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PEER-REVIEWED CONFERENCE REPORT

Trastuzumab Deruxtecan Effective in Second-line and Neoadjuvant Setting

Trastuzumab deruxtecan has superior clinical efficacy in second-line and neoadjuvant settings, as shown by the DESTINY-Breast02/03 and TRIO-US B-12 TALENT trials.

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Baseline CTC Count Can Guide First-line Treatment

CTC count before treatment can guide treatment decisions between chemotherapy and single-agent endocrine therapy, the STIC CTC trial showed.

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Low-dose Tamoxifen Prevents Breast Cancer Recurrence

Low-dose tamoxifen for 3 years significantly lowers recurrence from non-invasive breast cancer for 10 years without adverse events, the TAM-01 trial showed.

read more on PAGE 12

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Letter from the Editor

Dear reader,

Please start the new year with our congress report of the 2022 San Antonio Breast Cancer Symposium.

Here are some key points:

- Checkpoint inhibitors are relevant in the neo-adjuvant treatment of early triple-negative breast cancer. Whether targeting both PD-L1 and Lag-3 (a new target) is superior to single targeting remains to be seen.
- Trastuzumab deruxtecan outperforms other current second-line treatments for metastatic, Her2-positive breast cancer and may represent an option in the neo-adjuvant setting.
- Combining endocrine treatment with a CDK4-antagonist is not only less toxic than combination chemotherapy – it actually provides superior disease recurrence-free survival.
- Genomic analysis may not only prevent overtreating patients with early breast cancer in terms of chemotherapy, but they may also give hints on the duration of adjuvant endocrine treatment. Other assessments may identify patients benefitting from the addition of checkpoint inhibition to neo-adjuvant treatments. A pre-therapeutic circulating tumour cell count might (further?) identify patients requiring adjuvant chemotherapy.
- What to do after the failure of initial CDK4-antagonist/endocrine first-line treatment in metastatic HR-positive breast cancer? Some studies give answers.
- Did you consider de-escalation in the adjuvant treatment of ductal carcinoma in situ? Maybe you will after reading about the TAM-01 study.

I'm sure you'll find some practice-changing features in our report.

Yours, sincerely,
Stefan Rauh

Biography

Dr Stefan Rauh is currently working as oncologist/haematologist in the oncology department of Centre Hospitalier Emile Mayrisch, Esch, Luxembourg. He is mainly involved in clinical work but also in research and teaching activities and is interested in public policy and international cooperation projects in oncology. He is a member of the ESMO Practicing Oncologist's Working Group since 2011 (chair 2014–2018), member of the ESMO Public Policy Committee, and has been an ESMO Executive Board member in 2015–2016. He is interested in survivorship of cancer patients and has published a clinician's handbook on this topic: Survivorship Care for Cancer Patients.

Conflict of Interest Statement:
Nothing to declare.

Early-Stage Breast Cancer

Anti-PD-1/anti-LAG-3 combination highly effective in HER2-negative breast cancer

Paclitaxel/cemiplimab/fianlimab is a highly effective combination as neoadjuvant therapy in both triple-negative breast cancer (TNBC) and HR-positive/HER2-negative breast cancer. In addition, the ImPrint signature identifies patients with the greatest benefit from checkpoint inhibitor-based therapy, results from I-SPY 2 showed.

Addition of anti-PD-1 therapy to neoadjuvant chemotherapy has shown to significantly improve the pathologic complete response (pCR) and event-free survival in patients with TNBC [1]. In melanoma, addition of an anti-LAG-3 antibody to anti-PD-1 therapy has shown to significantly improve progression-free survival [2]. The neoadjuvant I-SPY 2 trial (NCT01042379) evaluated the efficacy and safety of the addition of the anti-PD-1 antibody cemiplimab plus the anti-LAG-3 antibody fianlimab to neoadjuvant treatment with paclitaxel. Prof. Claudine Isaacs (Georgetown University Medical Center, DC, USA) presented the results [3].

A total of 76 patients with HER2-negative, treatment-naïve breast cancer received neoadjuvant treatment with paclitaxel/cemiplimab/fianlimab for 12 weeks; 350 patients treated with paclitaxel alone served as a control. Addition of cemiplimab/fianlimab to paclitaxel increased the pCR rate: 44% versus 21% (all patients), 53% versus 29% (TNBC), and 36% versus 14% (HR-positive/HER2-negative). In addition, the residual cancer burden class was downshifted across all subtypes. RCB 0/1 class was 37% in the control arm versus 64% in the study arm in all patients, 48% versus 70% for TNBC patients, and 29% versus 60% for HR-positive/HER2-negative patients.

ImPrint, a 53-gene signature of neoadjuvant immunotherapy response, has recently been developed [4]. In the I-SPY-2 trial, a positive ImPrint score was able to identify patients with the greatest benefit from checkpoint inhibitor-based therapy. The pCR rate in TNBC patients with a positive ImPrint score was 82% when treated with paclitaxel/cemiplimab/fianlimab compared with 32% in TNBC patients with a negative ImPrint score. The pCR rate in HR-positive/HER2-negative patients with a positive ImPrint score was 91% when treated with paclitaxel/cemiplimab/fianlimab compared with 28% in HR-positive/HER2-negative patients with a negative ImPrint score. Addition of fianlimab and cemiplimab to paclitaxel was associated with an increased incidence of immune-related adverse events as well as 3 cases (5%) of type 1 diabetes.

"Paclitaxel/cemiplimab/fianlimab is a highly-effective combination for neoadjuvant therapy in both TNBC and HR-positive/HER2-negative breast cancer," concluded Prof. Isaacs. "In addition, the ImPrint signature identified patients with the greatest benefit from checkpoint inhibitor-based therapy."

1. Schmid P, et al. N Engl J Med 2022;386:556–567.
2. Tawbi HA, et al. N Engl J Med. 2022;386:24–34.
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MammaPrint test predictive for benefit of extended endocrine therapy

In addition to predicting the benefit of adjuvant chemotherapy in patients with early breast cancer, the 70-gene MammaPrint test also predicts who benefits from extended endocrine therapy, results from the IDEAL and NSABP-B42 trials showed.

Previously, the MINDACT study (NCT00433589) showed that the 70-gene MammaPrint test is able to predict the benefit of adjuvant chemotherapy in patients with early breast cancer [1,2]. ER-positive patients with a MammaPrint low-risk score do not benefit from adjuvant chemotherapy and are thus preferably treated with an extended endocrine therapy. However, some low-risk patients may be more likely to derive benefits from extended endocrine therapy than others, depending on their risk of late recurrence. Therefore, genomic classifiers that predict the risks of late recurrence may assist with treatment decisions.

