ASCO 2022 Breast Cancer Updates

Alida Podrumar¹

¹ Nassau University Medical Center, East Meadow, New York, USA

Corresponding author: Alida Podrumar; e-mail: apodruma@numc.edu

Abstract

Data presented at ASCO 2022 provide new perspectives of therapy for patients with breast cancer. Starting with the plenary session with DESTINY-Breast04 we are turning a new page in the treatment of metastatic human epidermal growth factor receptor 2 (HER2)-low breast cancer patients. The results of the DESTINY-Breast04 trial open a new therapeutic option for half of the patients with metastatic breast cancer, establishing HER2-low metastatic breast cancer as a targetable population with trastuzumab deruxtecan. The indications for antibody drug conjugates are expanding to patients with metastatic hormone receptor positive endocrine resistant disease based on TROPICS-02. From the multitude of clinical trials with antibody drug conjugates, we can envision that this will be likely the new way to deliver chemotherapy in the future. Differences in survival within the three cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in upfront metastatic hormone positive breast cancer are emerging. We have data on continuation of ribociclib beyond disease progression on CDK4/6 in the MAINTAIN trial. The FAKTION trial does prove the benefit of the AKT inhibitor capivasertib and does highlight the importance of an extended molecular panel of the phosphatidylinositol3-kinase PI3K pathway. Furthermore, the exploratory analysis of KEYNOTE- 522, examining the correlation of event free survival and residual cancer burden after neoadjuvant treatment in patients with triple negative breast cancer does demonstrate a benefit of pembrolizumab extending to patient which did not achieve pathologic complete response, mainly by a decrease in residual cancer burden. Advances in biomarkers of response to immunotherapy are needed. For early stage breast cancer studies are in support of de-escalation of radiotherapy for low risk breast cancer patients and confirming the lack of benefit of adjuvant chemotherapy for elderly patients, even with high genomic grade index.

Keywords: HER2 low breast cancer, antibody drug conjugates, CDK4/6 inhibitors, immunotherapy, triple negative breast cancer

1. Introduction

This review will provide an overview of the most important clinical trials presented at ASCO 2022, discuss clinical implications and highlight some existing questions in the field. The treatment landscape of HER2-low metastatic breast cancer has changed. There are new developments for patients with endocrine sensitive hormone receptor positive breast cancer. The indications for antibody drug conjugates are extending from triple negative
breast cancer (TNBC) to the endocrine resistant space. Historically TNBC has been difficult to treat. With first proven activity in the metastatic disease setting, the role of immune checkpoint inhibitors (ICI) in early stage TNBC has been recently established. Patients with residual disease after neoadjuvant chemotherapy are at the highest risk of relapse and continue to remain a therapeutic challenge.

2. HER2-low breast cancer

HER2-low is a breast cancer subgroup currently defined by immunohistochemical (IHC) analysis with IHC 1+ and 2+ in absence of HER2 gene amplification by fluorescent in situ hybridization (FISH) (1). It comprises approximately half of all breast cancers and is found more frequently in hormone receptor (HR) positive disease 63% than in HR-negative 34%[1,2]. A comparison of different molecular subtypes of breast cancer does show that the HR status is the major determinant of the biology of HER2-low breast cancer. The HR-positive subgroup is enriched with luminal subtypes, the HR-negative subtype is predominantly basal like (2).

While the HER2 expression in HER2-positive breast cancer is stable over time, studies have shown instability of HER2-low over time and a change of HER2 from low to zero and vice versa in the process of cancer progression to metastasis. This process did occur regardless of the HR status (3).

Regarding prognosis, no statistically significant differences in overall survival (OS) were observed between HER2-low and HER2-negative groups, prognosis being mostly dependent on HR status (2).

Historically only HER2-positive breast cancer did benefit from HER2 targeted therapy. Adjuvant Herceptin in patients with early stage HER2-low breast cancer was tested in the large, randomized phase III NSABP B47 trial enrolling 3270 patients with HER2-low breast cancer. One year of adjuvant trastuzumab plus chemotherapy vs. chemotherapy alone did unfortunately not improve disease-free survival (DFS) and OS (4).

