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Implementing Precision Medicine After SABCS 2025: Molecular Insights Driving Next-Generation Breast Cancer Care

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Abstract

Every year, the San Antonio Breast Cancer Symposium (SABCS) serves as the major catalyst for new developments across all fronts and disciplines in breast cancer, from prevention and early detection to the pathophysiology and management of metastatic breast cancer. Although novel agents and practice-changing clinical trials receive the lion's share of the audiences' attention, several translational studies are reported that enhance significantly our understanding of breast cancer. This review highlights the most impactful clinical translational studies and discusses the clinical perspective and application of the knowledge gained.

Take Home Messages

1. In patients with early-stage triple negative breast cancer who receive preoperative chemotherapy and do not achieve a complete pathologic response, biomarkers on the residual disease that capture the biology of the residual tumor and antitumor immune response and not just extent, can refine the risk of recurrence.
2. Despite compelling prognostic associations between circulating tumor DNA detection and relapse in early breast cancer, no interventional trial has demonstrated so far that acting on circulating tumor DNA results improves patient outcomes.
3. In metastatic hormone receptor positive and Her2-positive breast cancer, a chemotherapy-free regimen consisting of trastuzumab, pertuzumab, endocrine therapy, and ribociclib is a rational 1st line regimen yielding progression-free and overall survival noninferior to chemotherapy-containing regimens.

Introduction

Developments in breast cancer are now coming with a breakneck pace. Novel drugs and treatment paradigms in early stage breast cancer alter the biology of residual and recurrent disease and generate new gaps in the knowledge. As our therapies become more effective (and simultaneously more toxic), novel technologies and biomarkers hold promise in rationalizing our diagnostic and treatment approaches. Every year, the San Antonio Breast Cancer Symposium (SABCS) heralds the major changes in the treatment landscape in breast cancer and the new directions in breast cancer research. Insightful translational research is frequently eclipsed by practice-changing clinical trials with novel agents; nonetheless, it is the translational research that advances our understanding of breast cancer and brings about changes in the treatment paradigm. The scope of this review is to highlight some of the most impactful clinical translational studies presented at SABCS, discuss the gaps in the knowledge that they address, synthesize the knowledge gained from complementary abstracts and presentations, and place the results and the emerging concepts in a clinical frame of reference. Key limitation of this review is that the presented abstracts are not practice-changing; they are however, deeply practice-informing and set the stage for novel research directions. We organize this review into 5 thematically related categories: dissecting the biology of residual disease, tumor evolution, circulating tumor DNA, precision medicine in early-stage and metastatic breast cancer.

1. Dissecting the Biology of Residual Disease.

From the early dichotomous distinction between pathologic complete response (pCR) and residual disease, the field has moved to the residual cancer burden as a metric to capture the effect of preoperative chemotherapy[1] realizing that patients with residual disease can have very disparate outcomes. However, a limitation of the residual cancer burden is that it does not capture changes in tumor biology after preoperative chemotherapy. Three abstracts dissecting the biology of residual disease in early-stage triple negative breast cancer (TNBC) were presented.

On the first day of the meeting, Dr. Holtschmidt *et al* reported on the prognostic significance of tumor infiltrating lymphocytes (TILs) and the proliferation marker Ki67 of residual triple-negative breast cancer (TNBC) after preoperative (neoadjuvant) chemotherapy.[2] Using a cutoff of 15% for Ki67 and 50% for TILs, Dr. Holtschmidt *et al* stratified 640 patients with residual disease after preoperative chemotherapy to 4 different strata in terms of risk for distant relapse and overall survival. Patients with a Ki67 $\leq$ 15% and TILs $\geq$ 50% had the most favorable outcomes (5 year distant disease-free survival and overall survival of 83.7% and 92%) while patients on the opposite spectrum (Ki67 $>$ 15% and TILs $<$ 50% on the residual disease) had significantly higher risk for relapse and more than 7 times higher risk of death (with the respective figures being 42.4% and 48%). As expected, patients with limited residual disease (ypT1 ypN0) were more likely to have lower Ki67 and higher TILs compared to counterparts with more extensive residual disease ($>$ ypT1 ypN0). Strengths of the study include the central assessment of Ki67 and TILs. An important limitation however is that the assessments were performed in a fraction of patients with residual disease (n = 640/1505); in most patients (n = 865/1505), samples of their residual disease were not available or evaluable.[2]

