Editorial Commentary

New progress in early breast cancer treatment in 2021

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Treatment for breast cancer (BC) has gradually changed from localized therapy dominated by radical mastectomy to systemic therapy based on molecular subtypes. Endocrine therapy (ET) is one of the most important treatment approaches for hormone receptor positive (HR$^+$) BC patients. Currently, escalation of ET in the postoperative period is receiving increasing attention, including the addition of CDK4/6 inhibitors (CDK4/6i), use of ovarian function suppression (OFS) in the premenopausal period, and prolonging the duration of ET, which have achieved significant therapeutic benefits. Another new direction for HR+ patients is how to use polygenic risk score (PRS) to identify patients with low risk of recurrence, who could be spared from chemotherapy. As for human epidermal growth factor receptor 2-positive (HER2$^+$) BC, HER2-targeted monoclonal antibodies such as trastuzumab in combination with chemotherapy is currently the standard of neoadjuvant therapy. Their combination with tyrosine kinase inhibitors (TKI) can theoretically inhibit HER2 signaling more comprehensively, which also have exhibited great responses in clinical trials. The addition of TKI may be a good choice, especially when patients have achieved a poor response from dual HER2$^-$ blockade with pertuzumab and trastuzumab (HP). The selection of HER2$^-$ targeted therapy in the chemotherapy-free neoadjuvant setting is one of the likely future directions for exploration. In contrast to the two aforementioned BC subtypes, triple-negative breast cancer (TNBC) lacks well-defined molecular targets. Its treatment landscape has improved from the era of chemotherapy to that of immunotherapy and targeted therapy, with an abundance of exciting results from clinical trials available to guide clinical practice. Currently, discovery and application of biological markers are urgently needed to better identify the population who would benefit from certain treatment, thus paving the way for precision medicine. Dramatic research progress has been achieved in the fields of neoadjuvant therapy and adjuvant therapy across different molecular subtypes of breast cancer, which are of significant clinical value in aiding clinical decisions. This article will briefly review and summarize these relevant progresses in early BC treatment in 2021.

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

For HR$^+$/HER2$^-$ BC patients, ET is the standard of care. In the neoadjuvant setting, chemotherapy had always been the first choice. However, more and more clinical trials found that the efficacy of neoadjuvant ET was not weaker than that of chemotherapy for some HR$^+$/HER2$^-$ patients, with less adverse effects and good patient compliance. Particularly, in certain patients, the emergence of a novel molecularly targeted drug named CDK4/6i has been associated with therapeutic benefits similar to those of chemotherapy. As mentioned at the 2020 European Society for Medical Oncology (ESMO) Annual Meeting, the NeoPAL trial (1) for the first time compared the efficacy of CDK4/6i in combination with letrozole versus chemotherapy (letrozole-palbociclib combination *vs.* 3FEC-3T) in the neoadjuvant setting for high-risk HR$^+$/HER2$^-$ BC patients, and found similar clinical responses between the two groups, such as residual cancer burden (RCB) rates. The RCB rates of 0, I, II, and III were observed in 3.8% (2/52), 3.8% (2/52), 51.9% (27/52), and 40.4% (21/52) of patients receiving letrozole/palbociclib compared to 5.9% (3/51), 9.8% (5/51), 37.3% (19/51), and 47.1% (24/51) in patients undergoing chemotherapy, respectively. There was

also no significant difference in 3-year invasive disease-free survival (iDFS) [hazard ratio (HR) =0.83; 95% confidence interval (CI): 0.31 to 2.23; P=0.71] between the two groups. Besides, the emergence of giredestrant (GDC-9545), a novel oral selective estrogen receptor degrader (SERD) drug, provided another orally administered drug option . Giredestrant is a highly potent, nonsteroidal, oral, SERD. It achieves robust ER occupancy, leading to ER being unable to activate the transcription of targeted genes, while also promoting the degradation of ER protein, thereby blocking ER signaling completely, and inhibiting the proliferation of tumor cells, unaffected by the status of ESR1 mutation. The phase II CoopERA study was conducted in HR+/HER2– early BC patients (2). Its primary efficacy endpoint was Ki-67 score change from baseline to Week 2 of neoadjuvant therapy. Two-week relative Ki-67 reduction was greater with giredestrant than with anastrozole (75% *vs.* 67%, P=0.0433). This result had statistical significance and arrived at the primary efficacy endpoint, showing that giredestrant decreased Ki-67 expression better than aromatase inhibitors (AIs). Its secondary efficacy endpoint was complete cell cycle arrest (CCCA) rate at Week 2. At Week 2, 19.6% of tumors exhibited CCCA with giredestrant versus 12.8% with anastrozole (Δ 6.86%; 95% CI: –4.25% to 17.97%). These results have presented new therapeutic choices for HR^+ BC patients.