Trastuzumab deruxtecan (T-DXd) is a new generation antibody drug conjugate (ADC) linking HER2 to the topoisomerase inhibitor deruxtecan (DXd), a diffusible cytotoxic moiety via a cleavable linker. One humanized monoclonal HER2 antibody is linked to this potent cytotoxic payload with a drug-antibody ratio of 8:1. When the ADC is internalized, the linker is cleaved by lysosomal enzymes, facilitating the cytotoxic effect chemotherapy. In comparison to trastuzumab-emtansine (TDM1), where DM1 is trapped inside the target cells, DXd is diffusible in the neighboring cells, being effective in tumor cells with lower degree of HER2 expression - the bystander effect (5,6).

DESTINY-Breast04 was the first randomized phase III multicenter trial for patients with HER2-low metastatic breast cancer. It did randomize 557 patients 2:1 to T-DXd vs physicians’ choice of chemotherapy. Majority of patients (88.8%) were HR-positive and 11.3 % were HR-negative. All patients had a history of at least one prior chemotherapy but not more than two lines of chemotherapy. In the HR-positive patients the median progression free survival (PFS) was increased from 5.4 month to 10.1 month in the T-DXd arm with a hazard ratio of 0.51 and a p < 0.0001. Similar results were reported also in the entire group of patients with an improvement in median PFS from 5.1 to 9.9 month in the T-DXd group with a hazard ratio 0.5 and p < 0.0001, a 50% decrease in risk of disease progression. Among all patients there was a 6 month improvement in median OS from 16.8 to 23.4 month with T-DXd hazard ratio 0.64 p = 0.001. A subgroup analysis did confirm the benefit in all patient categories: IHC 1+, IHC 2+, prior use of CDK 4/6, irrespective of the number of prior chemotherapies. Results of an exploratory analysis of the HR-negative HER2-low breast cancer group did also show an improvement in median PFS from 2.9 to 8.5 month with a hazard ratio of 0.46 (95% CI, 0.24 to 0.89) and a more than doubled median OS of 18.2 month hazard ratio of 0.48 (95% CI, 0.24-0.95) with T-DXd (7).

Regarding toxicity, interstitial lung disease (ILD) is included in the black box warning of this drug and did occur in 12.1% of patients within the T-DXd arm and 3 patients (0.8%) died of ILD. The median time to onset of ILD was 4-5 month into therapy (7). In DESTINY-Breast04 patients did undergo CT chest every 6 weeks,
a strategy difficult to implement in clinical practice. In clinic we have to focus on proactive monitoring of patient’s pulmonary symptoms. ILD is treated per guidelines. Symptomatic ILD – grade 2 should lead to permanent discontinuation of T-DXd and prompt initiation of systemic corticosteroid treatment at 1 mg/kg/day prednisone for at least 14 days followed by a gradual taper over at least 4 weeks. For grade 1 asymptomatic ILD T-DXd is interrupted, steroids are started until ILD resolves to grade 0. If ILD resolves in ≤28 days from date of onset, the dose of T-DXd is maintained. If ILD resolves in >28 days from date of onset, T-DXd dose should be reduced by one dose level (8). On August 5, 2022, the Food and Drug Administration (FDA) approved T-DXd for patients with metastatic HER2-low breast cancer based on the positive results of DESTINY-Breast 04 trial results.

The concept of HER2-low continues to evolve. As per the data presented in DESTINY-Breast04 the level of HER2 expression by IHC 1+ vs 2+ did not correlate with treatment response. The DAISY trial is reporting a 30% response rates with T-DXd in patients with HER2 IHC 0 breast cancer [9], raising a critical question: which is the lowest level of HER2 expression associated with response to T-DXd? Can the effect of T-DXd in HER2- negative breast cancer patients be explained by the bystander effect? Do we need a more sensitive method than IHC to better select patients for T-DXd? It should be remembered that ASCO CAP guidelines define HER2 zero by less than 10% of cells with positive HER2 staining. The expression of HER2 on mass spectrometry is dependent on the level of IHC, but even IHC 0 has a low level of HER2 expression. The reported concordance among pathologist, especially in distinguishing between IHC 1+ and IHC 0 is as low as 26% (10).

