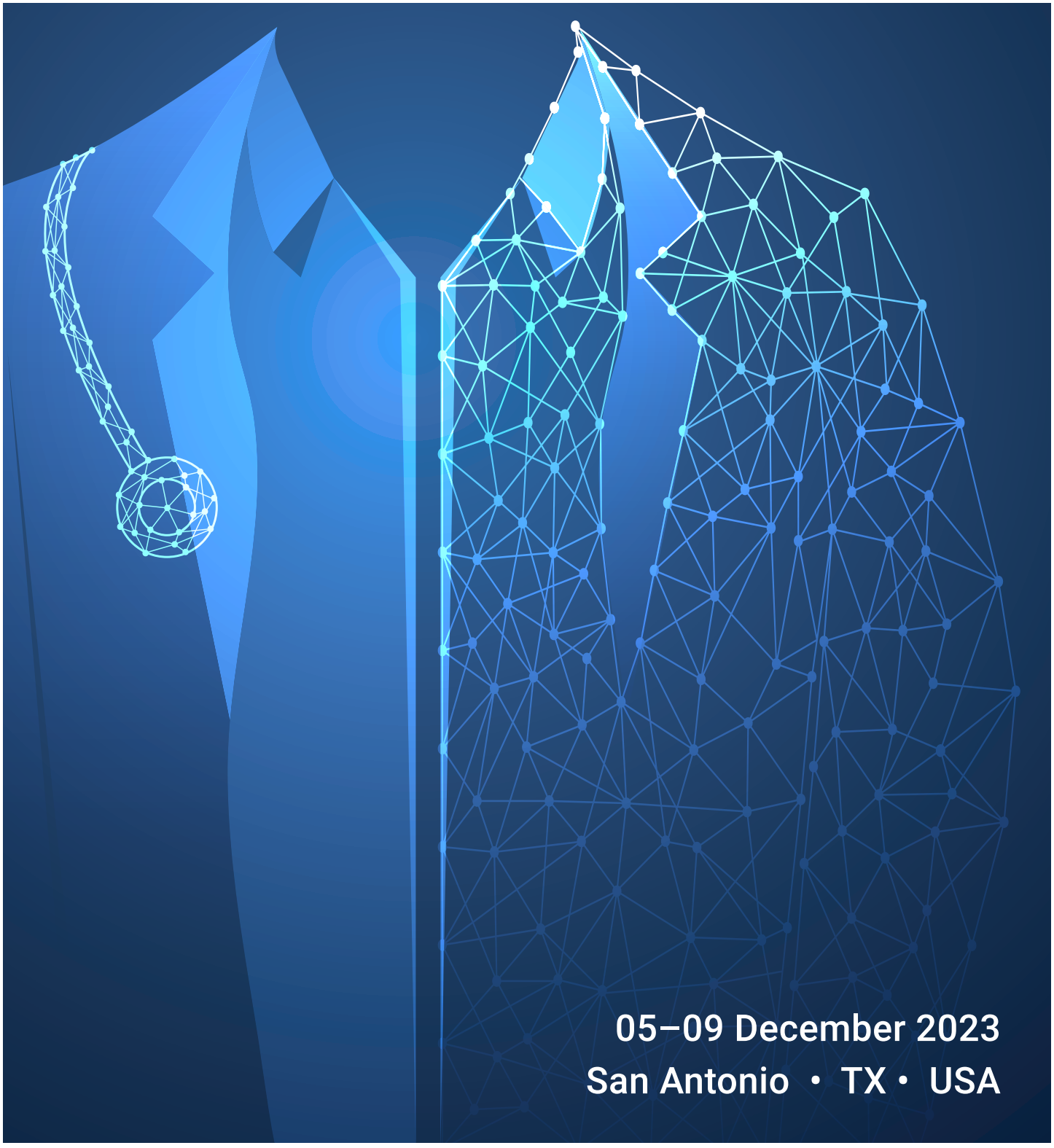
MEDICOM
MEDICAL PUBLISHERS

Medicom Conference Report Highlights

SABCS 2023

San Antonio Breast Cancer Symposium



05–09 December 2023
San Antonio • TX • USA

COLOPHON

Editor	Dr Rachel Giles
Medical Writer	Dr Marten Dooper
Publishing Director	Paul Willers
Editorial Operations Manager	Dr Rosalie Molenaar
Medical Project Manager	Rune Bruls
Editorial Coordinator	Dr Joery Goossens
Production Manager	Anouk Neijenhoff
Graphic Design	MOOZ grafisch ontwerp
Printing	GVO drukkers & vormgevers B.V.

Editor Conflict of Interest: no conflicts.

MEDICOM
MEDICAL PUBLISHERS

Head Office
Medicom Medische Uitgeverij B.V.
Laarderhoogtweg 25
1101 EB Amsterdam
The Netherlands

Postal address
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom-publishers.com
www.medicom-publishers.com

Contents

Early Breast Cancer

Highest benefit of neoadjuvant nivolumab in breast tumours with high PD-L1 expression and/or low ER expression

The benefit of neoadjuvant nivolumab is highest in patients with high PD-L1 expression and low oestrogen receptor (ER) expression, according to the results of an exploratory biomarker analysis of CheckMate 7FL.

Recently, results from the phase 3 CheckMate 7FL trial (NCT04109066) showed the benefit of the addition of nivolumab to neoadjuvant chemotherapy and adjuvant endocrine therapy in patients with newly diagnosed high-risk, high-grade ER-positive/HER2-negative primary breast cancer [1]. In the overall population, pathological complete response (pCR) rates with nivolumab were significantly improved compared with controls (24.5% vs 13.8%; OR 2.05; 95% CI 1.29–3.27; P=0.0021). The benefit of nivolumab was greater in the PD-L1-positive population (combined positive score [CPS] ≥1%).

Dr Sherene Loi (Peter MacCallum Cancer Centre, Australia) presented the results of an exploratory biomarker analysis of CheckMate 7FL [2]. "The aim of this biomarker study was to further define the patients who had greater magnitude of benefit with the addition of nivolumab to neoadjuvant chemotherapy in the CheckMate 7FL trial," explained Dr Loi.

With respect to PD-L1 expression, the pCR rate benefit of nivolumab was greater with increased CPS scores. The between-group difference in pCR increased from 5.7% in patients with CPS <1 to 52.3% in patients with CPS ≥20. In addition, a greater benefit of nivolumab was observed in patients with tumours containing >5% stromal tumour-infiltrating cells (TILs).

High expression of ER was negatively correlated with a pCR rate benefit of nivolumab: nivolumab benefit was the highest in patients with low (<50%) ER expression, Dr Loi showed. In addition, low expression of progesterone receptor (PR) was associated with a greater benefit of nivolumab. No association between nivolumab benefit and Ki67 proliferation index was observed.

"This exploratory analysis shows that the nivolumab benefit on pCR rates was the highest in patients with tumours with higher PD-L1 expression, stromal TILs ≥5%, and low expression of ER and PR," concluded Dr Loi. Additional exploratory and correlative analyses are ongoing to further refine the patient subpopulation with primary ER-positive/HER2-negative breast cancer who could benefit from the addition of nivolumab to neoadjuvant chemotherapy.