Similar results were observed in a secondary analysis of the ECOG-ACRIN EA1131 clinical trial.[3] The EA1131 study was a prospective clinical trial that randomized patients with ≥ 1 cm residual disease in the breast after neoadjuvant chemotherapy to receive adjuvant platinum chemotherapy (carboplatin or cisplatin) or capecitabine.[4] Of note, the study was terminated after enrollment of 410 of planned 775 participants as it was determined that it would be unlikely that further follow-up would establish noninferiority or superiority of adjuvant platinum chemotherapy.[4] Using a 30% cutoff for stromal TILs in the residual disease alongside with intrinsic subtype of the residual disease (basal v nonbasal as determined by PAM50), Dr. Bavde *et al* found that most patients had low stromal TILs (93%) and patients with low stromal TILs and basal-like intrinsic subtype had the worst invasive disease-free survival.[3]

Along the same lines, correlative studies in the context of GALGB 40603 (Alliance) clinical trial reported by Dr. Rädler *et al* also highlighted the adverse prognostic impact of basal-like intrinsic subtype of residual disease.[5] As a reminder, the CALGB 40603 (Alliance) was a 2 x 2 randomized clinical trial in patients with stage II/III TNBC whereby the addition of carboplatin or bevacizumab to a neoadjuvant chemotherapy regimen of weekly paclitaxel, followed by dose-dense doxorubicin and cyclophosphamide, were shown to increase the rates of pCR; this increment in the pCR rates however, did not have a reflection on long-term outcomes.[6] In patients with moderate or minimal preoperative treatment effect (residual cancer burden II or III, respectively), conversion of a non-basal breast cancer to basal-like or maintenance of the basal-like intrinsic subtype with preoperative chemotherapy was associated with the highest risk of death.[5] Complementary to the results reported by Dr. Holtschmidt *et al*, residual tumors with excellent treatment effect (residual cancer burden I) had high fibroblast transcriptional signatures and low tumor and/or proliferation signatures.[5]

Collectively, the results of these studies indicate that biomarkers of the residual disease that capture the biology of the residual tumor and antitumor immune response and not just extent, can refine the risk of recurrence. Of note, the antitumor immune response is complex and the methodologies that are ready for clinical applications provide insights only regarding the presence or absence of immune cells. They do not provide any functional insights such activation status of the T cells or interactions with other cells which are highly relevant in the immunooncology era. Nonetheless, these observations have important implications in clinical practice: the 2 clinical trials that inform medical decisions regarding adjuvant therapy in residual disease (KEYNOTE 522[7] and CREATE X[8]) were conducted in isolation; ongoing clinical trials are evaluating the role of antibody drug conjugates in the adjuvant setting.[9,10] Better understanding of the risk of recurrence and the benefit of the adjuvant interventions can help us optimize treatment selection in patients with residual disease.

2. Tumor Evolution

Highly related to dissecting the biology of residual disease, was a poster spotlight session that focused on subtype conversion in early (and metastatic) breast cancer.

A. Subtype Conversion in Early-Stage Breast Cancer

In a meta-analysis that included more than 5000 patients with residual disease after preoperative chemotherapy, subtype conversion by immunohistochemistry occurred in 15-20%.[11] Similarly, in a study that focused on patients with inflammatory breast cancer, changes in the receptor status following preoperative therapy occurred at a very similar percentage (22%).[12] Subtype conversion, and especially loss of hormone receptors, was associated with worse overall survival.[11]

Even though subtype conversion is well recognized, whether adjuvant therapy should be tailored to the biology of the residual disease as opposed to the disease at diagnosis (as it is currently the practice) is unknown. Studies in the context of the randomized adjuvant KATHERINE clinical trial, support the use of adjuvant ado-trastuzumab emtansine in patients whose Her2(+) disease at diagnosis converts to Her2(-).[13] In clinical practice, residual disease that tests positive and/or amplified for Her2 prompts the decision for adjuvant Her2 targeted therapy with the prevailing perception that a Her2(+) clone emerged under preoperative therapeutic pressure.

