Review Article



# Expert review on systemic treatment in the St. Gallen International Breast Cancer Conference 2021

**Mingxi Lin[1,2#], Yizi Jin[1,2#], Jian Zhang[1,2]**

[1]Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; [2]Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

*Contributions:* (I) Conception and design: J Zhang; (II) Administrative support: J Zhang; (III) Provision of study materials or patients: J Zhang; (IV) Collection and assembly of data: M Lin, Y Jin; (V) Data analysis and interpretation: M Lin, Y Jin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

*Correspondence to:* Jian Zhang. Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Oncology, Shanghai Medical College, Fudan University, No. 270, Dong'an Road, Shanghai 200032, China. Email: syner2000@163.com.

**Abstract:** The 17th St. Gallen International Breast Cancer Consensus Conference was held in March 2021. The theme of this year's conference was "customizing local and systemic therapies". The conference focused on the controversies about the optimal primary treatment of early breast cancer. The St. Gallen expert panel reviewed substantial new evidences and voiced their expert opinions, hoping to provide guidance to clinicians. Despite that many randomized clinical trials provided evidence on managing breast cancer, not all the clinical scenarios can find definitive data to guide recommendations. When data from randomized clinical trials are lacking, the opinions of the St. Gallen expert panel can be used as an important reference for clinical decision making. However, the panelists' recommendations may often be affected by the treatment availability, which vary from country to country. As a result, from Chinese experts' perspectives, Professor Jian Zhang made an interpretation and comments of the expert opinions of the 17th St. Gallen Conference. This work focused on the field of systemic treatment, including neoadjuvant therapy (chemotherapy, HER2 targeted therapy and endocrine therapy), tailored post-neoadjuvant therapy based on neoadjuvant therapy response and adjuvant therapy. We hope this work could help clinicians understand the expert opinions of the 17th St. Gallen Conference better.

**Keywords:** St. Gallen; neoadjuvant therapy; adjuvant therapy; early breast cancer

Received: 06 June 2021; Accepted: 28 July 2021; Published: 31 July 2021.
doi: 10.21037/tbcr-21-7
**View this article at:** https://dx.doi.org/10.21037/tbcr-21-7

## Introduction

The 17th St. Gallen International Breast Cancer Consensus Conference was held in March 2021. This conference is a multidisciplinary and global meeting. Experts, who actively engaged in clinical or basic research of breast cancer, constituted the Consensus Panel. 74 panelists participated and voted in this conference (1). This conference focused on the controversies about the optimal primary treatment of early breast cancer, including the fields of genetics, pathology, imaging, neoadjuvant/adjuvant therapy, surgery, and radiation therapy (2). The goal of the meeting was to discuss the practical issues in the management of breast cancer, and provide guidance to clinicians. The St. Gallen expert panel agreed that data from randomized clinical trials had the highest level of evidence. However, when data are lacking, the opinions of the St. Gallen expert panel can be used as an important reference for clinical decision making. From Chinese experts' perspectives, Professor Jian Zhang made an interpretation and comment of the discussion results of the 17th St. Gallen International Breast Cancer Consensus Conference in the field of systemic treatment.

## Neoadjuvant therapy

### *Neoadjuvant therapy for HR+/HER2– breast cancer*

For postmenopausal women with low-risk genomic signature or low-grade breast cancer, if neoadjuvant therapy is needed, there was no superiority for neoadjuvant chemotherapy over neoadjuvant endocrine therapy: (I) agreed: 98.2%; (II) disagreed: 1.8% (abstain: 3).