1. Loi S, et al. Abstract LBA20, ESMO 2023, 20–24 October, Madrid, Spain.
2. Loi S, et al. Biomarker results in high-risk estrogen receptor positive, human epidermal growth factor receptor 2 negative primary breast cancer following neoadjuvant chemotherapy ± nivolumab: an exploratory analysis of CheckMate 7FL. Abstract GS01-01, SABCS 2023, 5–9 December, San Antonio, TX, USA.

(More) axillary surgery does not influence long-term recurrence

The intensity of axillary surgery in patients with early breast cancer does not influence long-term recurrence, results from an individual patient-data meta-analysis of 30 randomised trials showed.

In early breast cancer, the optimal management of the axilla is uncertain. To better understand the long-term (>10 years follow-up) benefits and risks of different approaches, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) undertook an individual patient-data meta-analysis of randomised trials, comparing varying types of axillary treatment. Dr Gurdeep Mannu (University of Oxford, UK) presented the results [1].

For this meta-analysis, information was available on 20,273 women in 30 trials of axillary surgery or axillary radiotherapy. The trials took place between 1958 and 2009; median follow-up was 10.0 years (IQR 7.4–11.5). The results were split up for trials in the 'pre-sentinel lymph node biopsy' (pre-SLNB) era (1950–1990s) and the 'sentinel lymph node biopsy' (SLNB) era (1990s–2010s).

Trials in the pre-SLNB era compared axillary dissection versus no axillary dissection in node-negative disease, axillary radiotherapy versus no axillary radiotherapy, axillary dissection versus axillary radiotherapy, and more versus less axillary surgery. Trials in the SLNB era compared further surgery versus no further surgery in SLN-negative patients, further surgery versus no further surgery in SLN-positive patients, and axillary clearance versus axillary radiotherapy in SLN-positive patients. The majority (25/30) of the recorded trials compared no/less surgery versus (more) surgery.

The meta-analysis showed that there was no difference in 10-year locoregional recurrence, distant recurrence, breast cancer-specific mortality, or any death between less or more surgery. This was the case for both node-negative and (sentinel) node-positive patients, both in the pre-SLNB era and the SLNB era. However, in patients who underwent more surgery, the incidence of lymphoedema was doubled compared with patients with no/less surgery.

In addition, the meta-analysis showed no difference in recurrence or morbidity between axillary dissection versus axillary radiotherapy. However, axillary radiotherapy was associated with less lymphoedema.

Dr Mannu summarised that "more axillary surgery did not reduce recurrence but did increase lymphoedema. In addition, surgery did increase lymphoedema versus radiotherapy."

1. Mannu GS, et al. Overview of axillary management in early breast cancer. Abstract GS02-05, SABCS 2023, 5–9 December, San Antonio, TX, USA.

Neoadjuvant chemotherapy may help patients skip regional nodal irradiation

For patients whose breast cancer converted from lymph node-positive to lymph node-negative disease after neoadjuvant chemotherapy, skipping adjuvant regional nodal irradiation (RNI) did not increase the 5-year risk of disease recurrence or death, according to results from the NRG Oncology NSABP B-51/RTOG 1304 clinical trial.

For patients who undergo upfront surgery, the benefit of adjuvant RNI is well established in patients with pathologically positive axillary lymph nodes [1]. Patients who present with axillary node involvement, receive neoadjuvant chemotherapy, and are found to be pathologically node-negative at surgery have lower loco-regional recurrence rates compared with those who remain pathologically node-positive [2].

The phase 3 NSABP B-51/RTOG 1304 study (NCT01872975) evaluated the benefit of RNI in node-positive patients who are found to be node-negative (ypN0) after neoadjuvant chemotherapy. The study enrolled 1,641 patients with T1–3, N1, M0 breast cancer who converted to ypN0 after neoadjuvant chemotherapy and who had undergone either mastectomy or breast-conserving surgery. Participants were randomised 1:1 to RNI or no RNI. Participants in the no RNI arm who had breast-conserving surgery received whole breast irradiation. The primary outcome was invasive breast cancer recurrence-free interval (IBCRFI). Prof. Eleftherios Mamounas (Orlando Health Cancer Institute, FL, USA) presented the results [3].

After a median follow-up of 60 months, no difference in IBCRFI was observed between treatment arms (HR 0.88; 95% CI 0.60–1.29; P=051). Five-year estimates of IBCRFI were 91.8% and 92.7% for the no RNI and RNI arm, respectively. In addition, isolated loco-regional recurrence, distant recurrence, disease-free survival, and overall survival were not significantly different between the no-RNI and RNI arms.

Toxicities of grade 2–4 were more common in patients in the RNI arm. Radiation dermatitis of grade 3 occurred more with RNI (5.7% vs 3.3%).

"Our findings suggest that downstaging cancer-positive regional lymph nodes with neoadjuvant chemotherapy can allow some patients to skip adjuvant RNI without adversely affecting oncologic outcomes. Follow-up of patients for long-term outcomes continues," Prof. Mamounas summarised.

1. McGale P, et al. Lancet. 2014;383:2127-2135.
2. Mamounas EP, et al. J Clin Oncol. 2012;30:3960-3966.
3. Mamounas EP, et al. Loco-regional irradiation in patients with biopsy-proven axillary node involvement at presentation who become pathologically node-negative after neoadjuvant chemotherapy: primary outcomes of NRG Oncology/NSABP B-51/RTOG 1304. Abstract GS02-07, SABCS 2023, 5-9 December, San Antonio, TX, USA.

No radiotherapy after breast-conserving surgery is safe in selected younger patients

Avoiding radiotherapy after breast-conserving surgery in selected younger (50–69) post-menopausal patients appears not to increase the risk of recurrence nor to decrease survival, as is suggested by results of the single-arm IDEA trial.

Radiotherapy is recommended after lumpectomy to improve local control of invasive breast cancer and a modest survival benefit. However, the absolute benefit of radiotherapy is not the same for all subgroups of patients, and survival benefit appears restricted to those with a large absolute reduction in recurrence (>10–20%). Multiple studies have shown a low risk of ipsilateral breast events or other recurrences for selected patients: those aged 65–70 or older, with stage I breast cancers, and treated with breast-conserving surgery and endocrine therapy without adjuvant radiotherapy.

The prospective, single-arm IDEA trial (NCT02400190) aimed to evaluate if younger post-menopausal patients could also be successfully treated without radiotherapy, adding a genomic assay (Oncotype DX) to the classic selection factors. IDEA enrolled 200 post-menopausal patients aged 50–69 years, with pT1N0 unifocal invasive breast cancer, with margins 2 mm or wider after breast-conserving surgery, whose tumours were oestrogen receptor (ER)-positive, progesterone receptor (PR)-positive, and HER2-negative, with Oncotype DX 21-gene recurrence risk score ≤18, who were willing to avoid radiotherapy and to take at least 5 years of endocrine therapy and surveillance on study. Primary endpoint was the rate of breast cancer recurrence at 5 years of follow-up after breast-conserving surgery. Dr Reshma Jagsi (Emory University School of Medicine, MI, USA) presented the results [1].