B. Subtype Conversion in Recurrent Breast Cancer

Subtype conversion by immunohistochemistry and more so conversion at the level of gene expression is common upon diagnosis of recurrence. Paired analyses of primary tumors and metastases in the context of the AURORA US Metastasis Project indicate that clinical and intrinsic subtype switching occur in 28.6% and 45.9% of patients, respectively.[14] Luminal A breast tumors, which clinically represent indolent, strongly hormone receptor-positive tumors, constituted the intrinsic subtype with the most frequent conversion upon recurrence.[14] In clinical practice, when a diagnosis of recurrence is made, receptor studies are repeated on the diagnostic biopsy and further medical decisions are made accordingly; the receptor status of the primary tumor does not inform medical decisions in the metastatic setting. Conversions at the level of gene expression (which are not always coordinate with clinical subtype switching or have a coordinate change in immunohistochemistry) may explain the natural history of recurrent disease, e.g. accelerated course in a patient with originally luminal A breast cancer whose tumor converted to the more aggressive luminal B or Her2 enriched upon recurrence. Nonetheless, currently subtype testing beyond immunohistochemistry and next-generation sequencing for actionable mutations has no clinical utility in the metastatic setting.

3. Circulating Tumor DNA

A. Early stage breast cancer

In early-stage breast cancer, circulating tumor DNA (ctDNA) is an emerging tool for risk stratification, real-time monitoring of treatment effect and surveillance for recurrence in the adjuvant setting.

Neoadjuvant Setting

The PHERGain clinical trial evaluated prospectively a PET-guided pathologic complete response-adapted strategy to omit chemotherapy in early stage Her2(+) breast cancer.[15,16] The primary results of the trial have been reported; key findings of the trial were that 37.9% of the patients were able to omit chemotherapy and the 3-year Invasive Disease-Free Survival (IDFS) with the risk-adapted approach was excellent (94.8%).[16] In the context of this trial, blood samples were collected at baseline, cycle 3 day 1, and prior to definitive surgery, and a tissue-free DNA methylation-based assay was performed. It is noteworthy that, even though the assay did not require primary tumor tissue to be performed (this requirement constitutes the major bottleneck for tumor tissue-informed ctDNA assays), 19% of the submitted samples were not suitable for analysis. Key findings of the study include:

- ctDNA detection at baseline correlated with the stage of the disease and nodal involvement; more advanced disease was considerably more likely to be ctDNA(+) at diagnosis (33.3% for stage I vs. 93.2% for stage III).
- ctDNA status at diagnosis did not correlate with achievement of pCR. In other words, detection of ctDNA at diagnosis did not preclude the achievement of a pCR and patients with ctDNA(+) and ctDNA(-) (or undetectable for accuracy) disease were equally likely to achieve a pCR.
- Early ctDNA clearance (conversion from ctDNA(+)/detectable to ctDNA(-)/undetectable status) was associated with achievement of pCR. Persistence of ctDNA at the time of surgery was infrequent (17% of patients) and was associated invariably with the presence of residual disease. Despite the administration of postoperative systemic therapy, patients with detectable ctDNA at surgery still had a 5 times greater risk for an IDFS event at 3 years compared with their counterparts with ctDNA clearance.
- Lastly, the study found a strong association between baseline ctDNA status and outcomes (3-year IDFS); the association between ctDNA status after 2 cycles of preoperative treatment and outcomes did not reach statistical significance but there was a clear trend. Altogether, ctDNA(-) status at diagnosis and ctDNA clearance with preoperative therapy were predictive of favorable outcome at 3 years.[15]

