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7–10 DECEMBER 2021

PEER-REVIEWED CONFERENCE REPORT

Newcomer: a Selective Estrogen Receptor Degrader

First results from EMERALD showed clinical benefit of elacestrant over standard endocrine therapy in patients with ER-positive/HER2-negative metastatic breast cancer who progress on CDK4/6 inhibitor plus endocrine therapy.

read more on PAGE 6

Neoadjuvant Pembrolizumab + Chemotherapy Benefits TNBC

KEYNOTE-522 showed improved outcome survival of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab versus neoadjuvant chemotherapy alone, in TNBC patients.

read more on PAGE 11

Genomic Guidance in HER-2 Negative Disease

Should metastatic HER2-negative patients be switched early to targeted agents, based on next generation sequencing? SAFIR02-BREAST gives important insights on the application and decision-making value of genomic testing.

read more on PAGE 18

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Contents

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Letter from the Editor

Dr Stefan Rauh

Dear colleagues,

Another year has passed – and so has the San Antonio Annual Breast Cancer Symposium 2021 (SABCS)! Here is our conference report, with more than 20 news-packed pages for you!

For the anthracycline believers (in adjuvant treatment), new support is presented and certainly new fuel for pros and cons discussions. Additionally, there is enough food for thought concerning the right adjuvant hormonal treatment in premenopausal women.

Don't consider anti-oestrogens old stuff. There's a newcomer: a **S**elective **E**strogen **R**eceptor **D**egrader (elacestrant). Concerning new substance classes, CDK7 inhibitors in hormone-sensitive, HER2-negative metastatic breast cancer also make an appearance.

Find further evidence with clear positioning of immune checkpoint inhibitors in neoadjuvant or metastatic triple-negative breast cancer (TNBC) – and more on conjugates in TNBC and HER2-positive disease.

Should metastatic HER2-negative patients be switched early to targeted agents, based on next generation sequencing? The SAFIR02-BREAST trial gives important insights on the use and decision-making, also based on ESMO's ESCAT score.

You knew it all along – they confirmed it: Metformin did not make it, again… No effect was detected in early breast cancer, but even though – after all those trials – it still did not work in cancer, it does just fine in diabetes!

As always, I just picked a few samples. Please take the time to go through our exciting report, yourself.

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

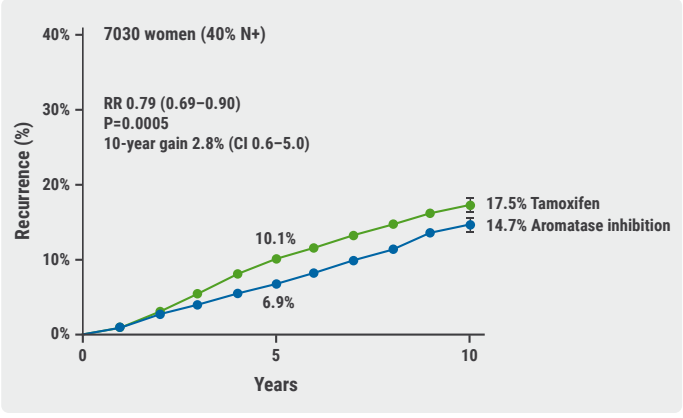
Aromatase inhibitors outperform tamoxifen in premenopausal women

In premenopausal women with early-stage breast cancer, adjuvant ovarian suppression can be combined with tamoxifen or an aromatase inhibitor. A meta-analysis of 4 randomised controlled trials showed that aromatase inhibition outperforms tamoxifen.

For women with early-stage, hormone receptor (HR)-positive breast cancer, adjuvant treatment with tamoxifen reduces their 15-year risk of breast cancer recurrence and death by about a third [1]. Aromatase inhibitors are even more effective than tamoxifen in postmenopausal women but, used alone, are ineffective in premenopausal women due to compensatory ovarian oestrogen production [2]. A meta-analysis was performed on individual patient data from 4 randomised-controlled trials, including 7,030 premenopausal women with oestrogen receptor (ER)-positive breast cancer: ABCGS12 (NCT00295646), TEXT (NCT00066703), SOFT (NCT00066690), and HOBOE (NCT00412022). All women received ovarian suppression or ablation and were randomised to receive either an aromatase inhibitor or tamoxifen for 3 years (in ABCSG12), or 5 years (in SOFT, TEXT, and HOBOE). Median follow-up was 8.0 years. Ms Rosie Bradley (University of Oxford, UK) presented the results [3].

The average annual rate of recurrence was 21% lower (RR 0.79; 95% CI 0.69–0.90; P=0.0005) for women allocated to an aromatase inhibitor compared with tamoxifen with an absolute 10-year gain in recurrence of 2.8% (14.7% vs 17.5%; see Figure).

Figure: Recurrence of breast cancer after aromatase inhibition or tamoxifen treatment [3].



The absolute 10-year gain in distant recurrence was 1.9% (10.2% vs 12.1%). In addition, no significant absolute gain in breast cancer mortality was observed (6.8% vs 7.2%). The greatest benefit from aromatase inhibition was seen in years 0–4 (RR 0.68; 99% CI 0.58–0.80) during the period when treatments differed, with no further benefit or loss of benefit in years 5–9 (RR 0.98; 99% CI 0.73–1.32). Limited follow-up data was available beyond year 10. In contrast to the findings of the meta-analysis of aromatase inhibition versus tamoxifen in postmenopausal women, aromatase inhibition appeared ineffective in N4+ disease.

Based on these results, Ms Bradley concluded that: "Using an aromatase inhibitor rather than tamoxifen, in premenopausal women receiving ovarian suppression, reduces the risk of breast cancer recurrence by about 20% compared with tamoxifen. Aromatase inhibition comes with more bone fractures, but no increase in non-breast cancer mortality."

1. Early Breast Cancer Trialists' Collaborative Group. Lancet 2011;378:771–784.
2. Early Breast Cancer Trialists' Collaborative Group. Lancet 2015;386:1341–1352.
3. Bradly R, et al. Aromatase inhibitors versus tamoxifen in pre-menopausal women with estrogen receptor positive early stage breast cancer treated with ovarian suppression: A patient level meta-analysis of 7,030 women in four randomised trials. GS2-04, SABCS 2021 Virtual Meeting, 7–10 December.

Concurrent taxane plus anthracycline most beneficial in reducing risk of breast cancer

A meta-analysis based on data of 18,203 early-stage breast cancer patients demonstrated anthracycline plus taxane to reduce the risk of breast cancer recurrence by 15% compared with taxane alone. The treatment did not significantly increase number of deaths from cardiovascular disease or leukaemia.

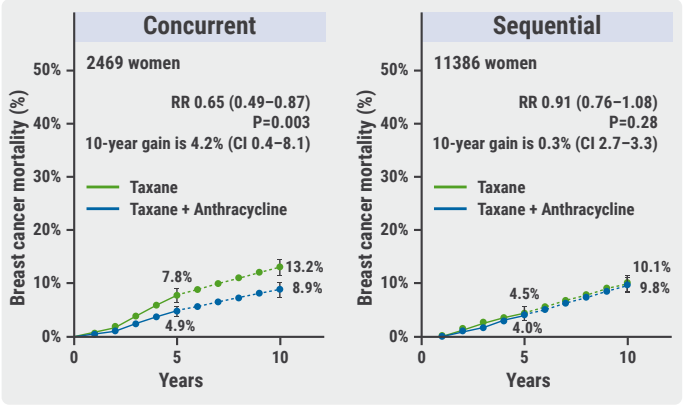
Anthracycline-containing and taxane-containing chemotherapy regimens reduce the rate of early-stage breast cancer recurrence by about a third compared with no chemotherapy. However, concerns about the increased risks of cardiac toxicity and leukaemia have resulted in treatment regimens without anthracycline. To better characterise the benefits and risks of anthracycline and taxane chemotherapy in early-stage breast cancer patients, a meta-analysis was performed based on individual data of 18,203 participants from 16 randomised-controlled trials starting before 2010.

All trials included at least 6 cycles of chemotherapy in each arm. Primary outcomes were recurrence and cause-specific mortality. Dr Jeremy Braybrooke (University Hospitals Bristol NHS Foundation Trust, UK) presented the results [1].

Three trials compared 6 courses of concurrent anthracycline, docetaxel, and cyclophosphamide versus docetaxel and cyclophosphamide alone; 8 trials compared sequential anthracycline plus taxane versus higher cumulative dose of docetaxel plus cyclophosphamide; 3 trials compared anthracycline plus taxane versus higher cumulative dose of taxane ± capecitabine; and 2 trials compared anthracycline plus taxane versus higher cumulative dose of taxane plus carboplatin.

Results show that patients treated with an anthracycline and taxane combination had on average 15% lower rates of breast cancer recurrence (RR 0.85; P=0.0003) than those receiving a taxane schedule without anthracycline, with an absolute reduction of 3.1% in 10-year recurrence (16.4% vs 19.0%). The 10-year risk of death from breast cancer was reduced by 1.6% (10.4% vs 12.0%; RR 0.87; P=0.02). The proportional reduction in recurrence was greatest in the 6 trials of concurrent anthracycline, docetaxel, and cyclophosphamide versus docetaxel plus cyclophosphamide (RR 0.58). By contrast, in trials of sequential anthracycline plus taxane versus the higher cumulative dose of docetaxel plus cyclophosphamide, no significant benefit from anthracycline was detected (RR 0.92). Also for breast cancer mortality, concurrent anthracycline plus taxane (vs taxane alone RR 0.65; 95% CI 0.49–0.87; P=0.003) outperformed sequential anthracycline plus taxane (vs taxane alone RR 0.91; 95% CI 0.76–1.08; P=0.28; see Figure).

Figure: Breast cancer mortality in concurrent (left) versus sequential (right) treatment [1].



No significant increases in deaths without recurrence or death from cardiovascular disease or leukaemia were observed, though longer follow-up is needed to fully assess the risks. Individual patient level data on toxicity and/or quality of life were not available.

"This meta-analysis demonstrates that the addition of anthracycline to taxane chemotherapy, compared with taxane alone, reduced the risk of breast cancer recurrence by 15% with larger proportional reductions in trials of concurrent anthracycline compared with sequential anthracycline. In addition, anthracycline did not significantly increase death from cardiovascular disease or leukaemia," summarised Dr Braybrooke.

1. Braybrooke J, et al. Taxane with anthracycline versus taxane without anthracycline: An individual patient-level meta-analysis of 16,500 women with early-stage breast cancer in 13 randomised trials. GS2-06, SABCS 2021 Virtual Meeting, 7–10 December.

Reduced risk of recurrence with ovarian suppression plus tamoxifen/exemestane

An updated analysis of 2 randomised trials – SOFT and TEXT – showed long term persistence of benefits of ovarian suppression plus endocrine therapy (exemestane or tamoxifen) versus tamoxifen alone for premenopausal women with hormone receptor (HR)-positive breast cancer.

In the SOFT (NCT00066690) trial, 3,066 premenopausal women with HR-positive early breast cancer were randomised to 5 years of adjuvant tamoxifen alone or to ovarian suppression treatment (OFS) plus either tamoxifen or the aromatase inhibitor exemestane. TEXT (NCT00066703; n=2,672) had a similar design but without a single-agent tamoxifen arm. About 2,500 women did not receive additional chemotherapy. In a previous combined analysis of these studies after 5 years of follow-up, adjuvant treatment with exemestane plus OFS was shown to outperform tamoxifen plus OFS [1]. Now, Dr Meredith Regan (Dana-Farber Cancer Institute, MA, USA) presented the updated results after a longer follow-up [2].

After 12 to 13 years of follow-up, the distant metastasis-free survival rates were 88.4% with exemestane plus OFS and 86.6% with tamoxifen plus OFS (HR 0.83; P=0.03). The overall survival rates were 90.1% versus 89.1%, a non-significant difference. Tamoxifen alone, meanwhile, led to a 12-year distant metastasis-free survival rate of 84.8% and a 12-year overall survival rate of 86.8%. Low-risk patients who received no chemotherapy had a 12-year overall survival rate exceeding 95%, regardless of the endocrine strategy, including tamoxifen alone. A subgroup analysis showed that patients younger than 35, and those who received neoadjuvant chemotherapy prior to enrolment, benefited most from OFS. Within those

2 subgroups, tamoxifen plus OFS led to a 10% absolute improvement in 12-year overall survival versus tamoxifen alone, and the exemestane plus OFS combination increased the absolute difference versus single-agent tamoxifen to 15%.

"Meaningful relative reductions in distant recurrence and death persist with longer follow-up for use of ovarian suppression with either endocrine therapy versus tamoxifen alone," said Dr Regan. "Absolute reductions are more substantial for those at higher risk, on the order of a 10% reduction in death, emphasising appropriate selection of patients to receive ovarian suppression. Notably, for those patients with low clinical-risk features who did not receive chemotherapy, the longer follow-up continues to support the use of tamoxifen alone," concluded Dr Regan.

1. Pagani O, et al. N Engl J Med 2014;371:107–118.
2. Regan MM, et al. Randomized comparison of adjuvant aromatase inhibitor exemestane (E) plus ovarian function suppression (OFS) vs tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): update of the combined TEXT and SOFT trials. GS2-05, SABCS 2021 Virtual Meeting, 7–10 December.

Metformin does not improve outcomes in patients with early-stage breast cancer

The phase 3 CCTGMA.32 trial showed no benefit of metformin in both patients with hormone receptor (HR)-positive and HR-negative moderate/high risk, early-stage breast cancer.

Clinical and epidemiologic evidence has linked hyperinsulinemia, insulin resistance, obesity, and diabetes to poor breast cancer outcomes. Metformin is an inexpensive, widely available, and well-tolerated drug that promotes modest weight loss and lowers insulin. In addition, metformin is a potential anti-cancer agent; indirectly by lowering the circulating insulin levels and directly by activating adenosine monophosphate-activated protein kinase (AMPK) [1]. CCTGMA.32 (NCT01101438) is a phase 3, randomised, double-blind, placebo-controlled adjuvant trial of metformin versus placebo in early-stage breast cancer. Dr Pamela Goodwin (Lunenfeld-Tanenbaum Research Institute, Canada) presented the results [2].