Among the 186 participants with clinical follow-up of at least 56 months, overall and breast cancer-specific survival rates at 5 years were both 100%; 2 deaths occurred

beyond 5 years. Recurrence-free survival rate at 5 years was 99%. There were 2 recurrences: 1 isolated ipsilateral axillary recurrence at 21 months and 1 ipsilateral breast event at 49 months; 6 additional patients recurred beyond 5 years.

"These results show a very low risk of relapse for post-menopausal patients with stage I cancers, avoiding radiotherapy using a genomic assay in combination with classic clinical and biological features for treatment selection, including patients younger than 60 years," Dr Jagsi concluded. "However, long-term follow-up beyond the 5-year required period of endocrine therapy will be important to determine if the risk of recurrence increases, particularly after discontinuation of endocrine therapy. In addition, results from ongoing randomised trials are needed to determine whether the option of avoiding initial radiotherapy can be offered to a broader group of women than current guidelines recommend."

1. Jagsi R, et al. Five-year outcomes of the IDEA trial of endocrine therapy without radiotherapy after breast-conserving surgery for postmenopausal patients age 50-69 with genomically-selected favorable stage I breast cancer. Abstract GS02-08, SABCS 2023, 5–9 December, San Antonio, TX, USA.

HER2-Positive Breast Cancer

Tucatinib improves PFS in metastatic, HER2-positive breast cancer

Addition of tucatinib to trastuzumab emtansine (T-DM1) extended progression-free survival (PFS) among patients with unresectable locally advanced or metastatic HER2-positive breast cancer, according to results from the HER2CLIMB-02 trial.

HER2-positive breast cancer has a predilection to spread to the brain, and when this occurs, prognosis is poor. A previous phase 2 trial, HER2CLIMB (NCT02614794), found that the addition of tucatinib to a regimen containing the HER2-targeted antibody trastuzumab and the chemotherapy capecitabine significantly improved PFS and overall survival (OS) in heavily pretreated patients, including those with brain metastases [1,2]. Preclinical data has shown that the combination of tucatinib and T-DM1 results in enhanced antitumor activity compared with either agent alone [3]. In addition, in a phase 1b/2 study, the combination of tucatinib and T-DM1 demonstrated encouraging antitumor activity, including intracranial responses, with a manageable safety profile [4].

The phase 3 HER2CLIMB-02 trial (NCT03975647) evaluated the efficacy of the combination of tucatinib and T-DM1 in patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who had progression after treatment with trastuzumab and a taxane. A total of 463 patients were enrolled and 1:1 randomised to receive tucatinib plus T-DM1 or placebo plus T-DM1; 44.1% had brain metastases at baseline. Median prior lines of systemic therapy in the metastatic setting was 1 (range 0–8). Primary outcome of the study was PFS, secondary outcomes were OS and PFS in patients with brain metastases. Prof. Sara Hurvitz (Fred Hutchinson Cancer Center, WA, USA) presented the results [5].

Median PFS in patients treated with tucatinib/T-DM1 was 9.5 months, versus 7.4 months in patients treated with placebo/T-DM1 (HR 0.76; 95% CI 0.61–0.95; P=0.0163). In patients with brain metastases, median PFS was 7.8 months and 5.7 months, respectively (HR 0.64). OS data are not yet mature.

Based on these outcomes, Prof. Hurvitz concluded that "this is the second randomised study including patients with brain metastases demonstrating that a tucatinib-containing regimen delays disease progression in patients with previously treated HER2-positive, unresectable locally advanced or metastatic breast cancer."

1. Murthy RK, et al. N Engl J Med 2020;382:597-609.
2. Curigliano G, et al. Ann Oncol. 2022;33:321-329.
3. Olson D, et al. Cancer Res Commun. 2023;3:1927-1939.
4. Borges VF, et al. JAMA Oncol. 2018;4:1214-1220.
5. Hurvitz S, et al. HER2CLIMB-02: Randomized, double-blind phase 3 trial of tucatinib and trastuzumab emtansine for previously treated HER2-positive metastatic breast cancer. Abstract GS01-10, SABCS 2023, 5–9 December, San Antonio, TX, USA.

OS benefit of adjuvant T-DM1 in early breast cancer with residual disease after neoadjuvant therapy

In patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant therapy, adjuvant treatment with trastuzumab emtansine (T-DM1) improves both invasive disease-free survival (IDFS) and overall survival (OS), according to updated results of the phase 3 KATHERINE trial.

Patients with HER2-positive early breast cancer who have residual disease after receiving neoadjuvant chemotherapy plus HER2-targeted therapy have a worse prognosis than those who have no residual disease [1]. Interim results from the phase 3 KATHERINE

trial (NCT01772472) demonstrated a higher 3-year IDFS rate in these patients after adjuvant treatment with 14 cycles of T-DM1 versus 14 cycles of trastuzumab. OS was not significantly different between both arms at the time of this interim analysis [2]. Prof. Sibylle Loibl (Goethe University, Germany) presented results from the final IDFS and an updated OS analysis [3].

In KATHERINE, 1,386 patients with HER2-positive early breast cancer who had residual disease after receiving neoadjuvant chemotherapy plus HER2-targeted therapy with trastuzumab were 1:1 randomised to receive 14 cycles of T-DM1 or 14 cycles of trastuzumab within 12 weeks after surgery. The primary endpoint was IDFS, key secondary endpoints were OS and distant recurrence-free survival (DRFS).

With a median follow-up of 8.4 years, T-DM1 sustained the improvement in IDFS over trastuzumab; 7-year IDFS rates were increased from 67.1% with trastuzumab to 80.8% with T-DM1 (HR 0.54; 95% CI 0.44–0.66]; P<0.0001). In addition, 7-year OS rates were significantly increased from 84.4% with trastuzumab to 89.1% with T-DM1 (HR 0.66; 95% CI 0.51–0.81; P=0.0027). Both IDFS and OS benefit was observed across all prespecified subgroups.

No new safety issues emerged with longer follow-up and cardiac toxicity was rare in both arms (0.7%).

Based on these results, Prof. Loibl concluded that "KATHERINE demonstrates a significant improved OS and sustained IDFS in patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant therapy who are treated with T-DM1 versus trastuzumab post-surgery." Follow-up is ongoing for the final OS analysis.

1. Cortazar P, et al. Lancet 2014;384:164-172.
2. von Minckwitz G, et al. N Engl J Med 2019;380:617-628.
3. Loibl S, et al. Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis. Abstract GS03-12, SABCS 2023, 5–9 December, San Antonio, TX, USA.

Atezolizumab improves pCR in HER2-positive early breast cancer

Addition of atezolizumab to neoadjuvant therapy for patients with HER2-positive early breast cancer increases pCR rates, first results of the APTneo Michelangelo trial demonstrated. An exploratory analysis suggests an additional benefit with anthracyclines.