Two additional studies presented at SABCS 2025 reported complementary results to the above with an emphasis on the association between early ctDNA clearance and favorable outcomes. The first study was conducted in the context of the I-SPY platform trial and early ctDNA clearance was associated with achievement of pCR or excellent treatment effect (RCB I).[17,18] The second correlative study was conducted in the context of the Neo-N open-label randomized phase 2 clinical trial.[19] The trial enrolled patients with stage I/II TNBC who received preoperative chemotherapy consisting of a carboplatin-paclitaxel backbone alongside

nivolumab at 2 different schedules, nivolumab lead-in followed by concurrent nivolumab chemotherapy vs. upfront concurrent nivolumab chemotherapy. Patients who achieved ctDNA clearance at the 5 +/- 1 week time point had a pCR rate of 63% and a 3-year event-free survival of 90.6%; ctDNA persistence was associated uniformly with residual disease at surgery and a 3-year event-free survival of 45.5%.[19]

Adjuvant setting

The PALLAS study was a large, international, randomized phase III trial of 2 years of adjuvant palbociclib added onto an endocrine therapy backbone in HR+/HER2-negative breast cancer.[20] The primary results of this trial have been reported; with longer follow up, the addition of palbociclib did not confer any benefit in terms of IDFS.[20] Tumor-informed minimal residual disease (MRD) testing by ctDNA was performed in a US cohort of 420 patients at 3 postoperative time points: first day of investigational therapy, on-treatment at approximately 6 months, and at the end of the 2-year interventional period.[21] The majority of patients (92%) were MRD-negative (or undetectable) and had excellent outcomes with a 5-year distant recurrence free interval of 93%. Similar to correlative studies conducted in the MONARCHE clinical trial,[22] the risk of recurrence in MRD-negative patients was not zero; approximately 5% of patients who were MRD-negative at the end of the interventional period developed a recurrence.[21] On the opposite end of the spectrum, the few patients who were MRD-positive on the first day or at the end of the interventional period had a 15 and 21.5 times, respectively, higher risk for distant recurrence compared with their MRD-negative counterparts.[21]

The second study following the same theme was the LEADER study, a prospective phase 2 clinical trial that enrolled patients with pathologic stage IIA or greater after completion of definitive surgery with curative intent and who were receiving adjuvant endocrine therapy.[23] The trial entailed surveillance by means of a tumor-informed ctDNA assay. Key difference from the PALLAS correlative study was that the trial entailed a ctDNA-informed intervention: upon ctDNA detection, ribociclib 400 mg PO daily continuously for 12 months was added to the endocrine regimen.[23] Note that the study preceded the approval of ribociclib in the adjuvant setting.[24] Most patients (89%) were persistently ctDNA negative throughout the surveillance period yielding a negative predictive value for serial testing conducted over the course of one year of 98.1%. ctDNA was detected in a small fraction of patients (11%) and in the majority of these patients (87%) ctDNA was detected on their first test. Of the ctDNA-positive patients, one-third had radiographic evidence of recurrence. Patients with favorable ctDNA changes with ribociclib (ctDNA decrease, 25%; complete clearance, 25%) were considerably more likely to have lower pre-intervention ctDNA levels than their counterparts with ctDNA persistence or increase.[23] Lower pre-intervention ctDNA levels may reflect more indolent recurrent disease and/or disease earlier in the course of recurrence, whereas persistent or rising ctDNA levels may reflect more aggressive disease, recurrence further advanced in its course, and lack of therapeutic benefit with the addition of ribociclib. Clinical and/or radiographic recurrence was delayed by 16.5 months in the group with favorable ctDNA changes vs. 5.3 months in the counterpart group.[23] The study is very small to show that long-term outcomes can be improved with intervention upon molecular relapse which constitutes the crux of MRD testing in clinical practice. Nonetheless, it is worth highlighting the clearance of ctDNA in some patients with ribociclib and the results of this trial can set the stage for a larger study investigating a biomarker-driven use of CDK4/6 inhibitors in the adjuvant setting.