After standard therapy, 3,649 non-diabetic patients were randomised to metformin (850 mg twice daily, 5 years) or placebo. After the second interim analysis (median follow-up of 29.5 months), intervention was stopped for patients who were HR-negative (n=1,116). In HR-positive patients, the incidence of both invasive disease-free survival (IDSF) events and overall survival (OS) events were evenly distributed between both treatment arms at 96 months of follow-up (IDSF: HR 1.01; 95% CI 0.84–1.21; P=0.93; OS: HR 1.10; 95% CI 0.86–1.41; P=0.47).

"Therefore, metformin should not be used as an adjuvant breast cancer treatment in this population," concluded Dr Goodwin. "Of note, this recommendation should not be extrapolated to the use of metformin to treat diabetes in breast cancer patients."

1. Goodwin PJ, et al. Clin Oncol. 2009;27:3271–3273.
2. Goodwin PJ, et al. CCTGMA.32, a phase III randomized double-blind placebo controlled adjuvant trial of metformin (MET) vs placebo (PLAC) in early breast cancer (BC): Results of the primary efficacy analysis (clinical trials.gov NCT01101438). GS1-08, SABCS 2021 Virtual Meeting, 7–10 December.

Omitting sentinel lymph node biopsy improves arm symptoms

Patients with early-stage breast cancer have better quality of life outcomes when forgoing a sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND), results from the INSEMA trial showed. Patients had improved arm symptoms and functioning with omitting SLNB versus ALND.

Despite increasing evidence disfavouring ALND for loco-regional control, it remains part of the guidelines for breast cancer treatment. In an attempt to re-evaluate standard local therapy, the INSEMA trial (NCT02466737) was designed to assess non-inferiority of avoiding SLNB or completion ALND (cALND) in early-stage, clinically node-negative breast cancer patients. First, 5,154 patients were randomised 1:4 to no SLNB and SLNB. Patients with pN1a(sn) metastasis in the SLNB arm were 1:1 randomised to either SLNB alone (no further surgery) or cALND. Primary outcome data are expected to be complete in 2024. Patient-reported outcomes were assessed at baseline as well as at 1, 3, 6, 12, and 18 months after final axillary surgery. Prof. Bernd Gerber (University of Rostock, Germany) presented the results [1].

Of 4,124 patients undergoing a SLNB, 485 patients were randomised between SLNB alone and cALND. Overall, recruited patients presented with low-risk breast cancer. All quality-of-life baseline parameters were well-balanced between arms. There were significant and persistent differences for the breast symptoms and arm symptoms scores favouring the no SLNB group in all post-baseline assessments. However, these differences were clinically meaningful only for the arm symptoms score (BRAS). In particular, lower pain and arm or shoulder scores, swelling in arm or hand, and arm mobility favoured no SLNB over SLNB in the first randomisation (P<0.001). In addition,

in patients who underwent a second randomisation, there were significant and clinically meaningful differences for the BRAS scores, which were better in the SLNB group compared with the cALND group.

"This first randomised trial investigating the omission of SLNB in clinically node-negative patients shows that omitting SLNB improves arm symptoms with no relevant differences in other quality of life scales. In addition, in patients who underwent SLNB, omitting cALND improved arm symptoms," concluded Prof. Gerber.

1. Gerber B, et al. Patient-reported outcomes (PROs) for the intergroup sentinel mamma study (INSEMA, GBG75, ABCSG43): Persistent impact of axillary surgery on arm and breast symptoms in early breast cancer. GS4-03, SABCS 2021 Virtual Meeting, 7–10 December.

HR-positive/HER2-negative Breast Cancer

Addition of palbociclib to standard endocrine therapy does not improve outcome in adjuvant treatment

Although adjuvant therapy with CDK4/6-inhibitors has shown to benefit patients with advanced/metastatic hormone receptor (HR)-positive/HER2-negative breast cancer, the final analysis of the PALLAS trial showed no benefit of adjuvant palbociclib for patients with early HR-positive/HER2-negative breast cancer.

The use of CDK4/6 inhibitors combined with endocrine therapy is a standard of care for advanced HR-positive/HER2-negative breast cancer, supporting the rationale to study CDK4/6 inhibition in the early breast cancer setting. PALLAS (NCT02513394) is a randomised, phase 3, open-label trial in which patients with stage 2–3 HR-positive/HER2-negative early breast cancer were randomised to receive either 2 years of palbociclib with adjuvant endocrine therapy or endocrine therapy alone. A total of 5,761 patients (median age 52 years, range 22–90) were enrolled; 17.6% had stage 2A disease and 82.1% stage 2B/3. Of all randomised patients, 82.5% had received prior (neo)adjuvant chemotherapy. After a protocol-planned, second interim analysis in May 2020, the study crossed the futility threshold [1]. Now, Prof. Michael Gnant (Medical University of Vienna, Austria) presented the results of the final analysis of PALLAS [2].

After a median follow-up of 31 months, invasive disease-free survival (iDFS) was similar between the 2 arms, with 3-year iDFS of 89.3% for palbociclib plus endocrine therapy and 89.4% for endocrine therapy alone (HR 0.96; 95% CI 0.81–1.14). Subgroup analyses revealed no significant interactions between treatment effect and other factors (including risk category).

"With the full number of events, this analysis of the PALLAS trial shows that the addition of 2 years of palbociclib to ongoing adjuvant endocrine therapy does not improve survival endpoints for patients with stage 2–3 HR-positive/HER2-negative early breast cancer," concluded Prof. Gnant.

1. Mayer EL, et al. Lancet Oncol. 2021; 22: 212-222.
2. Gnant M, et al. Adjuvant palbociclib in HR+/HER2- early breast cancer: Final results from 5,760 patients in the randomized phase III PALLAS trial. GS1-07, SABCS 2021 Virtual Meeting, 7–10 December.

The SERD elacestrant improves outcomes for patients unresponsive to endocrine therapy

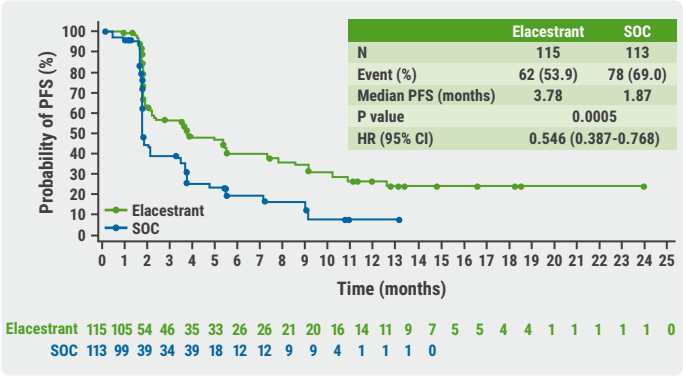
According to the first results of the EMERALD trial, elacestrant shows clinical benefit over standard endocrine therapy in patients with oestrogen receptor (ER)-positive/HER2-negative metastatic breast cancer who progress on CDK4/6 inhibitor plus endocrine therapy.

At the moment, endocrine therapy plus CDK4/6 inhibitor is the mainstay for the management of ER-positive/HER2-negative metastatic breast cancer. However, most patients eventually experience disease progression, including development of *ESR1* mutations (mESR1). Elacestrant, an oral selective oestrogen receptor degrader (SERD), demonstrated preclinical and clinical activity in a phase 1 trial in ER-positive metastatic breast cancer, including responses in patients with prior fulvestrant, CDK4/6 inhibitor, and mESR1 tumours, thus forming the rationale for the phase 3 EMERALD trial (NCT03778931) [1].

EMERALD enrolled 477 postmenopausal patients (228 with mESR1) with ER-positive/HER2-negative metastatic breast cancer who had received 1–2 prior lines of endocrine therapy and ≤1 line of chemotherapy in the metastatic setting, and who had prior progression on endocrine therapy plus a CDK4/6 inhibitor. Patients were randomised 1:1 to elacestrant (400 mg orally daily) or standard of care (investigator's choice of fulvestrant or an aromatase inhibitor). Dr Aditya Bardia (Massachusetts General Hospital, MA, USA) presented the results [2].

A 30% reduction in the risk of progression in the elacestrant arm in all patients was measured (HR=0.697; P=0.0018) and a 45% reduction in the risk of progression in patients with mESR1 (HR=0.546; P=0.0005; see Figure). Progression-free survival rate at 12 months was 22.3% with elacestrant versus 9.4% with standard of care in all patients and 26.8% versus 8.2% in the mESR1 subgroup. For both endpoints, results in key prespecified subgroups – including visceral metastases, number of prior lines of therapy, and pre-treatment with fulvestrant – were consistent with the overall outcome. The prespecified interim overall survival analysis planned at the time of the final progression-free survival analysis demonstrated a trend in favour of elacestrant in all patients and in patients with mERS1 (HR=0.751 and 0.592, respectively).

Figure: Probability of progression-free survival for elacestrant versus standard of care in patients with *ESR1*-mutatedtumours [2].



PFS, progression-free survival; SOC, standard of care

"Elacestrant is the first oral selective oestrogen receptor degrader to demonstrate a statistically significant and clinically meaningful improvement of progression-free survival in patients with ER-positive/HER2-negative metastatic breast cancer in the second-line and third-line settings, including for patients whose tumours harbour *ESR1* mutations," said Dr Bardia.

1. Bardia A, et al. J Clin Oncol 2021;39:1360–1370.
2. Bardia A, et al. Elacestrant, an oral selective estrogen receptor degrader (SERD), vs investigator's choice of endocrine monotherapy for ER+/HER2- advanced/metastatic breast cancer (mBC) following progression on prior endocrine and CDK4/6 inhibitor therapy: Results of EMERALD phase 3 trial. GS2-02, SABCS 2021 Virtual Meeting, 7–10 December.

Consistent overall survival benefit of ribociclib in advanced breast cancer

In 3 trials, addition of ribociclib to endocrine therapy improved overall survival in postmenopausal patients with locally advanced/metastatic hormone receptor (HR)-positive/HER2-negative breast cancer. Exploratory analyses now demonstrated consistent overall survival benefit in several subgroups of patients.

Addition of the CDK4/6 inhibitor ribociclib to endocrine therapy significantly improves progression-free and overall survival in patients with locally advanced/metastatic HR-positive/HER2-negative breast cancer, as was shown in the phase 3 MONALEESA-2, -3, and -7 trials (NCT01958021, NCT02422615, NCT02278120) [1–3]. Based on data from these 3 phase 3 trials, 2 retrospective, exploratory analyses of the overall survival were done in subgroups of patients.

Prof. Lisa Carey (University of North Carolina School of Medicine, NC, USA) presented results of the association of intrinsic subtypes with overall survival using tumour samples pooled from all 3 trials [4]. The intrinsic subtyping was based on the gene expression profile of the tumour samples. Of 997 tumour samples that were analysed, 54.4% appeared to be Luminal A-type, 27.9% Luminal B-type, 14.7% HER2-enhanced, and 3.0% basal-like. Overall survival data were consistent in the intent-to-treat population (n=2,066) and the biomarker population (n=997). Intrinsic subtype was prognostic for overall survival, both with or without ribociclib: Luminal A>Luminal B>HER-enhanced>basal-like. In all subtypes but basal-like, ribociclib improved overall survival: HR 0.75 and P=0.021, HR 0.69 and P=0.023, HR 0.60 and P=0.018, and HR 1.89 and P=0.148, respectively.

"These pooled data show that ribociclib has consistent benefit in Luminal A, Luminal B, and HER-enhanced tumour types. Patients with basal-like tumours seem not to benefit from palbociclib. However, due to the small sample size these results should be interpreted with caution," summarised Prof. Carey.

The second exploratory analysis evaluated the association between overall survival and location of metastases, number of metastatic sites, and prior therapy of patients in the MONALEESA-2 trial (n=668). Dr Joyce O'Shaughnessy (Baylor University Medical Center, TX, USA) presented the results.

Overall survival benefit of ribociclib in patients with or without bone-only metastases appeared to be consistent with that in the intention-to-treat population [5]. At 5- and 6-years follow-up, overall survival benefit of ribociclib was seen both in patients with

and without liver metastases. Similarly, overall survival benefit of ribociclib was observed at 5- and 6-years follow-up with liver or lung metastases. In addition, overall survival benefit of ribociclib was independent of the number of metastatic sites and independent of prior (neo)adjuvant chemotherapy or endocrine therapy. "So, this exploratory subgroup analysis demonstrated benefit of ribociclib independent of metastatic side, metastatic number, and/or prior therapy," concluded Dr O'Shaughnessy.

1. Hortobagyi GN, et al. Ann Oncol 2021;32(suppl5):S1283–S1346.
2. Slamon DJ, et al. N Engl J Med 2020;38:514–524.
3. Im S-A, et al. N Engl J Med 2019;381:307–316.
4. Carey LA, et al. Correlative analysis of overall survival by intrinsic subtype across the MONALEESA-2, -3, and -7 studies of ribociclib + endocrine therapy in patients with HR+/HER2– advanced breast cancer. GS2-00, SABCS 2021 Virtual Meeting, 7–10 December.
5. O'Shaughnessy J, et al. Overall survival subgroup analysis by metastatic site from the phase 3 MONALEESA-2 study of first-line ribociclib + letrozole in postmenopausal patients with advanced HR+/HER2– breast cancer. GS2-01, SABCS 2021 Virtual Meeting, 7–10 December.

Premenopausal women benefit from adjuvant chemotherapy next to endocrine therapy

The phase 3 RxPONDER trial evaluated the benefit of adjuvant chemotherapy followed by endocrine therapy in women with hormone receptor (HR)-positive/HER2-negative, early-stage breast cancer and 1–3 positive nodes. Updated results confirmed that the menopausal status makes the difference in this population.