In the adjuvant setting, there have been some new studies about the duration of adjuvant ET for post-menopausal HR+ early BC patients. In 2021, the *New England Journal of Medicine* (*NEJM*) published the results of the Austrian Breast Cancer Study Group trial 16 [ABCSG-16; Secondary Adjuvant Long-Term Study with Arimidex (SALSA)] trial (3), which showed that in postmenopausal women with HR+ early BC who had received 5 years of adjuvant ET, extending anastrozole by 5 years provided no benefit over a 2-year extension, with similar DFS (73.9% *vs.* 73.6%, HR =0.99, 95% CI: 0.85 to 1.15, P=0.90) and OS (87.3% *vs.* 87.5%, HR =1.02, 95% CI: 0.83 to 1.25), but was associated with a greater risk of adverse effects. The risk of clinical bone fracture was higher in the 5-year group than in the 2-year group (6.3% *vs.* 4.7%; HR =1.35; 95% CI: 1.00 to 1.84). However, on 17 September, 2021, *Lancet Oncology* published the results of the Letrozole Adjuvant Therapy Duration [LEAD; Gruppo Italiano Mammella 4 (GIM4)] study (4), showing that in postmenopausal BC patients who received 2–3 years of tamoxifen, extended treatment with 5 years of letrozole led to a significant improvement in survival compared with 2–3 years of letrozole. In the intention-to-treat (ITT) population, 12-year DFS (67% *vs.* 62%; HR =0.78, 95% CI: 0.65 to 0.93; P=0.0064) and 12-year OS (88% *vs.* 84%; HR =0.77; 95% CI: 0.60 to 0.98; P=0.036) were both higher in the extended group than the control group. Therefore, postoperative tamoxifen for 2–3 years followed by letrozole for 5 years should be considered one of the optimal standard endocrine treatments for postmenopausal patients with HR+ BC. For premenopausal women with HR^+ early BC, the 2021 San Antonio Breast Cancer Symposium (SABCS) presented the updated results of the 12-year follow-up of the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) (5). Generally, adjuvant exemestane plus OFS, as compared with tamoxifen plus OFS, showed a sustained benefit in DFS (80.5% *vs.* 75.9%, HR =0.79, 95% CI: 0.70 to 0.90). The 12-year follow-up of the SOFT trial showed again that the combination of OFS (with either tamoxifen or exemestane) resulted in persistent long-term benefits in premenopausal HR+ BC patients. Compared to tamoxifen used alone, OFS plus tamoxifen led to a 1.4% reduction in the risk of distant recurrence (86.2% *vs.* 84.8%) and a 2.2% reduction in the mortality rate (89.0% *vs.* 86.8%), while OFS plus exemestane led to a 3.0% reduction in the risk of distant recurrence (87.8% *vs.* 84.8%) and a 2.6% reduction in the mortality rate (89.4% *vs.* 86.8%). Besides, the 2021 SABCS presented a meta-analysis obtaining data from four randomized clinical trials [ABCSG XII, SOFT, TEXT, and Hormonal BOne Effects-2 (HOBOE) trials] to further compare OFS plus AI versus OFS plus tamoxifen (6). The results showed that OFS plus AI reduced the risk of recurrence more compared with OFS plus tamoxifen, and the main benefit was seen in the first 5 years after treatment initiation, with a 3.2% reduced risk of recurrence (6.9% *vs.* 10.1%, P=0.0005). The combination of ET with OFS reduced the risk of BC recurrence and improved survival for premenopausal HR+ BC patients.

In recent years, CDK4/6i has become a new hot spot in BC research. The results from the series of the Palbociclib Ongoing Trials in the Management of BC (PALOMA), MONARCH [Abemaciclib as monotherapy (MONARCH 1), in combination with fulvestrant (MONARCH 2), or with AI (MONARCH 3) for advanced BC], and the Mammary Oncology Assessment of LEE011's (Ribociclib's) Efficacy and Safety (MONALEESA) trials have established CDK4/6i combined with ET as a new standard of care in the first-line therapy for $HR^+/HER2^-$ advanced BC patients (7). However, whether the use of CDK4/6i can improve DFS

