Highlights from the 2018 annual meeting of the San Antonio Breast Cancer Symposium (SABCS)

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SUMMARY

From the 4-8th of December, the San Antonio Riverwalk again formed the background of the most important breast cancer congress in the world. This report will summarise eight top stories presented during the 2018 San Antonio Breast Cancer Symposium (SABCS). For a more complete overview of studies presented at the meeting, we refer to the congress website www.sabcs.org.

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ADJUVANT T-DM1 IMPROVES THE INVASIVE DISEASE-FREE SURVIVAL IN PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER WITH RESIDUAL INVASIVE DISEASE AT SURGERY FOLLOWING NEOADJUVANT CHEMOTHERAPY AND TRASTUZUMAB

The goal of the phase III KATHERINE trial was to determine if treating patients at higher risk for recurrence following neoadjuvant therapy (i.e. patients with persisting invasive breast cancer at surgery) with the antibody-drug conjugate T-DM1 instead of the standard therapy of trastuzumab would reduce the risk of recurrence without an unacceptable increase in toxicity.[1] KATHERINE is an open-label study of 1,486patients with HER2-positive early-stage breast cancer who received neoadjuvant chemotherapy plus HER2-targeted therapy that included a taxane and trastuzumab, followed by surgery. All patients had residual invasive disease in the breast or axillary lymph nodes. Within 12 weeks of surgery, patients were randomly assigned (1:1) to T-DM1 (3.6 mg/kg IV every three weeks) or trastuzumab (6 mg/kg IV every three weeks), for 14 cycles. The primary endpoint was invasive disease-free survival (IDFS). The median age of patients in KATHERINE was 49 years, with one out of five patients being younger than 40 years of age. Three quarters of patients previously received anthracyclines and 22% had residual disease of 1cm or less and negative axillary nodes (ypT1a, ypT1b, ypT1mic and ypN0). IDFS events occurred in 12.2% of patients in the T-DM1 arm as compared with 22.2% on the trastuzumab arm (HR[95%CI]: 0.50[0.39-0.64]; p< 0.001) (*Figure 1*) and this IDFS benefit was seen irrespective of age, race, the clinical stage at diagnosis, the hormone-receptor status, the type of preoperative HER2-directed therapy, the pathological nodal status after preoperative therapy and the primary tumour stage. At 3-years the IDFS rate with T-DM! was 77%, which was 11.3% less

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Keywords: breast cancer, T-DM1, adjuvant, triple-negative breast cancer, pathological complete response, tamoxifen, carcinoma in situ, circulating tumor cells, axilla, whole breast irradiation, partial breast irradiation.