HR+/HER2– breast cancer had lower response rates for neoadjuvant chemotherapy than other biological subtypes. When neoadjuvant therapy is needed (for example, to downstage breast cancer), neoadjuvant endocrine therapy may be a low-toxicity alternative option. Semiglazov *et al.* compared neoadjuvant chemotherapy (doxorubicin with paclitaxel) with neoadjuvant endocrine therapy (anastrozle or exemestane) in HR+ breast cancer patients (3). Clinical objective response (both 64%) and rates of pathological complete response (6% *vs.* 3%) were similar in both treatment groups. A meta-analysis (4) included over 20 studies also showed that neoadjuvant endocrine therapy gained similar response rates to neoadjuvant chemotherapy. TransNEOS trial (5) included 295 patients with HR+/HER2– breast cancer, and 21-gene recurrence score (RS) test was performed before neoadjuvant endocrine therapy. The response rates were 54% for patients with RS <18, but only 22% for RS >31. The American College of Surgeons Oncology Group (ACOSOG) Z1031 study confirmed that after 16-18 weeks of neoadjuvant endocrine therapy (aromatase inhibitor), half patients could undergo successful breast conserving surgery (6). 2021 ASCO guideline recommended that neoadjuvant endocrine therapy with aromatase inhibitor could be given to postmenopausal patients with HR+ breast cancer (7).

However, in China, the adoption of neoadjuvant endocrine therapy into clinical practice is still slow. This is probably because the pathological complete response (pCR) rates of neoadjuvant endocrine therapy are low, and this endpoint lacks of significantly prognostic value. Moreover, 21-gene test has not been verified by large samples in China.

Patients with ER+ breast cancer and residual disease after neoadjuvant endocrine therapy should be offered adjuvant chemotherapy: (I) if the patient has excellent clinical response with node-negative residual cancer? (i) Agreed: 0.0%, (ii) disagreed: 100.0% (abstain: 3); (II) if the patient has residual positive lymph nodes? (i) Agreed: 52.9%, (ii) disagreed: 47.1% (abstain:7); (III) if the patient has >5 cm residual tumor? (i) Agreed: 77.2%, (ii) disagreed: 22.9% (abstain: 1).

The neoadjuvant endocrine therapy could not only improve surgical outcome but also be used to adjust adjuvant treatment therapy. Ellis *et al.* utilized preoperative endocrine prognostic index (PEPI) to evaluate tumor response to neoadjuvant endocrine therapy (8). PEPI score 0 represented pT1/pT2, N0, Ki-67≤2.7%, and ER Allred score>2 measured on surgical specimen after neoadjuvant endocrine therapy. They found patients with PEPI score 0 had extremely low risk of relapse. The ACOSOG Z1031B also used PEPI score to examine the risk of relapse (9). For patients with PEPI score 0, the 5-year relapse risk was only 3.6% without adjuvant chemotherapy, supporting omitting adjuvant chemotherapy in this group. Moreover, the prospective WSG-ADAPT HR+/HER2– trial (10) used biomarkers (RS scores and Ki-67 index) to assess which patient should receive adjuvant chemotherapy after 3-week neoadjuvant endocrine therapy. In this study, patients with RS 0–11 or RS 12–25 plus Ki-67≤10% (assessed after 3-week neoadjuvant endocrine therapy) were spared adjuvant chemotherapy. As a result, de-escalation of therapy with no chemotherapy may be recommended for patients with excellent clinical response after neoadjuvant endocrine therapy. On the other hand, residual positive lymph nodes or >5cm residual tumor might represent lower endocrine sensitivity, and adjuvant chemotherapies are needed.

### *Neoadjuvant therapy for HER2-positive breast cancer*

For HER2-positive breast cancer with clinically positive lymph nodes, the preferred neoadjuvant regimen should include taxane and trastuzumab, combined with: (I) anthracycline: 61.8%; (II) pertuzumab: 12.7%; (III) pertuzumab plus platinum: 23.6% (abstain: 1).