in the adjuvant setting for HR$^+$/HER2$^-$ BC patients is not yet clear. All three Food and Drug Authority (FDA)-approved CDK4/6 inhibitors––palbociclib (PALLAS, PENELOPE-B), abemaciclib (Monarch E), and ribociclib (NATALEE)—have been, and continue to be, explored in the adjuvant setting for early BC. According to results of the PALbociclib CoLlaborative Adjuvant Study (PALLAS) trial presented at the 2021 SABCS, the addition of 2 years of palbociclib to standard adjuvant ET did not decrease the risk of recurrence or metastasis over ET alone in stage II–III HR$^+$/HER2$^-$ BC patients (8). The 4-year iDFS rate was 84.2% with palbociclib plus ET and 84.5% with ET alone (HR =0.96; 95% CI: 0.81 to 1.14; P=0.65). So far, the only positive outcomes for CDK4/6i have come from the MonarchE study (9). The 2021 *Annals of Oncology* updated the results from MonarchE study with 27 months median follow-up, showing benefits in iDFS (HR =0.70, 95% CI: 0.59 to 0.82; nominal P<0.0001) and distant relapse-free survival (dRFS) (HR =0.69, 95% CI: 0.57 to 0.83; nominal P<0.0001) for abemaciclib + ET over ET alone. The absolute improvements in 2- and 3-year iDFS rates were 2.7% (92.7% *vs.* 90.0%) and 5.4% (88.8% *vs.* 83.4%), respectively. This indicated that the abemaciclib benefit extended beyond the 2-year treatment period. Compared to ET alone, addition of CDK4/6i further decreased the risk of recurrence in HR$^+$/HER2$^-$ BC patients. Based on these results, the FDA approved combined abemaciclib with ET for patients with HR$^+$/HER2$^-$, node-positive, early BC at high risk of recurrence. At the same time, the 2021 Committee of Breast Cancer Society (CBCS) Guidance recommended that abemaciclib plus ET may be offered to patients with either at least four positive axillary lymph nodes or high-risk patients with one to three positive axillary lymph nodes, meeting the inclusion criteria of the MonarchE trial (10). Differences in patient selection, drug schedule, mechanisms on drug efficacy, medication compliance, and follow-up periods could partially explain the divergent outcomes for the above trials evaluating CDK4/6i in the adjuvant setting for early BC patients. More clinical trials are needed to explore the suitable population for adjuvant combined CDK4/6i with ET to achieve the curing of HR$^+$/HER2$^-$ early BC patients.

PRS can be used to spare some low-risk patients from chemotherapy, which helps to explore de-escalation strategies of adjuvant therapy in HR$^+$/HER2$^-$ BC patients. As confirmed by the Trial Assigning Individualized Options for Treatment (Rx) (TAILORx) study (11), 21-gene recurrence score (RS) had application value in predicting chemotherapy benefits in axillary node-negative HR$^+$/HER2$^-$ BC patients. In 2021, the *NEJM* published the latest results of the Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer (RxPONDER) trial about predicting chemotherapy benefits using RS in HR$^+$/HER2$^-$ BC patients with 1–3 positive lymph nodes and a RS of 25 or lower (12). Among premenopausal patients, 5-year iDFS was 89.0% with ET alone and 93.9% with chemotherapy plusET (HR =0.60; 95% CI: 0.43 to 0.83; P=0.002). Among postmenopausal patients, 5-year iDFS was 91.9% in the ET alone group and 91.3% in the chemotherapy plus ET group, with no chemotherapy benefit (HR =1.02; 95% CI: 0.82 to 1.26; P=0.89), indicating that postmenopausal patients with similar characteristics to those in this study can safely omit chemotherapy. However, for premenopausal patients, whether the benefit came from direct cytotoxic effect from chemotherapy or secondary to ovarian ablation is still not clear. Further studies are expected to answer the question of whether OFS will be able to replace chemotherapy.

