San Antonio Breast Cancer Symposium (SABCS) 2019 - Metastatic Breast Cancer Updates

Summary by Anne Loeser

SABCS is an annual symposium 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, as was the case this year.

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 2019. This material has likewise been incorporated into a comprehensive paperback and eBook about MBC entitled, ***"The Insider's Guide to Metastatic Breast Cancer,"*** which is also available in a complimentary .pdf. For additional information please visit https://www.insidersguidembc.com/about

Special thanks to the Metastatic Breast Cancer Alliance (MBCA) for sponsoring my attendance at the symposium, which in turn enabled this document to be compiled for MBC patients worldwide.

A major debt of gratitude to Eli Lilly for establishing the Patient Advocate Lounge at SABCS 2019, where patient advocates were able to unwind, enjoy refreshments, and converse with each other in a relaxed setting.

Kudos to the Tigerlily Foundation (a non-profit that supports young breast cancer survivors in underserved and difficult-to-reach communities) for initiating the highly-attended "Young Women's Metastatic Breast Cancer Disparities Fireside Chat" to discuss disparities in cancer care and outcomes, along with potential solutions regarding these critical issues.

A heartfelt congratulations to patient advocates Christine Hodgdon and Julia Maues, and to the many advocates and researchers who participated in the new "GRASP" (Guiding Researchers and Advocates to Scientific Partnerships) Program successfully piloted this year. This initiative brought together patient advocates and scientists for poster walk-throughs designed to enhance joint communication and mutual understanding.

General Notes from the Conference

1. **Overview of MBC Drugs and Combinations that were FDA-Approved in 2019:**

    a. In Feb. 2019, the FDA approved the subcutaneous injection consisting of Herceptin (Trastuzumab) and Hyaluronidase-oysk **(Herceptin Hylecta)** for the treatment of HER2- overexpressing breast cancer.

    b. In March 2019, the FDA) granted an accelerated approval for **Tecentriq (Atezolizumab) in combination with Abraxane (nab-paclitaxel)** for the initial treatment of Triple Negative Breast Cancer (TNBC) MBC patients whose tumors are PD-L1 positive. This combination therapy is the first FDA-approved regimen for metastatic breast cancer to include an immunotherapy drug.

    c. In April 2019, the FDA expanded the approval of **Ibrance (Palbociclib) with either an Aromatase Inhibitor (Letrozole, Arimidex, Aromasin) or Faslodex (Fulvestrant) to include men** with hormone receptor positive, HER2 negative MBC.

    d. In May 2019, the FDA approved **Piqray (Alpelisib), an oral PIK3 inhibitor, in combination Faslodex** for the treatment of postmenopausal women (as well as men) with hormone receptor positive, HER2 negative MBC with a PIK3CA mutation who had progressed on or after an endocrine-based treatment regimen.

    e. During the first half of 2019, the FDA approved three biosimilar intravenous drugs to Herceptin (Trastuzumab): **SB3** (Ontruzant; trastuzumab-dttb), **Trazimera** (trastuzumab-qyyp), and **Kanjinti** (trastuzumab-anns).

    f. Immediately following SABCS 2019, the FDA granted accelerated approval to **Enhertu** (fam-**Trastuzumab Deruxtecan**-nxki, also known as **DS-8201)** for patients with unresectable or metastatic HER2-positive breast cancer who had received 2 or more prior anti–HER2-based regimens in the metastatic setting.

2. As is the case for immunotherapy treatments, substantial research is underway regarding therapies based upon genes and **biomarkers.** Biomarkers represent substances, structures, or processes that can be measured in the body that may influence or predict the incidence of outcome or disease. They may reflect the effects of treatments, interventions, and even unintended environmental exposure. In clinical trials and in oncology clinics, biomarkers are increasingly used as eligibility criteria for specific therapies and as measurements of response to treatment.