In the NSABP-B42 trail (NCT00382070), which compared 5 years of adjuvant letrozole with 10 years of letrozole, only patients with a MammaPrint 'low but not ultralow' score had a benefit of 10 years over 5 years of endocrine therapy [3]. To confirm these findings, data from the IDEAL trial (Eudra-CT 2006-003958-16) was analysed. In this trial, no superiority of 5 over 2.5 years (after the first 5 years) of endocrine therapy was

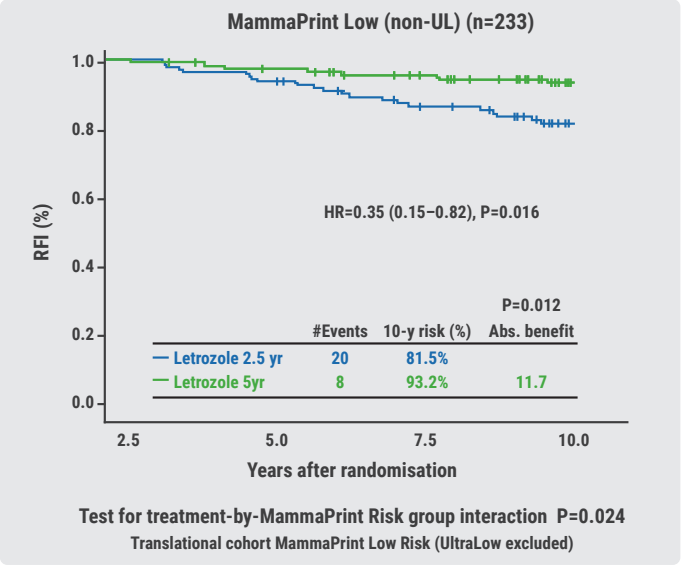
observed [4]. Recently, a subgroup analysis was performed based on MammaPrint risk scores. Dr Laura van 't Veer (UCLA, CA, USA) presented the results [5].

As expected, patients with a MammaPrint high-risk score did not benefit from extended endocrine therapy. However, in patients with a MammaPrint 'low but not ultralow risk' the recurrence-free survival, recurrence-free interval, and breast cancer-free interval were significantly improved with 5 years over 2.5 years of endocrine therapy (HR 0.32, 0.35, and 0.48, respectively; see Figure). This resulted in an absolute benefit of approximately 10 months for each of these endpoints.

The latest updates from the TAILOR-X trial (NCT00310180), with 12 years follow-up, also showed the risk of overtreatment [6]. Patients with early ER-positive/HER2-negative breast cancer with a mid-range Oncotype DX risk score (11–25) were better of skipping chemotherapy.

Based on these results, Dr van 't Veer concluded that MammaPrint is predictive of extended endocrine therapy benefit. MammaPrint high-risk patients can avoid extended endocrine therapy overtreatment, while MammaPrint 'low but not ultralow risk' patients significantly benefit from extended endocrine therapy.

Figure: MammaPrint low-risk tumours derive the most extended endocrine therapy benefit [5]



RFI, recurrence-free interval; non-UL, not ultralow.

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HR-positive/HER2-positive Breast Cancer: Trastuzumab-Deruxtecan

Trastuzumab deruxtecan effective in both second-line and neoadjuvant setting

In patients with ER-positive/HER2-positive breast cancer, the antibody-drug conjugate trastuzumab deruxtecan (T-DXd) has (superior) clinical efficacy in the second-line as well as in the neoadjuvant setting, results from the DESTINY-Breast02, DESTINY-Breast-03, and TRIO-US B-12 TALENT trials showed.

DESTINY-Breast02

In DESTINY-Breast01 (NCT03248492), T-DXd demonstrated robust activity in a pre-treated patient population with HER2-positive metastatic breast cancer, leading to regulatory approvals globally [1]. However, DESTINY-Breast01 was a modestly sized, single-arm, phase 2 trial. DESTINY-Breast02 (NCT03523585) was designed to confirm the results of DESTINY-Breast01 in a randomised, phase 3 trial. Dr Ian Krop (Yale Cancer Center, CT, USA) presented the primary results [2].

The study enrolled 608 patients with previously-treated, HER2-positive, unresectable or metastatic breast cancer. Over 70% of patients had 2 or 3 prior lines of therapy, all patients were pre-treated with trastuzumab and/or trastuzumab emtansine (T-DM1). Patients were randomised

2:1 to receive T-DXd or treatment of physicians' choice (TPC: trastuzumab/capecitabine or lapatinib/capecitabine). The primary endpoint was progression-free survival (PFS).

T-DXd appeared to be superior to chemotherapy-based treatment: the median PFS in the T-DXd arm was 17.8 months versus 6.9 months in the TPC arm (HR 0.359; P<0.000001). PFS rate at 24 months of follow-up was 42.2% versus 13.9% (see Figure). PFS benefit of T-DXd over TPC was observed in all pre-specified subgroups. The median overall survival (OS; key secondary endpoint) was 39.2 months compared with 26.5 months in the T-DXd arm and the TPC arm, respectively (HR 0.658; P=0.0021). In the TPC arm, 26% of patients received T-DXd in the post-trial setting. The objective response rate was 69.7% in the T-DXd arm versus 29.2% in the TPC arm (14% vs 5% complete response, respectively). No new safety signals were observed for T-DXd. Drug-related interstitial lung disease (any grade) was observed in 10.4% and interstitial lung disease grade ≥3 was observed in 1.2% of patients treated with T-DXd.

"DESTINY-Breast02 confirms the favourable benefit/risk profile of T-DXd in patients with advanced HER2-positive metastatic breast cancer, as previously demonstrated by DESTINY-Breast01," Dr Krop concluded.

DESTINY-Breast-03

The DESTINY-Breast03 trial (NCT03529110) compared the efficacy and safety of T-DXd with those of T-DM1 in patients with HER2-positive, unresectable or metastatic breast cancer that progressed on or after first-line treatment. A total of 524 patients were 1:1 randomised to receive T-DXd or T-DM1. The primary endpoint was PFS and the key secondary endpoint was OS. At the previously reported PFS interim analysis, in the T-DXd arm, the risk of disease progression or death was reduced by 72% [3]. Prof. Sara Hurvitz (David Geffen School of Medicine, CA, USA) presented the updated results based on 169 OS events [4].