Will list here few clinical trials being conducted in the HER2-low space. DESTINY-Breast06 is investigating upfront T-DXd in patients with HR-positive HER2 low metastatic breast cancer and includes a group of HER2-ultralow patients with IHC 0-1. Preclinical data suggest that HER2-positive tumors are immunogenic, enriched in tumor infiltrating lymphocytes (TIL) and have high level of programmed death-ligand 1 (PDL1) expression (11,12). In order to further improve the treatment and prognosis of HR-negative HER-2 low patients, a group of patients with poor prognosis, DESTINY- Breast08 is studying the combination of T-DXd with immunotherapy (IO). The TALENT trial is the first neoadjuvant trial with T-DXd and endocrine therapy with a pathologic complete response (pCR) endpoint [13]. Given the reported activity in the brain of T-DXd in HER2-positive breast cancer (14), T-DXd activity in patients for HER2-low with brain metastasis is being analyzed in the DEBRA trial.

3. HER3 positive breast cancer

Another target is HER3, expressed in up to 30-50% of breast cancers and associated with a poor prognosis (15). Historically given the lack of the kinase domain, HER3 cannot be targeted with tyrosine kinase inhibitors and HER3 directed monoclonal antibodies have limited activity. Dr. Krop was reporting at ASCO 2022 results of the phase 1/2 study of patritumab deruxtecan in HER3 expressing metastatic breast cancer. Analysis of 118 patients, 113 HR-positive, 53 HR-negative and 43 HER2-positive did report an overall response rate (ORR) of 30% in HR-positive/HER2 negative, 22.6% in HR-negative and 42.9% HER2-positive patients with a median PFS of 7.4 month in HR-positive, 5.5 month in HR-negative and 11 month in HER2-positive breast cancer patients. A direct relationship between HER3 expression and patritumab deruxtecan activity could not be demonstrated. The mechanism of action of patritumab deruxtecan in the HER3 low patients is not very well understood and could be explained by the ADC potency, bystander effect and high drug to antibody ratio. Regarding safety, the most common toxicities observed were gastrointestinal and hematologic with neutropenia and thrombocytopenia. ILD did occur in 6.6% of patients; although primarily grade 1 and 2, there was one fatal ILD event (16).

4. Metastatic HR-positive breast cancer

While a cross trial comparison shows similar PFS with the three cyclin- dependent kinase 4 and 6 (CDK4/6) inhibitors in first line metastatic breast cancer when combined with
aromatase inhibitors, ribocilcib is reporting OS (17), including in combination with fulvestrant (18). The final OS analysis of the addition of palbociclib to frontline letrozole in postmenopausal women with HR-positive HER2-negative breast cancer patients in PALOMA-2 concluded that the addition of palbociclib to letrozole did not significantly improve OS. The median OS in both arms was around 50 months. Given the long follow up on this trial, with a median of 90 months, patients were lost for follow-up and survival data were missing (19). How should we interpret these differences? Is one CDK4/6 inhibitor better than the other? Mature OS data of Monarch 3 trial with upfront abemaciclib and aromatase inhibitor are expected in 2023. A second interim analysis of the Monarch 3 trial presented at ESMO 2022 does show a favorable OS, although with no statistical significance (20). In clinic a discussion with the patient should reflect these differences in efficacy as well as differences in toxicity profile.

The treatment of patients progressing on first line CDK4/6 endocrine therapy raises important questions, including the benefit of continuation of the CDK 4/6 after disease progression. The MAINTAIN trial, a multicenter randomized, placebo-controlled phase II trial of 120 patients found a significant PFS benefit with a median PFS increase from 2.8 month to 5.3 month and a hazard ratio of 0.57 (95% CI: 0.39-0.95) \( p=0.006 \) when patients with HR-positive HER2-negative metastatic breast cancer changed endocrine therapy and received ribociclib following progression on CDK4/6 inhibitor. Most patients had previously received palbociclib. PFS was seen in all subgroups independent of the prior duration of the CDK 4/6, presence of visceral metastasis (21). How are we going to use this data for our patients in clinic? With the change of the endocrine therapy and the CDK4/6 inhibitor at the same time, it is difficult to clearly discern the contribution of ribociclib as the second CDK 4/6 inhibitor. PADA-1 trial data [22], while changing the endocrine partner by using serial estrogen receptor 1 (ESR1) mutation tracking, is also providing evidence for CDK 4/6 maintenance. Continuation of ribociclib could be an option in the absence of PIK3CA mutations, in patients with a slow disease progression. For more date we are awaiting the results of the Capitello 291 trial with the AKT inhibitor capivasertib and fulvestrant vs fulvestrant in patients with metastatic HR-positive breast cancer with progression on AI and CDK 4/6. In order to further redefine the importance of molecular alterations, a subset analysis of patients with PIK3CA/AKT1/PTEN alteration is planned in this study (23).