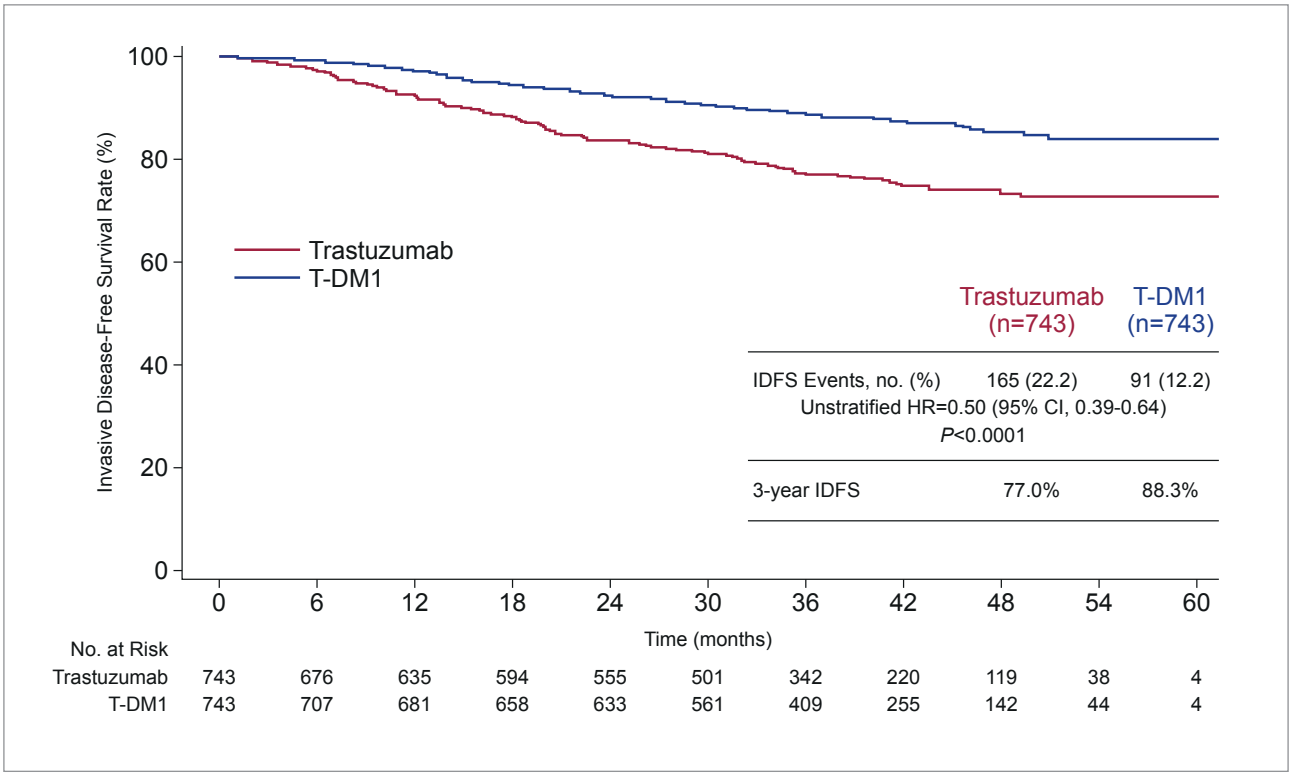


FIGURE 1. IDFS in the phase III KATHERINE trial.[1]

than the 88.3% seen with trastuzumab. T-DM1 also outperformed trastuzumab with respect to the incidence of distant recurrence (10.5 *vs.* 16.3%; HR[95%CI]: 0.60[0.45-0.79]) and locoregional recurrence (1.1% *vs.* 4.6%). The safety data were consistent with the known manageable toxicities of T-DM1, with expected increases in adverse events (AEs) associated with T-DM1 compared to trastuzumab (more fatigue, nausea, decreased platelet count, ALS/AST increase, epistaxis and sensory neuropathy). The incidence of grade 3/4 AEs with T-DM1 was 25.7% as compared to 15.4% with trastuzumab with a rate of AE-related treatment discontinuation of 18.0% with T-DM1 and 2.1% with trastuzumab.[1]

The authors concluded that the KATHERINE data could form the foundation of a new standard of care in this population and increase the use of neoadjuvant therapy in HER2-positive early breast cancer.

ADJUVANT CAPECITABINE DOES NOT LEAD TO A SIGNIFICANT OUTCOME IN PATIENTS WITH EARLY-STAGE TRIPLE-NEGATIVE BREAST CANCER

Results of the phase III GEICAM/CIBOMA trial indicate that adjuvant capecitabine for patients with early-stage triple negative breast cancer (TNBC) after completion of surgery and standard chemotherapy does not result in a significant improvement in the disease free (DFS) and overall survival (OS).[2] In total, 876 patients with operable, node-positive (or node-negative with tumour size ≥ 1 cm), centrally confirmed hormone receptor-negative, HER2-negative early breast cancer who had received 6-8 cycles of standard anthracycline and/or taxane-containing chemotherapy or 4 cycles of doxorubicin-cyclophosphamide (for node-negative disease) in the (neo)adjuvant setting, were included in the trial. Patients were randomized to either 8 cycles of capecitabine (1,000 mg/m^2 bid, days 1-14, every 3 weeks) or observation. The primary endpoint was DFS.[2]