3. At least **five new types of drugs** are being studied for MBC patients:

   a. **Oral SERDs**: Currently, the sole Selective Estrogen Receptor Degrader (SERD) available for hormone receptor positive MBC patients is Faslodex (Fulvestrant), which is administered as two intramuscular injections in the buttocks. Due to its limited bioavailability and to the discomfort its administration may sometimes cause, oral SERDs are under study:

      i. RAD-1901/Elacestrant by Radius (Phase 3 - Recruiting)
      ii. SAR-439859 by Sanofi (Phase 1/2 - Recruiting)
      iii. ZN-C5 by Zeno (Phase 1/2 - Recruiting)
      iv. GDC-9545 by Genentech (Phase 1 - Recruiting)
      v. G1T48 by G1 Therapeutics (Phase 1 - Recruiting)
      vi. LSZ102 by Novartis (Phase 1 - Recruiting)
      vii. AZD-9833 by Astra Zeneca (Phase 1 - Recruiting)
      viii. LY3484356 by Eli Lilly (Phase 1 - Recruiting)

   b. **SERCAs (Selective Estrogen Receptor Covalent Antagonists):** Existing FDA-approved hormonal therapies include SERMS (Tamoxifen and Fareston), SERDs (Faslodex), and Aromatase Inhibitors. SERCAS are a new series of compounds with unique modes of inhibition that target wild-type and mutant estrogen receptor alpha (ER*a*). SERCAs inactivate the estrogen receptor by targeting an amino acid that is not found in other hormone receptors, thus producing a different activity profile than SERMS and SERDS. The SERCA H3B-6545 is currently being tested in a recruiting Phase 1/2 clinical trial.

   c. **ShERPAs:** Selective human Estrogen Receptor Partial Agonists (ShERPAs) represent a new class of drugs that mimic the effects of estradiol in endocrine-resistant breast cancer cells. An active (non-recruiting) Phase 1 study of a ShERPA called TTC-352 is currently underway.

   d. **SARMs (Selective Androgen Receptor Modulators)**: The majority of hormone receptor positive breast tumors express the Androgen Receptor (AR), as do a moderate number of HER2 positive tumors and nearly one-third of triple-negative breast cancers. SARMs are drugs that can exert varying effects on ARs in different tissues, and there is currently one active (non-recruiting) SARM clinical trial for TNBC MBC patients whose tumors are AR positive.

   e. **BCL-2 Inhibitors:** BCL-2 is a cell survival protein best known for its roles in inhibiting apoptosis (cell death) and promoting oncogenesis (the transformation of normal cells into cancer cells). The majority of breast cancers are BCL-2 positive, and a Phase 2 study of the BCL-2 inhibitor Venetoclax is currently recruiting.

4. **Studies for Heavily Pre-treated Patients:** Encouragingly, studies are underway to determine the effect of experimental therapies on heavily pre-treated patients, and several of these studies such as SUMMIT, DESTINY-Breast-01, and KEYNOTE-890 are described below.

5. **Dosing and Toxicities:** Drug toxicity remains an area of concern, especially because most MBC patients will undergo treatment for the rest of their lives. In a workshop about drug-related toxicities, Medical Oncologist Dr. Aditya Bardia encouraged researchers to identify the Optimal Biological Dose (OBD) of drugs in clinical trials in order to reduce toxicity without impacting efficacy. He likewise discussed the concept of "Patient-Centered Dosing" - a collaboration between Medical Oncologists and their patients that considers an array of patient-specific factors when determining the best drug dosage for that patient.

6. **Central Nervous System (CNS) Metastases:** Since patients are living longer with MBC as the result of receiving more effective therapies, the chance of developing CNS metastases increases. Yet many MBC patients with CNS metastasis are excluded from clinical trials, especially those with active brain metastases that may be unresponsive to therapy. At SABCS 2019, patient advocates urgently voiced the need for change because unless patients with CNS metastases are included in clinical trials, they will continue to endure a sub-optimal prognosis.

7. **Under-represented Topics:**

   a. **Leptomeningeal Disease (LM):** Leptomeningeal disease is a form of CNS metastasis in which cancer cells migrate to cerebrospinal fluid (CSF) or to the lining of the brain or spinal cord. Of all metastatic sites, LM is the most difficult to treat, and MBC patients with LM have the worst prognosis - circumstances that warrant intensive and compassionate study.

   b. **Lobular Metastatic Breast Cancer (LMBC):** Lobular breast cancer more closely resembles a spider web than a solid tumor and therefore can be difficult to identify on scans. Patients with LMBC respond differently to certain therapies than those with ductal MBC (for example, hormone receptor positive lobular patients are less likely to respond to Tamoxifen). Due to the unique characteristics of LMBC and the fact that at least 10% of all MBC patients have this type of disease, more studies are needed. Furthermore, these patients should not be routinely excluded from clinical trials if their disease is difficult to track via scans because other mechanisms (such as liquid biopsy) may be viable for determining their response to treatment.