Although may be with less clinical impact, since patients with prior treatment with CDK4/6 inhibitors were not included, the phase II FAKTION study of fulvestrant plus capivasertib or placebo after progression on aromatase inhibitors is drawing attention to the importance of an expanded group of molecular markers PIK3CA activating mutations, AKT1 E17K mutation and PTEN alterations on next generation sequencing (NGS) or plasma by circulating tumor DNA (ctDNA). The expanded testing did identify pathway alterations in 25% of patients initially classified as mutation negative. In patients with pathway alterations capivasertib and fulvestrant was associated with an improvement in median PFS of 12.8 month vs 4.6 month with fulvestrant and placebo, hazard ratio of 0.44 (95%CI:0.26-0.72 \( p=0.0014 \)) and an improvement in median survival of 38.9 month vs 20 month with a hazard ratio 0.46 (95% CI:0.27-0.79) \( p=0.0047 \) (24).

5. New antibody drug conjugate data

TROPICS-02 Phase III Trial is the first trial to investigate an ADC in HR-positive patients, refractory to endocrine therapy. It did evaluate the ADC sacituzumab govitcan in HR-positive HER2-negative heavily pretreated metastatic breast cancer patients with progression on endocrine therapy, two to four prior lines of chemotherapy and 85% of liver metastasis. This trial is reporting a median PFS of 5.5 month with sacituzumab govitcan vs 4 month in the physician’s choice chemotherapy with a hazard ratio 0.66 (95% CI:0.53-0.83) \( p=0.0003 \). Although the improvement does seem to be modest the analysis at 6, 9 and 12 month shows an increase in the percentage of patients free of progression with a flattening of the PFS curves and a tripling of number of patients progression free at 1 year (25). OS was updated at ESMO 2022 with a median OS of
benefit of 3.2 month OS in favour of sacituzumab govitecan hazard ratio 0.79 (95% CI: 0.65-0.96; \( P = .02 \)) (26).

There are now two ADC with activity in metastatic HR-positive breast cancer resistant to endocrine therapy. Data comparing sacituzumab govitecan and trastuzumab deruxtecan are not available. Sacituzumab govitecan was added to the National Comprehensive Cancer Network (NCCN) as a treatment option for patients with HR-positive HER2-negative patients with disease progression on prior endocrine therapy, CDK4/6 inhibitors and at least two lines of chemotherapy (including taxanes), reinforcing the clinical activity of this treatment in a patient population where the need is the highest.

6. Early stage triple negative breast cancer

The phase III Keynote-522 trial led to the FDA approval of pembrolizumab in the neoadjuvant therapy of early-stage breast TNBC based on benefit in pCR and event free survival (EFS). 1174 patients with stage II or III TNBC were randomized in a 2:1 ratio to neoadjuvant therapy with four cycles of pembrolizumab or placebo every 3 weeks plus paclitaxel and carboplatin, followed by four cycles of pembrolizumab or placebo plus anthracycline- cyclophosphamide. After surgery patients did continue adjuvant pembrolizumab or placebo for a total duration of one year of therapy. In a final analysis the improvement in pCR was 7.5% (95% CI 1.6-13.4) in the pembrolizumab arm (27). A clinically and statistically significant 3-year EFS improvement from 76.8% to 84.5% hazard ratio 0.63 (95% CI, 0.48–0.82; \( P<.001 \)) was observed in the control versus pembrolizumab arm (28) and led to the FDA approval of pembrolizumab for neoadjuvant therapy in early stage TNBC on July 26, 2021.