In the era of effective anti-HER2 therapies, the contribution of anthracyclines has always been controversial. Whether the addition of anthracyclines in neoadjuvant therapy would offer benefit in HER2-positive breast cancer remains unclear. TRAIN-2 (11,12) and TRYPHAENA (13) were the two key trials addressing this question. The TRAIN-2 directly compared the 9 cycles of anthracycline-free regimen [paclitaxel + carboplatin + trastuzumab + pertuzumab (PCbHP)] with the anthracycline-containing regimen [5-fluorouracil + epirubicin + cyclophosphamide (FEC) + HP for 3 cycles followed by PCbHP for 6 cycles]. The study found that the addition of anthracycline did not improve pCR rates or event-free survival (EFS) in neoadjuvant therapy. However, the 9-cycle treatment regimen was not the

standard therapy. The TRYPHAENA trail also compared the 6-cycle anthracycline-containing regimen (FEC + HP for 3 cycles followed by docetaxel[T]+HP for 3 cycles) and the 6-cycle anthracycline-free regimen (TCbHP). The two treatment arms had similar pCR rates, corroborating the results from TRAIN-2. However, the primary objective of TRYPHAENA was to evaluate tolerability and safety. The efficacy results should not be over-interpreted. As a result, more evidences are needed to support the elimination of anthracycline in neoadjuvant therapy.

For HER2-positive breast cancer patients with clinically positive lymph nodes, if the neoadjuvant chemotherapy and trastuzumab plus pertuzumab (HP) are given and the tumor achieves pCR, expert panel agreed that the preferred adjuvant anti-HER2 therapy is: (I) HP irrespective of baseline stage: 55.6%; (II) HP if baseline stage 3: 22.2%; (III) H alone: 22.2% (abstain: 5).

For HER2-positive patients with clinically negative lymph node, if neoadjuvant HP are given and the tumor chieves pCR, experts agreed that: (I) H alone would be enough: 69.6%; (II) HP if baseline stage 1/2: 12.5%; (III) HP if baseline stage 2: 17.9% (abstain: 3).

For patients with a pCR after neoadjuvant chemotherapy, trastuzumab and pertuzumab, no data supported the administration of continued trastuzumab plus pertuzumab or trastuzumab alone, to complete the 1-year duration of anti-HER2 therapy. A pCR following neoadjuvant chemotherapy is often associated with improved prognosis. However, a small group of patients would still experience a relapse. It's of great interest to identify patients with high risk of relapse despite a pCR and propose the addition of pertuzumab beyond trastuzumab and chemotherapy. Huober *et al.* performed a pooled retrospective analysis to identify factors associated with relapse despite a pCR (14). 2,188 patients with pCR were included. The investigators found that the initial positive lymph node was significantly related with shorter disease-free survival (cN+ *vs.* cN0, HR =1.70, 95% CI: 1.2–2.4, P=0.002). The 6-year follow-up of APHINITY trial (15) demonstrated that patients with positive lymph nodes would benefit from adding pertuzumab to standard adjuvant therapy. The 6-year invasive disease-free survival was 83% with placebo and 88% with pertuzumab (HR =0.72, 95% CI: 0.59–0.87). For patients with negative lymph nodes, no difference was seen. As a result, for patients with cN+ and received pCR after neoadjuvant therapy, the addition of pertuzumab is recommended. The seven-year follow-up of the APT trial (16) suggested that patients with N- and small HER2-positive breast cancer had minimal risk of disease recurrence. The seven-year disease-free survival of adjuvant paclitaxel and trastuzumab was 93.3% (95% CI: 90.4–96.2). As a result, for patients with cN– breast cancer and pCR after neoadjuvant therapy, trastuzumab alone would be enough.

### *Neoadjuvant therapy for triple negative breast cancer (TNBC)*

For patients with TNBC, if standard neoadjuvant chemotherapy is given, an immune checkpoint inhibitor is not needed: (I) agreed: 90.8%; (I) disagreed: 9.6% (abstain: 4).

Although Keynote522 (17) and IMpassion031 (18) trials suggested that the addition of immune checkpoint inhibitors may augment pCR, the toxicity and long-term survival outcomes are still unclear. And immune checkpoint inhibitors targeting PD1/PDL1 have not gained indications in China. The biomarker for clinical benefit of immune checkpoint inhibitor was not definite. We do not regularly recommend the addition of immune checkpoint inhibitors in neoadjuvant therapy for patients with TNBC.