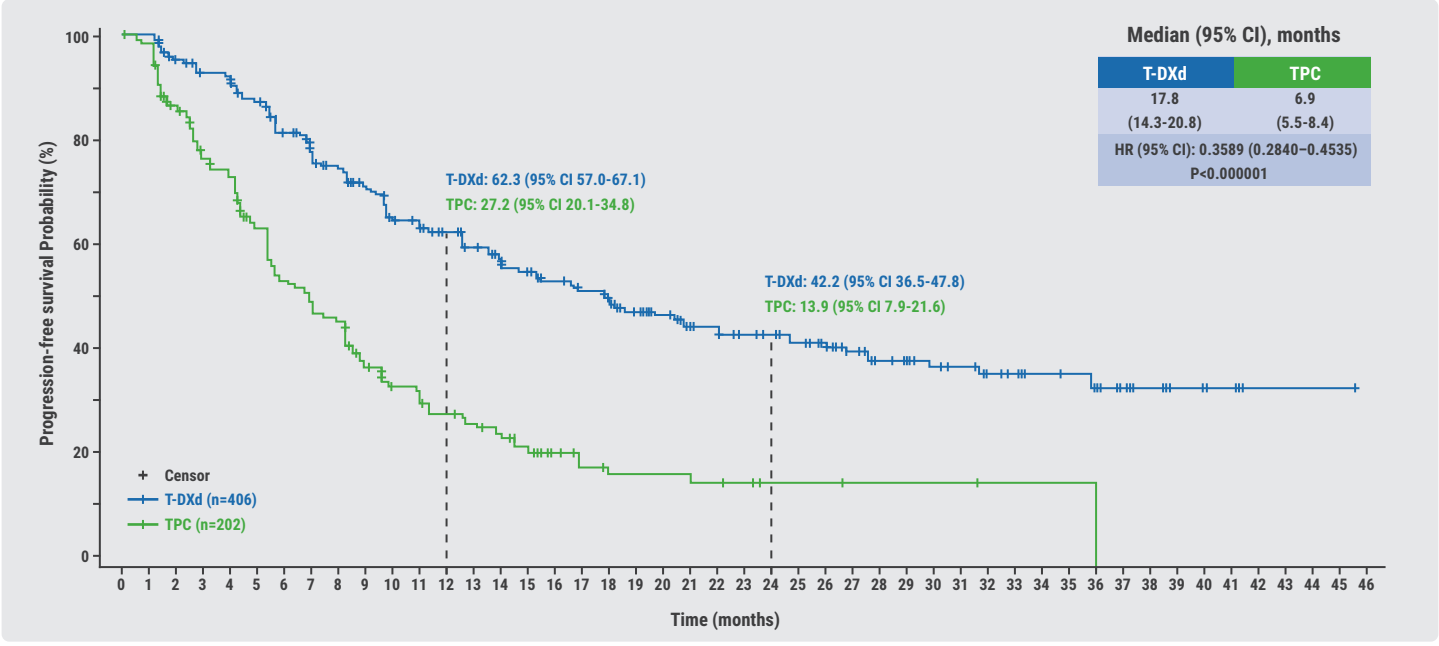
The median OS was not yet reached for either treatment arm. However, the HR was statistically significant in favour of T-DXd versus T-DM1 (HR 0.64; P=0.0037). The OS rates at 24 months were 77.4% and 69.9%, respectively. The updated median PFS was 28.8 months versus 6.8 months (HR 0.33; P<0.000001). The ORR was 78.5% for T-DXd and 35% for T-DM1 (21.1% vs 9.5% complete response, respectively).

Based on these results, Prof. Hurvitz concluded: "These updated results further support the use of T-DXd as the second-line standard-of-care in patients with HER2-positive metastatic breast cancer."

TRIO-US B-12 TALENT

In addition, Prof. Aditya Bardia (Harvard Medical School, MA, USA) presented the first results of the phase 2 TRIO-US B-12 TALENT trial (NCT04553770) [5]. This study evaluated the efficacy of T-DXd as a neoadjuvant treatment for patients

Figure: Progression-free survival of T-DXd by blinded independent central review [2]



T-DXd, trastuzumab deruxtecan; TPC, treatment of physicians' choice.

with localised HR-positive/HER2-low breast cancer. Because of the bystander effect of antibody-drug conjugates, HER2-low breast cancer is actionable by T-DXd. This was recently demonstrated in patients with metastatic, HER2-low breast cancer [6]. The efficacy of (neo-adjuvant) T-DXd in localised HER2-low breast cancer is not known. Given the cross-talk between ER and HER2, addition of endocrine therapy to T-DXd was also evaluated in this setting.

TRIO-US B-12 TALENT enrolled 58 patients with HR-positive/HER2-low, stage II or III breast cancer. Patients were randomised 1:1 to receive T-DXd (6 or 8 cycles) or T-DXd plus anastrozole followed by surgery. The primary objective was to evaluate the pathological complete response (pCR) in breast and lymph nodes. Secondary objectives were the objective response rate (ORR) and the change in HER2 and safety.

Of the patients treated with T-DXd, 5% achieved pCR (RCB-0) and 10% achieved near-pCR (RCB-I). The ORR in these patients was 68% (8% complete response). Of the patients treated with T-DXd plus anastrozole, 0% achieved pCR and 15% achieved near-pCR. The ORR in these patients was 58% (8% complete response). Of note, at data cut-off, surgical outcomes were pending for 24% of patients treated with T-DXd and 31% of patients treated with T-DXd plus anastrozole.

"These first results demonstrate preliminary evidence of clinical activity of neoadjuvant T-DXd in HR-positive/HER2-low localised breast cancer. Addition of endocrine therapy does not appear to enhance the efficacy of T-DXd," concluded Prof. Bardia.

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6. Modi S, et al. N Engl J Med. 2022;387:9–20.

HR-positive/HER2-negative Advanced Metastatic Breast Cancer

Benefit of adjuvant abemaciclib continues to deepen at longer follow-up

With additional follow-up, the benefit of adjuvant abemaciclib for patients with HR-positive/HER2-negative, node-positive, high-risk early breast cancer continues to deepen in magnitude after completion of treatment, results from the monarchE study showed.

Adjuvant therapy with the CDK4/6 inhibitor abemaciclib combined with endocrine therapy demonstrated significant improvement in invasive disease-free survival (IDFS) and distant recurrence-free survival (DRFS) in high-risk, HR-positive/HER2-negative, node-positive early breast cancer after 2 years of follow-up [1,2]. To evaluate the efficacy of abemaciclib after completion of the therapy, an analysis was completed 2 years after the primary outcome analysis. Prof. Stephen Johnston (The Royal Marsden NHS Foundation Trust, UK) presented the results of this analysis [3,4].

The phase 3 monarchE trial (NCT03155997) enrolled 5,637 patients who were 1:1 randomised to receive abemaciclib for 2 years plus endocrine therapy (≥5 years) or endocrine therapy alone. All patients were high-risk based on either clinical pathological features (Cohort 1, n=5120) or on the Ki-67 test (Cohort 2, n=517). After a median follow-up of 42 months, IDFS curves between the 2 treatment arms continued to widen in favour of abemaciclib. The absolute benefit of abemaciclib in IDFS 4-year rate was 6.4% compared with 2.8% after 2 years and 4.8% after 3 years of follow-up. HR for IDFS improved from 0.782 in the first year of follow-up to 0.602 after 4 years of follow-up.

Likewise, DRFS benefit of abemaciclib persisted beyond completion of abemaciclib: The absolute benefit of abemaciclib in DRFS 4-year rate was 5.9% compared with 2.5% after 2 years and 4.1% after 3 years of follow-up. HR for DRFS improved from 0.725 in the first year of follow-up to 0.581 after 4 years of follow-up. Addition of abemaciclib to endocrine therapy did improve IDFS and DFRS both in Cohort 1 and Cohort 2. Ki-67 score showed to be prognostic for a poor outcome, but not predictive of abemaciclib efficacy. Although the overall survival data are not yet mature, there was a numerical difference in deaths (157 vs 173) and number of patients with metastatic disease (125 vs 249) in favour of the abemaciclib arm.

"These data further support the addition of adjuvant abemaciclib to endocrine therapy for patients with HR-positive/HER2-negative, node-positive, high-risk early breast cancer," concluded Prof. Johnston.

