

## **SABCS 2021 Highlights for Patients with MBC**

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The San Antonio Breast Cancer Symposium (SABCS) is an annual conference providing state-of-the-art information regarding the biology, diagnosis, and treatment of all stages of breast cancer to an international audience of physicians, researchers, and patient advocates. Often the results of clinical trials are presented at the conference, and when favorable outcomes are reported from a later-phase study, the experimental drug or combination of drugs may be FDA approved shortly afterwards.

The purpose of this recap, which contains links to studies where possible, is to provide information about metastatic breast cancer (MBC) that was delivered at SABCS in 2021. The information is arranged by disease subtype for ease of reference.

This material is included in my comprehensive paperback and eBook entitled, “*The Insider’s Guide to Metastatic Breast Cancer*,” which is also available as a complimentary [.pdf](#). The Guide includes material about approved MBC therapies in the US, Canada, Europe and Australia, symptom and side effect mitigation, cutting-edge research, and more. If you like the way this SABCS information is presented and want to start the New Year with science-based MBC information, follow this [link](#) to *The Insider’s Guide to Metastatic Breast Cancer*.

Last but not least, heartfelt congratulations to patient advocates Christine Hodgdon, Julia Maues, and to the many individuals who participated in the “GRASP” (Guiding Researchers and Advocates to Scientific Partnerships) Program! This initiative brought together patient advocates and scientists for SABCS Poster walk-throughs designed to enhance joint communication and mutual understanding.

### **FOR INDIVIDUALS WITH HORMONE RECEPTOR (HR) POSITIVE, HER2 NEGATIVE MBC:**

#### **Elacestrant:**

Possibly the most pivotal news divulged at the conference pertained to a study of an endocrine therapy drug called Elacestrant for patients with HR+, HER2- MBC. Elacestrant is an oral SERD (Selective Estrogen Receptor Degradar) somewhat similar to (but different than) Faslodex, an FDA-approved SERD that is injected in the buttocks. The Phase 3 EMERALD trial enrolled 477 postmenopausal patients who had received one or two prior lines of endocrine therapy without chemotherapy in the metastatic setting. All patients had progressed on prior CDK4/6 inhibitor treatment. Patients were randomized to receive either Elacestrant or standard of care endocrine therapy consisting of either Faslodex or an Aromatase Inhibitor. At 6 months, the median Progression Free Survival (PFS) for patients taking Elacestrant was 34.3%, vs. 20.4% for patients taking the standard of care. For patients with ESR1 mutations, PFS at 6 months was 40.8% for patients taking Elacestrant vs. 19.1% for patients taking the standard of care.

Researchers acknowledged a study limitation in that all patients enrolled received prior CDK 4/6 inhibitor treatment, so the clinical benefit of Elacestrant for patients who have not received CDK 4/6 inhibitor therapy is undetermined. Given these results, it is possible that Elacestrant may be FDA-approved for a subset of HR+, HER2- patients in 2022. **From:** [Elacestrant extends PFS among certain women with metastatic breast cancer \(healio.com\)](#)

#### **ARV-471:**

ARV-471 is an oral experimental drug (called a PROTAC inhibitor) that degrades estrogen receptors by targeting specific proteins. It was studied in a Phase 1 dose escalation trial that enrolled 60 patients who were heavily pretreated with a median of four prior therapies. All patients had previously taken CDK4/6 inhibitors, 80% had taken Faslodex, and 78% received prior chemotherapy. Of the 47 patients who were evaluable for Clinical Benefit (confirmed complete response, partial response, or stable disease) the Clinical Benefit Rate was 40%. **From:** <https://www.pfizer.com/news/press-release/press-release-detail/arvinas-and-pfizer-announce-protacr-protein-degrader-arv>

## **OP-1250:**

OP-1250 is a Complete Estrogen Receptor Antagonist (CERAN) and a Selective ER Degradable (SERD) currently being studied for the treatment of MBC. A Phase 1 dose escalation study of this oral drug enrolled 41 heavily pre-treated patients; 95% had previously received at least one prior CDK4/6 inhibitor, 68% had previously taken Faslodex, and 42% received prior chemotherapy in the advanced setting. Overall, patients received a median of 3 prior lines of anti-cancer therapies. Of 39 patients whose circulating tumor DNA (ctDNA) was assessed, ESR1 mutations were detected in 49% at baseline. The study found that Clinical Benefit Rate was 46%. <https://www.globenewswire.com/news-release/2021/11/30/2342885/0/en/Olema-Oncology-Announces-First-Clinical-Data-on-OP-1250-in-Advanced-ER-HER2-Breast-Cancer.html>