The median age of patients in the trial was 50 years, approximately 30% of women were premenopausal and 60% had stage II disease (15% stage I, 20% stage III). The majority of patients (55%) was node-negative while an additional 30% had 1-3 positive nodes (approximately 15% had 4 or more positive nodes). In total, 71.7% had a basal phenotype and 67.5% received chemotherapy based on anthracyclines and taxanes. Three quarters of patients underwent an axillary lymph node dissection and approximately 80% also received radiotherapy. After a median follow-up of 7.4 years, the DFS was not significantly improved in patients treated with capecitabine (5-year DFS rate 79.6% *vs.* 76.8%; HR[95%CI]: 0.82[0.63-1.06]; p= 0.136). Also with respect to OS there was no difference between adjuvant capecitabine and observation (5-year OS: 86.2% *vs.* 85.9%; HR[95%-CI]: 0.92[0.66-1.28]). In subgroup analyses, the investiga-

tors found that among the 248 patients with non-basal-like disease, as defined by immunohistochemistry, patients randomized to adjuvant capecitabine were 49% less likely to experience a disease event (5-year DFS: 82.6% *vs.* 72.9%; HR[95%CI]: 0.53[0.307-0.913]) and 52% less likely to die (5-year OS: 89.5% vs. 79.6%; HR[95%CI]: 0.42[0.21-0.81]) compared with those randomized to observation. This is an intriguing finding but should be interpreted with caution because the interaction test was negative for DFS (p= 0.0694), although it was statistically significant for OS (p= 0.0052).[2]

PATHOLOGICAL COMPLETE RESPONSE AFTER NEOADJUVANT CHEMOTHERAPY AND IMPACT ON BREAST CANCER RECURRENCE AND MORTALITY

While the prognostic significance of pathological complete response (pCR) after neoadjuvant chemotherapy is relatively well established, the impact of adjuvant therapy in modulating relationship between pCR and long-term outcomes is less clear. To address this question, a meta-analysis of 52 studies including 27,895 patients was performed. Attainment of pCR, as compared to absence of pCR, was associated with significantly reduced disease recurrence overall (HR[95%-CI]: 0.31[0.24-0.39]), and in triple negative(HR[95%CI]: 0.18[0.10-0.31]), human epidermal growth factor 2-positive (HER2+) (HR[95%CI]: 0.32[0.21-0.47]), and trended towards significance for HR-positive breast cancer (HR[95%CI]: 0.15[0.02-1.10]). Similarly, pCR after neoadjuvant chemotherapy was also associated with reduced mortality overall (HR[95%CI]: 0.22[0.15-0.30]), and among all three major disease subtypes. The association of pCR with reduced recurrence was similar among studies where patients received subsequent adjuvant chemotherapy (HR[95%CI]: 0.34[0.18-0.61]) and those without adjuvant chemotherapy (95% HR[95%CI]: 0.36[0.27-0.54]) (*Figure 2*). The investigators concluded that the similar outcomes with/without adjuvant chemotherapy in patients who attain pCR after neoadjuvant chemotherapy likely reflects tumour biology and suggests adjuvant chemotherapy could potentially be abbreviated in certain circumstances and highlights the need for further research to evaluate clinical utility of escalation/de-escalation strategies in the adjuvant setting based on neoadjuvant response for patients with localized breast cancer.[3]

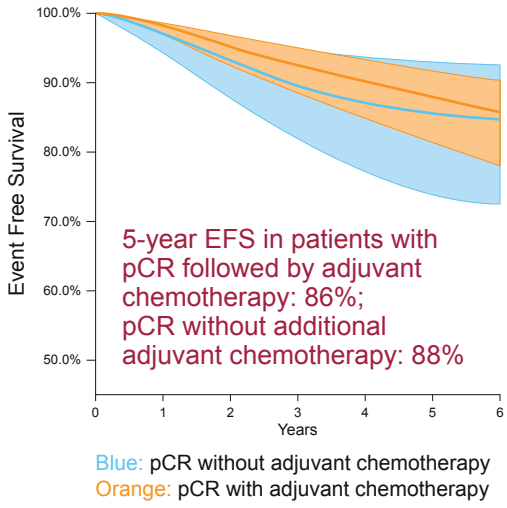
DELAYING THE INITIATION OF ADJUVANT CHEMOTHERAPY NEGATIVELY IMPACTS THE OUTCOMES OF TNBC