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2. Harbeck N, et al. Ann Oncol. 2021;32:1571–1581.
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First-line ribociclib plus endocrine therapy outperforms combination chemotherapy

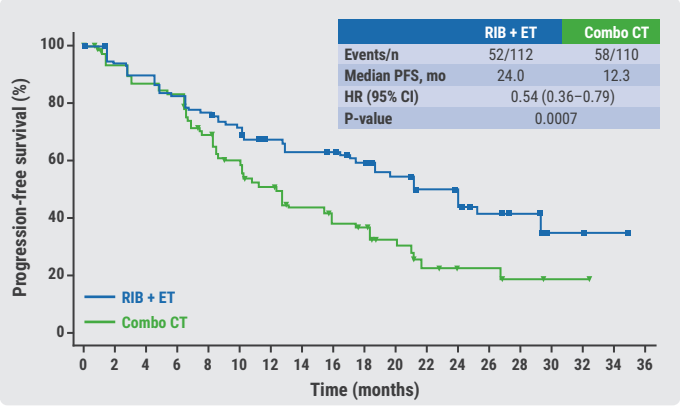
Results from phase 2 RIGHT Choice trial, the first prospective, head-to-head study comparing a CDK4/6 inhibitor plus endocrine therapy versus combination chemotherapy, showed superior progression-free survival (PFS) of ribociclib plus endocrine therapy over combination chemotherapy in patients with aggressive, HR-positive/HER2-negative advanced breast cancer.

In patients with advanced breast cancer with aggressive disease features features, like rapidly progressing or highly symptomatic disease, including life-threatening visceral crisis, combination chemotherapy is the standard-of-care [1]. The phase 2 RIGHT Choice trial (NCT03839823) compared the efficacy and safety of ribociclib plus endocrine therapy with combination chemotherapy in patients with aggressive, HR-positive/HER2-negative advanced breast cancer. Dr Yen-Shen Lu (National Taiwan University Hospital, Taiwan) presented primary results [2].

The trial randomised 222 patients with no prior systemic treatment for advanced breast cancer 1:1 to receive ribociclib plus letrozole or anastrozole or a physicians' choice combination chemotherapy (docetaxel/capecitabine, paclitaxel/gemcitabine, or capecitabine/vinorelbine). The primary endpoint was PFS.

After a median duration of 24 months, 45.5% of patients in the ribociclib arm and 23.6% of patients in the chemotherapy arm were still on treatment. The median PFS was 24.0 months for patients treated with ribociclib plus endocrine therapy versus 12.3 months for patients treated with combination chemotherapy (HR 0.54; P=0.0007; see Figure). PFS benefit of ribociclib plus endocrine therapy was observed across most subgroups of patients. The median time to treatment failure was longer in the ribociclib than the chemotherapy arm (18.6 vs 8.5 months; HR 0.45). Time to onset of response, overall response rate, and clinical benefit rate were similar in both treatment arms.

Figure: Ribociclib plus endocrine therapy has greater PFS benefit than combination chemotherapy [2]



RIB + ET, ribociclib plus endocrine therapy; Combo CT, combination chemotherapy; PFS, progression-free survival; mo, months.

Based on these first results, Dr Lu concluded that "first-line ribociclib plus endocrine therapy offers an efficacious and clinically meaningful treatment option for patients with aggressive, HR-positive/HER2-negative advanced breast cancer."

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Treatment options beyond CDK4/6 inhibition

Endocrine therapy plus a CDK4/6 inhibitor is the standard first-line treatment for HR-positive/HER2-negative metastatic breast cancer. However, tumours eventually develop hormonal resistance. An optimal therapy beyond CDK4/6 inhibition still has to be established. In a number of studies, the efficacy of different treatments beyond CDK4/6 inhibition were evaluated.

PACE

The phase 3 PACE trial (NCT03147287) was designed to explore the activity of continuation of CDK4/6 inhibitor beyond progression, with a change of endocrine therapy to fulvestrant, and to explore the addition of PD-L1 inhibition. Dr Erica Mayer (Dana-Farber Cancer Institute, MA, USA) presented the results [1].

PACE enrolled 220 patients with ER-positive/HER2-negative metastatic breast cancer who progressed on CDK4/6 inhibition plus endocrine therapy. Participants were randomised 1:2:1 to receive fulvestrant alone, fulvestrant/palbociclib, or fulvestrant/palbociclib/avelumab (triple therapy). The primary objective was to study the superiority of fulvestrant/palbociclib over fulvestrant alone.

Fulvestrant with palbociclib beyond progression did not improve PFS compared with fulvestrant alone: median PFS was 4.8 months for fulvestrant alone versus 4.6 months for fulvestrant/palbociclib (HR 1.11; P=0.62). However, triple therapy did numerically increase the median PFS to 8.1 months (HR vs fulvestrant: 0.75; P=0.23). The PFS rates at 12 months were 17.5%, 13.1%, and 35.6% for fulvestrant alone, fulvestrant/palbociclib, and triple therapy, respectively. In addition, an exploratory analysis of baseline mutation status showed favourable outcomes of fulvestrant/palbociclib versus fulvestrant alone in patients with a mutation in *PIK3CA*, *ERR1*, or *Rb1*.

"Among patients with HR-positive/HER2-negative metastatic breast cancer, combining palbociclib with fulvestrant beyond progression on prior CDK4/6 inhibition did not significantly improve PFS compared with using fulvestrant alone. However, the observed longer PFS when a PD-L1 inhibitor was added to fulvestrant/palbociclib is an intriguing signal in this population and deserves further study," Dr Mayer concluded.

EMERALD & SERENA-2

Both the EMERALD and SERENA-2 trials explored the efficacy of a next-generation, selective oestrogen-receptor degrader (SERD), elacestrant and camizestrant, respectively. Elacestrant has demonstrated a statistically significant improvement in PFS and a manageable safety profile compared with a single-agent endocrine therapy in the EMERALD trial (NCT03778931) [2].

EMERALD enrolled 477 patients with advanced/metastatic ER-positive/HER2-negative breast cancer who progressed on CDK4/6 inhibition. Participants were 1:1 randomised to receive elacestrant or standard-of-care (SOC) endocrine therapy (fulvestrant, anastrozole, letrozole, or exemestane). Prof. Virginia Kaklamani (University of Texas Health Sciences Center, TX, USA) presented the results from a post-hoc analysis of EMERALD on the impact of duration of prior CDK4/6 inhibition on PFS [3].