   c. **Epigenetics:** The field of epigenetics involves genetic control by factors other than a person's inherited DNA. It is widely acknowledged that epigenetic changes can switch genes on or off. Nutritional factors, drugs, chemicals, and environmental compounds can alter the epigenome in either a beneficial or harmful manner. Epigenetics requires further study relative to cancer, especially with regard to controllable factors that can render standard therapies more effective and their side effects more bearable.

Updates for Patients with Any Subtype of MBC

Oral Taxol (paclitaxel): According to a Phase 3 clinical trial of 402 MBC patients that compared an oral formulation of the chemotherapy drug paclitaxel (Taxol) with the current FDA-approved intravenous (IV) form, the oral version elicited a better response and increased survival. Results indicated that 40.4% of patients on the oral formulation (consisting of oral paclitaxel and Encequidar, which increases drug bioavailability) had a confirmed tumor response, compared with 25.5% in the IV group. Furthermore, the median Overall Survival was 27.9 months for the oral group compared with 16.9 months for the IV group. Importantly, the incidence of neuropathy was 17% in the oral group compared with 57% in the IV group, and was less severe when it occurred. Hair loss (alopecia) was also reduced in the oral group. Conversely, neutropenia (low neutrophil white blood count), infection, and gastrointestinal side effects were higher in the oral group, although these symptoms were generally low-grade. https://www.ajmc.com/conferences/sabcs-2019/oral-paclitaxel-reveals-superior-confirmed-response-survival-in-patients-with-metastatic-breast-cancer-compared-to-iv-paclitaxel

Updates for Patients with Hormone Receptor Positive, HER2 Negative MBC

The Combination of a CDK4/6 Inhibitor with Endocrine Therapy is the Standard-of-Care as First-Line Treatment: Based upon superior Overall Survival data from multiple clinical trials, the combination of a CDK4/6 inhibitor - Ibrance (Palbociclib), Kisqali (Ribociclib), or Verzenio (Abemaciclib) - with endocrine therapy is now the standard of care as first-line treatment option for pre-, peri-, and postmenopausal patients (and men) with hormone receptor positive, HER2 negative MBC.

It was reported that both Verzenio and Kisqali show evidence of being effective against visceral disease and being able to penetrate the Blood Brain Barrier (BBB). Verzenio also appears to be a particularly effective therapy for harder-to-treat hormone receptor positive patients with Progesterone negative and/or high-grade MBC.

In 2019, the FDA issued a warning that Ibrance, Kisqali, and Verzenio may cause rare but severe inflammation of the lung, although the overall benefit is still considered greater than the risks.

CDK4/6 Resistance: Researchers have identified the following biomarkers that may be indicative of resistance to CDK4/6 inhibitors:

- De Novo (Initial) Resistance:
  - Rb1 loss
  - FAT1 loss via the Hippo Pathway
  - CCNE1 overexpression
  - FGFR1 amplification

- Acquired Resistance:
  - Rb1 loss
  - ERBB2 (HER2) mutation
  - PTEN loss of function mutations
  - AKT amplification
  - AURKA amplification

A key question is whether additional lines of CDK4/6 treatment may benefit patients after previous CDK4/6 therapy has failed. In response, the Moffitt study of Verzenio and the TRINITI-1 "triplet" study below have shown encouraging early results:

Moffitt Study of Verzenio (Abemaciclib) after Prior Ibrance (Palbociclib) Progression: A SABCS 2019 poster presented by the Moffitt Cancer Center depicted study results of 28 heavily pre-treated hormone receptor positive, HER2 negative MBC patients who had previously progressed on Ibrance with endocrine therapy and had subsequently taken Verzenio (either as monotherapy or in combination with endocrine therapy). Of these patients, 23 (82.1%) had visceral involvement and 9 (32.1%) had brain metastases. These patients had received a mean of 5.4 prior lines of therapy, including chemotherapy. A total of seven (25%) patients had a durable response to Verzenio. Of those patients 3 had a longer Progression Free Survival (PFS) compared with their prior PFS on Ibrance. Of the patients with durable response, 5 had available genomic profiling: 2 (28.5%) patients had an ESR1 mutation and 3 (42.8%) had PIK3CA mutations. It was concluded that age, duration of previous Ibrance-based therapy, number of prior therapies, presence of visceral or brain metastatic disease, number of mutations, and presence of ESR1 or PIK3CA mutations did not affect PFS on Verzenio-based therapy.