Morante *et al.* retrospectively analysed the medical records of 687 TNBC patients who received adjuvant chemotherapy at Instituto Nacional de Enfermedades Neoplasicas between 2000 and 2014.[4] The mean age at diagnosis of the included patients was 49 years and most patients had stage II (60.1%) or III (29.45%) disease. They received either anthracyclines or anthracyclines and taxane-based chemotherapy (96.1%). The median follow-up was 101 months and the median time to starting adjuvant chemotherapy (TTC) was 41 days. In total, 189 patients started the treatment at or before 30 days, 329 started it from 31 to 60 days115 started it between days 61to 90 and 54 started it more than 90 days after surgery.[4] As the time to starting adjuvant chemotherapy increased, the 10-year DFS rate decreased. In fact, the 10-year DFA rate was 81.4%, 68.6%, 70.8%, and 68.1% among patients who started the treatment at or before 30 days after surgery, 31 to60 days after surgery, 61 to 90 days after surgery, and more than 90 days after surgery, respectively. The 10-year OS rate also decreased with a longer TTC at 82%, 67.4%, 67.1%, and 65.1% for the four groups of patients, respectively. The researchers then studied how the extent of delay in starting chemotherapy was associated with an increased risk for disease recurrence and death. They found that compared with patients who started adjuvant chemotherapy in the first 30 days after surgery, risk for disease recurrence was increased by 92% for those who delayed starting the treatment for 31 to60 days after surgery, by 138% for those who delayed starting the treatment for 61 to 90 days after surgery, and by 147% for those who delayed starting the treatment for more than 90 days after surgery. The risk of death compared with patients who started adjuvant chemotherapy in the first 30 days after surgery increased by 94%, 145%, and 179% for the three groups, respectively.[4]

It needs to be stressed that this was only a retrospective analysis of a single institution experience, but the results do indicate that delaying adjuvant therapy leads to a worse outcome in TNBC.

LOW DOSE TAMOXIFEN FOR THE PREVENTION OF RECURRENCE IN WOMEN WITH OPERATED HORMONE SENSITIVE BREAST DUCTAL OR LOBULAR CARCINOMA IN SITU

In the phase III TAM-01 trial, De Censi *et al.* randomly assigned 500 women with ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), and atypical ductal hyperplasia (ADH) who had been treated with surgery and, if needed, radiotherapy, to be treated with either low-dose tamoxifen (5 mg/day) or placebo. Treatment continued for 3 years, and patients were seen by the research team every 6 months and had a mammogram annually. After a median follow-up of 5.1 years, 14 (5.5%) of the 253 patients in the low-dose tamoxifen arm and 29 (11.3%) of the 247 patients in the placebo



Adjuvant Chemotherapy	Hazard Ratio (pCR and EFS)	95% PI
Yes[1]	0.36	0.19-0.67
No[2]	0.36	0.27-0.54

pCR was associated with significantly improved EFS in both groups, and there was no significant difference in Hazard Ratios between the two groups[3].

[1] > 90% of patients received adjuvant chemotherapy
[2] No more than 10% of patients received adjuvant chemotherapy
[3] Paired T-test (difference in log-HR: 0.02, 95% PI: -0.75-0.73; p = 60)

FIGURE 2. Association of pCR to neoadjuvant chemotherapy with reduced recurrence was similar among studies where patients did or did not receive subsequent adjuvant chemotherapy.[3]

arm had disease recurrence or new disease, corresponding to a risk reduction of 52% in favour of low-dose tamoxifen (HR[95%CI]: 0.48[0.25-0.89]; p= 0.02).[5] Among the patients who had a recurrence or new disease in the opposite breast, 3 of the 14 in the low-dose tamoxifen arm had invasive breast cancer and 11 had breast intraepithelial neoplasia. In the placebo arm, 10 had invasive breast cancer and 18 had breast intraepithelial neoplasia. There were 12 serious AEs among the patients in the low-dose tamoxifen arm and 16 among those in the placebo arm. There was one case of endometrial cancer among the patients in the low-dose tamoxifen arm and none among those in the placebo arm. There was one venous thromboembolism in the tamoxifen arm and one pulmonary embolism in the placebo arm. There were no significant differences between the two arms in reporting of menopausal symptoms such as hot flashes, vaginal dryness, and pain during intercourse.[5]