Lastly, the c-TRAK-TN clinical trial was the first prospective phase 2 trial that evaluated the clinical utility of ctDNA testing in guiding therapy in TNBC.[25] The trial enrolled patients with early-stage TNBC deemed by clinical criteria to have at least moderate risk for relapse (residual disease following neoadjuvant chemotherapy, or stage II/III with adjuvant chemotherapy). Patients had completed their treatment with curative intent and were monitored by means of ctDNA. In the original design of the study, patients in whom ctDNA was detected were randomized in a 2:1 ratio to intervention vs. observation. The intervention consisted of staging investigations. If metastatic disease were detected by imaging, patients were treated per standard of care; otherwise, they were offered the option of pembrolizumab. Key finding of this trial (whose conduct was at least in part compromised by the coronavirus pandemic) was the very frequent detection of metastatic disease at the time of ctDNA detection (72%). Additionally, 28.5% of

patients with high-risk disease were already ctDNA positive at study entry. Collectively, in this trial there was minimal, if any, lead time for a meaningful intervention to alter the course of recurrent disease.[25] The original trial utilized a digital droplet PCR assay that tracked 1-2 tumor-private mutations. In a subsequent blood sample analysis with a tissue-free DNA methylation-based assay, Dr. Cunningham, *et al* found high concordance between the 2 assays, high accuracy in predicting relapse, and importantly, earlier ctDNA detection prolonging the lead time window for potential intervention.[26] The significant conclusion of this study is that improvements in the sensitivity of the ctDNA assay can lead to earlier detection of molecular relapse, setting the stage for earlier interventions to alter the natural history of recurrence.[26]

Despite compelling prognostic associations in the aforementioned studies and across multiple other retrospective data sets, no interventional trial has demonstrated so far that acting on ctDNA results improves patient outcomes in early breast cancer. Nonetheless, we may be soon reaching an inflection point, where ultrasensitive detection assays with high clinical validity are converging with effective treatments to establish clinical utility.

B. Metastatic breast cancer

The therapeutic landscape of Her2(+) metastatic breast cancer is currently undergoing major shifts.[27] Nonetheless, it is well known that 5-10% of patients will achieve a long-term remission with their first line of therapy raising the question of whether treatment breaks could be considered. MRD tracking could be leveraged to inform such decisions. In a real-world cohort of patients with Her2(+) metastatic breast cancer, Dr. Morganti *et al* found that MRD status at year 1 correlated with exceptional response, which for the purpose of this study was defined as being on first line therapy without progression for 3 years.[28] All patients with exceptional response had undetectable MRD at year 1 vs. 25% of patients with conventional response. Exceptional response did not preclude late progression; nonetheless, in nearly all cases, late progression was heralded by MRD detection. It is important to note that the study utilized an ultrasensitive, whole-genome, tumor informed MRD assay with a limit of detection lower compared to 1st generation MRD assays,[28] supporting the point that ultrasensitive MRD assays will reach eventually clinical utility.

4. Precision Medicine in Early-Stage Breast Cancer.

Two complementary studies, TBCRC 056 and OlympiaN, evaluated a chemotherapy-free preoperative regimen consisting of a PARP inhibitor (niraparib and olaparib, respectively) in combination with an anti-PD-1 antibody (dostarlimab, TBCRC 056)[29] or an anti-PD-L1 antibody (durvalumab, OlympiaN)[30] in early-stage hormone receptor-low or negative, Her2(-) breast cancer harboring germline *BRCA1/2* or *PALB2* mutations. Despite the differences in the eligibility criteria, study designs, and populations, the pCR rates in both trials were high (50% in the TBCRC 056[29] and 68% (cohort A) and 80% (cohort B) in OlympiaN[30]). One should note the early stage and absence of lymph node involvement (T1-2/N0) in the patient population of the latter study which may account for the unprecedented pCR rate. Progressive disease which constituted an important consideration in predecessor studies in the same setting with PARP inhibitors alone (20.8% with neoadjuvant talazoparib in early-stage TNBC[31]) was infrequent (TBCRC 056: 6.5%[29] and OlympiaN: 4-8%[30]). These provocative results set the stage for further investigation of a chemotherapy-free regimen in patients with germline *BRCA1/2* or *PALB2* mutations and even somatic *BRCA1/2* mutations; the OlympiaN study did include a patient with a *BRCA1* mutation who achieved a pCR with preoperative olaparib and durvalumab.[30]