TRINITI-1 Study - Kisqali (Ribociclib), Afinitor (Everolimus), and Aromasin (Exemestane) after Prior CDK4/6 Progression: The Phase 1/2 TRINITI-1 trial evaluated triplet therapy with Kisqali, Afinitor, and Aromasin among 95 men and postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer who received previous CDK 4/6 inhibitor therapy and up to three lines of prior therapy. The Clinical Benefit Rate at 6 months was 41.1% (which was four times the minimum threshold for the study), the Disease Control Rate was 61.1%, and the Overall Response Rate was 8.4%. The median Progression Free Survival was 5.7 months. https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7Be782030f-fd3f-47d2-9735-ad3c2d4cd2e6%7D/triplet-therapy-confers-benefit-among-certain-patients-with-advanced-breast-cancer?page=2

OTHER STUDY RESULTS FOR HORMONE RECEPTOR POSITIVE MBC PATIENTS

As previously mentioned, Piqray (Alpelisib) was FDA-Approved in 2019 for Hormone Receptor Positive, HER2 Negative Men and Postmenopausal Women who have progressed on prior endocrine therapy and whose tumors express the PIK3CA Mutation. Approval was based on the SOLAR-1 Phase 3 study in which Progression Free Survival for patients taking Piqray and Faslodex was 11.0 months, vs. 5.7 months for those taking Faslodex-only. The FDA has also approved the companion diagnostic tests "Therascreen PIK3CA RGQ PCR Kit" and "FoundationOne CDx" to detect the PIK3CA mutation. *(Some patients treated with Piqray have severe hyperglycemia [high level of glucose in the bloodstream], and the safety of Piqray in those with Type 1 or uncontrolled Type 2 diabetes is unknown).*

SUMMIT "Basket" Trial Results - Nerlynx (Neratinib) + Herceptin (Trastuzumab) + Faslodex (Fulvestrant) for Hormone Receptor Positive, HER2 Negative Pre-Treated Patients with the HER2 Mutation: A SABCS 2019 poster of this Phase 2 study highlighted the results of administering the combination of Neratinib, Herceptin, and Faslodex to 45 hormone receptor positive, HER2 negative patients with a HER2 mutation. These heavily pre-treated patients had received a median of 4 prior lines of therapy. The median Overall Response Rate was 53%, the median Progression Free Survival was 9.8 months, and the median Duration of Response is not estimable because 5 of 9 responses are still ongoing.

FAKTION Trial Results – Capivasertib (AZD5363) + Faslodex (Fulvestrant) vs. Faslodex Alone for Hormone Receptor Positive, HER2 Negative Pre-Treated Patients: This Phase 2 study compared the results of administering Capivasertib + Faslodex, vs. Faslodex alone in 140 hormone receptor positive, HER2 negative postmenopausal women who had relapsed on prior endocrine therapy. Capivasertib is a potent and selective inhibitor of AKT, which is a key node in the PI3K/AKT/mTOR signaling network. Patients were allowed a maximum of 1 line of prior chemotherapy and up to 3 lines of endocrine therapy for MBC. The median Progression Free Survival among patients receiving the combination was 10.3 months compared with 4.8 months for patients solely receiving Faslodex, and the median Overall Survival was 26.0 months versus 20.0 months respectively. https://www.onclive.com/conference-coverage/asco-2019/capivasertib-combined-with-fulvestrant-improves-pfs-in-er-breast-cancer

SAFIR02-IMMUNO Trial Results – Imfinzi (Durvalumab) vs. Chemotherapy in Pre-Treated Patients: This Phase 2 trial enrolled HER2 negative locally advanced and MBC patients who were required to have received prior first- or second-line chemotherapy. Among the 44 patients with PD-L1–positive disease across several MBC subtypes, the median Overall Survival was 26 months with the immunotherapy drug Durvalumab compared with 12 months with chemotherapy. For the "mixed" study population of patients with various breast cancer subtypes, median Overall Survival was 21.7 months with Durvalumab vs. 17.9 months with chemotherapy. https://www.targetedonc.com/conference/sabcs-2019/durvalumab-maintenance-may-improve-outcomes-in-triplenegative-breast-cancer