Neoadjuvant dual targeting of HER2 with trastuzumab/pertuzumab in addition to chemotherapy is the standard-of-care for high-risk HER2-positive breast cancer [1]. Prior findings have indicated that the immune system plays a central role in the prognosis and achieved response with HER2-directed approaches, and this has led to the exploration of pairing immune checkpoint inhibitors with HER2-directed antibodies.

The phase 3 APTneo trial (NCT03595592) evaluated the efficacy and safety of adding atezolizumab to neoadjuvant dual targeting of HER2 and chemotherapy, and the value of also using anthracyclines in this setting. APTneo enrolled 661 patients with operable or locally advanced HER2-positive breast cancer who had not been exposed to chemotherapy. Participants were randomised 1:1:1 to 3 arms. Participants in arm A received neoadjuvant trastuzumab/pertuzumab (HP) plus carboplatin/paclitaxel (CT) for 6 cycles, and another 12 cycles of HP after surgery. Patients in arm B1 received neoadjuvant anthracycline/cyclophosphamide (AC) plus atezolizumab for 3 cycles, followed by 3 cycles of HPCT plus atezolizumab; after surgery they received 12 cycles of HP plus atezolizumab. Patients in arm B2 received HPCT plus atezolizumab for 6 cycles, followed by surgery and adjuvant HP plus atezolizumab for 12 cycles. The primary aim of APTneo is to compare event-free survival (EFS) 5 years after randomisation, a secondary outcome is the rate of pathological complete response (pCR). Dr Luca Gianni (IRCCS Ospedale San Raffaele, Italy) presented the first results concerning pCR rates [2].

pCR rates (ypT0/is ypN0) were 52.0%, 61.9%, and 53.6% in arm A, arm B1, and arm B2, respectively. The pCR rate difference between arm A and arm B1 was statistically significant (P=0.022). In addition, in a multivariate analysis, PD-L1-positivity, oestrogen receptor (ER)-negativity, and the presence of ≥30% stromal tumour-infiltrating lymphocytes (TILs) were associated with a higher probability of pCR.

"These results show that the addition of atezolizumab to neoadjuvant therapy for patients with HER2-positive early breast cancer increases the pCR rate. In addition, an exploratory analysis suggests either a direct anthracycline effect or a mechanistic enhancement of anthracyclines with atezolizumab," concluded Dr Gianni. The study continues follow-up to assess the primary endpoint of EFS.

1. Cardoso F, et al. Ann Oncol. 2019;30:1194-1220.
2. Gianni L, et al. Pathologic complete response (pCR) of neoadjuvant therapy with or without atezolizumab in HER2 positive, early high risk and locally advanced breast cancer: APTneo Michelangelo randomized trial. Abstract LBO1-02, SABCS 2023, 5–9 December, San Antonio, TX, USA.

HR-Positive/HER2-Negative Breast Cancer

Adjuvant ribociclib improves IDFS in early breast cancer

The addition of the CDK4/6 inhibitor ribociclib to adjuvant endocrine therapy improves invasive disease-free survival (IDFS) of patients with early-stage HR-positive/HER2-negative breast cancer, the results of the phase 3 NATALEE trial showed.

Although early breast cancer is treated with curative intent, a considerable risk of disease recurrence remains (27% to 37% for stage II and 46% to 57% for stage III HR-positive/HER2-negative breast cancer) [1]. In patients with advanced HR-positive/HER2-negative breast cancer, the addition of a CDK4/6 inhibitor to endocrine therapy has been shown to increase disease-free and overall survival, while maintaining quality of life [2].

The phase 3 NATALEE trial (NCT03701334) evaluated the addition of the CDK4/6 inhibitor ribociclib to endocrine therapy in 5,101 patients with early-stage HR-positive/HER2-negative breast cancer. Participants were randomised 1:1 to adjuvant treatment with ribociclib (400 mg/day for 3 years) plus endocrine therapy (for at least 5 years) or treatment with endocrine therapy alone. Dr Gabriel Hortobagyi (MD Anderson Cancer Center, TX, USA) presented final results on IDFS, which was the primary endpoint [3]. As of the data cut-off, the median follow-up was 34 months.

The trial met its primary endpoint, as the addition of ribociclib to adjuvant endocrine therapy significantly improved the 3-year IDFS rate: 90.7% versus 87.6% (HR 0.749; P=0.0006). The absolute IDFS benefit at 3 years follow-up was 3.1%. IDFS benefit was observed in all prespecified subgroups. The risk of invasive disease was reduced by 30.0% for stage II disease (3-year IDFS: 94.2% vs 92.6%; HR 0.700) and by 24.5% for stage III disease (3-year IDFS: 88.1% vs 83.8%; HR 0.755). In addition, the 3-year distant disease-free survival rate was significantly improved in patients treated with ribociclib: 92.9% versus 90.2% (HR 0.749; P=0.001). The overall survival data are not yet mature.

"These results further emphasise the significant IDFS benefit of ribociclib in a broad population of patients with HR-positive/HER2-negative early breast cancer at risk of recurrence," Dr Hortobagyi concluded. However, to put this into perspective, about 30 patients have to be treated with ribociclib for 3 years to receive an IDFS benefit for 1 patient, one of the attendants remarked.

1. Pan H, et al. N Engl J Med 2017;377:1836-1846.
2. Harbeck N, et al. Ther Adv Med Oncol. 2020;12:1758835920943065.
3. Hortobagyi GN, et al. Ribociclib + nonsteroidal aromatase inhibitor as adjuvant treatment in patients with HR+/HER2− early breast cancer: final invasive disease-free survival analysis from the NATALEE trial. Abstract GS03-03, SABCS 2023, 5–9 December, San Antonio, TX, USA.

Addition of inavolisib to palbociclib and fulvestrant reduces risk of progression

Combining inavolisib, a selective PI3Kα inhibitor, with palbociclib and fulvestrant improves progression-free survival (PFS) over palbociclib/fulvestrant in patients with *PIK3CA*-mutated, HR-positive/HER2-negative advanced breast cancer recurring on or within 12 months of endocrine therapy, according to results from the INAVO120 study.

There is an unmet need for more effective treatments that overcome resistance in patients with *PIK3CA*-mutated HR-positive/HER2-negative breast cancer [1]. Inavolisib is an oral, potent, and selective PI3Kα inhibitor that promotes the degradation of mutant p110α, which may improve the therapeutic window. In a phase 1 study (NCT03006172) the triplet inavolisib/palbociclib/fulvestrant had a manageable safety profile and demonstrated promising antitumour activity in *PIK3CA*-mutated HR-positive/HER2-negative breast cancer [2].

The phase 3 INAVO120 study (NCT04191499) aimed to assess the efficacy of the addition of inavolisib versus placebo to palbociclib / fulvestrant in patients with *PIK3CA*-mutated, HR-positive/HER2-negative advanced breast cancer who recurred on or within 12 months of endocrine therapy and who had no prior therapy for advanced/metastatic breast cancer. INAVO120 enrolled 325 patients, who were 1:1 randomised to inavolisib/palbociclib/fulvestrant or placebo/palbociclib/fulvestrant until progression of disease or toxicity. The primary endpoint was PFS. Prof. Komal Jhaveri (Memorial Sloan Kettering Cancer Center, NY, USA) presented the primary analysis results [3].