HER2-positive BC

Treatment de-escalation and escalation for HER2$^+$ early BC is a major focus of our discussion. Coordinated by West German Study Group (WSG), Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early Breast Cancer (ADAPT) is by far the largest prospective randomized controlled clinical trial with an umbrella protocol design focused on exploring early predictive surrogate markers for individualized treatment de-escalation in early BC across all molecular subtypes. The 2021 SABCS reported the latest results of the ADAPT-HR-/HER2+ trial (13). In this trial, patients were randomized to receive either neoadjuvant pertuzumab (P) + trastuzumab (T) alone, or neoadjuvant P + T + paclitaxel (Pac). After 12-week neoadjuvant Pac + P + T, an excellent pathological complete response (pCR) rate of 90.5% was observed, and a clinically meaningful pCR rate of 34% after P+T alone was also achieved. Besides, pCR was strongly associated with improved iDFS. In the chemotherapy-free P + T arm, no pCR was observed in patients with low HER2 expression [immunohistochemistry (IHC) 1+/2+ and fluorescence in situ hybridization (FISH) positive] and/or basal-like subtype. After a median follow-up of 5 years, there were no significant differences between study arms in iDFS (HR =0.32, 95% CI: 0.07 to 1.47; P=0.144), dDFS (HR

=0.34, 95% CI: 0.04 to 2.80; P=0.313), and OS (HR =0.41, 95% CI: 0.05 to 3.55; P=0.422). These results showed that chemotherapy-free HER2-targeted therapy can also achieve excellent pCR rates and survival, and the survival benefits were irrespective of further adjuvant chemotherapy use. Chemotherapy-free regimens may be promising for those with early responses, with high HER2 expression and non–basal-like tumors. The 2021 ESMO discussed the results from the translational research of WSG-ADAPT TP trial (14). Biomarkers may predict outcomes following de-escalated neoadjuvant therapy in $HR^+/HER2^+$ early BC when comparing ado-trastuzumab emtansine (T-DM1) with or without ET to trastuzumab plus ET in pCR and OS. Baseline tumor immunogenicity (PD-L1IC and CD8) may be associated with higher pCR rates and favorable outcomes, while PIK3CA mutation was correlated with poor outcome even after T-DM1 treatment, providing a theoretical basis for guiding future independent randomized controlled studies about chemotherapy-free strategies designed in a reasonable and scientific way.

As for neoadjuvant treatment strategies, new data has become available for combination treatment with pyrotinib, a small molecule TKI investigated within China. As reported in 2021 SABCS, the PHAse 2 trial of DuRvalumab in Advanced Endometrial Cancer (PHAEDRA) trial was the first clinical trial in China to compare the efficacy and safety of adding pyrotinib to trastuzumab and docetaxel versus placebo, trastuzumab, and docetaxel as neoadjuvant treatment in HER2-positive BC patients (15). The study showed that total (t)pCR rates were 41.0% (73 of 178) in the pyrotinib arm and 22.0% (39 of 177) in the placebo arm (difference, 19.0%; 95% CI: 9.5% to 28.4%; one-sided P<0.0001). Objective response rate (ORR) was 91.6% in the pyrotinib arm but only 81.9% in the placebo arm. The 2021 ESMO published the results of another prospective, multicenter clinical trial studying the addition of pyrotinib in early or locally advanced HER2-positive BC patients with no response to two cycles of neoadjuvant therapy (16). In this study, tpCR rate was 29.0% (9/31) following the addition of pyrotinib to TCH (trastuzumab, docetaxel, carboplatin) treatment, and 14.3% (3/21) for those who continued TCH. This study demonstrated the improved efficacy of pyrotinib + TCH in patients with early or locally advanced HER2-positive BC who did not respond after 2 cycles of TCH in the neoadjuvant setting, and also emphasized the importance of early efficacy assessment during neoadjuvant therapy. Additionally, a meta-analysis with four studies (CALGB40601, CHER-LOB, NSABP-B41, NeoALTTO) included showed chemotherapy combined with trastuzumab (T) plus lapatinib (L) dual blockade could lead to improved outcomes compared to chemotherapy combined with T alone (17). The risk of disease relapse was 38% lower with the combination chemotherapy plus LT group than with the chemotherapy plus T group (HR =0.62; 95% CI: 0.46 to 0.85). Dual blockade also led to a 65% reduction of risk of death (HR =0.65; 95% CI: 0.43 to 0.98). These findings showed the great clinical value of neoadjuvant TKI in improving pCR and prognosis when combined with T and chemotherapy compared to chemotherapy plus T alone, suggesting that the addition of TKI may also be a good choice in clinical practices.

TNBC

Unlike the above BCs which are HR^+ or $HER2^+$, TNBC has no clearly defined target. Taxanes and anthracyclines remain the main and active therapeutic choices in TNBC. In 2021, great research progress has been made in the (neo)adjuvant treatment of TNBC to guide clinical practice. New targeted therapies and immunotherapies have gradually become a focus of TNBC treatment to prolong survival, improve life quality, and hold the promise of a cure.