The RxPONDER trial (NCT01272037) evaluated the benefit of chemotherapy followed by endocrine therapy versus endocrine therapy alone in patients who had an Oncotype DX Recurrence Score (RS) <25. A previous analysis of RxPONDER after a median follow-up of 5 years reported that invasive disease-free survival (IDFS) and distant disease-free survival (DDFS) differed by menopausal status [1]. In the current study, Dr Kevin Kalinsky (Emory University Winship Cancer Institute, GA, USA) reported updates on IDFS and DDFS with follow-up of 6.1 years, as well as distant recurrence-free intervals (DRFI), and post-hoc analyses in premenopausal women. DRFI was defined as time to distant recurrence or death from breast cancer [2].

Consistent with the results from the previous analysis, postmenopausal women continued to not have any IDFS or DDFS benefit with adjuvant chemotherapy, whereas premenopausal women continued to benefit from adjuvant chemotherapy, with a 5-year absolute benefit for IDFS and DDFS of 4.9% and 2.5%, respectively. In line with these results, chemotherapy improved in premenopausal patients (absolute 5-year benefit 2.4%) and not in postmenopausal patients. In premenopausal patients with RS 0–13, the absolute benefit was 2.3%; in premenopausal patients with RS 14–25, the benefit was 2.8%.

Among the premenopausal patients, 12.4% had micro-metastatic disease. Post-hoc analysis showed a trend for chemotherapy benefit for those with micro-metastatic disease (HR 0.44, absolute 5-year benefit 7.3%). However, only 22 IDFS events were present. In premenopausal patients (1,403) with macro-metastases, the absolute 5-year benefit of chemotherapy was 4.8%.

"This update of RxPONDER confirms that postmenopausal women with RS<25 do not benefit from adjuvant chemotherapy," concluded Dr Kalinsky. "In addition, premenopausal women with RS<25 continue to benefit from adjuvant chemotherapy resulting in a 44–46% decrease in IDFS, DRFS, and DRFS events."

1. Kalinsky K, et al. N Eng J Med 2021;385(25):2336–2347.
2. Kalinsky KM, et al. Updated results from a phase 3 randomized clinical trial in participants (pts) with 1-3 positive lymph nodes (LN), hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) < 25 randomized to endocrine therapy (ET) +/- chemotherapy (CT): SWOG S1007 (RxPONDER). GS2-07, SABCS 2021 Virtual Meeting, 7–10 December.

Promising anti-tumour activity of the CDK7-inhibitor samuraciclib plus fulvestrant

Efficacy of second-line treatment options for patients with oestrogen receptor (ER)-positive/HER2-negative metastatic breast cancer who progress on an aromatase inhibitor plus CDK4/6 inhibitor is poor. In a first-in-human, phase 2 trial, samuraciclib in combination with fulvestrant showed promising activity.

At the moment, there is no current agreed standard of care treatment for woman with ER-positive/HER2-negative metastatic breast cancer who progress on first-line treatment with CDK4/6 inhibitor plus aromatase inhibitor or selective oestrogen receptor degrader (SERD) [1-3]. CDK7 inhibition is a promising therapeutic strategy in cancer because it acts as a regulator of the cell cycle, transcription, and endocrine receptor signalling. Pre-clinical breast cancer models indicate the potential for synergy when the CDK7 inhibitor samuraciclib is combined with fulvestrant [4].

Prof. Charles Coombes (Imperial College London, UK) presented the results of a first-in-human, phase 2 trial with samuraciclib plus fulvestrant [5]. This single arm cohort assessed the tolerability and efficacy of samuraciclib in combination with standard dose fulvestrant in 31 patients with metastatic ER-positive/HER2-negative breast cancer who had previously received an aromatase inhibitor and a CDK4/6 inhibitor for advanced disease. The combination treatment was generally well tolerated, with adverse drug

reactions of note being grade 1–2 nausea, vomiting, and diarrhoea. Most patients stayed on treatment until disease progression. No neutropenia was observed. Clinical benefit rate at 24 weeks was 36%. Clinical benefit rate in TP53 wildtype patients was 53%. Median progression-free survival for TP53 wildtype patients was 32 weeks versus 7.9 weeks for TP53 mutant patients. In addition, liver metastases were a negative predictive factor: median progression-free survival for patients without liver metastases was over 48 weeks versus 11.9 weeks for patients with liver metastases.

"These first results demonstrate that samuraciclib has an acceptable safety profile with evidence of anti-tumour activity in combination with fulvestrant for patients with metastatic ER-positive/HER2-negative breast cancer who have progressed on their prior CDK4/6 inhibitor," concluded Prof. Coombes.

1. Cook MM, et al. Oncologist 2021;26:101–106.
2. Rugo HS, et al. Lancet Oncol 2021;22:489–498.
3. Lindeman GJ, et al. J Clin Oncol 2021;39(Suppl):1004.
4. Patel H, et al. Mol Cancer Therap 2018;17:1156–1166.
5. Coombes C, et al. Study of samuraciclib (CT7001), a first-in-class, oral, selective inhibitor of CDK7, in combination with fulvestrant in patients with advanced hormone receptor positive HER2 negative breast cancer (HR+BC). GS3-10, SABCS 2021 Virtual Meeting, 7–10 December.

ctDNA is prognostic and predictive for response to ribociclib plus letrozole

Pre-treatment circulating tumour DNA (ctDNA) and early dynamics of ctDNA represent promising prognostic and predictive biomarkers in patients with hormone receptor (HR)-positive/HER2-negative advanced breast cancer treated with ribociclib plus letrozole in the first line.

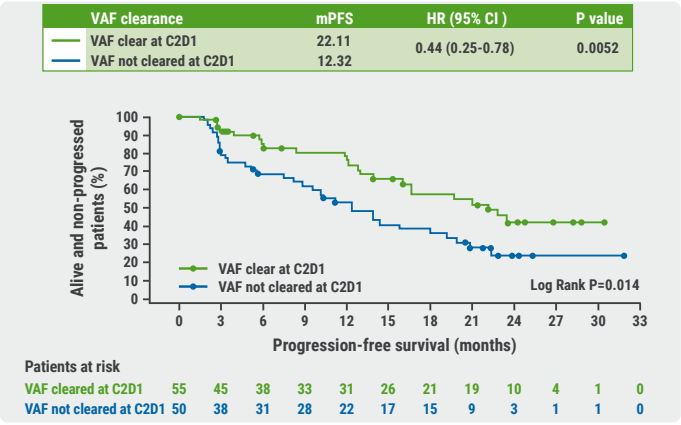
Patients with HR-positive/HER2-negative metastatic breast cancer benefit from treatment with ribociclib plus letrozole, the MONALEESA trials showed [1-3]. However, data on predictive biomarkers for response are limited and inconclusive. The aim of the phase 3 BioItaLEE trial (NCT03439046) was to assess the prognostic and predictive role of baseline and dynamic ctDNA in patients with HER-positive/HER2-negative advanced breast cancer treated in the first line with ribociclib plus letrozole. Dr Giampaolo Bianchini (San Raffaele Scientific Institute, Italy) presented the results. [4]

The study enrolled 287 postmenopausal patients. ctDNA was collected at baseline (D0; n=263), day 15 of cycle 1 (D15; n=238), day 1 of cycle 2 (C2D1; n=241), and at first imaging (FI, at approximately 12 weeks; n=206). ctDNA analysis covered the coding exons of 39 breast cancer-related genes. Median follow-up was 26.9 months and median progression-free survival (PFS) was 23.4 months.

At baseline, target mutations were detected in 43% of patients, whereas 57% of patients were wild-type, e.g. no mutation present. The absence of target mutations at D0 was associated with good prognosis. Median PFS was not reached for 'wild-type patients' and was 16.6 months for 'mutated patients' (HR: 0.41; P<0.0001). A significant reduction in mutated ctDNA was observed at D15 and C2D1 with a mean change of -64.3% and -68.6% compared with D0, respectively.

Clearance at D15 or C2D1 was associated with improved PFS compared with no clearance (HR 0.44; 95% CI 0.25–0.78; P=0.0052; see Figure). Median PFS in patients who had no clearance, clearance at D15, and clearance at C2D1 was 12.3 months, 21.9 months, and 22.1 months, respectively. Patients achieving clearance at D15 until C2D1 had the lowest risk of progression compared with those who had no clearance at any or both time points. Of the 150 patients without a detectable target mutation at baseline, 34 (22.7%) patients had detectable mutations at later timepoints (D15, C2D1 and/or FI). Median PFS in these patients was 15.9 months.

Figure: Variant allele frequency clearance at C2D1 is associated with improved progression-free survival [4].



C, Cycle; CI, confidence interval; D, day; HR, hazard ratio; mPFS, medium progression-free survival; VAF, variant allele frequency

Considering all time points individually, D15 was the most informative of patient outcome. The presence of a detectable mutation in baseline liquid biopsies appears to be a negative prognostic factor. Within this high-risk group, early mutation clearance during the first ribociclib plus letrozole cycle was informative of treatment benefit and associated with a lower risk of progression. In addition, monitoring of ctDNA in patients without baseline mutations demonstrated that the detection of new mutations was associated with worse outcome.

"So overall, pre-treatment and early dynamics of ctDNA represent promising prognostic and predictive biomarkers in patients with HR-positive/HER2-negative advanced breast cancer treated with ribociclib plus letrozole in the first-line," concluded Dr Bianchini. "Further studies are warranted to validate the clinical utility of these biomarkers."

1. Hortobagyi GN, et al. Ann Oncol 2021; 32 (suppl_5): S1283-S1346
2. Slamon DJ, et al. N Engl J Med 2020; 38: 514-524.
3. Im S-H, et al. N Engl J Med 2019; 381:307-316.
4. Bianchini G, et al. Circulating tumor DNA (ctDNA) dynamics in patients with hormone receptor positive (HR+)/HER2 negative (HER2-) advanced breast cancer (aBC) treated in first line with ribociclib (R) and letrozole (L) in the BioItaLEE trial. GS3-07, SABCS 2021 Virtual Meeting, 7–10 December.

Early switch to fulvestrant plus palbociclib beneficial for patients with *ESR1* mutation

Among patients with hormone receptor (HR)-positive/HER2-negative breast cancer treated with an aromatase inhibitor plus palbociclib, those who displayed a rising oestrogen receptor (*ESR1*) mutation, detected in their blood before disease progression, doubled their median progression-free survival (PFS) following a switch to fulvestrant plus palbociclib.

ESR1 mutations are known drivers of resistance to first-line aromatase inhibitors-based therapy in HR-positive/HER2-negative metastatic breast cancer patients. *ESR1* mutations predict resistance to aromatase inhibitors, but not to fulvestrant [1]. The randomised, multicentre, open-label, phase 3 PADA-1 trial (NCT03079011) aimed to evaluate the clinical benefit of a switch to fulvestrant plus palbociclib upon the detection of a rising *ESR1* mutation in blood (bESR1$_{mut}$). The PADA-1 trial enrolled 1,017 patients, who were treated in a first-line setting with an aromatase inhibitor plus palbociclib. The patients provided blood samples for *ESR1* mutation screening every 2 months. After a median time of 15.6 months, 172 patients demonstrated rising of bESR1$_{mut}$ during aromatase inhibitor plus palbociclib treatment (without clinical signs of progression). These patients were randomised to continuation of aromatase inhibitor plus palbociclib (standard arm, n=84) or to treatment with fulvestrant plus palbociclib (experimental arm, n=88). Prof. François-Clément Bidard (Institut Curie, France) presented the results [2].

After a median follow-up of 26 months after randomisation, the median PFS in the standard arm was 5.7 months versus 11.9 months in the experimental arm (HR=0.63; P=0.007), representing an absolute difference in median PFS of 6.2 months. The benefit of fulvestrant plus palbociclib over aromatase inhibitor plus palbociclib was observed across all prespecified subgroups.

Patients who progressed after continuing aromatase inhibitor plus palbociclib treatment were given the option to cross over to fulvestrant plus palbociclib. Among patients in the crossover cohort (n=47), the median second-PFS was 3.5 months, which is numerically shorter than the 6.2 months benefit of early switch to fulvestrant plus palbociclib.

Based on these results, Dr Bidard concluded that: "This first-of-its-kind liquid biopsy-based trial demonstrates that targeting bESR1$_{mut}$-associated resistance through a change in the endocrine partner of palbociclib is feasible and allows a doubling in the subsequent median PFS. The observed clinical benefit might justify the implementation of the PADA-1 treatment strategy as a valid option in clinical routine."

1. Turner NC, et al. Clin Cancer Res. 2020;26:5172–5177.
2. Bidard F-C, et al. Fulvestrant-palbociclib vs continuing aromatase inhibitor-palbociclib upon detection of circulating ESR1 mutation in HR+ HER2- metastatic breast cancer patients: Results of PADA-1, a UCBG-GINECO randomized phase 3 trial. GS3-05, SABCS 2021 Virtual Meeting, 7–10 December.

Triple-Negative Breast Cancer

Single-cell spatial analysis can predict response to neoadjuvant immunotherapy

A next-generation technology that allows the study of protein expression at the single-cell level and the location of the cells to be within the tumour microenvironment was feasible and provided information on the benefit of adding the immune checkpoint inhibitor atezolizumab to chemotherapy as neoadjuvant treatment for patients with early high-risk and locally advanced triple-negative breast cancer (TNBC).

Immune checkpoint inhibitors are effective in early and advanced TNBC. However, only a minority of patients benefit from it, making precision immuno-oncology a major unmet

need. Imaging mass cytometry enables high dimensional tissue imaging at subcellular resolution for assessment of TNBC ecosystems, providing information on cell type composition, functional status, and spatial organisation. Dr Giampaolo Bianchini (Ospedale San Raffaele, Italy) and colleagues investigated whether imaging mass cytometry could assist in the identification of ideal candidates for this therapeutic approach. They performed imaging mass cytometry analysis in the context of the phase 3 NeoTRIPaPDL1 trial (NCT02620280), which was designed to evaluate the addition of atezolizumab to the chemotherapeutics carboplatin and nab-paclitaxel as neoadjuvant therapy in patients with early high-risk and locally advanced TNBC.