At ASCO 2022 Dr. Pusztai did present an exploratory analysis of EFS by residual cancer burden (RCB) categories showing that the benefit of pembrolizumab is extending beyond the increase in pCR, by the effect of pembrolizumab in decreasing the RCB. The greatest benefit of pembrolizumab was seen in patients in the RCB-2 group. Patients with RCB-2 had an improvement in EFS of 75.7% vs 55.9% with placebo (HR 0.52; 95% CI: 0.32-0.82). Patients with RCB-0 and RCB-1 had very high 3-year EFS in both treatment arms and no statistically significant benefit for pembrolizumab was seen in these groups. Among patients with RCB-3, there was also no difference in 3 years of EFS, this group of patients representing likely a group of patients with primary refractory disease with no benefit of ICI (29).

Few clinical considerations merit further attention: To what extent does the chemotherapy regimen affect the responses to the neoadjuvant treatment? While different chemotherapy backbones have been used in different neoadjuvant studies, KEYNOTE- 522 regimen is the only study reporting outcomes, combining neoadjuvant carboplatin and anthracycline. Do we need both, do we need carboplatin or can an anthracycline free regimen be used? Impassion 031 and GeparNUEVO used a platinum based neoadjuvant chemoimmunotherapy regimen with favorable EFS results (30,31). The use of an anthracycline free, less toxic regimen is still controversial. Omission of anthracyclines in NeoTRIPaPD-1 trial led to no improvement in pCR with nab-paclitaxel/carboplatin/atezolizumab when compared to chemotherapy alone (32), suggesting that anthracyclines may lead to upregulation of the immune-related genes, resulting in a favorable tumor microenvironment (TME) (33). The benefit on pCR and safety of platinum-based, anthracycline free combination in neoadjuvant setting in the NeoSTOP trial (34), is further confirmed in the NeoPACT trial with the addition of pembrolizumab to carboplatin/docetaxel in the neoadjuvant setting, reporting a pCR of 58% (95%CI: 51-70%) and 2-year EFS of 89% (35).

Is adjuvant pembrolizumab needed in patients achieving a pCR to neoadjuvant therapy? GeparNUEVO did not use immunotherapy in the adjuvant part of the treatment course and is also reporting improvement of EFS (30). The planned OptimICE- pCR trial is expected to answer this question.

What is the best treatment of residual disease? KEYNOTE-522 did not include capecitabine treatment for residual disease. Considering the CREATE-X trial reported improvement in 5-year DFS 69.8% for capecitabine vs. 56.1% for observation with a hazard ratio
0.58 (95%CI 0.39-0.87) and OS 78.8% vs 70.3% hazard ratio 0.52 (95%CI 0.3-0.9) by escalation of post-neoadjuvant treatment with the addition of 4-6 cycles of adjuvant capecitabine (36), adjuvant capecitabine should be recommended for residual disease. Although capecitabine and pembrolizumab have overlapping toxicities, no major adverse side effects were mentioned with this combination. How can the OlympiA PARP inhibitor data in patients with gBRCA1 and gBRCA2 with residual disease be integrated in this treatment? We need to mention that OlympiA study did not include neoadjuvant IO and adjuvant olaparib was also not part of KEYNOTE-522. Supported by the benefit of adjuvant olaparib in gBRCA patients in OlympiA (37,38), the safety of the combination of olaparib and pembrolizumab, this combination should be recommended for patients with residual disease and gBRCA. Promising efficacy results of PARP inhibitors in metastatic breast cancer in patients with PALB2 and somatic BRCA mutation (39), might lead to the future use of PARP inhibitors in these mutations in early-stage disease.

PD-L1 status was not predictive of benefit for neoadjuvant pembrolizumab in the KEYNOTE-522 trial. While stromal and intra tumoral TIL have been confirmed to have prognostic value and are predictive of a good response to neoadjuvant therapy across multiple trials (40), there are not able to predict the response to the addition of ICI (30,31). A 27 gene -immunomodulatory signature score assay reported in a post hoc analysis NeoTRPaPDL1 is correlating with response to ICI (41). Emerging clinical trials are using TIL, to select patients for chemotherapy de-escalation strategies (42). In addition to the number of TIL the spatial relationship of the TIL with the cancer is a predictor of response to ICI. Currently following subgroups of tumor immune microenvironment are being described: the “immune deserted” subtype characterized by a low number of CD8 T cells, the “margin restricted” subtype with CD8 T cells restricted to tumor margins and fibrosis, the “inflamed “subtype displaying CD8 T cells within the epithelium and stroma, and the “stromal restricted” subtype with CD8 T cells restricted to the stroma (43). A better understanding of the tumor immune microenvironment may lead to better selection of patients able to benefit from immunotherapy. The impact of the gut microbiome composition on the response to neoadjuvant treatment in early stage TNBC is an emergent field of research (44). Recent publications show that patients exhibiting plasma circulating tumor DNA (ctDNA) after treatment for early-stage breast cancer have a worst prognosis and are more likely to relapse (45). Identification of ctDNA as a marker of minimal residual disease and its potential use to in an adaptive treatment approach is being investigated in ongoing clinical trials (46).