At a median follow-up of 21 months, the addition of inavolisib to palbociclib/fulvestrant significantly improved PFS over placebo: 15.0 versus 7.3 months (HR 0.43; 95% CI 0.32–0.59; P<0.0001). At 18 months, 46.2% of the participants in the inavolisib arm were progression-free, versus 21.1% in the placebo arm. A PFS benefit of inavolisib was seen in all prespecified subgroups. In addition, a benefit of inavolisib was observed in objective response rate (58.4% vs 25.0%) as well as in median duration of response (18.4 vs 9.6 months). A clear trend in overall survival benefit of inavolisib was observed (HR 0.64; 95% CI 0.43–0.97; P=0.0338).

The addition of inavolisib to palbociclib/fulvestrant did increase adverse event rates, in particular for hyperglycaemia (58.6% vs 8.6.%) and diarrhoea (48.1% vs 16.0%).

Based on these results, Prof. Jhaveri concluded that "inavolisib in combination with palbociclib and fulvestrant may represent a new standard-of-care for patients with *PIK3CA*-mutated, HR-positive/HER2-negative advanced breast cancer."

1. Cardoso F, et al. Ann Oncol. 2020;31:1623-1649.
2. Herrera-Abreu MT, et al. Cancer Res. 2016;76:2301-2313.
3. Jhaveri KL, et al. Inavolisib or placebo in combination with palbociclib and fulvestrant in patients with PIK3CA-mutated, hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer: Phase III INAVO120 primary analysis. Abstract GS03-13, SABCS 2023, 5–9 December, San Antonio, TX, USA.

Endocrine therapy response provides information on need of adjuvant chemotherapy

Endocrine therapy response and standard gene expression testing should be considered when deciding whether to use chemotherapy or not in patients with HR-positive/HER2-negative, N0–1, early breast cancer, according to findings from the multicentre ADAPTcycle trial.

Previously, findings from the prospective WSG-ADAPT HR+/HER2- trial (NCT01779206) showed that the 5-year distant disease-free survival (DDFS) rate associated with adjuvant endocrine therapy alone was 97% among patients who were pre-menopausal (or ≤50 years), had HR-positive/HER2-negative, N0–1, early breast cancer, had an Oncotype DX risk score ≤25, and who had achieved a response to short pre-operative endocrine therapy [1]. In contrast, other prospective trials (TAILORx, RxPONDER, MINDACT) suggest that, in pre-menopausal patients, adjuvant chemo/endocrine therapy has benefits over adjuvant endocrine therapy alone, even in case of a favourable gene expression profile [2–4]. To investigate possible explanations for the difference between these trial results, subgroup analyses were performed on patients enrolled in the phase 3 ADAPTcycle trial (NCT04055493). Prof. Oleg Gluz (Breast Center Niederrhein, Germany) presented the results [5].

Data was available from 4,334 patients (1,368 pre-menopausal, 2,966 post-menopausal) with clinical intermediate- to high-risk HR-positive/HER2-negative early breast cancer. Response to endocrine therapy (i.e. Ki67pos ≤10% after 2–4 weeks of pre-operative endocrine therapy) was observed in 48.2% of pre-menopausal patients and in 72.7% of post-menopausal patients. The data showed that adding ovarian function suppression to treatment with tamoxifen or aromatase inhibitors significantly increased the likelihood of (pre-operative) response to endocrine therapy in pre-menopausal patients: 34.7% with tamoxifen alone, 55.7% with tamoxifen plus ovarian function suppression, and 76.4% with aromatase inhibition plus ovarian function suppression. The latter was similar to the response seen in post-menopausal patients previously treated with an aromatase inhibitor. This association between type of (pre-operative) endocrine therapy and endocrine response was observed both in patients with Oncotype DX risk score ≤25 or >25, and was independent of menopausal status.

Based on these results, Prof. Gluz concluded that "with optimal endocrine therapy, no difference in endocrine therapy-sensitivity is observed between pre- and post-menopausal patients. Therefore, endocrine response should be considered in addition to gene expression testing for routine decision-making regarding chemotherapy use in HR-positive/HER2-negative, N0–1, early breast cancer, to maximise the number of patients in whom chemotherapy can be spared."

1. Nitz U, et al. J Clin Oncol. 2022;40:2557-2567.
2. Sparano JA, et al. N Engl J Med. 2019;380:2395-2405.
3. Kalinsky K, et al. N Engl J Med. 2021;385:2336-2347.
4. Piccart M, et al. Lancet Oncol. 2021;22:476-488.
5. Gluz O, et al. Impact of age and ovarian function suppression (OFS) on endocrine response to short preoperative endocrine therapy (ET): Results from the multicenter ADAPTcycle trial (n=4,334). Abstract LBO1-05, SABCS 2023, 5–9 December, San Antonio, TX, USA.

monarchE: No predictive biomarkers revealed with molecular profiling

The survival benefit of abemaciclib was recently demonstrated in the phase 3 monarchE trial. According to the molecular profiling of tumour samples, this benefit is consistent across all breast cancer-intrinsic molecular subgroups, for both high and low Oncotype DX risk scores, and for all most prevalent genomic alterations with the exception of *MYC* amplification.

Patients with node-positive, early breast cancer are at high risk of recurrence (up to 30% at 5 years) [1]. Previously, the monarchE trial (NCT03155997) showed a sustained benefit of 2 years of adjuvant abemaciclib to endocrine therapy in patients with HR-positive/HER2-negative, node-positive, high-risk early breast cancer with a hazard ratio of 0.68 for both invasive disease-free survival and distant relapse-free survival [2]. Molecular profiling was preformed to evaluate potential biomarkers that might predict the benefit of adjuvant abemaciclib in this patient population. Prof. Nick Turner (The Royal Marsden Hospital and Institute of Cancer Research, UK) presented the results [3].

Molecular profiling was performed in a subcohort (n=1,400) of the intention-to-treat population of monarchE. Whole-exome sequencing on baseline was performed in 1,173 tumour samples, RNA expression (Oncotype DX) was determined in 1,190 tumour samples at baseline. Patient characteristics and abemaciclib benefit were consistent in these 3 subpopulations.

A consistent abemaciclib treatment benefit was found across all intrinsic molecular subtypes (luminal A, luminal B, HER2-enriched, and basal). Abemaciclib benefit was also achieved regardless of Oncotype DX risk score (≤25 vs >25). Of all oncogenic mutations and copy number alterations with a prevalence ≥9%, only *MYC* amplification was associated with less benefit of abemaciclib. "However, this observation is based on a small sample size," Prof. Turner noted.

Prof. Turner concluded that "abemaciclib demonstrated a consistent benefit across all breast cancer-intrinsic molecular subgroups, for both high and low Oncotype DX risk scores, and for all most prevalent genomic alterations with the exception of *MYC* amplification. Future work will include the integration of additional exploratory and more comprehensive genomic and transcriptomic analyses with clinical outcomes from monarchE."

