The 2018 San Antonio Breast Cancer Symposium (SABCS) was fascinating this year! As opposed to several years ago when only sparse information about MBC was available at SABCS, this year it appeared that nearly half of the studies pertained to metastatic (as opposed to early stage) breast cancer.

The notes below have been incorporated into my 175-page book entitled, “The Insider’s Guide to Metastatic Breast Cancer.” If you would like a complimentary copy, please email your request to bestbird@hotmail.com (If you already have a copy of the book and want to receive an updated version, simply write “Repeat Customer” in the Subject Line of your email).

Notes:

Considerable research is being done regarding immunotherapy as a type of treatment for MBC, especially with regard to TNBC. As is the case for immunotherapy treatments, substantial research is underway regarding targeted therapies based upon biomarkers, and the results of some of these studies are provided below. Biomarkers represent substances, structures, or processes that can be measured in the body, and influence or predict the incidence of outcome or disease. They may reflect the effects of treatments, interventions, and even unintended environmental exposure. Therefore in oncology clinics and clinical trials, biomarkers are being increasingly used as eligibility criteria for specific therapies, and as measurements of response to treatment. Remember that it may take quite a while for treatment results to surface with regard to CDK4/6 inhibitors! For example, the median time to response for Verzenio (abemaciclib) has historically been 3.7 months.

Dr. Nikhil Wagle (a Medical Oncologist at Dana Farber who is also the Director of the MBC Project) stated in a presentation that “DNA sequencing does not tell the whole story” because it excludes:

- RNA expression
- Protein characteristics
- Epigenics, which are modifications to the expression of genes which do not involve changes to the genetic code itself
- The microenvironment/immune cell expression

6. Currently there are no definitive guidelines regarding the sequence of chemotherapy for TNBC MBC patients. As per a lecture at 2018 SABCS delivered by Dr. Roisin M. Connolly of Johns Hopkins School of Medicine, there are two potential clinical pathways for treating TNBC MBC:

a. If the patient’s tumor is PDL-1 positive, then the patient should ideally receive Atezolizumab with Abraxane because in the IMPassion130 trial, the median Overall Survival (OS) on the combination was 25 months vs. 15.5 months on Abraxane alone. However, this combination has not yet been FDA-approved as of Dec. 2018.

b. If the patient’s tumor is PDL negative, or the patient cannot obtain the above drug combination if their tumor is PDL-1 positive, then sequential single agent chemotherapy is recommended. Dr. Connolly advised that combination chemotherapy should only be given in the event of visceral crisis (severe organ dysfunction).

c. After the above, if the patient has a germline BRCA mutation, Talazoparib or Olaparib can be given.

7. Research is increasingly underway on the previously under-studied subset of MBC patients who are both Hormone Receptor (HR) positive and HER2 positive, sometimes referred to as “Triple Positive” (more about this later).


9. Talazoparib (Talzenna) and Olaparib (Lynparza) were both FDA-approved in 2018 for HER2 negative MBC patients with germline BRCA1 or BRCA2 mutations.
10. Oral SERDs (endocrine therapies similar to Faslodex) and oral SERMs (similar to Tamoxifen) are being studied, including GDC9545, SAR439859, RAD1901, LSZ102, and ZN-C5.

11. At least two new classes of drugs are currently being studied in MBC:

a. SERCAs (Selective Estrogen Receptor Covalent Antagonists): Current hormonal therapies include SERMS (Tamoxifen), SERDS (Faslodex), and Aromatase Inhibitors (Letrozole, Arimidex, and Aromasin). SERCAs are a new series of compounds with unique modes of inhibition that potently target both wild-type and mutant ERα, which can be indicative of hormonal therapy resistance. SERCAs inactivate the estrogen receptor by targeting a cysteine (amino acid) that is not present in other nuclear hormone receptors, leading to a different biological and activity profile than SERMS and SERDS. SERCAs such as H3B-6545 have begun being tested in clinical trials.