Forty-three protein-spanning cancer cells and the tumour microenvironment were assessed on pre-treatment, formalin-fixed, paraffin-embedded biopsies of 243 of the 280 enrolled patients. For each sample, 3 high-dimensional images were generated that encompassed the tumour, tumour-stroma interface, and adjacent stroma. The association of protein expression was assessed for epithelial and tumour-microenvironment cells, cell phenotypes, and the spatial tissue organisation with pathological complete response rate. Dr Bianchini presented the results [1].

By supervised clustering, 37 cell phenotypes were defined. PD-L1-positive tumours, high stromal tumour-infiltrating lymphocytes, and TNBC type were characterised by extreme heterogeneity and unique cell-type and spatial tumour microenvironment composition. Bulk protein expression analysis delivered only limited predictive information because it does not consider the cell compartment in which each protein is expressed. Several biomarkers demonstrated a significant association with pathological complete response rate. For example, high density of PD-L1-positive and IDO-positive antigen presenting cells, as well as high density of CD56-positive epithelial cells, was associated with higher pathological complete response rate in patients who received atezolizumab plus chemotherapy, but not in patients who only received chemotherapy (OR 4.5; p<0.001). In addition, high degree of spatial connectivity between epithelial cells and specific tumour-microenvironment cells correlated with a significant increase in the pathological complete response rate after atezolizumab.

"Our results demonstrate that imaging mass cytometry is feasible in a large, randomised trial and provides a comprehensive overview of TNBC at a single-cell level with special resolution, paving the way for its broad implementation in cancer research to aid precision immunology," concluded Bianchini. "Information on spatial data and on the interactions among specific cells in the tumour microenvironment might be informative about the benefit provided by an immune checkpoint inhibitor such as atezolizumab in addition to chemotherapy. However, all these findings will require independent validation."

1. Bianchini G, et al. Single-cell spatial analysis by imaging mass cytometry and immunotherapy response in triple-negative breast cancer (TNBC) in the NeoTRIPaPDL1 trial. GS1-00, SABCS 2021 Virtual Meeting, 7–10 December.

Neoadjuvant pembrolizumab plus chemotherapy benefits event-free survival in TNBC

Primary analysis of the KEYNOTE-522 trial showed a statistically significant and clinically meaningful improvement in the event-free survival (EFS) of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab versus neoadjuvant chemotherapy alone, in patients with early triple-negative breast cancer (TNBC).

Pembrolizumab showed anti-tumour activity and manageable safety in metastatic TNBC [1,2]. In addition, results from the phase 1b KEYNOTE-173 trial (NCT02622074) showed that pembrolizumab plus neoadjuvant chemotherapy had promising anti-tumour activity and manageable toxicity in patients with early-stage TNBC [3].

The phase 3 KEYNOTE-522 trial (NCT03036488) evaluated the efficacy and safety of pembrolizumab plus chemotherapy versus placebo plus chemotherapy as neoadjuvant therapy and pembrolizumab versus placebo as adjuvant therapy in patients with early-stage TNBC. A total of 1,174 patients with previously untreated, non-metastatic, centrally confirmed TNBC were randomised 2:1 to pembrolizumab or placebo, both given with 4 cycles of paclitaxel plus carboplatin, then with 4 cycles of doxorubicin or epirubicin plus cyclophosphamide (neoadjuvant phase). After definitive surgery, patients received pembrolizumab or placebo for 9 cycles or until recurrence or unacceptable toxicity (adjuvant phase). Dual primary endpoints were pathological complete response rate and EFS. The primary analysis showed a statistically significant and clinically meaningful improvement in EFS with pembrolizumab plus chemotherapy followed by pembrolizumab [4].

To assess the robustness and consistency of the primary EFS result, pre-specified sensitivity and subgroup analyses

for EFS were performed, including 2 that assessed the impact of different censoring rules and 3 that assessed the impact of different event definitions. Treatment effects on EFS were examined in pre-specified patient subgroups defined by nodal involvement (positive or negative), disease stage (1 or 3), menopausal status (premenopausal or postmenopausal), HER2 status (2+ by IHC but FISH- or 0–1+ by IHC), and LDH (>ULN or ≤ULN). Prof. Peter Schmid (Barts Cancer Institute, UK) presented the results of these analyses [5].

After a median follow-up of 39.1 months, the benefit of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab versus neoadjuvant chemotherapy alone was generally consistent with the primary EFS results for all 5 sensitivity analyses and in each subgroup evaluated. Hazard ratio (HR) for the sensitivity analyses varied from 0.63–0.65 (versus 0.63 in the primary analysis). Also, HR for the subgroup analyses was in line with the primary analysis: 0.58–0.73 (see Table).

Table: Hazard Ratio of subgroup analyses [5].

Subgroup analyses	HR (95% CI)
Nodal involvement	
Positive	0.65 (0.46–0.91)
Negative	0.58 (0.37–0.91)
Overall disease stage	
2	0.60 (0.42–0.86)
3	0.68 (0.45–1.03)
Menopausal status	
Premenopausal	0.62 (0.42–0.91)
Postmenopausal	0.64 (0.44–0.93)
HER2 status	
2+ by IHC (but FISH-)	0.73 (0.43–1.24)
0–1+ by IHC	0.60 (0.44–0.82)
LDH	
>ULN	0.65 (0.37–1.12)
≤ULN	0.63 (0.46–0.86)

IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; ULN, upper limit of normal; HR, hazard ratio.

"These results show a robust treatment benefit of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab for previously untreated non-metastatic TNBC. The EFS benefit was generally consistent across a broad selection of patient subgroups," concluded Prof. Schmid.

1. Adams S, et al. Ann Oncol 2019;30:397–404.
2. Adams S, et al. Ann Oncol 2019;30:405–412.
3. Schmid P, et al. Ann Oncol 2020;31:569–581.
4. Schmid P, et al. N Eng J Med 2020;382:810–821.
5. Schmid P, et al. KEYNOTE-522 study of neoadjuvant pembrolizumab + chemotherapy vs placebo + chemotherapy, followed by adjuvant pembrolizumab vs placebo for early-stage TNBC: Event-free survival sensitivity and subgroup analyses. GS1-01, SABCS 2021 Virtual Meeting, 7–10 December.

Early use of ctDNA testing can identify likelihood of relapse in TNBC

In the phase 2, proof-of-principle c-TRACK-TN trial circulating tumour DNA (ctDNA) surveillance was used in moderate or high-risk triple-negative breast cancer (TNBC) patients to start additional treatment with pembrolizumab.

A substantial part of patients presenting with TNBC relapse after primary treatment. In previous retrospective findings, ctDNA detection was highly predictive for relapse in patients with TNBC who completed their primary treatment [1,2]. The prospective, multicentre, phase 2 c-TRAK-TN trial (NCT03145961) piloted the prospective use of ctDNA assays in patients treated for early-stage TNBC who were at moderate or high-risk of relapse. Prof. Nicholas Turner (The Institute of Cancer Research, UK) presented primary results of c-TRAK-TN [3].

A total of 208 patients with trackable mutations who completed surgery and adjuvant chemotherapy underwent ctDNA testing at baseline. From these, 161 patients entered ctDNA surveillance every 3 months for 1 year. Patients who were ctDNA-positive were randomised between observation (e.g., standard follow-up) or intervention. In the intervention arm, patients underwent staging scans, and those without metastatic disease were offered pembrolizumab for a year. At 12 months, 27.3% of patients were ctDNA-positive. Patients in the high-risk group were much more likely to be positive for ctDNA at 12 months than those at moderate risk: 55.7% versus 11.8%. Seven patients relapsed without prior ctDNA detection.

Of the ctDNA-positive patients, 14 were assigned to observation and 32 were assigned to intervention. The rate of overt metastatic disease at time of ctDNA detection was 71.9% (23/32), substantially higher than expected. Nine patients were ctDNA-positive without metastatic disease and were offered pembrolizumab; 5 of them started treatment with pembrolizumab. None of these 5 patients exhibited ctDNA clearance after 6 months on pembrolizumab; 1 patient had sustained ctDNA suppression. For the 14 patients assigned to observation, lead time to relapse was a median 4.1 months. Four patients in the observation group remain recurrence-free. All became ctDNA negative after an initial ctDNA-positive result, although 2 have become ctDNA positive again. The 6-month recurrence-free survival rate with ctDNA clearance was 21.4%.

"Our findings have implications for future trial design, most importantly, to start ctDNA testing early and employ more sensitive ctDNA assays that track multiple variants," concluded Dr Turner. "Potentially, more frequent testing is advisable in the 0–6-month time points, given the rapidity of disease evolution."

1. Coombes RC, et al. Clin Cancer Res. 2019;25:4255–4263.
2. Garcia-Murillas I, et al. JAMA Oncol. 2019;5:1473–1478.
3. Turner N, et al. Primary results of the cTRAK TN trial: A clinical trial utilising ctDNA mutation tracking to detect minimal residual disease and trigger intervention in patients with moderate and high risk early-stage triple negative breast cancer. GS3-06, SABCS 2021 Virtual Meeting, 7–10 December.

Pembrolizumab plus chemotherapy benefits patients with combined positive score ≥10

Combined positive score (CPS) ≥10 is a reasonable cut-off to define patients with metastatic triple-negative breast cancer who benefit from pembrolizumab plus chemotherapy, subgroup analyses of KEYNOTE-355 show.

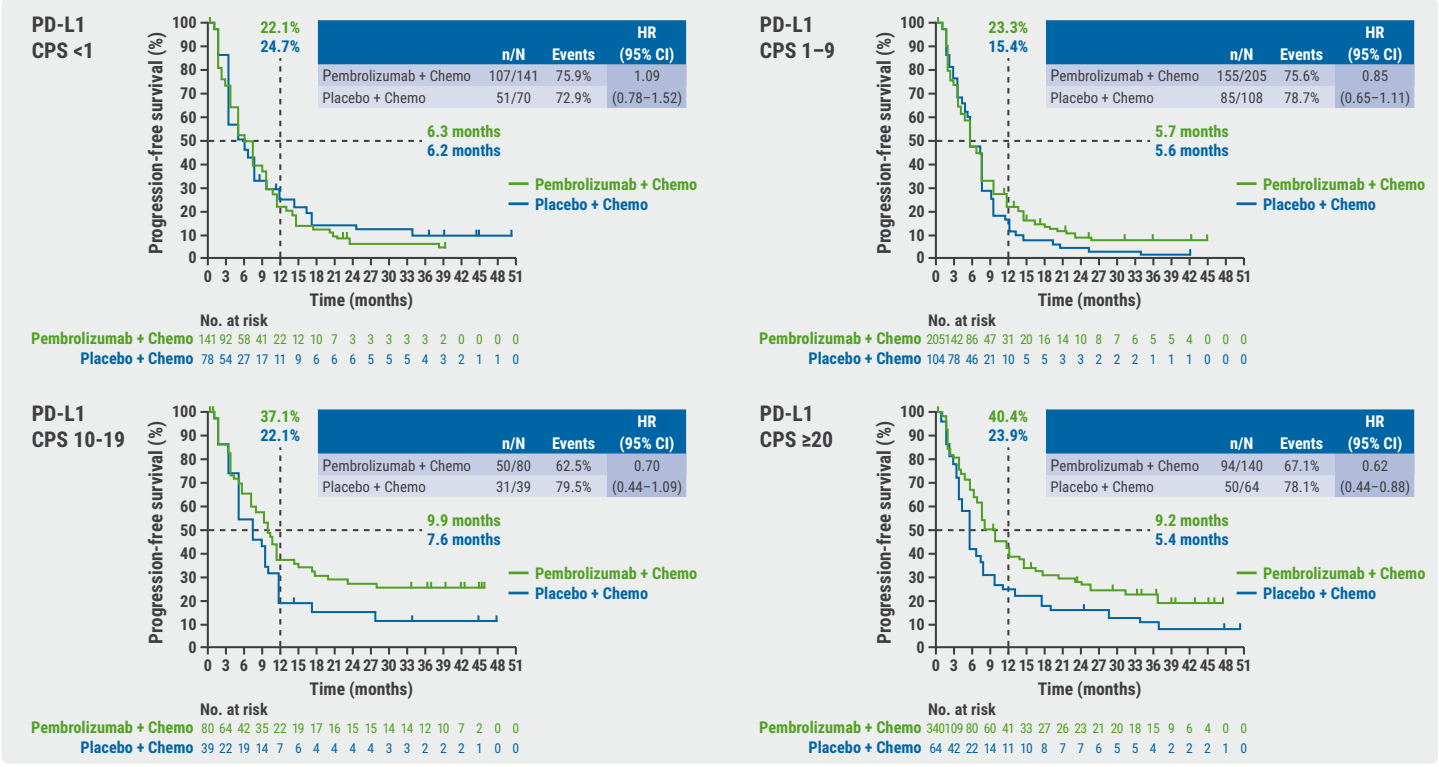
In the phase 3 KEYNOTE-355 trial (NCT02819518), first-line pembrolizumab combined with chemotherapy showed statistically significant improvements in overall survival (OS) and progression-free survival (PFS) compared with placebo plus chemotherapy in patients with previously untreated, locally recurrent, inoperable, or metastatic TNBC whose tumours expressed PD-L1 with a CPS ≥10 [1]. Additional analyses were done in subgroups of patients by additional CPS cut-offs to the primary results of KEYNOTE-355. Dr Javier Cortés (Vall d'Hebron Institute of Oncology, Spain) presented the results [2].

