Cancerworld

# Five San Antonio take-aways to improve care of breast cancer patients

Janet Fricker / 16 December 2022

**The 2022 San Antonio Breast Cancer Symposium, hosted in association with the American Association for Cancer Research (AACR), was held December 6–10, 2022**.

More than 8,000 researchers, clinicians, students, and patient advocates from 90 countries attended the meeting, which focused on the latest advances in the biology, aetiology, prevention, diagnosis and therapy of breast cancer.

Here we present a round-up of studies that caught our eye as offering important new information for clinicians.

## Interrupting endocrine therapy to pursue pregnancy is safe

**Women with breast cancer who pause endocrine therapy while attempting to conceive experienced short-term rates of breast cancer recurrence similar to breast cancer patients who did not pause therapy for pregnancy**. The POSITIVE trial (Abstract GS4-09), presented in the general session on the Friday, also found incidence of birth defects was low and was not associated with endocrine therapy exposure.

“The POSITIVE trial provides important data to support young patients with hormone receptor positive early breast cancer who are interested in pregnancy and taking a break from endocrine therapy to pursue one,” said study presenter Ann Partridge, Chair of Medical Oncology at Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School.

While breast cancer is most common in women older than 40 years, around 1 in 20 new diagnoses each year occur in women aged 40 years or less. Although retrospective studies have shown pregnancy after cancer to be feasible and safe, many women are concerned that breast cancer treatment might make it difficult to conceive or that pregnancy might exacerbate cancer recurrence.

Commonly young women with early-stage hormone-receptor-positive breast cancer are treated with endocrine therapy (ovarian function suppression, aromatase inhibitors, or selective oestrogen receptor modulators) taken for 5–10 years to prevent recurrence. Since endocrine therapy compromises conception, Partridge and colleagues set out to assess the effects of temporarily suspending endocrine treatment in women who wished to become pregnant.

Between December 2014 and December 2019, investigators enrolled 518 women aged less than 43 years desiring to become pregnant. Participants opted to pause endocrine therapy for approximately two years to try to conceive, following completion of between 18 and 30 months of adjuvant endocrine therapy. Patients were enrolled from 116 centres across 20 countries, and were advised to return to their endocrine treatment following pregnancy.

Results showed:

- The three-year recurrence rate of breast cancer was 8.9% (95%CI 6.3%–11.6%), similar to the 9.2% rate found in an external control cohort from the SOFT/TEXT trials ($n$=1,499) (NCT00066690; NCT00066703) examining adjuvant endocrine therapy in premenopausal women.
- Of 497 women followed for pregnancy status, 74% ($n$=368) had at least one pregnancy and 63.8% ($n$=317) had at least one live birth; 19% had at least one miscarriage; and 3% at least one medical abortion.
- A total of 365 babies were born, of which 8% were low birth weight and 2% had birth defects.
- To date, 76.3% of participants have resumed endocrine therapy.

“The incidence of birth defects was low and not associated with treatment exposure. Long-term follow-up both to monitor endocrine therapy resumptions and long-term disease outcomes, particularly in a hormone receptor-positive setting are ongoing,” concluded Partridge.

## Racial disparities in prometastatic tumour microenvironments

**Black patients with ER-positive, HER2-negative breast tumours treated with chemotherapy have increased concentrations of a ‘cellular complex’ facilitating metastasis**. The findings of the study (Abstract GS1-02), which featured in the Opening General Session, provide one reason why Black breast cancer patients experience worse outcomes.

“Our study provides a potential explanation for the persistent racial disparities in some forms of breast cancer that is not fully explained by disparities in social determinants of health, such as access to care or treatment,” said study presenter Maja Oktay, from Montefiore Einstein Cancer Center, New York.

Press briefing moderator Virginia Kaklamani, from UT Health San Antonio, commented, “The findings represent an important first-step toward better understanding of the biological differences between Black and White patients but also differences in cancer biology.”

Earlier research by Oktay and colleagues led to identification of three-cell structures in primary breast tumours consisting of an invasive tumour cell partially inserted into a blood vessel wall bound to an endothelial cell and a macrophage, with all three structures in direct and stable contact. The investigators named these structures ‘tumour microenvironment of metastasis’ (TMEM) doorways, since they act as ‘portals’ allowing tumour cells to enter the blood stream.

“With these three cells in close physical contact, there’s a special micro pharmacology that induces dissociation of endothelial cell junctions. These cells pull apart and create an opening through which content of the blood vessel can leak out and other cancer cells in the microenviroment can move in,” explained Oktay.

In earlier studies, the density of TMEM doorways in primary untreated tumours, as measured by the TMEM doorway score, was found to be prognostic for distant metastatic recurrence among patients with ER-positive, HER2-negative breast cancers. In other prior, studies, the investigators found neoadjuvant chemotherapy increased the density of TMEM doorways and resulted in prometastatic changes in tumour microenviroments for some women.