b. 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. Drugs such as Venetoclax (ABT-199) that target BCL-2 are now being studied. Venetoclax is a BCL-2 inhibitor that is currently approved for Chronic Lymphocytic Leukemia. In a study of 33 evaluable Hormone Receptor (HR) positive, BCL-2 positive patients who received the combination of Venetoclax and tamoxifen, the median Progression Free Survival (PFS) was 36 weeks overall. The median PFS was 23 weeks in those who received doses of Venetoclax at less than 800 mg., versus 51 weeks in those who received 800 mg of Venetoclax (the maximum dose in the study). In the 24 patients who received the maximum dosage, the ORR was 54% and the Clinical Benefit Rate (CBR) was 75%, with 1 Complete Response (4%) and 12 Partial Responses (50%). The median DOR was 42 weeks, and 8 patients from the 800-mg cohort remain on study treatment. From: https://www.onclive.com/conference-coverage/sabcs-2018/venetoclax-has-impressive-activity-in-eri-and-bcl2-breast-cancer

12. MBC studies based upon mutations:

a. PIK3CA Mutations in pre-treated Hormone Receptor+/HER2- Patients: In the SOLAR-1 Phase 3 clinical trial which compared Faslodex plus the targeted therapy Alpelisib (BLY719) versus Faslodex and placebo, postmenopausal patients with PIK3CA mutations (found via liquid or tumor biopsy) in the Faslodex/Alpelisib arm fared substantially better (median PFS 11.0 months) than similar patients in the Faslodex plus placebo arm (median PFS 5.7 months). Patients in this trial had received 1 or more lines of prior hormonal therapy but no chemotherapy. The ORR in the PIK3CA-mutant cohort was 26.6% in the Faslodex/Alpelisib arm compared with 12.8% in the Faslodex/placebo arm. These results, assessed after a median follow-up of 20 months, translated into a 35% reduction in the risk of progression or death in favor of Faslodex/Alpelisib arm. There was no advantage to providing Alpelisib in patients without a PIK3CA mutation. So encouraging were the results of this trial that a new "Managed Access Program" (NCT03706573) has been established to allow access to Alpelisib for eligible patients diagnosed with HR+ MBC who have a PIK3CA mutation. From: https://www.targetedonc.com/conference/esmo-2018/solar1-trial-results-demonstrate-a-benefit-for-genomic-testing-in-breast-cancer and https://clinicaltrials.gov/ct2/show/NCT03706573

b. HER2 or HER3 Mutations in Hormone Receptor Positive Patients: The SUMMIT Phase 2 trial sought to evaluate the safety and efficacy of Neratinib (Nerlynx) in Hormone Receptor (HR) positive patients who have solid tumors with activating HER2 or HER3 mutations. In the HER2-mutant, HR+ positive breast cancer cohort, 47 patients received Neratinib in combination with Faslodex (fulvestrant). In this group, 43 patients (92%) had HER2 negative disease, and the patients had received a median of 3 prior lines of therapy in the metastatic setting (range 0-11 prior regimens). All patients had been previously treated with hormonal therapy prior to entering the study, including 25 patients (53%) who had received prior Faslodex. 20 patients (43%) had received prior cyclin-dependent kinase 4/6 (CDK4/6) inhibitor therapy. Overall, 14 patients (30%) experienced an objective response, which included 4 patients with a complete response and 10
patients with partial responses, and 22 patients (47%) experienced clinical benefit (clinical benefit is defined as confirmed complete response or partial response or stable disease for at least 24 weeks). The median DOR was 9.2 months and the median PFS was 5.4 months. Patients who had received prior Faslodex or CDK4/6 inhibitor targeted therapy prior to entering the trial also benefited from the combination treatment. Of note, 6 patients (30%) with prior CDK4/6-inhibitor exposure demonstrated confirmed responses, with the duration of responses ranging from 4.5 - 14.8 months. Four patients were still on treatment at the time of data reporting. From: https://markets.on.nytimes.com/research/stocks/news/press_release.asp?docTag=201812060800BIZWIRE_USPRX____BW5252&feedID=600&press_symbol=44478224

c. Olaparib (a PARP inhibitor) is being studied in combination with Durvalumab (“Imfinzi”), a PD-L1 inhibitor, in HER2 negative MBC patients with BRCA1 or BRCA2 germline mutations in the Mediola study. The Mediola clinical trial consists of 25 pretreated MBC patients who had BRCA germline mutations and HER2 negative MBC. Twelve of these patients had HR positive tumors and 13 had TNBC. The combination demonstrated a Disease Control Rate (DCR) of 80%, and a 52% Overall Response Rate (ORR) which consisted entirely of partial responses. Responses were seen regardless of hormone receptor status, BRCA mutation type, or receipt of prior platinum-based chemotherapy. The longest response was ongoing at 308+ days, and the median DOR was not yet reached at the time of the analysis. Although medians have not yet been attained, the Kaplan-Meier curves indicated that approximately 70% of patients remained progression free, and most patients remained alive at the time of the analysis. From: http://www.onclive.com/web-exclusives/olaparibdurvalumab-combo-effective-for-brcamutant-breast-cancer