PD1/PDL1 testing should not affect the recommendation for the use of immune checkpoint inhibitor in neoadjuvant therapy: (I) agreed: 81.1%; (II) disagreed: 18.9%; (abstain: 6).

The Keynote522 trial indicated that the addition of pembrolizumab in neoadjuvant therapy could increase the percentage of patients with pCR (17). The benefits were observed in both PD-L1-positive population and PD-L1-negative population. The similar results were observed in IMpassion031 trial (18). As a result, the PD1/PDL1 testing should not affect the recommendation for the use of immune checkpoint inhibitor in neoadjuvant therapy.

All the patients with TNBC and residual disease after neoadjuvant therapy should receive adjuvant capecitabine: (I) agreed: 87.7%; (I) disagreed: 12.3% (abstain: 1).

TNBC has high relapse rate, especially for patients with residual disease after neoadjuvant therapy. The CREATE-X trial evaluated the value of adjuvant capecitabine in patients with residual disease after standard neoadjuvant therapy (taxane, anthracycline, or both) (19). The study revealed that adjuvant capecitabine could increase the rate of disease-free survival (74.1% in capecitabine group *vs.* 67.6% in control group, HR =0.70, 95% CI: 0.53–0.92). Among patients with TNBC, the capecitabine also increased the rate of disease-free survival (69.8% in capecitabine group *vs.* 56.1% in

control group, HR =0.58, 95% CI: 0.39–0.87) and the overall survival rate (78.8% *vs.* 70.3%, HR =0.52, 95% CI: 0.30–0.90). As a result, if the toxicities were tolerable, we recommended adjuvant capecitabine for TNBC that did not gain pCR after neoadjuvant therapy. Moreover, CBCSG010 trial (20) showed that the addition of capecitabine to standard adjuvant therapy could improve 5-year disease-free survival rates in TNBC patients (86.3% *vs.* 80.4%, HR =0.66, 95% CI: 0.44–0.99). And SYSUCC-001 trial (21) demonstrated the efficacy of maintenance therapy with low-dose capecitabine after standard adjuvant therapy for TNBC patients.

## Adjuvant therapy

### *Adjuvant therapy for HR-positive/HER2-negative breast cancer*

#### ER threshold for endocrine therapy

The appropriate threshold for "positive" ER expression for recommending adjuvant endocrine therapy in ER-positive breast cancers tested by IHC is: (I) greater than or equal to 1%: 50.0%; (II) greater than or equal to 10%: 50.0% (abstain: 3).

According to the most updated ASCO/CAP guideline for ER/PR testing, breast cancers with 1–10% cells staining ER positive have been classified into a new category of ER low positive (22). Due to the relative rarity of this subpopulation, the evidence on the endocrine therapy benefits for breast cancers with ER low positive remained limited, and no clinical trial has so far been designed to address this question. Previous retrospective studies demonstrated inconsistent results regarding the prognosis and endocrine responsiveness of ER low positive breast cancers. Several studies suggested that the biological behavior and clinical outcome of ER low positive tumors were more similar to the ER-negative and gained limited benefits from adjuvant endocrine therapy (23-25). A real-world data analysis of 17,216 patients in China also confirmed these findings. ER low positive breast cancer tended to have strongly aggressive clinicopathological features and a majority of them were treated with chemotherapy (26). However, there were still data from long-term follow up supporting patients with ER expression ≥1% may benefit from endocrine therapy (27).