Chemotherapy remains the most important treatment strategy in TNBC, with the value of carboplatin being increasingly recognized in recent years. In 2018, the Lancet published the outcomes of the addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess) study (18), showing a significant higher pCR rate in the paclitaxel plus carboplatin group than in patients receiving paclitaxel alone (58% *vs.* 31%, P<0.0001), but a non-significant pCR rate between the paclitaxel plus carboplatin plus veliparib group and the paclitaxel plus carboplatin group (53% *vs.* 58%, P=0.36). These results suggested that the improvement in pCR rate was due to carboplatin, without a substantial contribution from veliparib. Besides, as reported by ESMO in 2021, after 4.5 years median follow-up time, the event-free survival (EFS) was significantly higher in the paclitaxel plus carboplatin group than that in the paclitaxel alone group (79.3% *vs.* 68.5%; HR =0.57; 95% CI: 0.36 to 0.91; P=0.02) (19). No significant difference in EFS was found between the paclitaxel plus carboplatin plus veliparib group and the paclitaxel plus carboplatin group (78.2% *vs.* 79.3%; HR =1.12; 95% CI: 0.72 to 1.72; P=0.620).

These results indicated that the pCR benefit caused by the addition of carboplatin to paclitaxel translated into the EFS benefit, while the further addition of poly-ADP-ribose polymerase inhibitor (PARPi) had no impact on pCR nor EFS. The NeoCART study was the first head-to-head clinical trial comparing the efficacy and safety of neoadjuvant TCb (docetaxel and carboplatin) to that of EC-T (epirubicin, cyclophosphamide, and docetaxel) in TNBC, led by Kun Wang from Guangdong Provincial People's Hospital (20). The pCR rate was 61.4% following 6 cycles of TCb treatment and 38.6% in the 4EC-4T group, with a difference of 22.8% [odds ratio (OR) =2.52, P=0.033], confirming that the TCb regimen was superior to the standard EC-T regimen in the neoadjuvant setting for TNBC patients. Considering its efficacy and safety, the 2022 National Comprehensive Cancer Network (NCCN) guideline version 1.0 published the NeoCART study as the reference for docetaxel + carboplatin (4–6 cycles) in "HER2-negative invasive breast cancer".

In the adjuvant setting, the phase III PATTERN trial investigated the combination of paclitaxel and carboplatin (PCb) in TNBC (21), and was included in the 2021 American Society of Clinical Oncology (ASCO) and NCCN guidelines, claiming the important position of carboplatin-containing regimens in the adjuvant setting. In this study, 5-year DFS was longer in the PCb group compared with the CEF-T (cyclophosphamide, epirubicin, fluorouracil, and docetaxel) group (86.5% *vs.* 80.3%; HR =0.65; P=0.03). However, the phase III randomized controlled EA1311 trial showed that adjuvant platinum agents are unlikely to be noninferior or superior to capecitabine at improving iDFS for non-pCR TNBC patients after neoadjuvant chemotherapy (22). The 3-year iDFS for platinum was 42% (95% CI: 30% to 35%) versus 49% (95% CI: 39% to 59%) for capecitabine (HR =1.06; 95% CI: 0.62 to 1.81). As platinum agents failed to show noninferiority or superiority over capecitabine and were associated with more severe adverse effects than expected, this trial was terminated early. This trial further consolidated the importance of capecitabine as the standard therapy. Furthermore, the SYSUCC-001 study (23) was also included in the 2021 NCCN guideline, which evaluated the efficacy and adverse effects of low-dose capecitabine maintenance for 1 year after standard adjuvant chemotherapy in TNBC, and found a significant improvement of 5-year DFS in the capecitabine group over the observation group (82.8% *vs.* 73.0%; HR =0.64; P=0.027).