13. A study for HER2 positive, Hormone Receptor negative MBC patients:

In the PATRICIA Phase 2 study (also mentioned below for Triple Positive MBC patients), the combination of Ibrance and Herceptin demonstrated safety and efficacy in pre-treated patients with advanced HER2+ MBC. Investigators enrolled patients who had received 2 to 4 prior lines of therapy into 3 cohorts: 1 cohort contained patients with HR negative/HER2+ disease, and the other 2 cohorts included patients with ER+/HER2+ disease. Patients with HR negative/HER2+ breast cancer received Ibrance + Herceptin. At 6 months, 5 of 15 (33%) the patients in the ER-/HER2+ cohort attained Progression Free Survival (PFS). From: https://www.onclive.com/conference-coverage/sabcs-2018/palbociclib-combo-active-in-her2-breast-cancer

14. Treatments being studied for Hormone Receptor+/HER2+ (“Triple Positive”) MBC patients:

a. Aromatase Inhibitor + Herceptin (Trastuzumab) + Pertuzumab (Perjeta): The Phase 2 PERTAIN study enrolled 258 women with HER2-positive, HR positive locally advanced or MBC who were not previously treated with systemic non-hormonal therapy in the advanced-disease setting. Patients received either Herceptin (with or without a taxane for 18–24 weeks) plus an aromatase inhibitor (Arimidex or Letrozole), or else they received Herceptin (with or without a taxane for 18–24 weeks) plus Perjeta plus an aromatase inhibitor. The triplet combination of Herceptin (with or without a taxane), plus Perjeta and an aromatase inhibitor resulted in a median PFS of 18.9 months, compared to 15.8 months for Herceptin (with or without a taxane) plus an aromatase inhibitor. Furthermore, the DOR was significantly longer with the triplet (27.1 vs 15.1 months). From: http://www.ascopost.com/issues/january-25-2017/pertuzumab-trastuzumab-plus-aromatase-inhibitor-beneficial-in-metastatic-breast-cancer/

b. Aromatase Inhibitor + Herceptin (Trastuzumab) + Lapatinib (Tykerb): The "triplet" therapy combination of Lapatinib (Tykerb), Trastuzumab (Herceptin), and an aromatase inhibitor (AI) reduced the risk for death or progression by 38% in women with HER2+/HR+ MBC compared with those treated with a targeted agent plus an Aromatase Inhibitor (AI), according to findings from the Phase 3 ALTERNATIVE study. This clinical trial enrolled 355 patients who had undergone prior endocrine therapy and experienced disease progression during or after a prior regimen containing Herceptin plus chemotherapy in the adjuvant or neoadjuvant setting and/or in the first-line metastatic setting. The median PFS was 11 months for the triplet therapy combination versus 5.7
months for women assigned to Herceptin plus AI, and the median PFS also favored the triplet compared to Herceptin plus AI (8.3 months vs 5.7 months). Although OS data were immature at the time of this analysis, they trended in favor of the triplet therapy as opposed to Herceptin plus AI (median OS 46.0 vs 40.0 months). The researchers concluded that the PFS benefit obtained with Lapatinib plus Herceptin plus AI in patients with HER2-positive, HR-positive MBC who had been previously treated is clinically meaningful and robust, and that the triplet combination can potentially offer an effective and well-tolerated, chemotherapy-sparing alternative treatment regimen for patients for whom chemotherapy is not a viable option. From: http://www.onclive.com/web-exclusives/dual-her2-blockade-superior-for-pfs-in-her2hr-metastatic-breast-cancer

c. Ibrance and Herceptin, with or without Letrozole: In the PATRICIA Phase 2 study, the combination of palbociclib (Ibrance) and trastuzumab (Herceptin) demonstrated safety and efficacy in pre-treated patients with advanced HER2+ breast cancer, some of whom were also hormone receptor positive. Investigators enrolled patients who had received 2 to 4 prior lines of therapy into 3 cohorts: 2 cohorts contained patients with ER+/HER2+ disease, and 1 cohort contained patients with ER-/HER2+ disease. Patients with ER+/HER2+ breast cancer were randomized to receive Ibrance + Herceptin with or without letrozole. At 6 months, 6 (40%) of 15 patients with ER+/HER2+ MBC who received Ibrance and Herceptin without letrozole achieved PFS, and 8 (53%) of 15 ER+/HER2+ MBC patients who received Ibrance and Herceptin with letrozole were also progression-free. From: https://www.onclive.com/conference-coverage/sabcs-2018/palbociclib-combo-active-in-her2-breast-cancer