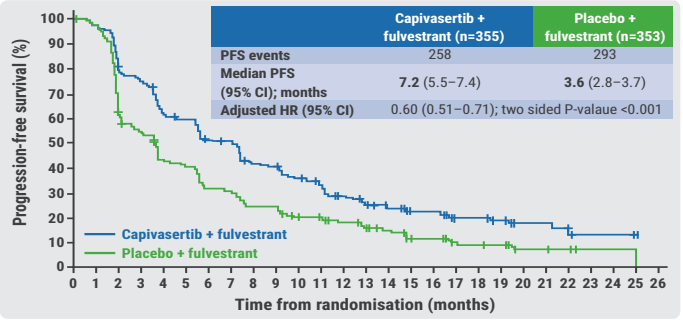
Longer duration of CDK4/6 inhibition proved to be associated with higher PFS rates, both in the elacestrant arm and the SOC arm. However, this was more pronounced in the elacestrant arm resulting in a larger absolute benefit of elacestrant with longer duration of CDK4/6 inhibition. The absolute benefit of elacestrant over SOC in the PFS rate at 18 months was 13.03% in patients with at least 6 month of CDK4/6 inhibition and 16.92% in patients with at least 18 months of CDK4/6 inhibition. The benefit of elacestrant over SOC was even more pronounced in patients with ESR1-mutated tumours. The absolute benefit of elacestrant over SOC in the PFS rate at 18 months was 20.70% in patients with at least 6 month of CDK4/6 inhibition and 30.68% in patients with at least 18 months of CDK4/6 inhibition.

Likewise, in the phase 2 SERENA-2 trial (NCT04214288), treatment with camizestrant after progression on CDK4/6 inhibition showed to be superior to treatment with fulvestrant. Again, the benefit of camizestrant over fulvestrant was more pronounced in patients with ESR1-mutated tumours [4].

CAPItello-291

Targeting the PI3K-AKT-mTOR intracellular pathway could be an alternative treatment option beyond CDK4/6 inhibition. The phase 3 CAPItello-291 trial (NCT04305496) evaluated the efficacy of capivasertib, an AKT inhibitor. A total of 708 patients with advanced HR2-positive/HER2-negative breast cancer who progressed after endocrine therapy (about 70% had CDK4/6 inhibition) were 1:1 randomised to receive capivasertib plus fulvestrant or placebo plus fulvestrant. The median PFS was significantly improved in the capivasertib arm compared with the placebo arm (7.2 vs 3.6 months; HR 0.60; P<0.001; see Figure) [5]. The overall survival data are not yet mature.

Figure: Investigator-assessed PFS for capivasertib versus placebo in the overall population [5]



PFS, progression-free survival.

VERITAC

Finally, result from the phase 1/2 VERITAC trial (NCT04072952) showed clinical activity of ARV-471, a selective, orally-administered PROTAC protein degrader that targets wildtype and mutant oestrogen receptor in patients with advanced HR-positive/HER2-negative, advanced/metastatic breast cancer who progressed after treatment with 1 or more lines of CDK4/6 inhibition [6]. The phase 3 VERITAC-2 trial (NCT05654623) will compare the efficacy of ARV-471 with fulvestrant beyond CDK4/6 inhibition.

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Triple-Negative Breast Cancer

ZNF689 deficiency promotes intratumour heterogeneity and resistance to immune checkpoint blockade in TNBC

In triple-negative breast cancer (TNBC), high intratumour heterogeneity (ITH) is associated with a poor response and resistance to immune checkpoint inhibitors. Efavirenz, a reverse-transcriptase inhibitor, showed to improve the efficacy of anti-PD-1 treatment in a mouse model.

TNBC is an aggressive disease characterised by remarkable ITH, which poses a significant therapeutic challenge [1]. However, the key determinants and underlying mechanisms of ITH in TNBC remain to be elucidated. To get more insight in this, both genetic and histologic ITH in 394 TNBC specimens were analysed. Dr Li-Peng Ge (Fudan University Shanghai Cancer Center, China) showed that genetic ITH and histologic ITH are highly correlated [2]. In addition, high ITH (genetic or histologic) is associated with immune-excluding tumour characteristics (low CD8, low tumour-infiltrating lymphocytes).

Results from 4 anti-PD-1-based clinical trials (NCT04613674, NCT04418154, NCT03805399, NCT04129996) demonstrated that high ITH is associated with poor efficacy outcomes. Transcriptomic analysis revealed *ZNF689* (a gene coding for Zinc Finger Protein 689) to be involved in ITH. Depletion of *ZNF689* in multiple mouse models significantly promoted ITH. In addition, it was shown that *ZNF689* eventually facilitated transcriptional silencing and that the reverse-transcriptase inhibitor efavirenz was able to decrease ITH. In a mouse model, efavirenz was able to augment anti-tumour immunity. Consistently, *ZNF689* expression positively correlated with favourable prognosis and responsiveness to anti-PD-1 treatment.

Based on these results, Dr Ge concluded that "*ZNF689* deficiency promotes ITH and targeting ITH with efavirenz can combat resistance to immune checkpoint inhibition in TNBC." To further explore the role of *ZNF689* and efavirenz in TNBC treatment, the phase 2, open-label, 3-arm Renaissance study (NCT05076682) recently started to test the efficacy and safety of the combination of efavirenz and anti-PD-1 therapy.

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Oestradiol represses anti-tumoural immune response to promote progression of brain metastases

Oestradiol promotes brain metastatic progression by stimulating an immunosuppressive brain microenvironment, results from a preclinical study showed. Therefore, oestrogen-depletion therapies could be used in combination with brain irradiation to promote a more effective anti-tumoural immune response.

Young age (<45 years) is a significant and independent predictor for the development of brain metastases in breast cancer, irrespective of the tumour subtype. In addition, the incidence of brain metastasis is higher in pre-menopausal women compared with post-menopausal women (53% vs 25%) [1]. Previously, it was shown that pre-menopausal levels of 17-β oestradiol (E2) promote brain metastasis of ER-negative breast cancer cells by inducing the secretion of pro-metastatic factors critical for early brain colonisation [2]. Ovariectomy in combination with the aromatase inhibitor letrozole prevented brain colonisation of TNBC human xenografts and murine models through paracrine activation of EGFR and TrkB, pathways involved in increased invasion and early tumour initiation [2].

Yet, it remains unknown to what extent E2-depleting therapies can decrease progression of established brain metastases in combination with current standard-of-care for brain metastasis (irradiation and immunotherapy). A study in mice was performed to assess how E2-depleting therapies alone or in combination with standard-of-care decrease the progression of existing brain metastases in TNBC. Dr Maria Contreras-Zarate (University of Colorado, CO, USA) presented the results [3].

The results showed that E2-withdrawal in combination with letrozole and radiation decreased brain metastatic burden significantly as compared with E2-treated mice, but not without radiation, suggesting that the effectiveness of E2 suppression to decrease progression of existing metastasis depends on the priming of the immune system by radiation. In line with this, no effects of E2 withdrawal in combination with letrozole and irradiation were observed in immunodeficient (NGS) mice. In addition, it was shown that E2 suppression activates immune-surveillance at early stages of brain colonisation and recruits T and B cells to the brain at later stages of metastatic progression.

"Our results support the hypothesis that oestradiol promotes brain metastatic progression by stimulating an immunosuppressive brain microenvironment," Dr Contreras-Zarate concluded. "Therefore, E2-depleting therapies like aromatase inhibitors and selective oestrogen modulators could be used in combination with brain irradiation to promote a more effective anti-tumoural immune response."

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3. Contreras-Zarate MJ, et al. Estradiol represses anti-tumoral immune response to promote progression of ER$^-$ brain metastases. Abstract GS5-07, SABCS 2022, 6–10 December, San Antonio, TX, USA.