## **Entinostat:**

Entinostat is an experimental oral Histone Deacetylase (HDAC) Inhibitor (a chemical compound that inhibits a certain class of enzymes called histone deacetylases). A Phase 3 trial randomized 354 patients who had progressed on prior endocrine therapy to either Entinostat in combination with Aromasin or Aromasin alone. Median PFS on the combination was 6.3 months vs. 3.7 months on Aromasin alone. **From:** <https://www.healio.com/news/hematology-oncology/20211209/entinostat-plus-exemestane-improves-pfs-in-hormone-receptorpositive-advanced-breast-cancer>

## **Nerlynx (Neratinib) Plus Faslodex Plus Herceptin for HR+, HER2- Patients with HER2 Mutant MBC:**

In the Phase 2 SUMMIT trial which included 33 patients with HR-positive, HER2 negative, HER2-mutated MBC who had previously received CDK4/6 inhibitors, the triplet regimen of Neratinib, Faslodex, and Herceptin induced an Objective Response Rate of 42.4%. The median Duration Of Response (DOR) was 14.4 months and the median Progression Free Survival was 7.0 months. **From:** <https://www.cancernetwork.com/view/neratinib-combo-yields-positive-orr-in-her2-mutant-metastatic-breast-cancer>

## **Enobosarm:**

Enobosarm is a first-in-class, oral nonsteroidal Androgen Receptor (AR) agonist designed to treat patients with AR-positive, ER-positive advanced breast cancer. Findings from the Phase 2 G200802 trial determined that Enobosarm elicited a Clinical Benefit Rate (CBR) of 32%. Patients who had greater than 40% AR staining experienced an Overall Response Rate of 50% and a CBR of 79%, but patients with an AR staining of less than 40% experienced an ORR of 0% and a CBR of 18%, indicating that AR expression may be a useful biomarker of response for treatment selection. **From:** <https://www.onclive.com/view/schwartzberg-on-bringing-seminal-observations-on-ar-from-bench-to-bedside-in-er-breast-cancer>

## **Enhertu:**

Enhertu is FDA-approved for HER2+ MBC patients. HR+, HER2- patients have either HER2 low expression (HER2 +1 or HER2 +2) or no HER2 expression (HER2 0). In the Phase 2 DAISY study, it was found that 38% of pretreated patients with HER2 low expression responded to Enhertu, as well as almost 30% of patients with HER2 0 expression. The activity in HER2 0 tumors just missed the prespecified cutoff for clinical success, and breast cancer specialists at SABCS 2021 were undecided as to whether the investigation of Enhertu should continue in that subgroup. In the HER2 0 group (which included HR+ patients as well as some TNBC patients), there was intriguing efficacy, and the question arose whether HER2 was totally absent or whether there was failure in detecting low-level HER2 expression via testing. (Historically, 63% of HR+ patients have cancer with HER2 low expression). **From:** <https://www.medpagetoday.com/meetingcoverage/sabcs/96154>

## **Patients with Rising ESR1 Mutations While Taking Ibrance with an Aromatase Inhibitor:**

As per the Phase 3 PADA-1 trial, patients with rising ESR1 mutations who were taking Ibrance in combination with an Aromatase Inhibitor (Letrozole, Arimidex, or Aromasin) in the first-line setting who switched to Faslodex plus Ibrance before disease progression had a doubling of PFS compared with patients who were not switched. At a median follow-up of 26 months, the median PFS was 11.9 months in patients who switched to Faslodex, vs. 5.7 months for patients who did

not switch. Patients who remained on Ibrance with an Aromatase Inhibitor who subsequently developed progression and switched to Faslodex had a median PFS of 3.5 months, so there appears to be a benefit of switching from an Aromatase Inhibitor to Faslodex prior to progression when ESR1 mutations arise.

As an aside, ESR1 mutations can be detected in the blood by cell-free circulating DNA analysis. These mutations are detected in less than 5% of patients at metastatic relapse but are identified in 30% to 40% of patients at progression following first-line Aromatase Inhibitor-based therapy. **From:** <https://www.targetedonc.com/view/pfs-doubles-with-fulvestrant-palbociclib-following-ai-palbociclib-in-hr-positive-her2-negative-mbc>

### **For Patients with Liver or Lung Metastasis:**

Kisqali plus Letrozole appears to be more effective than Ibrance plus Letrozole as first-line therapy for patients with liver or lung metastasis. At SABCs 2021, it was reported that at 6 years, the Overall Survival (OS) for patients with liver or lung metastasis who took Kisqali and Letrozole was 40.5%, vs. 31.2% for patients taking Ibrance and Letrozole. And for MBC patients without liver or lung metastasis, the 6 year OS was 48.6% on Kisqali plus Letrozole, vs. 33.2% on Ibrance plus Letrozole.