MEDIOLA Trial Results – Lynparza (Olaparib) plus Imfinzi (Durvalumab) in HER2 Negative BRCA Mutated MBC Patients: MEDIOLA was a Phase 1/2 study evaluating the combination of Olaparib, an FDA-approved PARP inhibitor, with the immunotherapy drug Durvalumab in HER2 negative patients with advanced solid tumors harboring BRCA mutations. For MBC patients with hormone receptor positive disease, the median Progression Free Survival (PFS) was 9.9 months, and the median Overall Response Rate was 69.2%. By number of prior lines of chemotherapy, the median PFS was 11.7 months for patients with 0 or 1 prior lines, and 6.5 months in those with 2 prior lines. Overall, patients exhibiting responses showed durable benefit, with a median Duration of Response of 9.2 months. https://www.targetedonc.com/news/olaparib-plus-durvalumab-show-durable-activity-in-germline-brca-breast-ovarian-cancer

Verzenio (Abemaciclib) for Patients with Brain Metastases: In a study of 58 hormone receptor positive, HER2 negative MBC patients with brain metastases who took Verzenio, 52 were evaluable for evaluation of Objective Intracranial Response Rate (OIRR), the primary endpoint of this study. These patients had received a median of 4 prior systemic therapies in the metastatic setting. Three patients had a confirmed response for an OIRR of 6%, and 38% demonstrated a reduction in the sum of their intracranial targeted lesions. The intracranial clinical benefit rate, which consisted of patients with response and those who had stable disease for at least 6 months, was 25%, and the median Progression Free Survival was 4.4 months. https://www.targetedonc.com/news/newer-treatments-and-combinations-emerging-for-breast-cancer-brain-metastases

Updates for Patients with HER2 Positive MBC

The current standard-of-care treatment for patients with HER2-positive, hormone receptor negative MBC is first-line Herceptin (Trastuzumab) plus Pertuzumab (Perjeta) and a Taxane, followed by second-line trastuzumab emtansine (T-DM1) for patients who have disease progression. Whereas there had previously been no standard of care for third-line treatment and beyond, this changed immediately after SABCS 2019 based upon the results of the DESTINY-Breast01 study below.

Notably, many of the following studies apply HER2 positive patients who are also hormone receptor positive ["Triple Positive"], and the MonarcHER trial was specifically designed for this population.

Enhertu (Trastuzumab Deruxtecan/DS-8201) has been granted FDA Accelerated Approval based upon DESTINY-Breast01 Trial Results Disclosed at SABCS 2019: Immediately following the DESTINY-Breast01 trial results announced at SABCS 2019, the FDA conferred accelerated approval to Enhertu (fam-Trastuzumab Deruxtecan-nxki/DS-8201) for the treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting. The Phase 2 DESTINY-Breast01 study evaluated the HER-2 directed Antibody Drug Conjugate (ADC) Trastuzumab Deruxtecan in HER2-positive MBC patients (53% of whom were also hormone receptor positive) who had received prior treatment with trastuzumab emtansine (TDM-1). HER2+ patients with stable brain metastases were also included. In this clinical trial, 184 patients who had undergone a median of six previous treatments received the recommended dose of Trastuzumab Deruxtecan. Response to therapy was reported in 112 (61%) patients, the median Duration Of Response was 14.8 months, the median Progression Free Survival (PFS) was 16.4 months, and the median Overall Survival has not yet been reached. Markedly, the median PFS for the 24 patients with brain metastases was 18.1 months. https://www.onclive.com/conference-coverage/sabcs-2019/t-dxd-shows-potential-to-establish-new-standard-of-care-in-advanced-her2-positive-breast-cancer and https://www.onclive.com/web-exclusives/fda-approves-trastuzumab-deruxtecan-for-her2-breast-cancer