7. Early-stage HR-positive breast cancer

The prognosis of patients with early-stage low risk HR-positive breast cancer is very good and overtreatment of this patients should be avoided. LUMINA trial is a phase III study of 500 patients 55 years or older with invasive ductal cancer stage I HR-positive, luminal A, defined as ER\geq 1%, PR >20 %, HER2-negative and Ki 67 \leq 13.25%, grade 1 or 2, omitting radiation therapy after lumpectomy, sentinel node biopsy and endocrine therapy. The study is reporting a 5 year follow up a with a 2.3% local recurrence rate, concluding that patients with low-risk breast cancer can forgo radiation therapy after breast conserving surgery and endocrine therapy (47). Can we now omit radiation therapy? Ki 67 reproducibility is of concern and clinical trials using genomic signatures to guide omission of radiation for patients with low-risk breast cancers are ongoing. LUMINA provides further evidence of omitting radiation therapy in elderly patients, but the safety of omitting radiation therapy in younger patients with longer life expectancy is still to be confirmed in additional studies.

The phase III randomized ASTER 70s trial for patients more than 70 years of age with early-stage HR-positive tumors, high genomic grade index, did confirm that there was no benefit for adjuvant chemotherapy, providing additional evidence to an existing literature that older patients get no benefit from chemotherapy, even with high genomic grade index (48).
Regarding adjuvant denosumab, a long-term follow-up from the ABCSG-18 trial does provide evidence that addition of denosumab during adjuvant aromatase inhibitor therapy does lower the rate of fractures and is also associated with an improved bone metastases-free survival by 19% and OS by 20%[49]. The previously reported D-CARE trial with adjuvant denosumab did not show any benefit of denosumab in prevention of breast cancer recurrences but did include a higher risk patient population and HR-negative patients and [50]. The ABSCG-18 study findings are similar to the results with bisphosphonates, which are currently the guideline-recommended standard of care for bone-strengthening adjuvant treatment for early-stage breast cancer and therefore denosumab can be considered as adjuvant therapy for postmenopausal HR-positive patients.

8. Conclusions:

Last ASCO draws attention to numerous advances in the management of patient with breast cancer, the most notable one being the paradigm shift in the treatment of HER2-low breast cancer. The HER2-low landscape is continuing to evolve, the optimal cutoff predicting response to T-DXd is unfolding. We have much to learn on sequencing ADC, as more are available for use in our patients. We expect further data in the post CDK4/6 inhibitor space for HR-positive metastatic breast cancer. Further research is needed to establish how to best select patients who benefit from immunotherapy.

Abbreviations:
ADC – antibody drug conjugate
AKT – protein kinase B
CDK4/6 – cyclin dependent kinase 4/6
c_tDNA – circulating tumor DNA
DFS – disease free survival
EFS – event free survival
ESR1 – estrogen receptor 1
FDA – Food and Drug Administration
FISH – fluorescent in situ hybridization
HER – human epidermal receptor
HR – hormon receptor
IHC – immunohistochemistry
ILD – interstitial lung disease
NCCN – National Comprehensive Cancer Network
NGS – next generation sequencing
PALB2 – partner and localizer of BRCA2
PARP – poly (adenosine diphosphate-ribose) polymerase
PCR – pathologic complete response
PDL1 – programmed death ligand 1
PIK3CA – phosphatidylinositol 3-kinase
PTEN – phosphatase and tensin homolog
ORR – overall response rate
OS – overall survival
TDXD – trastuzumab deruxtecan
TDM1 – trastuzumab emtansine
TIL – tumor infiltrating lymphocytes
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