In the current study, Oktay and colleagues performed a retrospective multi-institutional study of TMEM doorway scores and macrophage density in 183 women (96 self-identified as Black and 87 as White) who had undergone neoadjuvant chemotherapy.

TMEM doorway scores were determined in residual breast cancer tissue after pre-operative chemotherapy using a previously validated multiplex staining and automated scoring technique. Investigators analysed the relationship between distant-recurrence-free survival (DRFS), macrophage density, and TMEM scores.

Results showed 49% of Black women had metastasis versus 34.5% of White women, and that Black women were more likely to undergo mastectomy than White women (69.8% vs 54%), and had higher-grade tumours.

Tumours from Black patients had more macrophages and higher TMEM doorway scores than tumours from White patients in the entire cohort and the ER-positive/HER2-negative cohort, but not in the triple-negative subset.

Adjusting for age, lymph node status, race, surgery type and tumour grade, size and subtype, investigators found patients with high TMEM scores showed approximately twice the risk for distant recurrence as those with low or intermediate TMEM scores (RR=2.01; 95%CI 1.17–3.44).

“Based on these data, we formulated the hypothesis that racial disparity in distant recurrence-free survival among patients with residual ER-positive/HER2-negative disease is due to enhanced prometastatic response to chemotherapy in Black women compared to White women,” explained Oktay. The study, she added, also suggests neoadjuvant chemotherapy increases the TMEM doorway score, producing prometastatic changes in the tumour microenvironment in some women, thereby uncovering a previously unrecognised mechanism of chemotherapy resistance.

The findings suggest that giving patients TMEM doorway inhibitors, such as rebastinib (a selective inhibitor of macrophage recruitment) alongside neoadjuvant chemotherapy might improve outcomes for Black women and help to eliminate outcome disparities in ER-positive HER2-negative breast cancer.

# Trastuzumab deruxtecan confirmed as standard of care in metastatic HER2-positive breast cancer

**Second-line treatment with trastuzumab deruxtecan (T-DXd) resulted in significantly longer overall survival in comparison with trastuzumab emtansine (T-DM1) in women with HER2-positive metastatic breast cancer**. The DESTINY-Breast03 phase III study (Abstract GS2-02) found that patients treated with T-DXd showed improvements in overall survival as well as continuation of the progression-free survival benefit seen in an earlier analysis. The study was published simultaneously in *The Lancet*.

“For patients with HER2-postive breast cancer who experience disease progression following initial treatment in the metastatic setting, T-DXd has shown significant improvement in survival compared to T-DM1, further confirming this medicine as the new standard of care,” said study presenter Sara Hurvitz, from the University of California Los Angeles.

Two antibody-drug conjugates utilizing trastuzumab to seek HER2-expressing cells and deliver cytotoxic drug payloads have been approved as second-line treatment for metastatic HER2 breast tumours. In the case of T-DXd, the drug conjugate induces cell death by inhibiting topoisomerase; while in the case of T-DM1 the drug conjugate kills cells by disrupting microtubule assembly.

The DESTINY-Breast03 study included 524 patients previously treated with trastuzumab and a taxane in the metastatic or (neo)adjuvant setting who experienced recurrences within six months. Between July 2018 and June 2020 they were randomised 1:1 to T-DXd ($n$=261) or T-DM1 ($n$=263). The current presentation follows an earlier presentation reporting median progression-free survival results at ESMO Congress 2021, which also favoured T-Dxd.

In the latest results, median overall survival was not reached in either arm, although patients treated with T-DXd had a 36% lower risk of death than those treated with T-DM1 (HR 0.64, 95%CI 0.47–0.87, $P$=0.0037). After 12 months, 94.1% of patients in the T-DXd arm were alive versus 86% in the T-DM1 arm; and after 24 months 77.4% of patients in the T-DXd arm were alive versus 69.9% in the T-DM1 arm.

The median progression-free survival for patients treated with T-DXd was 28.8 months, compared with 6.8 months for patients treated with T-DM1 (HR 0.33, 95%CI 0.26–0.43, $P$<0.0001). Objective responses were observed in 78.5% of patients receiving T-DXd versus 35% treated with T-DM1. Furthermore, 21.1% of patients treated with T-DXd had a complete response, compared with 9.5% treated with T-DM1.

Consistent overall survival benefits were observed across key subgroups, including those with and without baseline brain metastases, previous treatment with pertuzumab, baseline visceral disease, and by hormone receptor status.

Grade 3 or higher treatment-related adverse events were observed in 56.4% of patients treated with T-DXd versus 51.7% treated with T-DM1. There were no grade 4 or 5 events in either group. Although drug-related interstitial lung disease/ pneumonitis was observed in 15.2% of patients treated with T-DXd versus 3.1 % with T-DM1, Hurvitz noted new cases were mild or moderate in severity.