We think the possible benefit of endocrine therapy in the ER-low-positive patients should not be denied based on the current evidence. Considering the relative low toxicity of endocrine therapy, we endorse that adjuvant endocrine therapy can be considered in patients with ER expression ≥1%. In the clinical practice for this subpopulation, more clinicopathological factors (such as tumor size, stage, histopathological types, Ki-67 index, etc.) should be considered to decide the administration of endocrine therapy. For those who have positive lymph nodes, the IHC tests for involved lymph nodes can also provide clues for treatment decisions. The controversial evidence also indicated that prospective studies are needed to help determine the threshold.

#### Extended endocrine therapy

For node-positive ER-positive HER2-negative breast cancers, what is the optimal duration of the endocrine therapy? (I) 5 years: 11.3%; (II) 7 to 8 years: 34.0%; (III) 10 years: 52.8%; (VI) indefinite: 1.9% (abstain: 1).

For premenopausal high-risk patients who received 5 years of OFS + Tam, do you prolong treatment? (I) Yes, additional 5 years of OFS + Tam: 4.1%; (II) Yes, additional 5 years of Tam only: 44.9%; (III) Yes, additional 5 years of AI (+ OFS if still premenopausal): 40.8%; (IV) No: 10.2% (abstain: 7).

Prolonged adjuvant endocrine therapy should be considered in ER-positive breast cancer patients with high-risk factors (such as positive lymph nodes, grade 3, >T2, Ki-67>30%, etc.) after 5-year standard therapy if tolerable. It is also noteworthy that prolonged adjuvant AI treatment contributes greatly to the prevention of second breast cancers. Yet the optimal duration and treatment regimens for extended adjuvant endocrine therapy remained controversial. For postmenopausal patients, NSABP-B42 (28) trial showed that the extension of endocrine therapy with aromatase inhibitors (AI) for additional 5 years decreased the recurrence risk, while IDEAL (29) and ABCSG-16 (30) demonstrated that extension with AI for additional 2 to 2.5 years yielded comparable benefit compared with additional 5 years. For premenopausal patients, although 10-year tamoxifen treatment did not demonstrate significant improvement in OS for node-negative patients compared with the 5-year regimen in NSABP B-14 (31), the results from ATLAS (32) and aTTom (33) endorsed the 10-year tamoxifen therapy due to its benefit for risk reduction. For premenopausal patients who received 5 years of OFS + Tam/AI, although there lacks straightforward proof from clinical trial, we still consider the extension of endocrine therapy based on the evidence of decreasing long-term recurrence risk. The combined analysis of TEXT & SOFT study demonstrated

that patients with high risks benefit more from 5 year of OFS + AI compared with OFS + Tam in the long term (34). Therefore, if the premenopausal patient had higher risks such as having ≥4 positive nodes, aged ≤35, and/or grade 3, additional 5 years of more escalated therapy, i.e., OFS+AI should be preferred. The side effect of long-term tamoxifen such as an increased risk of thrombosis and endometrial cancer should also be considered.

**CDK4/6 inhibitors**

Should patients with ER-positive cancers and 4 or more positive lymph nodes receive adjuvant CDK4/6 inhibitor therapy with abemaciclib? (I) Yes: 54.0%; (II) No: 46.0% (abstain: 7).

Should patients with ER-positive cancers and 1–3 positive lymph nodes and with grade 3, or/and T3, or high Ki-67 receive adjuvant CDK4/6 inhibitor therapy with abemaciclib (i.e., Monarch-E eligibility)? (I) Yes: 43.6%; (II) No: 53.7% (abstain: 3).

In ER-positive, HER2-negative breast cancer, should Ki-67 testing (in combination with other prognostic markers) be used to select adjuvant treatment with CDK 4/6 inhibitors? (I) Yes: 39.6%; (II) No: 60.4% (abstain: 4).