At the time of the final analysis, the median follow-up was 44 months. Of all patients, 25% had a CPS<1, 37% had a CPS 1–9, 14% had a CPS 10–19, and 24% had a CPS>20. In the primary analyses, the hazard ratios for OS were 0.73 in the CPS≥10 subgroup, 0.86 in the CPS≥1 subgroup, and 0.89 in the intent-to-treat population. Hazard ratios for PFS were 0.66, 0.75, and 0.82, respectively. In the additional analyses, hazard ratios for OS were 0.97 in the CPS<1 subgroup, 1.09 in the CPS 1–9 subgroup, 0.71 in the CPS 10–19 subgroup, 0.72 in the CPS≥20 subgroup, and 0.89 in the intent-to-treat population. Hazard ratios for PFS were 1.09, 0.85, 0.70, 0.62, and 0.82, respectively (see Figure).

Based on these results, Dr Cortés concluded that: "CPS≥10 is a reasonable cut-off to define patients with metastatic triple-negative breast cancer who will benefit from pembrolizumab plus chemotherapy."

1. Rugo HS, et al. LBA16, ESMO Virtual Annual Meeting 2021, 16–21 September.
2. Cortes J, et al. Final results of KEYNOTE-355: Randomized, double-blind, phase 3 study of pembrolizumab + chemotherapy vs placebo + chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer. GS1-02, SABCS 2021 Virtual Meeting, 7–10 December.

Figure: Progression-free survival in PD-L1 patients with combined positive score cut-offs of: <1, 1–9, 10–19, and ≥20 [2].



CPS, combined positive score; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval

Neratinib plus trastuzumab plus fulvestrant shows encouraging clinical activity

Both patients with heavily pretreated hormone receptor (HR)-positive/*HER2*-mutated, HER2-negative metastatic breast cancer and patients with heavily pretreated *HER2*-mutated metastatic triple-negative breast cancer (TNBC) have encouraging responses to treatment with neratinib plus trastuzumab plus fulvestrant.

HER2 mutation in the absence of gene amplification or protein overexpression is a unique mechanism of oncogenetic addiction to HER2 signalling [1]. Neratinib has demonstrated encouraging clinical activity either as a single agent or in combination with fulvestrant in *HER2*-mutated, *HER2*-non-amplified metastatic breast cancer [2]. Addition of trastuzumab to neratinib plus fulvestrant showed encouraging clinical activity with durable responses in the phase 2 SUMMIT trial (NCT01953926). Early data also suggest that neratinib plus fulvestrant plus trastuzumab improves clinical benefit in patients with *HER2*-mutated, *HER2*-non-amplified metastatic breast cancer [3].

Based on these findings, SUMMIT has recently been expanded to include a randomised comparison of neratinib plus fulvestrant plus trastuzumab ('triplet') versus fulvestrant plus trastuzumab ('doublet') versus fulvestrant alone ('mono') in 21 patients with HR-positive/*HER2*-mutated, HER2-negative metastatic breast cancer who were exposed to CDK4/6 inhibitors. Prior to starting this randomised portion of the trial, 26 patients were already enrolled in a non-randomised cohort receiving neratinib plus fulvestrant plus trastuzumab. In another SUMMIT cohort, 18 patients with *HER2*-mutant TNBC were enrolled in a non-randomised cohort and received neratinib plus trastuzumab. Dr Komal Jhaveri (Memorial Sloan Kettering Cancer Center, NY, USA) presented the results [4].

In the non-randomised, triplet-treated patients (n=26) objective response rate was 46.2% (all partial response), clinical benefit rate was 57.7%, and median progression-free survival was 8.2 months. In the randomised, triplet-treated patients (n=7) objective response rate was 28.6% (14.3% complete response, 14.3% partial response), clinical benefit rate was 28.6%, and median progression-free survival was 6.2 months. No responses were seen in de doublet-treated and mono-treated patients.

These results are in line with the hypothesis that neratinib is critical for the inhibition of *HER2* mutations. Based on these results the doublet-cohort and mono-cohort were closed. In the combined randomised and non-randomised triplet cohort (n=33) objective response rate was 42.4% (3% complete response, 39.4% partial response), clinical benefit rate was 51.5%, and median progression-free survival was 7.0 months. In the TNBC cohort (n=18) objective response rate was 33.3% (5.6% complete response, 27.8% partial response), clinical benefit rate was 38.9%, and median progression-free survival was 6.2 months (see Table).

Table: Baseline characteristics and efficacy of TNBC patients treated with neratinib plus trastuzumab [4].

Baseline characteristics	TNBC (N+T; n=18)
ECOG performance status, n (%)	
0	9 (50.0)
1	9 (50.0)
Histological type, n (%)	
Lobular	3 (16.7)
Ductal	7 (38.9)
Mixed ductal and lobular	0
Other	8 (44.4)
Median number of prior anti-cancer regimens (range)	3.5 (7–7)
Efficacy	**TNBC (N+T; n=18)**
Objective response (confirmed CR/PR), n (%)	6 (33.3)
CR	1 (5.6)
PR	5 (27.8)
Best overall response (confirmed or unconfirmed PR or CR), n (%)	7 (38.9)
Median DOR, months (95% CI)	not estimable
Clinical benefit, n (%)	7 (38.9)
Median PFS, months (95% CI)	6.2 (2.1–8.2)
Median duration of treatment, months (range)	4.4 (0.3–15.4)

CR, complete response; PR, partial response; CI, confidence interval; DOR, duration of response; PFS, progression-free survival

Based on these result, Dr Jhaveri concluded that "the combination regimen of neratinib plus fulvestrant plus trastuzumab demonstrates encouraging clinical activity in patients with heavily pretreated HR-positive/*HER2*-mutated, HER2-negative metastatic breast cancer who had previously received CDK4/6 inhibitors."

1. Nayar U, et al. Nat Genet 2019;51:207–216.
2. Smyth LM, et al. Cancer Discov 2020;10:198–213.
3. Jhaveri K, et al. PD1-05, SABCS 2020 Virtual Symposium, 8–11 December.
4. Jhaveri K, et al. Neratinib + fulvestrant + trastuzumab for hormone receptor-positive, HER2-mutant metastatic breast cancer and neratinib + trastuzumab for triple-negative disease: Latest updates from the SUMMIT trial. GS4-10, SABCS 2021 Virtual Meeting, 7–10 December.

Phase 1–3 Trials

Datopotamab deruxtecan shows promising anti-tumour activity

Updated results from the phase 1 TROPION PanTumor01 study confirm promising anti-tumour activity and a manageable safety profile of the antibody-drug conjugate datopotamab deruxtecan in patients with previously treated advanced/metastatic triple-negative breast cancer (TNBC).

Effective treatment options for patients with advanced or metastatic TNBC that have relapsed or are refractory to standard treatment are limited. Over-expression of TROP2 was reported to predict poor prognosis in various solid tumours, including breast cancers [1]. Datopotamab deruxtecan is an antibody-drug conjugate consisting of a humanised anti-TROP2 IgG1 monoclonal antibody conjugated to a potent topoisomerase I inhibitor payload. Preliminary results from the multi-centre, open-label, phase 1 TROPION-PanTumor01 study (NCT03401385) demonstrated that datopotamab deruxtecan has encouraging anti-tumour activity and a manageable safety profile in patients with TNBC [2]. Dr Ian Krop (Dana-Farber Cancer Institute, MA, USA) presented updated results from the TNBC cohort [3].

A dose of datopotamab deruxtecan, 6 mg/kg intravenously, was given every 3 weeks to 42 patients. Two patients with TNBC received datopotamab deruxtecan 8 mg/kg prior to selection of 6 mg/kg for dose expansion. The median follow-up was 7.6 months. The overall response rate was 34%; the disease control rate was 77%. Median duration of response was not yet reached, with the majority of responses ongoing at data cut-off. All-cause treatment-emergent adverse events (any grade, grade ≥3) were observed in 98% and 45% of patients, respectively. Fatal adverse events were not observed. Dose reduction occurred in 18% of patients, treatment discontinuation occurred in 2% of patients. The most common adverse events (any grade) included nausea (58%), stomatitis (53%), alopecia (35%), vomiting (35%), and fatigue (33%). No cases of interstitial lung disease were observed.

"Datopotamab deruxtecan demonstrates promising anti-tumour activity with a manageable safety profile in previously treated patients with advanced/metastatic TNBC," concluded Dr Krop. "A phase 3 trial is planned."

1. Zeng P, et al. Sci Rep. 2016;6:33658.
2. Bardia A. ESMO Breast Cancer Congress 2021. Abstract LBA4.
3. Krop IE, et al. Datopotamab deruxtecan in advanced/metastatic HER2- breast cancer: Results from the phase 1 TROPION-PanTumor01 study. GS1-05, SABCS 2021 Virtual Meeting, 7–10 December.

Trastuzumab deruxtecan outperforms trastuzumab emtansine

Both trastuzumab deruxtecan and trastuzumab emtansine have shown to improve progression-free survival (PFS) in patients with HER2-positive metastatic breast cancer. In a head-to-head comparison, trastuzumab deruxtecan proved to outperform trastuzumab emtansine.

Trastuzumab deruxtecan is a HER2-targeting, antibody-drug conjugate for the treatment of previously treated patients with advanced HER2-positive metastatic breast cancer, as was demonstrated by the DESTINY-Breast01 study (NCT03248492) [1]. Before, the EMILIA trial (NCT00829166) showed trastuzumab emtansine to be beneficial in this population [2]. In the phase 3 DESTINY-Breast03 (NCT03529110) trial the efficacy and safety of trastuzumab deruxtecan and trastuzumab emtansine are compared head-to-head in patients previously treated with trastuzumab and taxane. The primary analysis demonstrated trastuzumab deruxtecan to have a clinically meaningful and statistically significant improved PFS versus trastuzumab emtansine. Trastuzumab deruxtecan demonstrated superior PFS versus trastuzumab emtansine (HR 0.28; P<0.0001); median PFS was not reached for trastuzumab deruxtecan versus 6.8 months for trastuzumab emtansine; 12-month PFS rate was 79.7% versus 34.2%, respectively [3]. Now, Dr Sara Hurvitz (University of California, CA, USA) presented results from subgroup analyses of DESTINY-Breast03, including patients with brain metastases [4].

Median PFS favoured trastuzumab deruxtecan over trastuzumab emtansine independent of hormone receptor status, prior trastuzumab treatment, and number of prior lines of therapy. For patients with stable brain metastases at baseline (n=82), median PFS was 15.0 months for trastuzumab deruxtecan versus 3.0 months for trastuzumab emtansine (HR 0.25;

see Figure). Overall, confirmed overall response rate (ORR) for trastuzumab deruxtecan was 79.7% (16.1% complete response, 63.6% partial response) versus 34.2% (8.2% complete response, 25.5% partial response) for trastuzumab emtansine. In patients with stable brain metastases at baseline, ORR was 67.4% (4.7% complete response, 62.8% partial response) for trastuzumab deruxtecan versus 20.5% (0% complete response, 20.5% partial response) for trastuzumab emtansine. In addition, intracranial response rate in these patients was 63.9% (27.8% complete response, 36.1% partial response) for trastuzumab deruxtecan versus 33.4% (2.8% complete response, 30.6% partial response) for trastuzumab emtansine.

Overall, the safety profile of trastuzumab deruxtecan was manageable and comparable with its known safety profile. Adjudicated drug-related interstitial lung disease/pneumonitis was reported in 27 (10.5%) patients treated with trastuzumab deruxtecan and 5 (1.9%) patients treated with trastuzumab emtansine, with no grade 4 or 5 events.

"Consistent PFS and ORR benefits with trastuzumab deruxtecan versus trastuzumab emtansine were observed across subgroups in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and taxanes, including patients with brain metastases," concluded Dr Hurvitz.

1. Modi S, al. N Engl J Med 2020;382:610–621.
2. Verma S, Miles D, et al. N Engl J Med 2012; 367:1783-1791.
3. Cortés J, et al. Ann Oncol. 2021;32(suppl5):1283–1346.
4. Hurvitz S, et al. Trastuzumab deruxtecan (T-DXd; DS-8201a) vs. trastuzumab emtansine (T-DM1) in patients (pts) with HER2+ metastatic breast cancer (mBC): subgroup analyses from the randomized phase 3 study DESTINY-Breast03. GS3-01, SABCS 2021 Virtual Meeting, 7–10 December.

Nivolumab plus ipilimumab serve promising dual checkpoint inhibition

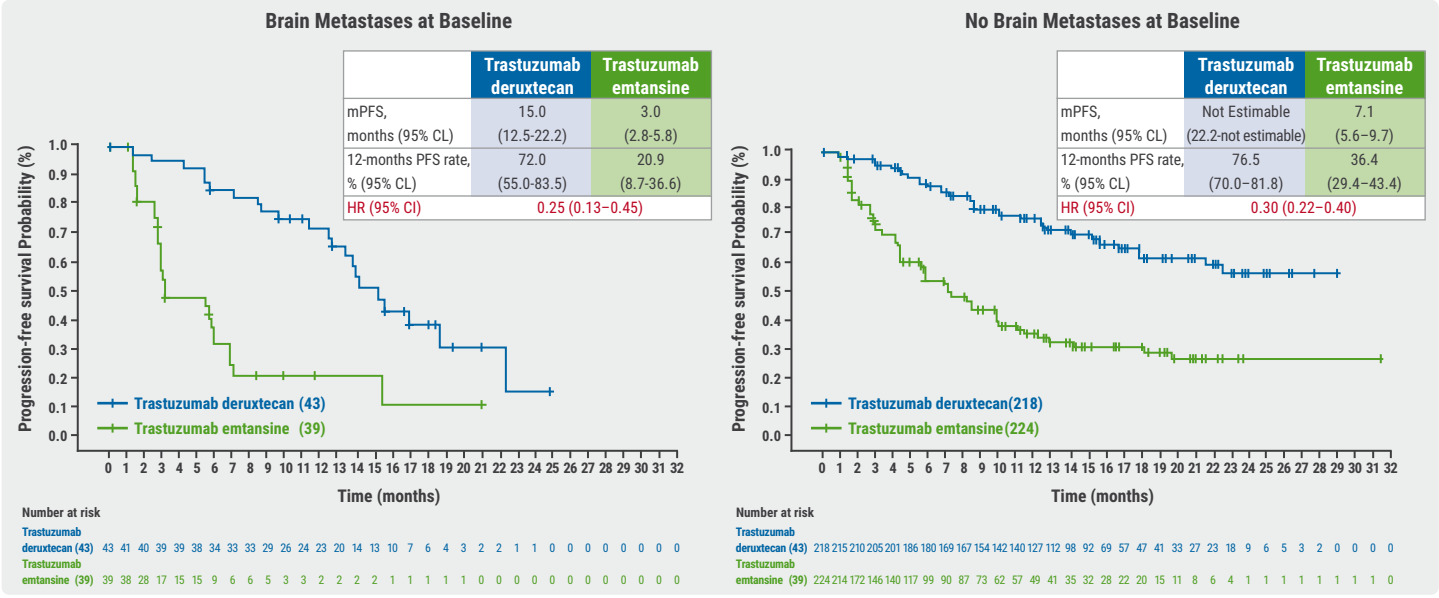
Dual checkpoint inhibition with nivolumab plus ipilimumab may be a promising treatment option for patients with HER2-negative metastatic breast cancer and high tumour mutational burden (TMB).