1. Sheffield KM, et al. Future Oncol. 2022;18:2667-2682.
2. Harbeck NA, et al. Annal of Oncol. 2023;34(suppl 2):S1256.
3. Turner N, et al. Genomic and transcriptomic profiling of primary tumors from patients with HR+, HER2-, node-positive, high-risk early breast cancer in the monarchE trial. Abstract GS03-06, SABCS 2023, 5–9 December, San Antonio, TX, USA.

No predictive biomarkers found in PALLAS

PAM50 subtype does not predict 5-year invasive disease-free survival (IDFS) nor benefit of adjuvant palbociclib in patients with stage II–III HR-positive/HER2-negative early breast cancer, as was shown by biomarker analysis of the phase 3 PALLAS trial.

The use of CDK4/6 inhibitors combined with endocrine therapy is a standard-of-care for advanced/metastatic HR-positive/HER2-negative breast cancer, supporting the rationale to study CDK4/6 inhibition in the early breast cancer setting. Recently, the phase 3 PALLAS trial (NCT02513394) did not show survival benefit of 2 years of adjuvant palbociclib plus endocrine therapy versus endocrine therapy alone in patients with stage II–III HR-positive/HER2-negative early breast cancer [1]. A protocol-defined biomarker analysis (TRANS-PALLAS) was performed in which genomic subtype (PAM50 intrinsic subtype) from whole-transcriptome RNA sequencing was used for analysis of prediction and prognosis. Dr Daniel Stover (The Ohio State University, OH, USA) presented the outcomes [2].

From the total study population of 5,796 enrolled patients, tumour samples of 1,748 patients (889 in the palbociclib arm, 859 in the placebo arm) were included in TRANS-PALLAS. Risk for 5-year IDFS in the TRANS-PALLAS cohort appeared to be significantly lower relative to the rest of the PALLAS population (P=0.0013).

Based on PAM50 determination, 72.1% of the tumours in the TRANS-PALLAS cohort were luminal A, 2.6% normal, 10.5% luminal B, 4.1% HER2-like, and 3.8% basal-like subtype. Although heterogeneity was observed in 5-year IDFS by PAM50 subtypes (87.1% IDFS in luminal A vs 75.8% IDFS in basal-like subtype), no statistically significant association was observed (P=0.066). Likewise, heterogeneity between PAM50 subtypes was found regarding palbociclib benefit (HR 1.33 in basal-like vs HR 0.25 in HER2-like subtype), but this interaction was also not statistically significant (P=0.145).

Both PAM50 risk of recurrence (ROR) score and PAM50 proliferation score were prognostic for 5-year IDFS. In addition, a potential interaction was observed for PAM50 ROR and PAM50 proliferation score with palbociclib treatment benefit (P=0.051).

Based on these outcomes. Dr Stover concluded that "the biomarker analysis revealed a higher than anticipated percentage of luminal A tumours in the TRANS-PALLAS cohort, indicating a lower-risk distribution of cancers in this population. PAM50 subtype did not appear to be prognostic or predictive for palbociclib benefit."

1. Gnant M, et al. J Clin Oncol. 2022;40:282-293.
2. Stover D, et al. Protocol-defined biomarker analysis in the PALLAS adjuvant trial (AFT-05; ABCSG-42): Genomic subtype derived from RNA sequencing of HR+/HER2- early breast cancer. Abstract GS03-07, SABCS 2023, 5–9 December, San Antonio, TX, USA.

Triple-Negative Breast Cancer

Olaparib maintenance has favourable safety profile in TNBC

In patients with previously untreated, locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC), maintenance olaparib/pembrolizumab shows similar efficacy outcomes compared with chemotherapy/pembrolizumab but with a more favourable safety profile, the results from KEYLYNK-009 demonstrated.

Patients with previously untreated, locally recurrent inoperable or metastatic TNBC can benefit from treatment with pembrolizumab (plus chemotherapy), as results from the phase 3 KEYNOTE-355 study (NCT02819518) showed [1]. There is a need for tolerable and effective regimens in this setting that maintain the clinical benefits after induction therapy. In pre-clinical tumour models, PARP inhibitors activated the STING pathway, upregulated PD-L1 expression, and showed synergistic antitumor activity when combined with anti-PD-(L)1 antibodies, regardless of *BRCA* status [2]. In addition,

phase 1 trials with anti-PD-(L)1 antibodies plus PARP inhibitors have demonstrated tolerable safety and promising antitumor activity in patients with advanced TNBC [3,4].

The phase 2 KEYLYNK-009 study (NCT04191135) evaluated the efficacy and safety of maintenance pembrolizumab plus olaparib versus pembrolizumab plus chemotherapy for patients with locally recurrent inoperable or metastatic TNBC who had clinical benefit from induction with first-line pembrolizumab plus platinum-based chemotherapy. The trial enrolled 460 patients with locally recurrent inoperable or metastatic TNBC not previously treated in the metastatic setting. Participants were treated with platinum-based chemotherapy plus pembrolizumab for 4–6 cycles (induction); those who had benefit from induction therapy (response or stable disease, n=27) were 1:1 randomised to post-induction therapy with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. The primary endpoints were progression-free survival (PFS) and overall survival (OS). Prof. Hope Rugo (UCSF Helen Diller Family Comprehensive Cancer Center, CA, USA) presented the results [5].

At a median follow-up of 17 months, median PFS (from randomisation) was almost identical in both treatment groups: 5.5 months for participants treated with olaparib/pembrolizumab and 5.6 months for participants treated with chemotherapy/pembrolizumab (HR 0.98; 95% CI 0.72–1.33; P=0.4556). In addition, no difference in median OS was observed between the groups. In a subgroup analysis, a positive trend for PFS was observed for patients with *BRCA*-mutated tumours when treated with olaparib/pembrolizumab (HR 0.70; 95% CI 0.33-1.48).

A lower incidence of treatment-related adverse events was reported in participants receiving olaparib/pembrolizumab versus chemotherapy/pembrolizumab.

"Stopping chemotherapy in patients responding to induction therapy with chemotherapy/pembrolizumab and treating them with maintenance olaparib/pembrolizumab shows similar efficacy outcomes compared with continued chemotherapy/pembrolizumab, but with a more favourable safety profile," concluded Prof. Rugo.

1. Cortes J, et al. N Engl J Med 2022;387:217-226.
2. Wang Z, et al. Sci Rep. 2019;9:1853.
3. Domchek SM, et al. Lancet Oncol. 2020;21:1155-1164.
4. Vinayak S, et al. JAMA Oncol. 2019;5:1132-1140.
5. Rugo HS, et al. Pembrolizumab plus olaparib vs pembrolizumab plus chemotherapy after induction with pembrolizumab plus chemotherapy for locally recurrent inoperable or metastatic TNBC: randomized, open-label, phase 2 KEYLYNK-009 study. Abstract GS01-05, SABCS 2023, 5–9 December, San Antonio, TX, USA.