According to the interim analysis of Monarch-E, abemaciclib combined with endocrine therapy significantly improved iDFS (P=0.01, HR =0.75, 95% CI: 0.60–0.93) and DRFS (P=0.01, HR =0.72, 95% CI: 0.56–0.92) versus endocrine therapy alone (35). In the subgroup analysis stratified by lymph nodes, patients with 4-9 positive lymph nodes benefited the most (iDFS: HR =0.69, 95% CI: 0.48–0.99), which could serve as solid evidence supporting the use of abemaciclib in this subpopulation. For patients with 1-3 positive lymph nodes, the iDFS improvement was less significant (HR =0.71, 95% CI: 0.48–1.06). It should be noted that although the subgroup analyses were prespecified, the subgroup results were exploratory in nature due to statistical reasons.

Among the three adjuvant CDK inhibitor trials, Monarch-E was the only trial demonstrated positive results. Compared with Monarch-E, the PALLAS trial enrolled more patients with N0 or N1 pathological nodal status. The negative results of PALLAS (36) might be the reason why more clinicians were cautious on the addition of CDK4/6 inhibitor in patients with 1-3 positive lymph nodes and other high-risk factors. Another issue is how to determine the "high-risk" population. Anatomic stage mainly identifies patients with high risk of early relapse, while biological risk may predict recurrence risk in the long run. Apart from clinical risk, biological risk was also considered in the eligibility of Monarch-E, and a greater absolute benefit was observed in patients with high Ki-67 (37). Meanwhile, patients with high Ki-67 tend to have other combined high-risk features, so we believe that Ki-67 index alone may not serve as the decisive factor of using CDK 4/6 inhibitors. In addition, for patients with available genomic assays, those who have high genomic scores can also be classified as having high biological risk, and the opportunity of using CDK 4/6 inhibitors may be considered in this population in the future.

The median follow-up period of Monarch-E was approximately 19 months, which was shorter than PALLAS and Penelope B. We expect the results from long-term follow-up to confirm the status of adjuvant CDK4/6 inhibitor therapy in high-risk ER-positive patients.

**Multi-gene panel testing**

Are there postmenopausal patients with clinical presentations meeting the criteria of the MINDACT, TAILORx, RxPonder and similar trials with low-risk signatures and or recurrence scores (RS) ≤25 who should receive chemotherapy? (I) No: 51.1%; (II) Yes, if RS 21–25: 6.4%; (III) Yes, if extensive LVI: 0.0%; (IV) Yes, pT3pN1: 12.8%; (V) Yes, if 3 positive LN: 8.5%; (VI) Yes, pT3pN1 or 3 positive LN: 21.3% (abstain: 10).

For premenopausal women with node-negative breast cancers and recurrence score 16–25, or other lower-range genomic signature, the recommended treatment is: (I) Tam: 22.5%; (II) OFS with Tam or AI: 53.1%; (III) chemotherapy and endocrine therapy: 24.5% (abstain: 8).

Consider the experiences from ADAPT, MINDACT, TAILORX and RxPONDER, and other trials examining the role of endocrine therapy +/– chemotherapy in ER-positive HER2-negative breast cancer. For a patient with stage 3 (i.e., high anatomic stage), postmenopausal ER positive breast cancer. The preferred treatment is endocrine therapy and adjuvant chemotherapy (as opposed to endocrine therapy alone): (I) regardless of biomarkers: (i) Yes: 67.9%; (ii) No: 32.1% (abstain: 0); (II) at very high stage such as if N3(≥10+LN) or T3N2: (i) Yes: 96.4%; (ii) No: 3.6% (abstain: 1); (III) if grade 1 or 2 lobular breast cancer: (i) Yes: 48.0%; (ii) No: 51.9% (abstain: 4); (IV) if grade 1/low grade/ Ki-67 <10%: (i) Yes: 37.3%; (ii) No: 62.8% (abstain: 5); (V) if recurrence score is <11: (i) Yes: 34.0%; (ii) No: 61.0% (abstain: 8); (VI) if recurrence score is <25: (i) Yes: 58.3%; (ii) No: 41.7% (abstain: 9).