In the open-label, multicentre, phase 2 NIMBUS trial (NCT03789110), the efficacy and safety of dual checkpoint inhibition with nivolumab plus low-dose ipilimumab was evaluated in patients with hyper-mutated breast cancer with a TMB≥9 mutations/megabase (mut/Mb). Dr Romualdo Barroso-Sousa (Hospital Sírio-Libanês, Brazil) presented the results [1].

The NIMBUS study included 30 patients with HER2-negative metastatic breast cancer (70% HR-positive, 30% triple-negative breast cancer) and a TMB of at least 9 mut/Mb (median 10.9 mut/Mb). The median number of prior chemotherapy lines was 1.5 and the maximum was 3. Patients received nivolumab (3 mg/kg every 2 weeks) plus ipilimumab (1 mg/kg every 6 weeks) until disease progression, unacceptable toxicity, or up to 24 months.

During a median 9.7 months of follow-up, there were 5 (16.7%) confirmed objective responses, all of which were partial. A further 6 (20%) patients had stable disease during follow-up. Median duration of response was 12.1 months, while median progression-free survival and overall survival were a respective 1.4 and 19.3 months. Exploratory analyses revealed that in patients with a high TMB (≥14 mut/Mb) the overall response

Figure: Progression-free survival of patients with and without brain metastases treated with trastuzumab deruxtecan or trastuzumab emtansine [4].



mPFS, median progression-free survival; PFS, progression-free survival.

rate was 60% versus 8% in the 25 patients with a TMB of 9–13 mut/Mb. Median progression-free survival and median overall survival were 9.5 months and not reached in patients with a TMB≥14 mut/Mb versus 1.4 months and 8.8 months in patients with a TMB of 9–13 mut/Mb.

Based on these results, Dr Barrosso-Sousa concluded that: "this study supports the use of checkpoint inhibitors among patients with HER2-negative metastatic breast cancer and TMB. However, the study does not answer the question whether dual checkpoint inhibition is better than pembrolizumab monotherapy."

1. Barroso-Sousa R, et al. Nimbus: A phase 2 trial of nivolumab plus ipilimumab for patients with hypermutated her2-negative metastatic breast cancer (MBC). GS2-10, SABCS 2021 Virtual Meeting, 7–10 December.

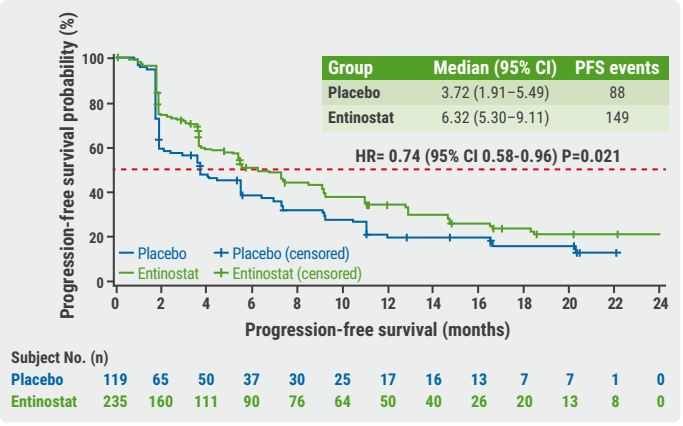
Entinostat plus exemestane improves progression-free survival in Chinese patients

Patients with advanced hormone receptor (HR)–positive/HER2-negative breast cancer derived greater progression-free survival (PFS) benefit when treated with entinostat plus exemestane versus matched placebo, according to results from a Chinese, phase 3 study.

Entinostat is a potent, once weekly, orally bioavailable, class 1 selective histone deacetylase inhibitor. In breast cancer, disruption of oestrogen-mediated signalling results in acquired resistance to hormonal therapy. Entinostat is hypothesised to re-sensitise these cells to endocrine treatment. Prof. Binghe Xu (Chinese Academy of Medical Sciences, China) presented results of a double-blind, placebo-controlled, phase 3 (NCT03538171) trial evaluating the efficacy and safety of entinostat plus exemestane versus placebo plus exemestane in patients with HR-positive/HER2-negative advanced breast cancer who progressed on prior endocrine therapy [1].

A total of 354 patients were randomised 2:1 to entinostat (5 mg weekly) or placebo. Both groups received exemestane daily (25 mg). Treatment was given until disease progression or unacceptable toxicity. Median PFS was 6.32 months in patients treated with entinostat versus 3.72 months in patients treated with placebo (HR 0.74; P=0.021; see Figure). Median overall survival was not reached in both treatment arms (HR 0.75 in favour of entinostat). Overall response rates (ORR) were 15.7% and 10.1% and clinical benefit rates were 37.4% and 32.8%, respectively. Ad-hoc subgroup analysis of PFS showed that entinostat plus exemestane outperformed exemestane alone across all pre-specified subgroups, except for those who received prior fulvestrant. Regarding safety, the most common adverse events were hematologic toxicities, including neutropenia (43.8%), leukopenia (6.4%), thrombocytopenia (8.5%), and anaemia.

Figure: Progression-free survival of entinostat plus exemestane versus placebo plus exemestane treatment [1].



PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

"The entinostat plus exemestane combination significantly improved PFS compared with exemestane alone in patients with advanced, HR-positive/HER2-negative breast cancer that progressed after previous endocrine therapy," concluded Prof. Xu. "Entinostat plus exemestane can offer meaningful clinical benefit in these patients."

1. Xu B, et al. A randomized control phase III trial of entinostat, a once weekly, class I selective histone deacetylase inhibitor, in combination with exemestane in patients with hormone receptor positive advanced breast cancer. GS1-06, SABCS 2021 Virtual Meeting, 7–10 December.

Efficacy of pyrotinib plus capecitabine confirmed in previously treated patients

Patients with previously treated HER2-positive metastatic breast cancer who received pyrotinib plus capecitabine had longer overall survival than patients who received lapatinib plus capecitabine, according to updated results from the phase 3 PHOEBE trial.

Patients with metastatic HER2-positive breast cancer are typically treated with the HER2-targeted therapies trastuzumab and pertuzumab in combination with a taxane, but resistance to this regimen inevitably develops. Patients who progress on this standard therapy may then be treated with lapatinib plus capecitabine or with alternative HER2-targeted therapies, such as trastuzumab plus emtansine. Pyrotinib is an irreversible tyrosine kinase receptor inhibitor that targets HER2, as well as the related proteins HER4 and HER1. A prior phase 2 clinical trial found that pyrotinib plus

capecitabine led to clinical responses in previously treated patients with HER2-positive metastatic breast cancer [1]. The phase 3 PHOEBE trial (NCT03080805) compared lapatinib plus capecitabine versus pyrotinib plus capecitabine in this patient population. Prof. Binghe Xu (Chinese Academy of Medical Sciences, China) presented the results [2].

The PHOEBE trial enrolled 267 Chinese patients with HER2-positive metastatic breast cancer who had been previously treated with trastuzumab and taxanes and up to 2 previous lines of chemotherapy in the metastatic setting. Patients were randomised 1:1 to treatment with either pyrotinib plus capecitabine or lapatinib plus capecitabine. The median follow-up was 33.2 months in the pyrotinib arm and 31.8 months in the lapatinib arm. Pyrotinib plus capecitabine significantly improved median progression-free survival compared with that for lapatinib plus capecitabine: 12.5 months versus 5.6 months (HR 0.48; P<0.0001). Median overall survival was not reached for pyrotinib and was 26.9 months for lapatinib (HR 0.69; P=0.019). Two-year overall survival rates were 66.6% and 58.8%, respectively. The benefit of pyrotinib plus capecitabine was observed in most clinically relevant predefined subgroups (including metastatic disease, trastuzumab resistance, pathological grading, visceral lesions, ECOG performance status, oestrogen and progesterone receptor status, and previous lines of chemotherapy).

"In conclusion, these updated results from PHOEBE reaffirm pyrotinib plus capecitabine as an established treatment option in this population," said Dr Xu.

1. Ma F, et al. J Clin Oncol. 2019;37:2610–2619.
2. Xu B, et al. Updated overall survival (OS) results from the phase 3 PHOEBE trial of pyrotinib versus lapatinib in combination with capecitabine in patients with HER2-positive metastatic breast cancer. GS3-02, SABCS 2021 Virtual Meeting, 7–10 December.

Basic and Translational Research

Using genomics to match treatments improves outcomes

The use of multigene sequencing as a therapeutic decision tool improved the outcomes for patients with metastatic breast cancer when the genomic alterations identified were ranked in the I/II tiers of the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT), according to results from the SAFIR02-BREAST trial.

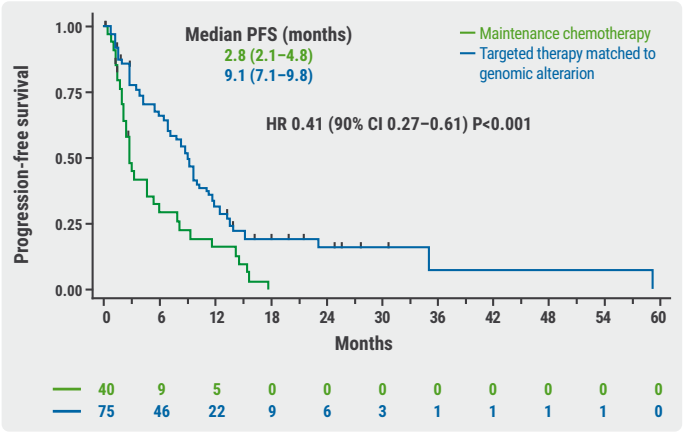
The aim of the phase 2 SAFIR02-BREAST study (NCT02299999) was to assess the clinical utility of multigene sequencing and DNA copy number analyses. The study enrolled patients with metastatic, HER2-negative breast cancer to evaluate whether targeted therapies guided by genomics improve progression-free survival (PFS) compared with maintenance chemotherapy. After 6 to 8 cycles of induction chemotherapy, patients without progressive disease who presented an actionable genomic alteration were randomised to targeted therapies matched to genomic alterations or maintenance chemotherapy. The researchers performed a pooled analysis of this trial and the phase 2 SAFIR-PI3K trial (NCT03386162) that compared a combination of the PI3Kα-specific inhibitor alpelisib and the oestrogen-receptor antagonist fulvestrant with maintenance chemotherapy in patients with *PIK3*CA-mutated metastatic breast cancer.

The primary objective was to evaluate whether targeted therapies guided by genomics improves PFS compared with maintenance chemotherapy. A hierarchical testing was applied. The efficacy of targeted therapies was first tested in patients presenting an ESCAT I/II alteration [1]. If a P<0.1 was observed in the first step, subsequent analyses were performed in the intent-to-treat population. Prof. Fabrice André (Institut Gustave Roussy, France) presented the results of SAFIRE02-BREAST [2].

Out of the 1,462 patients enrolled, 238 (16%) had stable disease after 6–8 cycles of chemotherapy and carried known genomic alterations. These patients were subsequently randomised between maintenance chemotherapy (n=81) and targeted therapy (n=157). In the 115 patients presenting an ESCAT I/II genomic alteration, the median PFS was 9.1 months and 2.8 months in matched-targeted therapy and maintenance chemotherapy arms respectively (HR 0.41; 90% CI 0.27–0.61; P<0.001; see Figure). In the intent-to-treat population, there was no significant difference in the duration of PFS between the 2 arms (HR 0.77, P=0.109), suggesting that the ESCAT

classification was highly predictive of the benefits of targeted therapies matched to genomic alterations.

Figure: Progressive-free survival between ESCAT patients on maintenance chemotherapy versus targeted therapy [2].



PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

"Our study showed that genomic analysis improves the outcome of patients with metastatic breast cancer if they carry alterations classified as ESCAT I/II," commented Prof. André. "These findings suggest that genomics should be a part of the pathway of care, but it has no impact if the results of the identified gene alterations are not interpreted using a validated framework of actionability, like ESCAT."

1. Mateo J, et al. Ann Oncol. 2018;29:1895–1902.
2. André F, et al. Clinical utility of molecular tumor profiling: Results from the randomized trial SAFIR02-BREAST. GS1-10, SABCS 2021 Virtual Meeting, 7–10 December.

How tamoxifen can induce uterine cancer

Long-term use of tamoxifen is associated with an increased risk for the development of uterine cancer. New research shows that tamoxifen directly activates a signalling pathway (PIK3) that is a well-known driver of uterine cancer development.

Tamoxifen is widely used in the adjuvant treatment of oestrogen receptor–positive breast cancer and is an important drug for premenopausal and postmenopausal patients who cannot tolerate aromatase inhibitors. Despite the clear clinical benefit, an adverse effect of tamoxifen is a 2–7-fold increased risk of uterine cancer after 2–5 years of treatment, with further increased risk after 10 years [1]. Dr Kirsten Kübler (Broad Institute, MA, USA) presented results of preclinical research aiming to clarify the mechanism by which tamoxifen increases the risk of uterine cancer and finding approaches to prevent tamoxifen-associated uterine cancer (TA-UC) [2].