High pCR with neoadjuvant nivolumab/chemotherapy in stage I–II TNBC

A 12-week neoadjuvant, non-anthracycline chemotherapy regimen with nivolumab induced pathological complete response (pCR) rates over 50% in patients with stage I–II triple-negative breast cancer (TNBC), as was shown in a phase 2 Australian study.

For patients with stage II–III TNBC, neoadjuvant systemic therapy including immunotherapy is standard-of-care [1]. However, the optimal neoadjuvant regimen is not yet clear for all patients. Results from the GeparNuevo trial (NCT02685059) showed a higher pCR with a 2-week neoadjuvant immunotherapy 'lead-in' versus concurrent neoadjuvant chemo/immunotherapy [2]. Furthermore, the addition of immune checkpoint inhibition may allow shorter chemotherapy duration in selected patients.

The BCT1902/IBCSG 61-20 Neo-N trial aimed to investigate the strategies of a lead-in nivolumab monotherapy followed by chemotherapy versus concurrent nivolumab and chemotherapy. This phase 2 study enrolled 108 patients with stage I–IIB TNBC and randomised them 1:1 to receive either 1 dose of nivolumab followed 2 weeks later by nivolumab plus carboplatin/paclitaxel for 4 cycles (arm A) or 4 cycles of nivolumab plus carboplatin/paclitaxel followed by 1 dose of nivolumab, prior to surgery. The primary endpoint was pCR (ypT0/Tis ypN0). Dr Nicholas Zdenkowski (University of Newcastle, Australia) presented the first results [3].

No evidence was observed for differences in pCR rate between arms: 51% in arm A versus 55% in arm B. Multivariable logistic regression showed that high levels of tumour-infiltrating lymphocytes (TILs) might be a predictor of pCR (67% in high TILs vs 46% in low TILs; OR 2.47). In addition, expression of PD-L1 (≥1% SP-142) was associated with high pCR (71% in PD-L1 positive vs 33% in PD-L1 negative tumours).

"pCR rates in this study exceeded 50%, supporting a 12-week neoadjuvant, non-anthracycline chemotherapy regimen with nivolumab for patients with stage I–II TNBC. Patients with immune-enriched tumours, identified by high TILs or PD-L1 expression, had high pCR rates with just 12 weeks of treatment. However, this study did not support the hypothesis that lead-in nivolumab is associated with a pCR advantage," concluded Dr Zdenkowski. Event-free survival results are still immature.

1. Curigliano G, et al. Ann Oncol. 2023;34:970-986.
2. Loibl S, et al. Ann Oncol. 2019;30:1279-1288.
3. Loi S, et al. Randomized phase II study of neoadjuvant nivolumab (N) 2-week lead-in followed by 12 weeks of concurrent N+carboplatin plus paclitaxel (CbP) vs concurrent N+CbP in triple negative breast cancer (TNBC): (BCT1902/IBCSG 61-20 Neo-N). Abstract LBO1-03, SABCS 2023, 5–9 December, San Antonio, TX, USA.

Bilateral mastectomy and breast-conserving surgery have equal impact on breast cancer-specific mortality in pathogenic *BRCA1* carriers

Women with breast cancer with a pathogenic *BRCA1* variant who undergo bilateral mastectomy are significantly less likely to develop contralateral breast cancer. However, bilateral mastectomy is not significantly associated with a reduction in long-term breast cancer-specific mortality compared with breast-conserving surgery, as is shown by interim results from an international study.

Pathogenic variants in *BRCA1* and *BRCA2*, which are found in 3–4% of women with breast cancer, increase the risk of ipsilateral and contralateral breast cancer, as well as the risk of ovarian cancer. For this reason, many women with a *BRCA*-mutated unilateral breast cancer opt for bilateral mastectomy. However, it is not clear to what extent this operation impacts long-term breast cancer mortality. An international study, initiated at the University of Toronto, thus evaluated the differences in survival by surgical treatment in an international cohort of women with a *BRCA1* mutation and unilateral breast cancer. Dr Kelly Metcalfe (Women's College Research Institute Toronto, Canada) presented the interim results [1].

A total of 2,482 patients with stage I–III, *BRCA1*-mutated, unilateral breast cancer (mean age 43 years) were enrolled; 34.3% underwent breast-conserving surgery, 46% underwent unilateral mastectomy, and 19.7% underwent bilateral mastectomy.

Among those who had a unilateral mastectomy or breast-conserving surgery, the risk of contralateral breast cancer at 20 years was 27.5%. After experiencing a contralateral cancer, the hazard ratio for breast cancer-related death was 2.22 (95% CI 1.49–3.32; P<0.0001) compared with patients without contralateral breast cancer, regardless of age. Of all patients, 11.5% died of breast cancer during follow-up. The 15-year breast cancer-specific survival in the entire cohort was 82.9%. The survival was 78.7% for those who had a unilateral mastectomy, 86.2% for those who had breast-conserving surgery, and 88.7% for those who had bilateral mastectomies. Age was not correlated to survival.

"What we see from these data is that women with breast cancer with a pathogenic *BRCA1* variant who have bilateral mastectomy are significantly less likely to develop contralateral breast cancer. However, bilateral mastectomy is not significantly associated with a reduction in mortality compared with breast-conserving surgery," concluded Dr Metcalfe. "The cohort will require longer follow-up for definitive results, and additional analyses are ongoing."

1. Metcalfe KA, et al. Surgical treatment of women with breast cancer and a BRCA1 pathologic variant: an international analysis of the impact of bilateral mastectomy on survival. GS02-04, SABCS 2023, 5–9 December, San Antonio, TX, USA.

Living With & After Breast Cancer

Exercise programme improves quality of life for patients with metastatic breast cancer

Patients with metastatic breast cancer who took part in a 9-month structured exercise programme reported less fatigue and an improved quality of life compared with those who did not undergo the exercise programme, according to results from the PREFERABLE-EFFECT trial.

Breast cancer and its treatments can cause side effects such as fatigue, nausea, pain, and shortness of breath, which can decrease a patient's health-related quality of life. Previously, it has been proven that pre-operative exercise and exercise during adjuvant cancer treatment lead to improvements in cardiorespiratory fitness, strength, fatigue, and other patient-reported outcomes. Thus, the ASCO guideline advises that oncology providers should recommend regular aerobic and resistance exercise during active treatment with curative intent [1].

"However, at that moment, no evidence was available about the effect of exercise in patients with metastatic cancer," Prof. Anne May (University Medical Center Utrecht, the Netherlands) explained. To fill this gap in knowledge, the PREFERABLE-EFFECT trial (NCT04120298) aimed to investigate the effects of supervised and individualised exercise on fatigue and quality of life of patients with metastatic breast cancer [2].

A total of 357 patients with metastatic breast cancer and a life expectancy of more than 6 months were enrolled in the study. All participants in the trial received a physical activity tracker and generic exercise advice; 178 patients were randomly assigned to twice-weekly supervised exercise sessions, involving balance, resistance, and aerobic exercises, for 9 months. The control group was provided with usual care and a general exercise advise. The primary endpoints were cancer-related physical fatigue and health-related quality of life at 6 months.