Multi-gene panel testing has become a useful tool in

the selection of patients with ER-positive/HER2-negative breast cancer to receive de-escalation therapy. Meanwhile, according to the long-term outcome of MINDACT and TAILORx trial, the exploratory analyses indicated that the benefit of adding chemotherapy could be age-dependent, and a clinically relevant benefit was observed in patients with low genomic risk yet younger than 50 years (38,39). Therefore, the emission of chemotherapy in patients with low genomic risk should be handled with care. Chinese experts tend to add chemotherapy for ER-positive patients with positive lymph nodes unless the patient was postmenopausal, T1–3, and has low genomic risk. For premenopausal patients, we also prefer to add chemotherapy under most circumstances since a substantial proportion of premenopausal patients are likely to benefit from chemotherapy. For specific histological type and biomarkers such as Ki-67, the consideration of endocrine responsiveness should be balanced with tumor burden and node metastases.

### *Adjuvant therapy for HER2-positive breast cancer*

#### Escalated anti-HER2 therapy

Should patients with node-negative, HER2-positive breast cancers receive adjuvant pertuzumab (intravenous or subcutaneous formulation) in addition to trastuzumab? (I) Yes: 5.9%; (II) No: 94.1% (abstain: 6).

Should patients with HER2-positive breast cancers receive adjuvant neratinib after trastuzumab/pertuzumab as (neo)adjuvant therapy regimen, and/or trastuzumab emtansine-based therapy? (I) Yes: 1.9%; (II) Yes, only if ER-positive: 5.8%; (III) Yes, only if ER-positive and very high risk such as ≥4 positive lymph nodes: 63.5%; (IV) No: 28.9% (abstain: 5).

In the section of adjuvant therapy for HER2-positive breast cancer, a topic worth discussion is the target population for escalated anti-HER2 therapy. Since no significant clinical benefit was observed in the node-negative subgroup in APHINITY (15), a majority of experts agreed that the dual anti-HER2 blockade was not necessary in node-negative patients. The long-term follow-up data showed that adjuvant trastuzumab + chemotherapy (single HER2 blockade) was adequate for HER2-positive patients with negative lymph nodes and small tumor size. The APT trial showed the 7-year RFI was 97.5% after wTH treatment (40). The 2-year DFS of early-stage patients also reached 97.8% when treated with TC+H regimen (41).

Another escalated treatment strategy for high-risk HER2-positive patients incorporating neratinib was investigated in the ExteNET trial (42). The prespecified subgroup analysis showed that the extended adjuvant therapy with neratinib for 1 year after trastuzumab and chemotherapy significantly enhanced iDFS in ER-positive patients with a tolerable safety profile (43). The combination of trastuzumab + pertuzumab has successfully reduced the early recurrence of high-risk patients, while further strategies are needed to reduce the long-term recurrence risk for ER-positive patients in view of the biological characteristics of ER-positive breast cancer. Therefore, most experts agreed that additional neratinib is a reasonable choice for ER-positive patients with very high risk even if the patient has received prior dual HER2 blockade therapy.

#### Novel anti-HER2 strategies

For women with stage 1, HER2 positive breast cancers, should trastuzumab emtansine be used instead of paclitaxel/trastuzumab therapy? (I) Yes: 0.0%; (II) No: 68.5%; (III) Only under special circumstances: 31.5% (abstain: 2).

The phase II ATEMPT trial investigated T-DM1 *vs.* paclitaxel combined with trastuzumab (T + H) for stage I HER2-positive breast cancer in terms of toxicity and clinical benefit. The 3-year DFS for patients receiving T-DM1 reached 97.5% (95% CI: 95.9–99.3%), and T-DM1 was associated with less clinically relevant toxicities compared with T + H (44), yet the trial did not meet the preplanned statistical endpoint. There lacks sufficient data supporting the regular use of T-DM1 in stage 1, HER2-positive patients, while we also believe that some special conditions may justify the use of T-DM1, such as when cytotoxic chemotherapy is not acceptable for patients. It is worth noting that a meta-analysis involving 6,188 patients showed the incidence of T-DM1 induced thrombocytopenia was higher in Asian patients (45), so clinicians in China may be more cautious on the use of T-DM1, and careful surveillance is needed during the T-DM1 treatment.