Whole-exome sequencing was performed on 21 TA-UC samples obtained from the TAMARISK study [3]. These data were compared with molecular data from 544 *de novo* uterine cancers, cancers that were not associated with tamoxifen use. Most genomic alterations occurred at similar rates between TA-UC and *de novo* uterine cancers. The key exception was a significantly decreased frequency in patients with TA-UCs of mutations in the phosphoinositol-3-kinase (PI3K) signalling pathway, a well-known driver of uterine cancer development. Two essential components of the PI3K pathway were affected: the gene *PIK3CA* was mutated in 14% of TA-UCs versus 48% of *de novo* uterine cancers (P=0.003), and the gene *PIK3R1* was mutated in none of the studied TA-UCs versus 31% of *de novo* uterine cancers (P=0.001).

Additional studies in in vivo mouse models demonstrated that tamoxifen activates the PI3K pathway and increases cell proliferation in normal mouse uterine tissue through paracrine and autocrine effects, both of which are abrogated by the PI3K inhibitor alpelisib. "This suggested that the tamoxifen-driven increase in PI3K pathway signalling may, in effect, substitute for a *PIK3CA*- or *PIK3R1*-mutation to stimulate uterine cancer development," explained Dr Kübler. "Furthermore, the ability of a PI3K inhibitor to reduce cell proliferation in our mouse model raises the possibility that downregulating the PI3K pathway may prevent or significantly reduce TA-UC development, offering a potential future therapeutic and prevention strategy for specific high-risk patients undergoing tamoxifen therapy."

1. Davies C, et al. Lancet 2013;2381:805–816.
2. Kübler K, et al. Tamoxifen instigates uterine cancer development by activating PI3K signaling and supersedes PIK3CA driver mutations. GS2-09, SABCS 2021 Virtual Meeting, 7–10 December.
3. Hoogendoorn WE, et al. Breast Cancer Research and Treatment. 2008;112:99–108.

Loss of *ASXL1* tumour suppressor promotes resistance to CDK4/6 inhibitors

The pathways leading to CDK4/6 inhibitor resistance are not yet clear. Using a technique called 'accelerated mutagenesis,' researchers unravelled the role of *ASXL1* loss in CDK4/6 inhibitor resistance.

CDK4/6 inhibitors in combination with anti-oestrogens have prolonged survival of patients with oestrogen receptor (ER)-positive/HER2-negative metastatic breast cancer. However, this combination is not curative, mainly due to acquired drug resistance. Knowledge about mechanisms of such resistance remains incomplete. Dr Dhivya Sudhan (UT Southwestern Medical Center, TX, USA) reported results of new insights in the pathways leading to CDK4/6 inhibitor resistance [1].

Using CRISPR/Cas9 to delete the DNA mismatch repair gene *MSH2* in MCF7 and T47D ER-positive breast cancer cells, Dr Sudhan and colleagues obtained cells with drug resistance-associated mutations. Clones resistant to CDK4/6 inhibitors were selected and subjected to whole exome sequencing. Of the 10 genes recurrently mutated in the CDK4/6 inhibitor resistant cells, loss of *ASXL1* tumour suppressor was identified as top hit. Loss of *ASXL1* has been implicated in myeloid transformation through epigenetic reprogramming. In line with these findings, among 1,769 tumours from patients treated with CDK4/6 inhibitor (TEMPUS database), 37 exhibited *ASXL1* alterations. In addition, RNA sequencing of patient-derived organoids established from post-CDK4/6 inhibitor metastases, identified *ASXL1* mutations in 2/7 organoids (29%). Functional studies showed that loss of *ASXL1* was associated with maintenance of retinoblastoma phosphorylation in the presence of CDK4/6 inhibition, markedly higher levels of CDK2, CDK6, cyclins E and A, and downregulation of p21 and p27.

"We identified loss of *ASXL1* as a novel mechanism of resistance to CDK4/6 inhibition," concluded Dr Sudhan. "Knockdown of CDK2 and cyclin A restored sensitivity to CDK4/6 inhibitors and reduced viability of *ASXL1* deficient cells, suggesting that CDK2 inhibitors are a treatment approach against these drug-resistant tumours."

1. Sudhan DR, et al. Loss of ASXL1 tumor suppressor promotes resistance to CDK4/6 inhibitors in ER+ breast cancer. GS3-09, SABCS 2021 Virtual Meeting, 7–10 December.

Inducers of ferroptosis are potential drugs to target *p53*-mutated TNBC cells

Expression of a mutant *p53*-gene sensitises triple-negative breast cancer (TNBC) cells to death by ferroptosis. The experimental drug ML-162 induces ferroptosis in *p53*-mutated TNBCs and demonstrated anti-cancer activity *in vitro* and *in vivo*.

Up to 85% of TNBCs have a *p53* mutation as their oncogenic driver. Due to this high frequency of *p53* mutations in TNBCs, targeting *p53* mutants in a clinical setting could be highly attractive if pathways exist that, when inhibited, will induce the specific death of *p53*-mutant breast cancer cells, but not *p53*-wild type breast cells. Dr William Tahaney (MD Anderson Cancer Center, TX, USA) presented first results of the search for these pathways and drugs that can inhibit them [1].

In vitro and *in silico* drug screens identified 6 potential drugs that inhibit growth of *p53*-mutant TNBCs but not *p53*-wild type TNBCs. One drug, the perodixase inhibitor ML-162, was selected for further study and was found to induce death through ferroptosis, and not apoptosis or necroptosis. The effect of ML-162 was demonstrated in vivo by treating *p53*-mutant TNBC xenografts in nude mice with ML-162. This treatment significantly reduced tumour volume and induced lipid peroxidation, a hallmark of ferroptosis.

"In conclusion, our high-throughput screening demonstrated that several of the identified drugs suppress growth or induce death preferentially in *p53*-mutant TNBCs. One of these drugs, ML-162, induces death of *p53*-mutant TNBCs through induction of ferroptosis. Therefore, these studies provide the basic science foundation to further develop ferroptosis inducers for the targeted treatment of *p53*-mutant breast cancers," concluded Dr Tahaney.

1. Tahaney WM, et al. Inhibition of GPX4 induces preferential death of p53-mutant triple-negative breast cancer cells. GS1-09, SABCS 2021 Virtual Meeting, 7–10 December.

MAPK-pathway alterations are associated with resistance to anti-HER2 therapy

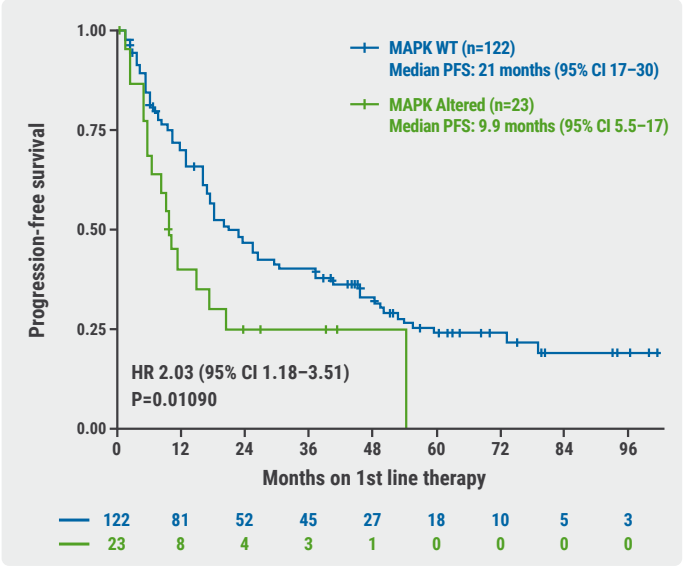
Genomic analysis of HER2-positive breast tumours identified pathways alterations associated with anti-HER2 resistance and new therapeutic vulnerabilities.

Resistance to anti-human epidermal growth factor receptor 2 (HER2)-therapy is common and more insight in the molecular pathways involved, could lead to new treatment strategies. Previous research demonstrated the involvement of alterations in the PI3K-pathway in resistance to anti-HER2 therapy [1,2].

To explore the role of the mitogen-activated protein kinase (MAPK)-pathway in anti-HER2 resistance, Dr Emanuela Ferraro (Memorial Sloan-Kettering Cancer Center, NY, USA) and colleagues performed next generation sequencing on 733 *HER2*-amplified tumours (385 primary, 348 metastatic) from patients with advanced HER2-positive breast cancer. Frequency of MAPK-pathway alterations was 9.8% in primary tumours and 15.6% in metastatic tumours [3,4]. Of note: frequency of PI3K-pathway alterations were 30.6% and 37.3%, respectively. Both PI3K-pathway alterations (mutant 13 months vs wildtype 23 months; P=0.0013) and MAPK-pathway alterations (mutant 9.9 months versus wildtype 21 months; P=0.01, see Figure) were associated with a statistically significant worse clinical outcome for progression-free survival. MAPK-pathway alterations were also independently associated with worse outcome after

correction for *PIK3CA* mutations, ERBB2 amplification, and oestrogen-receptor status (HR 2.24; P=0.0039). The causal involvement of MAPK-pathway in HER2-resistance was confirmed in additional *in vitro* studies, where MAPK-altered cell lines showed resistance to FDA approved HER2-inhibitors. In addition, HER2-resistant cell lines proved to be sensitive for MEK inhibitors.

Figure: Progression-free survival stratified by MAPK-pathway alteration [3,4].



MAPK, mitogen-activated protein kinase; WT, wildtype; PFS, progression-free survival; HR, hazard ratio.

"Our analysis uniquely identified MAPK-pathway alterations as additional potential drivers of resistance to anti-HER2 therapy. Inhibition of the PI3K or MAPK-pathway in such tumours may represent a new therapeutic strategy to extend the anti-HER2 benefit," concluded Dr Ferraro.

1. Berns K, et al. Cancer Cell. 2007;12:395–402.
2. Baselga J, et al. J Clin Oncol. 2014;32:3753–3761.
3. Ferraro E, et al. Genomic analysis of 733 HER2+ breast cancers identifies recurrent pathways alterations associated with anti-HER2 resistance and new therapeutic vulnerabilities. GS3-03, SABCS 2021 Virtual Meeting, 7–10 December.
4. Smith AE, et al. Nat Commun. 2021;12(1):6667.

Genomic signatures of DCIS define biology and correlate with clinical outcomes

Based on molecular analysis of 677 ductal carcinoma *in situ* (DCIS) samples, several subtypes of DCIS were identified as well as an 812-gene profile predictive for recurrence.

DCIS consists of a molecularly heterogeneous group of premalignant lesions, with variable risk of invasive progression. Understanding biomarkers for invasive progression could help individualise treatment recommendations based upon tumour biology and reduce overtreatment. As part of the National Cancer Institute's Human Tumor Atlas Network (HTAN), Dr Siri Strand (Stanford University, CA, USA) and colleagues conducted comprehensive genomic analyses on 2 large DCIS case-control cohorts with a 7.1-year median follow-up (TBCRC 038 and RAHBT) [1,2].

Gene expression analysis of 677 DCIS samples from 481 patients resulted in an 812-gene profile, which was predictive for recurrence (AUC 0.72). Based on the RNA expression of all coding genes, 3 clusters were identified, referred to as ER low, quiescent, and ER high. The ER-low cluster had significantly higher levels of ERBB2 and lower levels of ESR1 compared to quiescent and ER-high clusters. Quiescent cluster lesions were less proliferative and less metabolically active than ER high and ER-low subtypes. Based on DNA copy number aberrations, 6 subtypes of DCIS were identified. Focusing on the stromal component of DCIS from laser capture microdissection, 4 distinct DCIS-associated stromal clusters were identified. A "normal-like" stromal cluster with ECM organisation and PI3K-AKT signalling, a "collagen-rich" stromal cluster, a "desmoplastic" stromal cluster with high fibroblast and total myeloid abundance, mostly associated with macrophages and myeloid dendritic cells (mDC), and an "immune-dense" stromal cluster.

"Comprehensive genomic profiling in 2 independent DCIS cohorts with longitudinal outcomes shows distinct DCIS stromal expression patterns and immune cell composition. RNA expression profiles reveal underlying tumour biology that is associated with later ipsilateral breast events in both cohorts. These studies provide new insight into DCIS biology and will guide the design of diagnostic strategies to prevent invasive progression," said Dr Strand.

1. Strand SH, et al. The Breast PreCancer Atlas DCIS genomic signatures define biology and correlate with clinical outcomes: An analysis of TBCRC 038 and RAHBT cohorts. GS4-07, SABCS 2021 Virtual Meeting, 7–10 December.
2. Strand SH, et al. 2021 bioRxiv doi: 10.1101/2021.06.16.448585.

BRCA2 linked to inferior outcomes with CDK4/6 inhibitors plus endocrine therapy

An analysis of germline-somatic interactions in breast-cancer tumours revealed novel associations relevant to the disease's progression and treatment resistance. For example, carriers of the *BRCA2* mutation had inferior outcomes to treatment with first-line CDK4/6 inhibitors plus endocrine therapy.

Germline genetic alterations are established mediators of breast carcinogenesis, often giving rise to specific forms of genomic instability. *BRCA1/2* pathogenic variants are representative of this phenomenon through their induction of homologous recombination deficiency. While specific patterns of genomic instability may sensitise cancers to therapies such as Poly(ADP-ribose) polymerase inhibitors (PARPi) or platinum chemotherapy, their implications for lineage-directed therapies, such as endocrine therapy or CDK4/6 inhibitors, are unknown. Therefore, Dr Anton Safonov (Memorial Sloan-Kettering Cancer Center, NY, USA) and colleagues systematically investigated the patterns of association of germline alterations with specific somatic alterations and explored the resulting effect on clinical outcomes. The study included samples from 4,640 patients who underwent germline and matched tumour-tissue sequencing. Dr Safonov presented the results [1].