Basic and Translational Research

Resistance to CDK4/6 inhibitors is likely due to expansion of pre-existing resistant clones

In vitro studies using DNA barcoded cell-lines demonstrated that resistance to CDK4/6 inhibitors is likely due to the expansion of pre-existing resistant clones, suggesting that targeting resistance upfront could delay the acquisition of clinical resistance.

Multiple mechanisms of acquired resistance to CDK4/6 inhibitors have been identified in clinical and pre-clinical studies [1]. It remains unknown if these mechanisms are pre-existing or acquired during treatment. In addition, the role of *ESR1* mutations in resistance to CDK4/6 inhibitors (plus endocrine therapy) is largely unknown, as well as if the mechanisms of resistance to different CDK4/6 inhibitors are disparate.

To get more insight, Dr Cristina Guarducci (Dana-Farber Cancer Institute, MA, USA) studied the clonal dynamics and mechanisms of resistance *in vitro* using a DNA barcoded, doxycycline-inducible *ERS1*-mutant MCF7 cell line [2]. These cells express the *Y537S ERS1*-mutated oestrogen receptor (on top of the wildtype receptor) when treated with doxycycline. Cellular barcoding is a technique in which individual cells are labelled with unique nucleic acid sequences, termed barcodes, so that they can be tracked through space and time [3].

Cells with or without a mutated oestrogen receptor were treated – in triplicates – with escalating doses of palbociclib or abemaciclib until resistance. Clustering of identical barcodes in the resistant cells indicated that resistance to palbociclib was associated with the selection of pre-existing subclones.

In addition, expression of the mutant oestrogen receptor was associated with the selection of different palbociclib-resistant subclones. *ESR1* mutation was also associated with an earlier and more heterogeneous clonal selection compared with the wildtype receptor. Resistance to abemaciclib was also associated with the selection of pre-existing subclones. However, in abemaciclib-resistant cells, oestrogen-receptor wildtype cells and oestrogen-receptor mutant cells had a high number of overlapping selected clones. Again, *ESR1* mutation was associated with an earlier – but not more heterogenous – selection of subclones.

The barcodes enriched in palbociclib-resistant and abemaciclib-resistant cells were different. This difference was more pronounced in the setting of oestrogen-receptor wildtype cells compared with oestrogen-receptor mutated cells. Functional studies showed that palbociclib-resistant cells retained sensitivity to abemaciclib, while abemaciclib-resistant cells were cross-resistant to palbociclib.

"Resistance to CDK4/6 inhibitors is likely due to the expansion of pre-existing resistant clones, suggesting that targeting resistance upfront could delay the acquisition of clinical resistance. The clonal selection during the acquisition of resistance to palbociclib and abemaciclib is different, highlighting the differences between these 2 CDK4/6 inhibitors," concluded Dr Guarducci.

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Baseline CTC count can guide first-line treatment in HR-positive/HER-negative metastatic breast cancer

A single assessment of the circulating tumour cell (CTC) count before the start of treatment can guide the treatment decision between chemotherapy and single-agent endocrine therapy in HR-positive/HER2-negative metastatic breast cancer, results from the STIC CTC trial showed.

An elevated number of CTCs (≥5/7.5 mL) is an adverse prognostic factor for progression-free survival (PFS) and overall survival (OS) in patients with metastatic breast cancer [1]. The phase 3, randomised STIC CTC trial (NCT01710605), run before the introduction of CDK4/6 inhibitors for HR-positive/HER2-negative metastatic breast cancer, showed that CTC count was non-inferior to the clinician's choice – with respect to PFS – to guide first-line treatment selection between chemotherapy and endocrine therapy [2]. Prof. François-Clément Bidard (Institut Curie, France) presented the OS data of the STIC CTC trial [3].

The trial enrolled 755 patients with HR-positive/HER2-negative metastatic breast cancer who could receive either endocrine therapy or chemotherapy as a first-line treatment, according to their physician. In all patients, a baseline CTC count was performed, before randomisation of the participants. Participants were randomised to treatment according to physicians' choice (standard arm) or treatment based on CTC count (CTC arm: endocrine therapy if CTC <5/7.5 mL [CTC-low], chemotherapy if CTC ≥5/7.5 mL [CTC-high]). The median follow-up was 57 months.

In the standard arm, 272 participants with a clinically low-risk profile (Clin-low) were allocated to endocrine therapy and 103 participants with a clinically high-risk profile (Clin-high) to chemotherapy. In the CTC arm, 239 CTC-low participants were allocated to endocrine therapy and 138 CTC-high to chemotherapy. In 463 participants, treatment of physician's choice was concordant with treatment based on CTC count (Clin-high/CTC-high, Clin-low/CTC-low). In 292 participants, there was discordance between physicians' choice and treatment based on CTC count (n=189 Clin-low/CTC-high; n=103 Clin-high/CTC-low).

In participants with concordance between physician's choice and CTC count-based therapy, there was no difference in the OS between the arms. However, participants with Clin-low/CTC-high treatment based on CTC count (chemotherapy) had a statistically significant and clinically meaningful survival benefit compared with treatment according to physician's choice (endocrine therapy) with a median OS of 51.8 versus 35.4 months (HR 0.53; P=0.001). Therefore, in these patients, chemotherapy should be the treatment of first choice. In contrast, patients with Clin-high/CTC-low treatment based on CTC count did not have a different outcome compared with treatment based on physician's choice. Therefore, in these patients, endocrine therapy should be the treatment of first choice.

Based on these results, Prof. Bidard concluded that "A single assessment of the CTC count before the start of treatment can guide the treatment decision between chemotherapy and single-agent endocrine therapy in HR-positive/HER2-negative metastatic breast cancer."

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Germline pathogenic variants for breast cancer also increase contralateral breast cancer risk

In women carrying a germline pathogenic variant for breast cancer, like *BRCA1*, *BRCA2*, or *CHEK2*, the risk for contralateral breast cancer is also increased, data from a sub-analysis of the CARRIERS study shows.

Currently, the precise influence of germline pathogenic variants in *ATM, BRCA1, BRCA2, CHEK2*, and *PALB2* as well as the effects of factors like age, menopausal status, race/ethnicity, and adjuvant endocrine therapy on the risk to develop contralateral breast cancer is not well defined. Previously, the CARRIERS study provided estimates of the prevalence and risk of the variants *ATM, BRCA1, BRCA2, CHEK2*, and *PALB2* in the US population [1]. In the same cohort, 15,104 women (14,444 non-carriers) treated with ipsilateral surgery for unilateral invasive breast cancer were followed to study the risk of these genetic variants on a subsequent contralateral breast cancer (CBC) event. Prof. Siddhartha Yadav (Mayo Clinic, MN, USA) presented the results [2].

After a median follow-up of 11 years, 801 CBC events were observed. The 10-year cumulative incidence of CBC (from first breast cancer diagnosis) was significantly increased in carriers versus non-carriers of *BRCA1* (23% vs 4.3%), *BRCA2* (4.3% vs 17%), and *CHEK2* (4.3% vs 8%), but not for carriers of *ATM* (4.3% vs 4.0%). For *PALB2* carriers, the 10-year cumulative incidence of CBC was only increased in patients with ER-negative first breast cancer (5.4% vs 19.7%).