In recent years, immunotherapy has undergone rapid advances. Many studies about programmed death-1/programmed cell death-ligand 1 (PD-1/PD-L1) have demonstrated encouraging results in TNBC patients. The 2021 ESMO Annual meeting reported the updated follow-up outcomes of the KEYNOTE 522 trial (24), which aimed to compare four cycles of pembrolizumab plus paclitaxel and carboplatin (the pembro group) with placebo plus paclitaxel and carboplatin (the pbo group) in the neoadjuvant setting, followed by doxorubicin–cyclophosphamide or epirubicin–cyclophosphamide for 4 weeks in the neoadjuvant setting. The two groups then received an additional four cycles of pembrolizumab or placebo (9 cycles in total). After a median 39.1 months follow-up period, there was improvement in 36-month EFS rate in the pembro group over the pbo group (84.5% *vs.* 76.8%; P=0.00031), and the benefit was consistent across all subgroups. The pembro group showed significant improvements both in pCR and EFS, as well as a longer OS, thereby supporting the FDA approval as neoadjuvant therapy for TNBC patients. Long-term follow-up results are expected. The 2021 ASCO Annual meeting presented the latest results of the GaparNeuvo trial after 43.7 months median follow-up (25), which investigated the addition of durvalumab, a PD-L1 inhibitor, to standard neoadjuvant chemotherapy in patients with early TNBC. As previously reported, the pCR rate was 53.4% with durvalumab versus 44.2% in the placebo arm (adjusted OR =1.53; P=0.182), a nonsignificant difference. In the latest analysis, the durvalumab arm showed improvements in 3-year iDFS (85.6% *vs.* 77.2%, HR =0.48; 95% CI: 0.24 to 0.97; P=0.0398), dDFS (91.7% *vs.* 78.4%, HR =0.37; 95% CI: 0.13 to 0.74; P=0.0078), and OS (95.2% *vs.* 83.5%, HR =0.24; 95% CI: 0.08 to 0.72; P=0.0108) compared with the placebo arm, providing long-term survival data of combined immunotherapy with chemotherapy in early TNBC patients for the first time. In addition, a single-arm, open-label, phase II clinical trial was aimed at evaluating the efficacy and safety of neoadjuvant camrelizumab plus nab-paclitaxel and epirubicin for early TNBC and exploring the optimal chemotherapy regimens when used in combination with immunotherapy (26). This trial was conducted in China, and obtained the data of the domestically developed PD-1 inhibitor camrelizumab in the Chinese population. The pCR rate was about 74–81%, which is relatively high in the neoadjuvant setting for TNBC globally, and was beyond expectation. Although research on immunotherapy has achieved great progress in TNBC, there are still some patients who are unable to benefit from immunotherapy. Therefore, further study is warranted to find more effective

biomarkers to help select the appropriate target population that can benefit from immunotherapy.

In the field of targeted therapy, the 2021 ASCO Annual Meeting presented the results of the OlympiA study (27), which aimed to assess the use of adjuvant PARPi olaparib versus placebo in patients with germline BRCA1/2-mutant HER2$^-$ early BC after completion of standard chemotherapy. Compared with placebo, olaparib showed a significant benefit for iDFS (HR =0.58; 99.5% CI: 0.41 to 0.82; P<0.0001) and resulted in an 8.8% increase of 3-year iDFS (85.9% *vs.* 77.1%; 95% CI: 4.5% to 13.0%), and a 7.1% increase of 3-year dDFS (87.5% *vs.* 80.4%; 95% CI: 3.0% to 11.1%). Based on these outcomes, the FDA granted priority review for olaparib. In the neoadjuvant setting, NEOTALA was the first phase II clinical trial to evaluate the efficacy and safety of the PARPi talazoparib for patients with early germline BRCA1/2-mutant HER2$^-$ BC (28). Talazoparib has been shown to be the potent PARP inhibitor, with the currently strongest potential of trapping PARP-DNA complexes, and ability to reach efficacy at low concentration. The pCR rate of talazoparib was 45.8% and 49.2% for the evaluable and ITT populations, respectively, which is comparable to those observed with combination anthracycline and taxane-based chemotherapy regimen. Talazoparib was generally well tolerated, with no adverse effects attributed to this drug. To further select population suitable to targeted therapy, in the future, genetic testing for BRCA mutations may be made more available for high-risk early BC patients.

Summary

Although much groundbreaking progress has been made in BC clinical research in 2021 which have changed clinical practice decisions, there are still numerous challenges. Previously adjuvant chemotherapy was recommended for all HR+/HER2 early BC patients with positive axillary lymph node. By contrast, current research on clinical implementation of PRS has brought us to the realization that chemotherapy can be avoided in some low-risk postmenopausal BC patients, even with one to three positive lymph nodes. For premenopausal women, it is not clear if the chemotherapy benefit is secondary to ovarian ablation or to the cytotoxic effect from chemotherapy. Further research is needed to determine if chemotherapy can be replaced by OFS, thus premenopausal women can be treated with OFS plus ET alone. In addition, CDK4/6i have brought new hope to the treatment of HR$^+$/HER2$^-$ early BC patients. However, questions remain as to finding the suitable population for adjuvant CDK4/6i plus ET treatment, and how to individualize the treatment strategy when it comes to deciding which subpopulation of HR$^+$/HER2$^-$ BC patients may benefit from extended duration of ET, which need to be addressed in future studies. The combination with TKI may inhibit the HER2 pathway more comprehensively to benefit more HER2$^+$ BC patients, while we are still exploring how to select the suitable subpopulation of HR$^-$/HER2$^+$ patients for neoadjuvant targeted therapy with chemotherapy avoided. In lack of an ideal therapeutic target, TNBC has been the subject of intensive research on new treatment approaches recently, which paved the way from the era of chemotherapy to the era of targeted therapy and immunotherapy.