The most common germline pathogenic variants were *BRCA2*, *BRCA1*, *CHEK2*, *ATM*, and *PALB2*. Results confirmed previously established relationships, such as mutual exclusivity of germline *ATM* and *TP53* variants. Alterations in *TP53* were seen in 83% of germline *BRCA1* patients; however, this did not achieve significance when adjusted for receptor subtype (OR 3.90; 95% CI 1.34–11.38; Q=0.15).

Germline *BRCA2* was associated with a distinct somatic aberration profile compared with wild type. The most enriched somatic genes were variations in *RB1*, *AGO2* and *MYC*, respectively. The *RB1* enrichment was specific to *BRCA2* and was not seen with *BRCA1*.

Given that *RB1* is a well-established mechanism of CDK4/6 resistance, the effect of *BRCA2* status on the efficacy of CDK4/6 inhibitors in combination with endocrine therapy was investigated. Patients with germline *BRCA2* mutations were found to have relatively worse progression-free survival with endocrine therapy and CDK4/6 in first line and subsequent lines of therapy (HR 2.17; 95% CI 1.46–3.22; P<0.001).

"This finding raises the question whether hormone receptor positive patients with *BRCA2* should be treated with CDK4/6 inhibitors in the front-line setting as a standard or with PARP inhibitors instead?" Dr Safonov said.

1. Safonov A, et al. Comprehensive genomic profiling of patients with breast cancer identifies germline-somatic interactions mediating therapy resistance. GS4-08, SABCS 2021 Virtual Meeting, 7–10 December.

Miscellaneous

Olaparib is well tolerated as an additional treatment

Adjuvant treatment with the PARP-inhibitor olaparib showed beneficial effects for patients with *BRCA1/2* mutations and high-risk, HER2-negative, early-stage, primary breast cancer. In addition, patient-reported outcomes (PROs) demonstrated no negative impact on the quality of life.

OlympiA (NCT02032823) is a randomised, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy and safety of the PARP-inhibitor olaparib in patients with germline *BRCA1/2* mutations and high-risk, HER2-negative, early-stage, primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. A recently published interim analysis at a median follow-up of 2.5 years showed the 3-year invasive disease–free survival to be 85.9% in the olaparib group and 77.1% in the placebo group [1]. In the OlympiA trial, PROs were collected to inform the discussion between physicians and patients regarding the risks and benefits of additional adjuvant therapy. Dr Patricia Ganz (UCLA School of Medicine, CA, USA) presented the results [2].

A total of 1,836 patients were randomised (1:1) to 1 year adjuvant olaparib or placebo. PRO assessments were done at baseline and every 6 months up to 2 years. Data from 1,535 patients were available for these analyses. Baseline scores for fatigue were well balanced between study arms and clinically meaningfully lower in OlympiA patients compared with healthy women. Patients treated with olaparib experienced a higher increase in fatigue scores at 6 and 12 months compared with patients treated with placebo. However, this difference (-1.3 at 6 months, P=0.024 and -1.5 at 12 months, P=0.025) did not reach the prespecified border of a clinically meaningful

difference of 3 points. At 18 and 24 months, no differences in fatigue scores between patients treated with olaparib or placebo were observed. Scores for nausea and vomiting were clinically meaningfully higher in patients treated with olaparib at 6 months (P<0.001) and 12 months (P<0.001), but not at 18 and 24 months. Diarrhoea was not increased for either treatment group during the study. Physical functioning, emotional functioning, nor global health status was impaired over time for either treatment group.

"In conclusion, these results show that treatment with olaparib comes with a clinically meaningful increase in nausea and vomiting during the first year of treatment," said Dr Ganz. "Olaparib does not induce a clinically meaningful increase of fatigue, diarrhoea or a decrease in quality of life."

1. Tutt ANJ, et al. N Engl J Med 2021;384:2394–2405.
2. Ganz PA, et al. Quality of life results from OlympiA: A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high risk HER2 negative breast cancer. GS4-09, SABCS 2021 Virtual Meeting, 7–10 December.

Race effects the likelihood to develop lymphoedema following breast cancer treatment

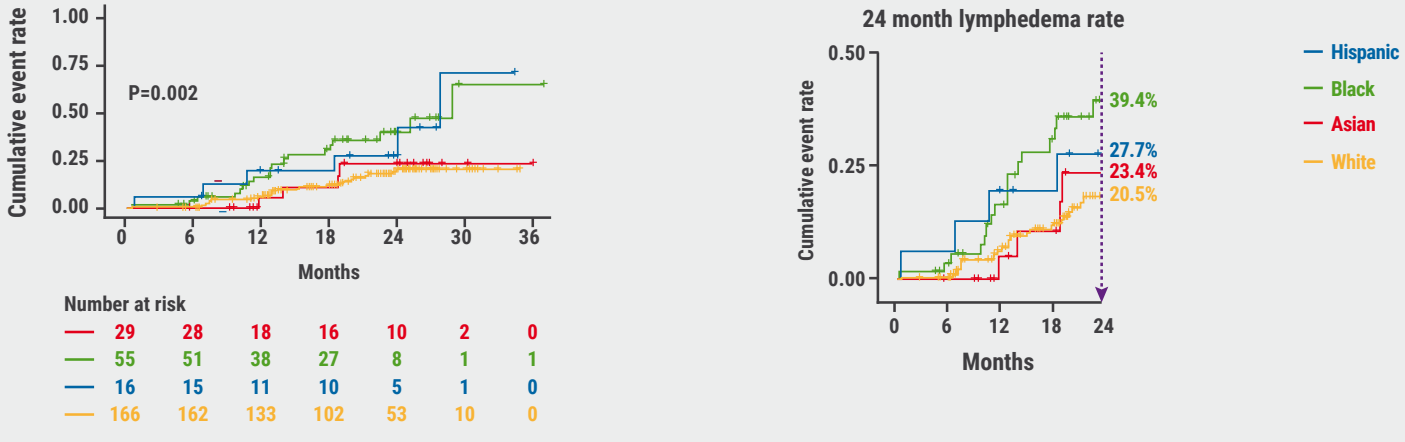
Development of breast cancer-related lymphoedema is not equally distributed between races. Black women experienced higher rates of breast cancer-related lymphoedema than White women, results of a prospective study show.

Lymphoedema is a well-known and quality-of-life lowering side effect of breast cancer treatment, particularly for women who undergo axillary lymph node dissection. Epidemiological and self-reported data suggest that Black women may be at increased risk of developing breast cancer related lymphoedema after axillary lymph node dissection, albeit that prospective clinical data is lacking. Dr Andrea Barrio (Memorial Sloan-Kettering Cancer Center, NY, USA) presented results from a prospective study investigating the impact of race and ethnicity on breast cancer related lymphoedema incidence and severity [1].

The study enrolled 304 patients and included 276 patients who had at least one longitudinal measurement after baseline included in the analysis. Sixty percent of the participants were White; 20% were Black; 11% were Asian; and 6% were Hispanic (3% did not report race or ethnicity). Black women were older (P=0.007), had higher baseline BMI (P<0.001), and were more likely to be clinically node-positive (P=0.016) compared to White, Asian, and Hispanic women. Both black and Hispanic women were more likely to undergo breast-conserving surgery (P=0.037) and receive nodal radiotherapy (P=0.02). Breast cancer-related lymphoedema was defined as a relative volume change of 10% or greater from baseline.

At a median follow-up of 1.6 years, 50 women developed breast cancer-related lymphoedema. The 24-month breast cancer-related lymphoedema rate was 20.5% for White women, 23.4% for Asian women, 27.7% for Hispanic women, and 39.4% for Black women (see Figure). Multivariate analysis showed that Black race was the strongest predictor of breast cancer-related lymphoedema development (OR 3.53; P<0.001) versus White women as reference category. Hispanic ethnicity was also associated with a higher incidence of breast cancer-related lymphoedema (OR 3.11). However, the number of Hispanic patients included was low. In addition, neoadjuvant chemotherapy was associated with a 2-fold increase (OR 2.07; P=0.017) of breast cancer-

Figure: Cumulative Incidence of Lymphedema by race/ethnicity [1].



related lymphoedema incidence. Among patients with lymphoedema, there was no difference in lymphoedema severity across racial and ethnic groups, with similar relative volume changes observed.

"The aetiology for the higher observed incidence of lymphoedema in Black women is unknown," said Dr Barrio. "It may be due to race-based differences in inflammatory reaction, tissue fibrosis, and lymphatic function. Future studies should address the biologic mechanisms behind racial disparities in lymphoedema development and develop possible preventive strategies."

In addition, analysis of the data from the I-SPY trial (NCT01042379) showed that race did not significantly affect several key measures of breast cancer treatment outcomes, including pathologic complete response (OR relative to White: 1.00 for Asian and 0.89 for Black) and event-free survival (HR relative to White: 1.10; P=0.73 for Asian and 1.37; P=0.13 for Black) [2].

1. Montagna G, et al. Impact of race and ethnicity on incidence and severity of breast cancer related lymphedema after axillary lymph node dissection: Results of a prospective screening study. GS4-01, SABCS 2021 Virtual Meeting, 7–10 December.
2. Kyalwazi B, et al. Analysis of clinical outcomes and expression-based immune signatures by race in the I-SPY 2 trial. GS4-02, SABCS 2021 Virtual Meeting, 7–10 December.

Sentinel lymph node staging is non-inferior to complete axillary lymph node dissection

Axillary lymph node dissection (ALND) is an effective procedure for axillary staging. However, it is associated with a significant risk of morbidity. The minimal invasive and less morbid sentinel lymph node biopsy (SLNB) is non-inferior to ALND, results of the SINODAR ONE trial show.

Sentinel lymph node (SLN) staging is currently used to avoid complete ALND in breast cancer patients. The SLN is the only site of axillary metastasis in ≥60% of cases. Therefore, the SINODAR ONE study (NCT05160324) evaluated whether SLNB is or is not inferior to ALND. The study enrolled 889 patients between 40–75 years with a primary invasive T1-T2 tumour, axillary nodes cN0, no more than 2 macro-metastatic SLNs, no distant metastasis, no neo-adjuvant therapy, and no previous invasive breast cancer. All patients underwent SLNB and were randomised 1:1 to standard (SLNB plus ALND) or experimental (only SLNB) treatment. Dr Damiano Gentile (Humanitas Research Hospital, Italy) presented the results [1].

Most patients (77.2%) received breast-conserving surgery, while 22.8% of patients underwent mastectomy. A median of 2 SLNs were removed in both arms. Overall, only 3 micro-metastatic SNLs were found: 1 in the standard arm and 2 in the experimental arm. No statistical difference was found between the 2 treatments in terms of survival and recurrence: 5-years overall survival was 98.9% versus 98.8% and 5-year recurrence-free survival was 96.3% versus 95.6% in the standard versus experimental arm, respectively (see Table).

Table: Recurrence-free survival and overall survival after SLNB versus ALND [1].

Outcomes	Standard treatment	Experimental treatment	P value
RFS rate (ITT)			
- 1-year	99.0%	98.9%	
- 3-year	97.9%	97.0%	0.511
- 5-year	96.3%	95.6%	
OS rate (ITT)			
- 1-year	99.5%	100%	
- 3-year	98.9%	98.8%	0.936
- 5-year	98.9%	98.8%	
RFS rate (PP)			
- 1-year	99.0%	99.0%	
- 3 year	98.0%	97.0%	0.491
- 5-year	96.4%	95.6%	
OS rate (PP)			
- 1-year	99.5%	100%	
- 3 year	99.2%	98.7%	0.753
- 5-year	99.2%	98.7%	

RFS, recurrence-free survival; OS, overall survival; ITT, intention-to-treat; PP, per-protocol

"We believe randomisation between ALND and SLN staging is no longer justified. We favour the omission of complete axillary dissection in international guidelines," concluded Dr Gentile.

1. Gentile D, et al. Preservation of axillary lymph nodes compared to complete dissection in T1-T2 breast cancer patients presenting 1-2 metastatic sentinel lymph nodes. A multicenter randomized clinical trial. Sinodar One. GS4-05, SABCS 2021 Virtual Meeting, 7–10 December.

One in 7 breast cancers detected during screening are overdiagnosed

A new model, based on data from the Breast Cancer Surveillance Consortium (BCSC), suggests that over-diagnosis of screen-detected breast cancer is less frequent than estimated from excess-incidence studies. However, the model also takes indolent tumours into account and produced a higher estimate than previous models that didn't consider this factor.

Breast cancer screening is subject to overdiagnosis, which is the mammographic detection of cancers that would not become symptomatic or otherwise cause harm in the absence of screening. Estimates of overdiagnosis based on excess incidence are prone to bias, and estimates based on models have been criticised for not explicitly accommodating indolent tumours. Dr Marc Ryers (Duke University Medical Center, NC, USA) and colleagues developed a model that accounts for the transition from healthy to preclinical and clinical disease, while allowing for a fraction of indolent preclinical tumours [1]. Based on data of 35,986 women, 82,677 screens, and 718 breast cancer diagnoses, the predicted overdiagnosis rate among screen-detected cases was 15.3% (95% Prediction Interval [PI] 9.7–25.2), where 6.0% (95% PI 0.2–19.0) was due to the detection of indolent cancers and 9.3% (95% PI 5.8–13.6) was due to competing mortality [2]. For a program of annual screening from age 50–74, the overall predicted overdiagnosis rate was 14.6% (95% PI 9.4–23.9).

"Our results indicate that overdiagnosis among screen-detected cancers is less frequent than estimated by excess-incidence studies and more frequent than estimated by previous modelling studies that did not account for indolent tumours," concluded Dr Ryser.

1. Ryser MD, et al. Am J Epidemiol. 2019;188:197–205.
2. Ryser MD, et al. Estimation of breast cancer over diagnosis in a US breast screening cohort. GS4-06, SABCS 2021 Virtual Meeting, 7–10 December.