In all patients but *ATM* carriers, the 10-year cumulative incidence of CBC was approximately 3 times higher in pre-menopausal patients compared with post-menopausal patients. CBC in carriers who were over 65 years at their first breast cancer diagnosis (n=153) was rare, with only 3 events at a median follow-up of 10 years. Race/ethnicity did not have any effect on CBC rates.

"The results of this study will aid in a more personalised approach to CBC risk management strategies in germline *ATM, BRCA1, BRCA2, CHEK2*, and *PALB2* pathogenic variant carriers based on relevant demographic and tumour characteristics," concluded Prof. Yadav.

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Low-dose tamoxifen still prevents recurrence from non-invasive breast cancer

Low-dose tamoxifen for 3 years significantly lowers recurrence from non-invasive breast cancer for 10 years without adverse events. Moreover, the low risk of death strengthens treatment de-escalation in DCIS, results from the TAM-01 trial showed.

Tamoxifen is effective in the adjuvant treatment of HR-positive breast cancer and for the prevention of breast cancer in at-risk women, including those with atypical ductal hyperplasia (ADH), lobular carcinoma *in situ* (LCIS), and ductal carcinoma *in situ* (DCIS). However, standard use of tamoxifen (20 mg/day for 5 years) is limited by its toxicity [1]. Previously, results from the phase 3 TAM-01 study (NCT01357772) showed that a low dose of tamoxifen (5 mg/day for 3 years) can halve the recurrence of breast intraepithelial neoplasia with limited toxicity [2]. Dr Andrea De Censi (Ospedali Galliera, Italy) now presented the 10 years of follow-up data from TAM-01 [3].

TAM-01 enrolled 500 patients with hormone-sensitive or unknown breast intraepithelial neoplasia, including ADH, LCIS, and DCIS who were randomised 1:1 to receive tamoxifen (5 mg/day) or placebo for 3 years. The cumulative incidence of neoplastic events after 10 years was 25 in the tamoxifen arm versus 41 in the placebo arm (HR 0.58; P=0.028) demonstrating a carry-over effect of low-dose tamoxifen. With respect to subgroups, a non-significant decrease of ipsilateral breast events (HR 0.68; P=0.227) and a significant decrease of contralateral breast events (HR 0.36; P=0.025) were observed. In the DCIS cohort (n=346), a 50% reduction (HR 0.50; P=0.02) of breast events was observed. The tumour characteristics of the breast neoplastic events were not different between the tamoxifen and placebo arm. Adverse events were not significantly increased in the tamoxifen arm versus the placebo arm.

Based on these results, Dr De Censi concluded that "Low-dose tamoxifen for 3 years significantly lowers recurrence from non-invasive breast cancer at 10 year without adverse events. Moreover, the low risk of death strengthens treatment de-escalation in DCIS."

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Endocrine interruption to pursue pregnancy does not impact short-term disease in breast cancer

Breast cancer patients who pause their endocrine therapy to try to get pregnant experienced short-term rates of breast cancer recurrence similar to women who do not pause therapy, according to results from the POSITIVE clinical trial.

Many young breast cancers survivors desire pregnancy. However, standard 5–10 years of adjuvant endocrine therapy compromises conception in women with hormone-positive disease. Although retrospective evidence shows that pregnancy after breast cancer does not worsen the disease outcome, regardless of HR status, women are often discouraged to get pregnant after breast cancer [1].

The POSITIVE trial (NCT02308085) prospectively evaluated outcomes of pregnancy after breast cancer and interruption of endocrine therapy to attempt pregnancy. The study enrolled 518 women (≤42 years) who had at least 18 and no more than 30 months of endocrine therapy for stage I–III HR-positive breast cancer and who desired to become pregnant. After enrolment, women had up to 2 years to attempt pregnancy, conceive, and breastfeed, including a 3-month washout period. Endocrine therapy resumption was strongly recommended after pregnancy to complete the full 5–10 years. The primary endpoint was breast cancer-free interval (BCFI). A cohort of 1,499 patients from the SOFT/TEXT trials were used as external controls [2]. Dr Ann Partridge (Dana-Farber Cancer Institute, MA, USA) presented the results [3].

The median time from breast cancer diagnosis to enrolment was 29 months and the median follow-up from enrolment was 41 months [4]. The cumulative incidence of both BCFI and distant relapse-free interval (DRFI) events at 3 years of follow-up were not statistically different in POSITIVE versus SOFT/TEXT: 8.9% versus 9.2% for BCFI and 4.5% versus 5.8% for DRFI (see Figure). In addition, no difference was observed in BCFI between women in the POSITIVE trial who became pregnant compared with women who did not become pregnant.

Of the 497 women who were followed for pregnancy status, 368 (74.0%) had at least 1 pregnancy, 317 (63.8%) had at least 1 live birth, with a total of 365 babies (15 sets of twins) born. Birth defects were low (2%) and not clearly associated with treatment exposure. At 48 months, 8% of patients had cancer recurrence or death before resuming endocrine therapy, 76% had resumed endocrine therapy, and 15% had not (yet) resumed endocrine therapy.

Based on these results, Dr Partridge concluded: "Temporary interruption of endocrine therapy to attempt pregnancy among women who desire pregnancy does not impact short-term disease outcomes. These data stress the need to incorporate patient-centred reproductive healthcare in the treatment and follow-up of young women with breast cancer."

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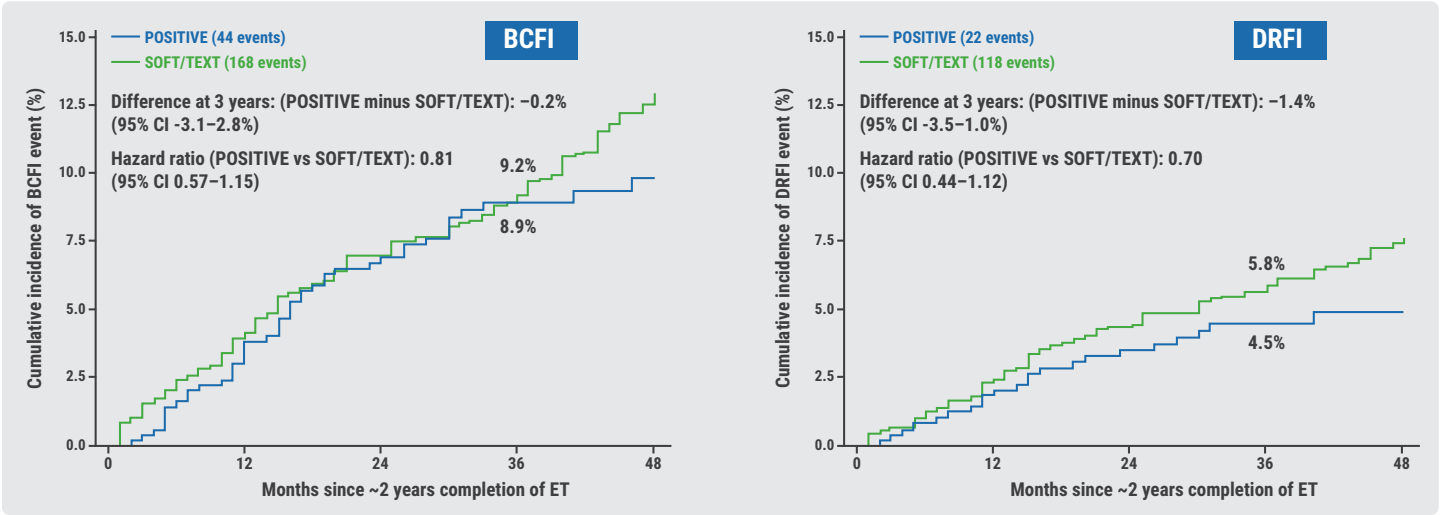
Figure: Cumulative incidence of BCFI and DRFI events in POSITIVE versus SOFT/TEXT trials [3]