It is possible that patients may obtain the same benefit, or partial benefit, from OFS instead of chemotherapy. A multitude of exciting research outcomes have been obtained to guide clinical practice. The choices of personalized precision therapy based on the patient's target profile have emerged as attractive treatment approaches. For example, PD-1 inhibitor plus chemotherapy can be given to patients with PD-L1 combined positive score (CPS) ≥10, while patients with germline BRCA-mutated BC can receive PARP inhibitors as treatment. To further realize individualized precision medicine, the discovery of reliable biomarkers for screening the target population who can benefit is currently in critical need. We are looking forward to more and more basic, clinical, and translational studies, which will offer evidence to clinical decision-making in a more individualized and precise way, and bring more survival benefits to BC patients.

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References

1. Delaloge S, Dureau S, D'Hondt V, et al. 63O Letrozole and palbociclib versus third generation chemotherapy as neoadjuvant treatment in luminal breast cancer: Survival results of the UNICANCER-NeoPAL study. Cancer Res 2021;81:PS12-03.
2. Hurvitz SA, Park YH, Bardia A, et al. LBA14 Neoadjuvant giredestrant (GDC-9545) + palbociclib (palbo) vs anastrozole (A) + palbo in post-menopausal women with oestrogen receptor-positive, HER2-negative, untreated early breast cancer (ER+/HER2– eBC): Interim analysis of the randomised, open-label, phase II coopERA BC study. Ann Oncol 2021;32:S1285-6.
3. Gnant M, Fitzal F, Rinnerthaler G, et al. Duration of Adjuvant Aromatase-Inhibitor Therapy in Postmenopausal Breast Cancer. N Engl J Med 2021;385:395-405.
4. Del Mastro L, Mansutti M, Bisagni G, et al. Extended therapy with letrozole as adjuvant treatment of postmenopausal patients with early-stage breast cancer: a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2021;22:1458-67.
5. Pagani O, Regan MM, Fleming GF, et al. Abstract GS4-02: Randomized comparison of adjuvant aromatase inhibitor exemestane (E) plus ovarian function suppression (OFS) vs tamoxifen (T) plus OFS in premenopausal women with hormone receptor positive (HR+) early breast cancer (BC): Update of the combined TEXT and SOFT trials. Cancer Res 2018;78:GS4-02.
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in pre-menopausal women with estrogen receptor positive early stage breast cancer treated with ovarian suppression: A patient level metaanalysis of 7,030 women in four randomised trials. San Antonio Breast Cancer Symposium 2021;23:382-92.
7. Breast Cancer Expert Committee of National Cancer Quality Control Center; Cancer Drug Clinical Research Committee of China Anti-Cancer Association. Consensus recommendations for the clinical application of CDK4/6 inhibitors in patients with hormone receptor positive, human epidermal growth factor receptor 2 negative advanced breast cancer. Zhonghua Zhong Liu Za Zhi 2021;43:405-13.
8. Gnant M, Dueck AC, Frantal S, et al. Abstract GS1-07: Adjuvant palbociclib in HR+/HER2- early breast cancer: Final results from 5,760 patients in the randomized phase III PALLAS trial. Cancer Res 2022;82:GS1-07.
9. Harbeck N, Rastogi P, Martin M, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol 2021;32:1571-81.
10. Chinese Anti-Cancer Association, Committee of Breast Cancer Society. Chinese Anti-Cancer Association Guidelines for Breast Cancer Diagnosis and Treatment (Version 2021). China Oncology 2021;31:954-1040.
11. Sparano JA, Gray RJ, Ravdin PM, et al. Clinical and Genomic Risk to Guide the Use of Adjuvant Therapy for Breast Cancer. N Engl J Med 2019;380:2395-405.
12. Kalinsky K, Barlow WE, Gralow JR, et al. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. N Engl J Med 2021;385:2336-47.