5. Precision Medicine in Metastatic Breast Cancer.

A. Hormone receptor-positive (HR(+)) and Her2(-) breast cancer

The current standard of care for first line therapy in metastatic HR(+)/Her2(-) breast cancer calls for endocrine therapy with an aromatase inhibitor alongside with a CDK4/6 inhibitor with ribociclib constituting the preferred CDK4/6 inhibitor.[32-34] In the respective phase 3 clinical trials, approximately 1 in 4 and 1 in 5 patients were able to achieve remissions sustained for over 4 and 5 years, respectively.[35] In an exploratory analysis presented by Dr. Razavi *et al*, clinicopathologic and molecular features associated with such sustained remissions included <3 metastatic sites at diagnosis, lower mean ctDNA fraction (potentially reflective of lower proliferation

rate, tumor cell turnover, and sites of metastatic involvement), and luminal A intrinsic subtype. Additionally, patients with prolonged sustained remission were less likely to harbor *TP53* alterations detected by ctDNA and cyclin E1 (encoded by *CCNE1*) overexpression in tumor tissue,[35] a known mechanism that compromises the efficacy of CDK4/6 inhibitors.[36]

The EPIK-B5 phase III clinical trial evaluated the addition of alpelisib to fulvestrant as a 2nd line therapy in patients with *PIK3CA* mutations who progressed on 1st line therapy consisting of aromatase inhibitor in combination with CDK4/6 inhibitor.[37] Key finding of the trial was the significant improvement in the progression-free survival with the addition of alpelisib (7.4 months) compared to fulvestrant alone (2.8 months).[37] While this study aligns with the current standard of care (in the predecessor registrational SOLAR-1 clinical trial, only 6% of patients had received a CDK4/6 inhibitor previously[38]), alpelisib is associated with significant toxicity, most notably hyperglycemia and rash Grade ≥3 of 33% and 13%, respectively, leading to frequent dose reductions (46%), interruptions (68.5%), and discontinuations (27.2%).[37]

B. Hormone receptor-positive (HR(+)) and Her2(+) breast cancer

While the first line therapy for Her2(+) metastatic breast cancer is intensified,[27] the multicenter phase 3 DETECT V clinical trial investigated a diametrically opposite approach: it randomized patients with HR(+)/Her2(+) metastatic breast cancer in the 1st to 3rd line setting to receive trastuzumab and pertuzumab combined with endocrine therapy or chemotherapy followed by maintenance endocrine therapy and dual Her2-targeted therapy.[39] The protocol was amended nearly half-way with the addition of ribociclib to both arms. The majority of patients (77%) enrolled in the first line setting. Key findings of the trial were the non-significant differences in progression-free and overall survival between the chemotherapy-free and -containing arms and the significant improvement in progression-free and overall survival in both arms with the addition of ribociclib. No prespecified subgroup of patients seemed to fare better with induction chemotherapy. As expected, the toxicity was significantly worse in the chemotherapy-containing arm and it was driven by diarrhea, fatigue, nausea, neuropathy, and mucositis.[39]

All conferences, and the SABCS alike, feature the work of many trainees, physicians, and investigators who are working diligently to reduce the burden of breast cancer worldwide and mitigate the daunting disparities. All this progress holds minimal significance if it cannot reach our patients, especially the most vulnerable and disadvantaged.

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