BCFI, breast cancer-free interval; DRFI, distant relapse-free interval; ET, endocrine therapy.

Miscellaneous

Racial disparity in the tumour microenvironment

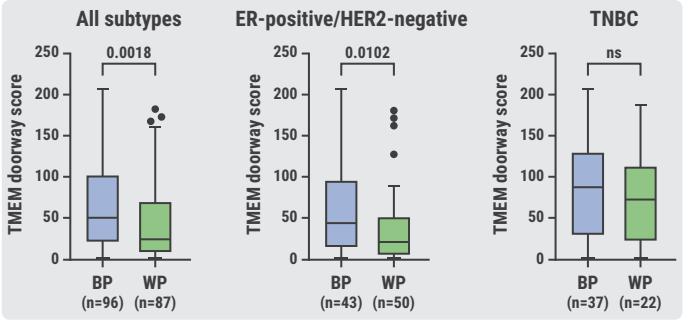
Residual tumours from Black patients with ER-positive/HER2-negative primary breast cancer treated with neoadjuvant chemotherapy have a higher score of a biomarker of distant metastatic recurrence than tumours from White patients.

Black patients with breast cancer have 40% higher death rates compared with White patients [1]. In line with this, Black race is associated with a higher risk of distant recurrence rate and a poorer survival in ER-positive/HER2-negative, but not in triple-negative breast cancer (TNBC) patients with residual disease after neoadjuvant chemotherapy [2].

Previous research showed that neoadjuvant chemotherapy can induce breast cancer metastasis by opening tumour microenvironment of metastasis (TMEM) doorways [3]. These TMEM doorways consist of three-cell structures in primary breast tumours in which an invasive tumour cell, partially inserted into a blood vessel wall, is bound to an endothelial cell and a macrophage. TMEM doorway density proves to be a prognostic marker for metastasis in breast cancer patients, especially in ER-positive/HER2-negative disease [4]. To evaluate the role of TMEM doorway density in the racial disparity in breast cancer outcomes, a retrospective study was done. Dr Burcu Karadal-Ferrena (Albert Einstein College of Medicine, NY, USA) presented the results [5].

The study included 183 patients (96 self-identified as Black, 87 as White) with HER2-negative disease and with residual disease ≥5 mm after neoadjuvant chemotherapy. Black patients had higher grade disease (76% vs 65% grade 3), higher rate of distant recurrence (49% vs 42%), and were more likely to undergo mastectomy (70% vs 62%), compared with White patients. Automated quantification of TMEM doorway density showed higher scores in ER-positive/HER2-negative Black patients compared with White patients (P=0.0102), but not in TNBC Black versus White patients (see Figure). In addition, a high TMEM doorway score was associated with worse disease recurrence-free survival in all ER-positive/HER2-negative patients, but not in TNBC patients.

Figure: TMEM doorway score higher in Black patients in the entire cohort and in the ER-positive/HER2-negative subtype [5]



TMEM, tumour microenvironment of metastasis; BP, Black patients; WP, White patients; TNBC, triple-negative breast cancer; ns, non-significant.

Based on these results, Dr Karadal-Ferrena concluded: "A high TMEM doorway score is an independent prognostic risk factor in patients with residual disease after neoadjuvant chemotherapy. Racial disparity in breast cancer outcomes may be due to a more pronounced increase in TMEM doorway density after neoadjuvant chemotherapy in Black patients." A limitation of the study, Dr Karadal-Ferrena said, was that neither TMEM doorway density at baseline nor the change in TMEM doorway score after neoadjuvant chemotherapy were evaluated.

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Chemo-endocrine therapy worse for cognition than endocrine therapy alone

Chemo-endocrine therapy has a greater negative effect on cancer-related cognitive impairment compared with endocrine therapy alone in both pre- and postmenopausal women, results from the RxPONDER PRO substudy showed.

Breast cancer treatment is associated with cancer-related cognitive impairment. However, the effect of endocrine therapy versus chemotherapy followed by endocrine therapy (chemo-endocrine therapy) is not well understood, nor is the impact of menopausal status [1,2]. Therefore, the impact of breast cancer treatment on cognition was explored in the RxPONDER PRO substudy (NCT01272037).

In this substudy, the 8-item Patient-Reported Outcomes Measurement Information System (PROMIS) Perceived Cognitive Function Concerns (PCF) questionnaire was completed at baseline and after 6, 12, and 36 months after randomisation of 568 patients (274 treated with chemo-endocrine therapy, 294 treated with endocrine therapy alone; 139 premenopausal, 429 postmenopausal). The primary endpoint of the substudy was the mean cognitive function score by treatment arm and menopausal status. Dr Irene Kang (City of Hope Orange County, CA, United States) presented the results [3].

In premenopausal participants treated with endocrine therapy alone, mean cognitive function score temporarily decreased after randomisation and returned to baseline value by 36 months. In contrast, in premenopausal patients treated with chemo-endocrine therapy the score decreased after randomisation and did not return to baseline value. The difference in longitudinal mean score between treatment arms (-3.02) was both statistically significant and clinically meaningful.

In postmenopausal participants treated with endocrine therapy alone, mean cognitive function score stayed stable during follow-up while in postmenopausal participants treated with chemo-endocrine therapy the score decreased after randomisation and did not return to baseline value. The difference in longitudinal mean score between treatment arms (-2.36) was statistically significant but not clinically meaningful.

The change in cognitive function was however heterogeneous. In both treatment groups and in both pre- and postmenopausal participants, most did not show a clinically meaningful worsening of cognitive function score during follow-up. Their score kept stable or was (clinically meaningful) better during follow-up. The odds of having worse cognitive function was highest in postmenopausal participants treated with chemo-endocrine therapy at 12 months after randomisation (OR 2.24; 95% CI 1.40–3.59).

"Chemo-endocrine therapy has a greater negative effect on cancer-related cognitive impairment compared with endocrine therapy alone both in pre- and postmenopausal women," concluded Dr Kang. "In addition, the effect of chemo-endocrine therapy seems to persist over time in a significant portion of patients."

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