CLINICAL UTILITY OF CIRCULATING TUMOUR CELL COUNT AS A TOOL TO CHOOSE BETWEEN FIRST LINE HORMONE THERAPY AND CHEMOTHERAPY FOR ER+ HER2- METASTATIC BREAST CANCER

In ER+ HER2- metastatic breast cancer patients, the choice between 1st line hormone therapy (HT, the recommended option) or chemotherapy (CT) is based on the absence of visceral crisis or adverse prognostic factors, without any proven/objective criteria. The phase III STIC CTC trial was set up to test whether circulating tumour cells (CTC) could help to customize the 1st line treatment choice in this setting.[6] The multicentre, phase 3, non-inferiority STIC CTC trial enrolled 778 patients with hormone receptor-positive, HER2-negative metastatic breast cancer to receive first-line treatment with chemotherapy or endocrine therapy. The choice of treatment was by random assignment, selected by clinically-driven choice or CTC-driven choice (CTC count not disclosed, HT or CT administered as decided a priori). In the CTC count arm, patients with low CTC levels (as defined as < 5 CTC/7.5 mL) received endocrine therapy, whereas patients with high CTC levels (as defined as ≥ 5 CTC/7.5 mL) received chemotherapy. The CTC count was non-inferior to the clinician's choice arms for the primary endpoint of PFS, with a median of 15.6 months (95%CI: 12.8-17.3) compared with 14.0 months (95%CI: 12.2-16.0) in the clinician's choice arm (HR[95%CI]: 0.92[0.80-1.06]), based on the pre-specified non-inferiority margin of 1.25. Also the OS was similar between arms, with a 2-year rate of 82.1% in the CTC count arm compared with 81.4% in the clinician's choice arm. The CTC count confirmed the clinician's choice in 67% of patients who received endocrine therapy and in 48% of patients who received chemotherapy. For discordant cases, CTC count that differed from clinician's choice resulted in a switch in therapy. In these cases, patients

who were switched to chemotherapy demonstrated a significantly prolonged PFS compared with endocrine therapy (median PFS: 15.5 *vs* 10.5 months). There was also a trend towards an improved OS with chemotherapy *vs*. endocrine therapy based on CTC count (median OS: 42.0 *vs*. 37.1 months). Patients who were switched to endocrine therapy based on low CTC count demonstrated no difference in PFS between arms.[6]

The authors concluded that high CTC count favours chemotherapy compared with endocrine therapy. As such, they argue that CTC count should be included in the decision algorithm for HR-positive, HER2-negative metastatic breast cancer patients.

RADIOTHERAPY OR SURGERY OF THE AXILLA AFTER A POSITIVE SENTINEL NODE IN BREAST CANCER PATIENTS: 10 YEAR FOLLOW UP RESULTS OF THE EORTC AMAROS TRIAL

Traditionally, patients early-stage invasive breast cancer who had cancer detected in a sentinel lymph node biopsy underwent axillary lymph node dissection, which is an effective but invasive surgical procedure that is associated with adverse side effects such as lymphedema and difficulties moving the arm. The phase III AMAROS clinical trial tested whether axillary radiotherapy could yield comparable outcomes to axillary lymph node dissection with fewer adverse side effects. Previously reported data with five-years of follow-up showed that lymphedema occurred significantly more often after axillary lymph node dissection than after axillary radiotherapy. During SABCS 2018 10-year follow-up data of this trial were reported.[7]