13. Harbeck N, Gluz O, Christgen M, et al. De-escalated neoadjuvant pertuzumab+trastuzumab with or without paclitaxel weekly in HR-/HER2+ early breast cancer: ADAPT-HR-/HER2+ biomarker and survival results. J Clin Oncol 2021;39:503.
14. Harbeck N, Nitz U, Christgen M, et al. LBA13 Predictive impact of biomarkers on pCR and survival after de-escalated neoadjuvant T-DM1 with or without endocrine therapy (ET) vs. trastuzumab+ET in HER2+/HR+ early breast cancer: WSG ADAPT TP trial. Ann Oncol 2021;32:S1285.
15. Wu J, Liu Z, Yang H, et al. Pyrotinib in combination with trastuzumab and docetaxel as neoadjuvant treatment. for HER2-positive early or locally advanced breast cancer (PHEDRA): A randomized, double-blind, multicenter, phase 3 study. Cancer Res 2022;82:PD8-08.
16. Yu ZG, Xiong B, Yang Z, et al. 155P The addition of pyrotinib in early or locally advanced HER2-positive breast cancer patients with no response to two cycles of neoadjuvant therapy: A prospective, multicenter study. Ann Oncol 2021;32:S428.
17. Guarneri V, Griguolo G, Miglietta F, et al. 117O Survival after neoadjuvant therapy with trastuzumab-lapatinib and chemotherapy in patients with HER2-positive early breast cancer: A meta-analysis of randomised trials. Ann Oncol 2021;32:S407.
18. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol 2018;19:497-509.
19. Loibl S, Sikov W, Huober J, et al. 119O Event-free survival (EFS), overall survival (OS), and safety of adding veliparib (V) plus carboplatin (Cb) or carboplatin alone to neoadjuvant chemotherapy in triple-negative breast cancer (TNBC) after ≥4 years of follow-up: BrighTNess, a randomized phase III trial. Ann Oncol 2021;32:S407-46.
20. Zhang L, Wu ZY, Li J, et al. Neoadjuvant docetaxel plus carboplatin vs epirubicin plus cyclophosphamide followed by docetaxel in triple-negative, early-stage breast cancer (NeoCART): Results from a multicenter, randomized controlled, open-label phase II trial. Int J Cancer 2022;150:654-62.
21. Yu KD, Ye FG, He M, et al. Effect of Adjuvant Paclitaxel and Carboplatin on Survival in Women With Triple-Negative Breast Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol 2020;6:1390-6.
22. Mayer IA, Zhao F, Arteaga CL, et al. Randomized Phase III Postoperative Trial of Platinum-Based Chemotherapy Versus Capecitabine in Patients With Residual Triple-Negative Breast Cancer Following Neoadjuvant Chemotherapy: ECOG-ACRIN EA1131. J Clin Oncol 2021;39:2539-51.
23. Wang X, Wang SS, Huang H, et al. Effect of Capecitabine Maintenance Therapy Using Lower Dosage and Higher Frequency vs Observation on Disease-Free Survival Among Patients With Early-Stage Triple-Negative Breast Cancer Who Had Received Standard Treatment: The SYSUCC-001 Randomized Clinical Trial. JAMA 2021;325:50-8.
24. Schmid P, Cortes J, Dent R, et al. VP7-2021: KEYNOTE-522: Phase III study of neoadjuvant pembrolizumab + chemotherapy vs. placebo + chemotherapy, followed by adjuvant pembrolizumab vs. placebo for early-stage TNBC. Ann Oncol 2021;32:1198-200.
25. Loibl S, Schneeweiss A, Huober JB, et al. Durvalumab improves long-term outcome in TNBC: results from the phase II randomized GeparNUEVO study investigating neodjuvant durvalumab in addition to an anthracycline/taxane based neoadjuvant chemotherapy in early triple-negative breast cancer (TNBC). J Clin Oncol 2021;39:506.
26. Wang C, Liu Z, Chen X, et al. 179P Neoadjuvant camrelizumab plus nab-paclitaxel and epirubicin for early triple-negative breast cancer: A single-arm, open-label, phase II study. Ann Oncol 2021;32:S436.
27. Tutt A, Garber JE, Kaufman B, et al. OlympiA: A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high-risk HER2-negative early breast cancer. J Clin Oncol 2021;39:LBA1.
28. Litton JK, Beck JT, Jones JM, et al. Neoadjuvant talazoparib in patients with germline BRCA1/2 (gBRCA1/2) mutation-positive, early HER2-negative breast cancer (BC): Results of a phase 2 study. J Clin Oncol 2021;39:505.

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