### **Effect of Proton Pump Inhibitors on the Efficacy of Ibrance:**

Proton-pump-inhibitors (PPIs) are frequently prescribed for the management of anticancer drug-related gastrointestinal (GI) symptoms. In a retrospective observation study of 112 patients who took the CDK4/6 inhibitor Ibrance with endocrine therapy, it was noted that patients taking PPIs had a shorter PFS than those who were not taking PPIs (14.0 versus 37.9 months). (NOTE: Several lines of evidence suggest no impact of PPIs on the bioavailability of Kisqali, another CDK4/6 inhibitor). **From:** [https://www.esmooopen.com/article/S2059-7029\(21\)00192-7/fulltext](https://www.esmooopen.com/article/S2059-7029(21)00192-7/fulltext)

## **FOR INDIVIDUALS WITH HER2 POSITIVE MBC:**

### **Pyrotinib:**

Pyrotinib is a tyrosine kinase receptor inhibitor that targets HER2, as well as the related proteins HER4 and epidermal growth factor receptor (EGFR), also known as HER1.

The PHOEBE trial enrolled 267 Chinese patients with HER2-positive MBC who had been previously treated with Herceptin and up to two previous lines of chemotherapy in the metastatic setting. Patients were randomly assigned to receive either Pyrotinib plus Xeloda, or Tykerb plus Xeloda. The study determined that patients treated with Pyrotinib plus Xeloda had a 31% lower risk of death than those treated with Tykerb plus Xeloda, with overall survival (OS) not reached in the Pyrotinib arm compared with an OS of 26.9 months in the Tykerb arm. Furthermore, patients in the Pyrotinib arm had significantly longer progression-free survival than those in the Tykerb arm (12.5 months vs 5.6 months), with a 52% lower risk of disease progression.

**From:** <https://www.aacr.org/about-the-aacr/newsroom/news-releases/investigational-therapy-pyrotinib-with-chemotherapy-may-improve-outcomes-in-patients-with-pretreated-her2-positive-breast-cancer/>

### **Zanidatamab:**

Zanidatamab is a bispecific antibody (an artificial protein that can bind to two different types of antigens or two different parts on the same antigen) that is administered intravenously. In a Phase 1 trial of 22 pre-treated HER2 positive MBC patients, a median follow-up at 7.1 months determined that Zanidatamab plus chemotherapy yielded a confirmed Objective Response Rate (ORR) of 36.4%. Specifically, when paired with Zanidatamab, the ORR was 27.3% with Navelbine, 42.9% with Xeloda, and 50% with Taxol. Additionally, the combination was associated with a clinical benefit rate (CBR) of 54.5%, a disease control rate of 86.4%, and a duration of response (DOR) ranging from 1.6 months to over 22.1 months. The median progression-free survival was 7.3 months. **From:** <https://www.onclive.com/view/bispecific-antibodies-like-zanidatamab-have-promise-in-heavily-pretreated-her2-breast-cancer>

**Enhertu** (already FDA-approved as a third or later-line therapy for HER2+ MBC Patients):

Enhertu showed statistically significant improvement in Progression Free Survival when compared with T-DM1 as second-line treatment for HER2-positive MBC, according to results from the global Phase 3 DESTINY-Breast03 trial which randomly assigned 524 previously treated patients to either drug. At a median follow-up of about 16 months, median Progression Free Survival was not reached with Enhertu and was 6.8 months with T-DM1. The benefit was observed across all prespecified subgroups, including patients with brain metastases. *(Based upon these results, it's feasible that Enhertu may ultimately be moved to second-line therapy in lieu of T-DM1).* **From:** <https://ascopost.com/news/september-2021/destiny-breast03-second-line-trastuzumab-deruxtecan-for-metastatic-her2-positive-breast-cancer/>

### **HER2+ Patients with Leptomeningeal Disease (LD):**

As per the TBCRC049 trial, HER2 positive patients with Leptomeningeal Disease who took the combination of Tukysa, Xeloda and Herceptin had a median Overall Survival (OS) of 10 months compared with an OS of 4 – 5 months for historical controls.

### **FOR INDIVIDUALS WITH TRIPLE NEGATIVE (TNBC) MBC:**

#### **Datopotamab Deruxtecan (Dato-DXd):**

Datopotamab Deruxtecan (Dato-DXd) is an Antibody Drug Conjugate (ADC) that was studied in the TROPION-PanTumor01 Phase 1 Trial. The 44 patients enrolled in the study had been treated with a median of three prior therapies in the metastatic setting, including taxanes, platinum-based chemotherapy, immunotherapy, other ADCs, and PARP inhibitors. The overall Objective Response Rate (ORR) was 34%, and in the subgroup of 27 patients who had not previously been treated with a TROP-2-directed drug (such as Trodelvy) the ORR was 52%. **From:** <https://pharmaphorum.com/news/az-daiichi-take-aim-at-gilead-in-triple-negative-breast-cancer/>

#### **Enhertu:**

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