Of the 4,806 patients with early-stage, clinically node-negative breast cancer who the enrolled in the trial, 1,425 went on to have a positive sentinel lymph node biopsy. In total, 744 of these patients had been randomly assigned to axillary lymph node dissection and 681 to axillary radiotherapy. After 10 years, 1.82% (11 out 681 patients) of those assigned to axillary radiotherapy had axillary recurrence, compared with 0.93% (7 out of 744 patients) of those assigned to axillary lymph node dissection. In addition, neither distant metastasis–free survival (DMFS, 78.2% *vs*. 81.7%) nor OS (81.4% *vs*. 84.6%) were significantly different between the two treatment arms. A significantly greater proportion of patients assigned to axillary radiotherapy went on to develop a second primary cancer than did patients assigned to axillary lymph node dissection: 11.0% *vs*. 7.7% (mainly due to a higher incidence of contralateral breast cancer in the patients treated with axillary radiotherapy). The main limitation of the study is that the size of the radiation field was greater than what is currently deemed necessary, which caused some morbidity that may now be avoided. There was also an imbalance in the number of patients who had a sentinel lymph node biopsy in the two arms and the number of recurrences was by far lower than expected, reducing the statistical power of the study. However, the researchers noted that these limitations do not adversely affect the conclusion from the trial data that axillary radiotherapy is not inferior to axillary lymph node dissections in terms of locoregional control.[7]

CONVENTIONAL WHOLE BREAST IRRADIATION VS. PARTIAL BREAST IRRADIATION FOR WOMEN WITH STAGE 0, I, OR II BREAST CANCER

Whole breast irradiation (WBI) following lumpectomy has comparable ipsilateral recurrence rates as mastectomy. Accelerated partial breast irradiation (PBI) treats the tumour bed area instead of the entire breast and as such reduces the radiation treatment time from 3-6 weeks to 5-8 days. The main purpose of the presented phase III study was to determine if accelerated PBI is equivalent to WBI in controlling for ipsilateral breast cancer recurrence in women who desire breast-conservation surgery.[8] In total, 4216 breast cancer patients who had recently received a lumpectomy with 0-3 positive axillary nodes were randomly assigned to treatment with WBI or PBI. Of these breast cancer patients, 25% had DCIS, 65% had stage I breast cancer, and 10% had stage II disease. Overall 81% of patients had HR-positive cancer, and 61% of patients were postmenopausal. In total 2,109 patients received WBI and 2,107 received PBI. Treatment with WBI was defined as daily treatment with 2 grays (Gy) of radiation totalling 50 Gy with a sequential boost to the surgical site; treatment with PBI was defined as twice daily treatment with 3.4-3.85 Gy totalling 10 treatments delivered via 3D external beam radiation or brachytherapy. The primary endpoint of the trial was evidence of ipsilateral breast tumour recurrence (IBTR).

There were 161 IBTRs as first events: 90 in the PBI arm and 71 with WBI (HR[90%CI]: 1.22[.94-1.58]). While the risk of recurrence was not statistically different between the two treatment arms, the hazard ratio did not meet the statistical criteria for treatment equivalence (the per protocol-defined margin to declare PBI and WBI equivalent regarding IBTR risk, the 90% CI for the observed HR had to lie entirely between 0.667 and 1.5). The proportion of patients who were IBTR-free 10 years after treatment was 95.2% among those who received PBI and 95.9% among those who received WBI. The difference in the 10-year relapse free interval (RFI) be-

tween the two treatment arms was statistically significant, favouring WBI (91.9% *vs.* 93.4%; HR[95%CI]: 1.32[1.04-1.68]; p=0.02). No statistical difference was seen with respect to OS, DFS and distant disease-free interval. Grade 3 toxicity was modestly higher in patients who received PBI *vs.* WBI (9.6% *vs.* 7.1%). Likewise, grade 4-5 toxicity was slightly higher in the PBI arm compared to WBI (0.5% *vs.* 0.3%).

Despite only small differences in IBTR (<1%) and RFI (1.5%) between the two treatment arms at 10 years, the researchers could not declare that WBI and PBI were equivalent in controlling local in-breast tumour recurrence because the HR between arms fell short of meeting statistical equivalence. However, these findings do suggest that the less burdensome radiation method of accelerated PBI may be an acceptable choice for many women. Additional analyses are underway to determine if specific cohorts may have advantages in local and regional relapse control between the two treatment arms.

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