HER2CLIMB Trial Results – Herceptin (Trastuzumab) plus Xeloda (Capecitabine), with or without Tucatinib (formerly ONT-380) among Pre-treated HER2 Positive Patients: The HER2CLIMB Phase 2 trial evaluated the triplet combination of the oral tyrosine kinase inhibitor Tucatinib (which crosses the Blood Brain Barrier) + Herceptin + Xeloda, compared with the doublet combination of Herceptin + Xeloda. The study enrolled 612 HER2-positive MBC patients with or without brain metastases who had previously taken Herceptin, Perjeta (Pertuzumab), and trastuzumab emtansine (TDM-1). Progression Free Survival (PFS) at 1 year was 33.1% in the triplet arm vs. 12.3% in the doublet arm, and the median duration of PFS was 7.8 months vs. 5.6 months, respectively. The Overall Survival (OS) rate at 2 years was 44.9% in the triplet arm vs. 26.6% in the doublet arm, and the median OS was 21.9 months vs. 17.4 months, respectively. Among patients with brain metastases (40% of which were untreated, or treated and progressing), the PFS rate at 1 year was 24.9% in the triplet arm vs. 0% in the doublet arm, and the median PFS was 7.6 months vs. 5.4 months, respectively. The Overall and Progression Free Survival results were consistent across all prespecified subgroups based upon age, race, hormone receptor status, geographic location, and other factors. Given these results, the combination of Tucatinib + Herceptin + Xeloda is likely to become FDA-approved for HER2 positive MBC patients in a late-line setting, and was conferred Breakthrough Therapy Designation on Dec. 18, 2019. https://www.esmo.org/Oncology-News/HER2CLIMB-and-DESTINY-Breast01-Findings-in-Heavily-Pretreated-HER2-positive-MBC and https://www.mdedge.com/hematology-oncology/article/214170/breast-cancer/tucatinib-called-game-changer-her2-positive

MonarcHER Trial Results for Triple Positive Pre-Treated MBC Patients Receiving either Verzenio (Abemaciclib) + Herceptin (Trastuzumab) + Faslodex (Fulvestrant), Verzenio + Herceptin, or Herceptin + Chemotherapy: In this Phase 2 study of 237 postmenopausal women with heavily pretreated hormone receptor–positive, HER2-positive advanced breast cancer, the combination of Verzenio, Herceptin, and Faslodex reduced the risk of disease progression or death by 33%. Patients were required to have received at least two prior HER2-directed therapies that included trastuzumab emtansine (T-DM1) and a taxane, but could not have included a CDK4/6 inhibitor plus Faslodex. Patients received either: Verzenio + Herceptin + Faslodex (Arm A), Verzenio + Herceptin (Arm B), or Herceptin + chemotherapy (Arm C). Progression Free Survival was 8.3 months for patients in Arm A, 5.6 months for Arm B, and 5.7 months for Arm C. The Overall Response Rate was 35.4%, 16.5% and 22.8% respectively, and the median Overall Survival has not yet been determined. https://www.ascopost.com/issues/november-10-2019/abemaciclib-benefits-patients-with-her2-positive-breast-cancer-in-monarcher-trial/

NALA Trial Results – Nerlynx (Neratinib) + Xeloda (Capecitabine) vs. Tykerb (Lapatinib) + Xeloda for Pre-Treated HER2 Positive Patients: In the Phase 3 NALA trial, 621 HER2 positive MBC patients who received two or more prior lines of therapy were given either Nerlynx + Xeloda, or Tykerb + Xeloda. The Progression Free Survival (PFS) curves began to separate after 6 months: 6-month PFS rates were 47% in the Nerlynx arm vs. 38% in the Tykerb arm, 1-year rates were 29% vs. 15%, and 18-month rates were 16% vs. 7% respectively. The mean Overall Survival was similar at 24.0 months for the Nerlynx arm compared with 22.2 months for the Tykerb arm. https://www.targetedonc.com/conference/asco-2019/phase-iii-nala-trial-results-in-higher-pfs-with-neratinib-combo-for-her2-breast-cancer

