative patients with mPFS 2.5 months. KATE2 study (69) suggested that trastuzumab emtansine (T-DM1) + atezolizumab versus T-DM1 did not show statistically significant difference in PFS in HER2$^+$ mBC patients who had previously treated by trastuzumab and taxane therapy. For patients with TIL ≥5% and/or PD-L1 positive (defined as IC score >1 based on SP142 detection), there was a better PFS benefit trend in combination therapy group.

Recommendation 15: no clear evidence of ICIs in HER2$^+$ mBC patients were established in efficacy benefits, safety and combination patterns. It is not recommended to routinely use ICIs in HER2$^+$ mBC (IIB, Grade N/A).

Conclusions

ICIs have transformed cancer treatment, significantly advancing the management of malignancies through pharmacology. Despite the many guidelines outlining specific regimens for BC immunotherapy, their implementation is impeded by the complexity of real-world clinical scenarios. This consensus provides comprehensive insights and culminating in 15 key recommendations, involving proper patient selection, optimized chemotherapy partner, predictive biomarkers, the scientific management of side effect, all aimed at enhancing the standardization and qualification of proper management of immunotherapy in clinical daily practice in the therapeutic area of BC.

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Footnote

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