At 3, 6, and 9 months, both quality of life and physical fatigue were significantly better in the patients who took part in the exercise programme than in the control patients. In addition, patients in the exercise group observed significantly less pain and dyspnoea.

Adherence to the exercise programme was good (77%).

Based on these findings, Prof. May suggested that "physicians and nurses should routinely recommend supervised exercise to patients with metastatic breast cancer; policymakers and insurance companies should ensure cost coverage for exercise programmes."

1. Ligibel JA, et al. J Clin Oncol 2022;40:2491-2507.
2. May AM, et al. Effects of a structured and individualised exercise program on fatigue and health-related quality of life in patients with metastatic breast cancer: the multinational randomized controlled PREFERABLE-EFFECT study. Abstract GS02-10, SABCS 2023, 5–9 December, San Antonio, TX, USA.

Fast menstrual resumption after interruption of endocrine therapy

Women who interrupt endocrine therapy to become pregnant almost all recover menses within 6 months. Younger age is associated with a shorter time to and a higher chance of pregnancy, as was shown by results of the POSITIVE trial.

The primary outcomes of the POSITIVE trial (NCT02308085) showed that, in women with previous HR-positive early breast cancer, temporary interruption of endocrine therapy to attempt pregnancy does not impact disease outcomes [1]. However, patient characteristics influencing menstrual resumption and time to pregnancy are not clear. In addition, uncertainty exists regarding the efficacy and safety of ovarian stimulation for fertility preservation and the use of assisted reproductive technologies to achieve pregnancy after endocrine therapy interruption. Therefore, the data of POSITIVE was further evaluated. Results were presented by Dr Hatem Azim (Monterrey Institute of Technology, Mexico) [2].

Of 516 patients included in POSITIVE, 273 (53%) reported amenorrhea at enrolment (which was after 18–30 months adjuvant endocrine therapy). Of these patients, 255 (94%) recovered menses within 1 year. A total of 368 (74%) patients reported at least 1 pregnancy. Age at enrolment was the only factor significantly associated with time to pregnancy. After 1 year, 64% of patients younger than 35 years were pregnant, compared with 38% of patients between 40–42 years; after 2 years this was 80% versus 50% (HR 0.40; 95% CI 0.29–0.56).

A total of 179 patients had undergone ovarian stimulation for embryo/oocyte cryopreservation at diagnosis and prior to enrolment, of whom 68 (37.9%) reported cryopreserved embryo transfer after enrolment. In addition, 215 patients reported using any assisted reproductive technology after enrolment, of whom 80 (37.2%) underwent ovarian stimulation for IVF or ICSI. Older age (>35 years) was significantly associated with a lower chance of pregnancy (OR 0.50; 95% CI 0.29–0.86). In addition, cryopreserved embryo transfer after enrolment was significantly associated with increased odds of becoming pregnant (OR 2.41; 95% CI 1.17–4.95). Ovarian stimulation did not influence breast cancer outcomes. "However, longer follow-up is needed," Dr Azim acknowledged.

In summary, most patients presenting with amenorrhea due to endocrine therapy resumed menses within 6 months after interrupting endocrine therapy. Younger age and cryopreserved embryo transfer were associated with, respectively, shorter time to pregnancy and higher pregnancy rates. "These data are of paramount importance for oncofertility counselling of young breast cancer patients," concluded Dr Azim

1. Partridge AH, et al. N Engl J Med 2023;388:1645-1656.
2. Azim HA, et al. Fertility preservation and assisted reproductive technologies (ART) in breast cancer (BC) patients (pts) interrupting endocrine therapy (ET) to attempt pregnancy. Abstract GS02-11, SABCS 2023, 5–9 December, San Antonio, TX, USA.

Pregnancy is not contraindicated in pathogenic *BRCA* carriers

More than 1 in 5 young women who are pathogenic *BRCA* carriers became pregnant after a diagnosis of early breast cancer. Their disease-free survival after pregnancy was comparable with those who did not become pregnant, as was shown by results of an international study.

A substantial proportion of young women with newly diagnosed breast cancer are interested in future fertility [1]. More than 12% of these young patients carry a germline pathogenic variant in the *BRCA1* or *BRCA2* genes [2]. Reproductive counselling of pathogenic *BRCA* carriers is complex, considering the psychological fear of transmitting the genetic variant to their offspring, the possible negative impact of deficient *BRCA* function on fertility potential, and the indication to undergo risk-reducing bilateral salpingo-oophorectomy at a young age. In addition, while several studies have demonstrated the safety of conceiving following breast cancer diagnosis and treatment, the evidence in pathogenic *BRCA* carriers is limited [3].

An international, multicentre, hospital-based, retrospective cohort study including young women with history of breast cancer and a pathogenic *BRCA* variant (NCT03673306) aimed to provide more solid evidence in the field. The study enrolled 4,732 patients, aged 40 years or younger, who were diagnosed with *BRCA1*- or *BRCA2*-mutated, stage I–III, invasive breast cancer. The primary endpoints were cumulative incidence of pregnancy after breast cancer and disease-free survival. Secondary endpoints were breast cancer-specific survival, overall survival, pregnancy, and foetal and obstetric outcomes. Dr Matteo Lambertini (University of Genova, Italy) presented the results [4].

After a median follow-up of 7.8 years, 659 of the participating women had at least 1 pregnancy, and 4,073 had no pregnancy. Cumulative incidence of pregnancy at 10 years was 22% (95% CI 21–24), with a median time from breast cancer diagnosis to conception of 3.5 years (IQR 2.2–5.3 years). In patients with HR-positive disease, cumulative incidence of pregnancy at 10 years was lower (18% vs 26%) and median time to pregnancy was longer (4.3 vs 3.2 years), compared with patients with HR-negative disease. Rates of pregnancy and foetal and obstetric complications were in line with the expectations in a population of women with similar age and no history of breast cancer.

Of note, no significant difference in disease-free survival was observed between women with or without a pregnancy after breast cancer (adjusted HR 0.99; 95% CI 0.81–1.20). The occurrence of pregnancy was associated with a lower rate of breast cancer-specific survival events (adjusted HR 0.60; 95% CI 0.40–0.88; P=0.009).

Dr Lambertini concluded that "this study showed that more than 1 in 5 young women who are pathogenic *BRCA* carriers became pregnant after a diagnosis of early breast cancer and that disease-free survival was comparable with those who did not become pregnant. Therefore, conceiving after proper treatment and follow-up for breast cancer should not be contraindicated in these women."

1. Ruddy KJ, et al. J Clin Oncol. 2014;32:1151-1156.
2. Copson ER, et al. Lancet Oncol. 2018;19:169-180.
3. Lambertini M, et al. J Clin Oncol. 2021;39:3293-3305.
4. Lambertini M, et al. Pregnancy after breast cancer in young women with germline BRCA pathogenic variants: results from an international cohort study. Abstract GS02-13, SABCS 2023, 5-9 December, San Antonio, TX, USA.