In future analyses, the DESTINY-Breast03 investigators hope to look at efficacy of T-DXd in patients with brain metastases and explore predictive markers of response. Studies are currently ongoing to determine the efficacy and safety of T-DXd in patients with HER2-positive metastatic breast cancer

in first-line settings (NCT04538742, DESTINY-Breast07; NCT04784715, and DESTINY-Breast09) and in early-stage disease (NCT05113251, DESTINY-Breast11, NCT04622319, and DESTINY-Breast05).

## Study supports omitting axillary lymph node dissection after downstaging to node negative

**Neoadjuvant chemotherapy downstaging positive lymph nodes to negative without axillary lymph node dissection resulted in low rates of invasive breast cancer recurrence using either targeted axillary dissection (TAD) or sentinel lymph node biopsy (SLNB)**. The retrospective study (Abstract GS4-02) found using TAD resulted in removal of fewer lymph nodes than SLNB alone.

“These results support omission of axillary lymph node dissection in patients who are successfully down-staged to node negative after neoadjuvant chemotherapy,” said study presenter Giacomo Montagna, a breast surgeon from Memorial Sloan Kettering Cancer Center, New York.

Data on the safety of omitting axillary lymph node dissection in node-positive patients downstaged to negative following neoadjuvant chemotherapy has been sparse. Additionally, there is no consensus on whether SLNB should be used alone or in combination with TAD. TAD is an innovative surgical procedure where a metallic marker is inserted into the suspicious node prior to neoadjuvant therapy, allowing targeted implantation of a radioactive iodine-125 seed following chemotherapy.

For the retrospective study, investigators set out to evaluate outcomes following omission of axillary lymph node dissection in a real-world cohort of breast cancer patients, and further explored whether there were differences between TAD and SLNB. The study reviewed outcomes for 1,144 consecutive patients diagnosed at 19 different centres between April 2013 and December 2020 with biopsy-proven T1-4 N1-3 breast cancer, all of whom received neoadjuvant chemotherapy. Altogether 666 patients underwent SLNB and 478 TAD, with a median follow-up of 4.2 years.

The two types of nodal assessment led to similar outcomes: the three-year axillary recurrence was 0.5% for TAD versus 0.8% for SLNB; three-year locoregional recurrence was 0.8% for TAD versus 1.9% for SLNB; and three-year invasive recurrence was 7.8% for TAD versus 7.3% for SLNB.

Results at five-years for TAD and SLNB combined were 1.0% for axillary recurrence, 2.7% for locoregional recurrence, and 10.0% for invasive recurrence.

The median number of sentinel nodes removed was 4.4 with SLNB and 3.9 with TAD ($P<0.001$), with 4.2 overall.

The investigators concluded that the main advantage of TAD was a reduction in the number of lymph nodes removed. An ongoing prospective study, Montagna added, is currently underway, exploring whether arm function and lymphoedema rates differ between TAD and SLNB.

## Physical activity reduces risk of death in breast cancer survivors

**Even moderate physical activity was associated with a significantly decreased risk of all-cause death in long-term breast cancer survivors**. The study (Abstract P3-03-15) found moderate physical activity was associated with a 60% decreased risk of death compared to women who were insufficiently active.

“This study suggests that survivorship care plans should consider incorporating physical activity because even moderate activity is vital for extending survival as well as health-related quality of life,” conclude the authors.

While there is strong evidence to support the protective effects of physical activity on risk of developing breast cancer, the impact on survival after breast cancer diagnosis has been controversial, with limited research undertaken among long-term survivors.

In the current study, Reina Haque and colleagues, from Kaiser Permanente Southern California, followed a cohort of 315 post-menopausal breast cancer survivors diagnosed with early-stage breast cancer between January 1996 and December 2012. Subjects, who were at least two years post initial diagnosis, answered the Godin-Shephard Leisure-Time Physical Activity Questionnaire (GSLTPAQ), assessing exercise over a typical seven-day period and providing a score summarising exercise patterns into three levels (active, moderately active, and insufficiently active).

Results showed that, over a maximum follow-up of 8.7 years after baseline (median 7.8 years), 45 subjects (14.3%) died due to all causes (five due to breast cancer). The mortality rates were 12.9 per 1,000 person years for active women, 13.4 per 1,000 person years for those who were moderately active, and 32.0 per 1,000 person years for insufficiently active women.

In multivariable analysis, compared to insufficiently active women, those who were active had a 58% decreased risk of death (HR 0.42, 95%CI 0.21–0.85), and those who were moderately active a 60% decreased risk of death (HR 0.40, 95%CI 0.17–0.95).