TBCRC-022 Trial Results – Nerlynx (Neratinib) + Xeloda (Capecitabine) for HER2 Positive Patients with Brain Metastases: This Phase 2 trial enrolled 47 MBC patients with measurable, progressive, HER2-positive brain metastases (92% after receiving CNS surgery and/or radiotherapy) who received the oral tyrosine kinase inhibitor Nerlynx (Neratinib) plus Xeloda. One group of patients had received prior Tykerb (Lapatinib) and the other did not. The difference in results was modest: the median Progression Free Survival was 3.1 months

among patients with prior Tykerb exposure vs. 5.5 months for patients with no prior exposure, and median Overall Survival was similar at 15.1 months vs. 13.3 months respectively. https://ascopubs.org/doi/10.1200/JCO.18.01511

SOPHIA Trial Results – Margetuximab + Chemotherapy vs. Herceptin (Trastuzumab) + Chemotherapy for Heavily Pre-treated HER2 Positive Patients: This Phase 3 trial enrolled 536 heavily pretreated patients with HER2-positive MBC (some of whom were also hormone receptor positive, and some who had brain metastases) in which one group received the immune-enhancing monoclonal antibody Margetuximab + chemotherapy, and the other group received Herceptin + chemotherapy. The Progression Free Survival was comparable at 5.7 months in the Margetuximab + chemotherapy arm vs. 4.4 months in the Herceptin + chemotherapy arm, and the median Overall Survival was 21.6 months vs. 19.8 months respectively. https://www.globenewswire.com/news-release/2019/12/11/1959336/0/en/MacroGenics-Presents-Results-from-the-SOPHIA-Study-of-Margetuximab-in-Patients-with-HER2-Positive-Metastatic-Breast-Cancer-at-the-San-Antonio-Breast-Cancer-Symposium.html

Updates for Patients with Triple Negative (TNBC) MBC

Tecentriq (Atezolizumab) in Combination with Abraxane (nab-paclitaxel) has been FDA-approved as Initial Treatment for TNBC Patients with PD-L1 Positive Tumors Based Upon the IMpassion130 Trial: Earlier this year, Tecentriq in combination with Abraxane was FDA-approved as first-line treatment for TNBC MBC patients whose tumors express programmed cell death ligand 1 (PD-L1). Approval was based on findings from the Phase 3 IMpassion130 trial which included 902 patients with unresectable locally advanced or metastatic TNBC who had received no prior chemotherapy. Patients received either Tecentriq and Abraxane, or Abraxane alone. In the PD-L1–positive sub-population, median Progression Free Survival (PFS) was 7.5 months for patients in the combination arm vs 5.0 months for patients in the Abraxane-only arm. and the median Overall Survival (OS) was 25 months vs. 15.5 months respectively. The FDA has specifically approved the VENTANA PD-L1 (SP142) Assay as a companion diagnostic device for selecting TNBC patients for this therapy. https://www.targetedonc.com/publications/targeted-therapy-news/2019/tto-nov12019/changes-bring-immunotherapy-to-the-forefront-of-the-breast-cancer-treatment

Tecentriq (Atezolizumab) + Ipatasertib + either Taxol (paclitaxel) or Abraxane (nab-paclitaxel) Trial Results in Previously Untreated Patients: This Phase 1b study administered Tecentriq + the oral AKT inhibitor Ipatasertib + either Taxol or Abraxane to 26 TNBC MBC patients who were previously untreated for advanced disease. The triplet demonstrated a confirmed Objective Response Rate of 73%, irrespective of tumor biomarker status such as PD-L1 or PIK3CA/AKT1/PTEN alterations. https://www.roche.com/media/releases/med-cor-2019-04-01.htm

TOPACIO/KEYNOTE-162 Trial Results – Zejula (Niraparib) plus Keytruda (Pembrolizumab) in Pre-treated TNBC Patients: This Phase 2 study enrolled patients with advanced or metastatic TNBC irrespective of BRCA mutation status or PD-L1 expression who had received prior platinum-based chemotherapy. Patients received the oral PARP inhibitor Zejula with the PD-L1 immunotherapy drug Keytruda. Among 47 evaluable patients, 10.5% had a Complete Response (CR), another 10.5% had a Partial Responses, 28% had stable disease, and 51% had progressive disease. In the 15 evaluable patients with tumor (not germline) BRCA mutations, the Overall Response Rate (ORR) was 47% and the median Progression Free Survival (PFS) was 8.3 months. However, in patients with BRCA wild-type tumors, the ORR was much lower at 11% and the median PFS was 2.1 months. Among 28 evaluable patients with PD-L1–positive disease, the response rate was 32% and the disease control rate was 50%. Among 13 patients with PD-L1–negative disease, the response rate was 8% and the disease control rate was 46%. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6567845/ and https://www.ascopost.com/News/60192