15. Treatments Being Studied for TNBC MBC patients:

a. The Phase 3 IMPassion130 trial, in which 902 MBC patients with previously untreated TNBC received either Abraxane alone, or a combination of Abraxane plus Atezolizumab (Tecentriq), indicated that patients receiving the combination had an improved median PFS (7.2 months vs. 5.5 months). Importantly, an interim OS analysis showed median survival of 21.3 months with the Atezolizumab/Abraxane regimen, versus 17.6 months with Abraxane alone. Notably, the Atezolizumab/Abraxane regimen conferred a considerable OS benefit to patients with PD-L1-positive TNBC (median 25 months on the combination arm vs. 15.5 months on Abraxane alone). At SABCS 2018, it was disclosed that the best responders were patients whose immune cells on or near the tumor expressed PD-L1. At SABCS 2018, Dr. Leisha A. Emens, co-leader of the Hillman Cancer Immunology and Immunotherapy Program, disclosed that the best responders were patients whose immune cells on or near the tumor expressed PD-L1, stating, "PD-L1 immune cell expression was the best predictor of clinical benefit."


b. The combination of Keytruda (Pembrolizumab) and Zejula (Niraparib), a PARP inhibitor, has shown promising and durable response rates in pre-treated TNBC MBC patients, regardless of their BRCA mutational status according to the Phase 1/2 trial called TOPACIO in which 46 TNBC patients were assessed. Among these patients, 15 had BRCA mutations and 5 had genetic alterations in other DNA repair genes. Three patients had complete responses, 10 had partial tumor reductions, and 10 had their disease stabilized with the treatment. This represents an ORR of 28% and a DCR of 50%. As expected, patients with BRCA mutations had the best response rates at 60%, followed by those with mutations in other DNA repair genes at 55%, and those who were positive for the PD-L1 protein — a biomarker that predicts response to Keytruda — at 36%. Overall, the 15 patients with BRCA mutations lived for a median of 8.3 months without their disease progressing, which is superior to the 3 - 5 months seen with standard chemotherapy, or with either agent alone. From: https://breastcancer-news.com/2018/06/18/zejula-keytruda-promising-response-rates-phase-1-2-trial-breast-cancer/?amp
16. HR+/HER2- Patients with Visceral Disease: It is noteworthy that Kisqali plus endocrine therapy appears to be highly effective for MBC patients with HR+/HER2- visceral disease. Nearly 60% of patients enrolled in the MONALEESA trials had visceral metastases such as lung and/or liver, and all benefited from treatment with Kisqali in combination with endocrine therapy. In patients with visceral metastases, Kisqali plus endocrine therapy yielded a median PFS of 24.4 months compared with a median PFS of 11.9 months for patients with visceral disease on endocrine therapy alone. Furthermore, the ORR of patients with visceral disease on the combination therapy closely resembled the ORR of patients with bone-only disease who were on the combination. From: https://www.pharmacypracticenews.com/Clinical/Article/12-18/Kisqali-Improves-Outcomes-and-Survival-Rates-in-Women-With-Metastatic-Breast-Cancer-/53612

17. Study of HER3 Overexpressed MBC Patients: U3-1402, an investigational antibody-drug conjugate (ADC) targeting HER3, induced objective response in more than 40% of 42 heavily pretreated patients with HER3-expressing breast cancer, according to results presented at the 2018 San Antonio Breast Cancer Symposium. The ORR was 42.9% (18/42), the median PFS was 8.3 months, and the overall disease control rate (DCR) was 90.5% (38/42). Most responses proved to be durable, as the median duration of response (DOR) was not yet reached (range, 2.8-13.8 months) after a median follow-up of 10.5 months. Twenty-one patients remained on treatment as of the November 6, 2018 data cutoff. From: https://www.onclive.com/conference-coverage/sabcs-2018/her3targeting-antibodydrug-conjugate-shows-encouraging-activity-in-advanced-breast-cancer