### *Adjuvant therapy for TNBC*

#### Adjuvant immunotherapy

Should patients with stage 2 or 3 TNBC, not treated in the neoadjuvant setting, but receiving adjuvant chemotherapy, also receive PD-1/PD-L1 targeted treatment with an immune checkpoint inhibitor? (I) Yes: 9.6%; (I) No: 90.4% (abstain: 5).

For the use of immunotherapy in early-stage TNBC,

we only have supporting evidence in neoadjuvant settings so far. Recent clinical trials such as KEYNOTE-522, IMPASSION031, and Geparneuvo (46) have revealed an augmented pCR after neoadjuvant therapy with ICIs, which indicated the potential of ICIs in the early-stage TNBC. Despite this, the use of neoadjuvant immunotherapy has not been widely acknowledged among Chinese experts due to the lack of data in Chinese patients and approval for indication. We believe that RFS and toxicity profile from long-term follow-up are needed, and predictive biomarkers are yet to be established. Several ongoing clinical trials are evaluating the use of ICIs in the adjuvant therapy for TNBC currently (NCT02826434, NCT03740893, NCT02954874, etc.), and we expect updates on results.

### PARP inhibitors

Based on the tolerability of Olaparib in advanced, BRCA1/2 associated breast cancer, I would recommend adjuvant Olaparib in BRCA1/2 associated early-stage breast cancer if the OlympiA data show which of the following: (I) overall survival benefit, only: 7.7%; (II) absolute iDFS at 3 years of >10%: 25.0%; (III) absolute iDFS at 3 years of >5%: 48.1%; (IV) absolute iDFS at 3 years of >2%: 19.2% (abstain: 5).

For *BRCA1/2*-associated breast cancer patients, Olaparib has demonstrated significant improvement in PFS for metastatic patients (47,48) and shown promising results in neoadjuvant settings (49). Based on the previous success, Olaparib has entered the arena of adjuvant therapy and has been under evaluation in the OlympiA trial. Since the aim of treating early breast cancer is to prevent recurrence, OlympiA sought to evaluate whether Olaparib can further reduce recurrence in germline *BRCA1/2*-mutated patients with high risks.

According to the recently published data, the interim analysis of OlympiA demonstrated an absolute 3-year iDFS of 8.8% in the Olaparib group (85.9% *vs.* 77.1%; HR: 0.58; 99.5% CI: 0.41–0.82; P<0.001), though the difference in OS between groups did not reach the interim-analysis boundary (50). This result was consistent with the most convincing answer among the panelist in St. Gallen BCC, and it promises to change the treatment landscape of early stage HER2-negative patients. Genetic testing of homologous repair mutations in early TNBC may help more patients gain benefits from this targeted therapy.

## Conclusions

The 17th ST. GALLEN International Breast Cancer Consensus Conference focused on the controversies about the optimal primary treatment of early breast cancer. A great number of treatment recommendations were given. The expert recommendations of the 17th ST. GALLEN conference could provide guidance to clinicians and the recommendations might suit the majority of patients in common clinical situations. However, clinicians should also aware that proper adjustments should be made according to the patient's socioeconomic status, complications, and tumor characteristics.

## Acknowledgments

*Funding*: None.

## Footnote

*Conflicts of Interest*: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tbcr-21-7). JZ serves as the unpaid editorial board member of *Translational Breast Cancer Research* from May 2021 to April 2023. The other authors have no conflicts of interest to declare.

*Ethical Statement*: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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doi: 10.21037/tbcr-21-7
**Cite this article as:** Lin M, Jin Y, Zhang J. Expert review on systemic treatment in the St. Gallen International Breast Cancer Conference 2021. Transl Breast Cancer Res 2021;2:17.