KEYNOTE-890 Trial Results – TAVO (tavokinogene telseplasmid/intratumoral IL-12) plus Keytruda (Pembrolizumab) in Pre-treated TNBC Patients: This Phase 2 trial provided the combination of TAVO IL12 therapy and the PD-L1 immunotherapy drug Keytruda to metastatic TNBC patients who were refractory to chemotherapy and had progressed after an average of three prior lines of therapy. (IL-12 is an immunotherapy that plays a significant role in priming and maintaining T-helper cells, activating natural killer cells, and regulating the reactivation and survival of memory T cells). Four (28.6%) of the evaluable 14 patients showed a rapid tumor reduction and had a confirmed partial response (including a deep partial response in a patient with multiple liver, bone, skin and nodal metastases and a short disease-free interval following neoadjuvant chemotherapy). All responses are ongoing (range 6 to 9 months) and the median Duration of Response has not yet been reached. Notably, 3 of the 4 responding patients' lesions were PD-L1 negative. An additional three (21.4%) of the 14 patients had stable disease. https://www.biospace.com/article/oncosec-presents-interim-data-of-28-5-percent-objective-response-rate-from-ongoing-keynote-890-study-evaluating-tavo-in-combination-with-keytruda-for-heavily-pretreated-late-stage-metastatic-triple-negative-breast-cancer-at-the-2019-san-antonio/

SAFIR02-IMMUNO Trial Results – Imfinzi (Durvalumab) vs. Chemotherapy in Pre-Treated Patients: This Phase 2 trial enrolled HER2 negative locally advanced and MBC patients, 82 of whom were TNBC. All patients were required to have received prior first- or second-line chemotherapy. Among the TNBC MBC patients in the trial, the median Overall Survival (OS) was 21 months on the

immunotherapy drug Imfinzi (Durvalumab) compared with 14 months on chemotherapy. Among the 44 patients with PD-L1–positive disease across several MBC subtypes, the median OS was 26 months with Imfinzi compared with 12 months with chemotherapy. https://www.targetedonc.com/conference/sabcs-2019/durvalumab-maintenance-may-improve-outcomes-in-triplenegative-breast-cancer

Colet Trial Results - Tecentriq (Atezolizumab) + Cotellic (Cobimetinib) + a Taxane in Previously Untreated Patients: In this Phase 2 study, 63 patients with locally advanced or metastatic TNBC were randomized to receive first-line treatment with Tecentriq + Cotellic (a MEK kinase inhibitor targeted therapy) paired with either Taxol (paclitaxel) or Abraxane (nab-paclitaxel). The response rate was 39% for PD-L1–positive patients and 20% for the PD-L1–negative group. In the Taxol group, 44% of patients with PD-L1–positive disease responded, whereas only 11% of PD-L1–negative patients responded. In the Abraxane group, 33% of PD-L1–positive patients responded, whereas 27% of PD-L1–negative patients responded. https://www.targetedonc.com/publications/targeted-therapy-news/2019/tto-nov12019/changes-bring-immunotherapy-to-the-forefront-of-the-breast-cancer-treatment

MEDIOLA Trial Results – Lynparza (Olaparib) plus Imfinzi (Durvalumab) in BRCA Mutated HER2 Negative MBC Patients: MEDIOLA was a Phase 1/2 study evaluating the combination of Lynparza (Olaparib), an FDA-approved PARP inhibitor, with the immunotherapy drug Imfinzi (Durvalumab) in patients with advanced solid tumors who harbor BRCA mutations. In the TNBC group, the median Progression Free Survival was 4.9 months and the Objective Response Rate was 58.8%. By number of prior lines of chemotherapy, the median PFS was 11.7 months for patients with 0 or 1 prior lines, and 6.5 months in those with 2 prior lines. Overall, patients exhibiting responses showed durable benefit, with a median Duration Of Response (DOR) of 9.2 months. https://www.targetedonc.com/news/olaparib-plus-durvalumab-show-durable-activity-in-germline-brca-breast-ovarian-cancer