# Breast Cancer RESEARCH REVIEW™

Making Education Easy

Issue 1 – 2020


## In this issue:



**Abbreviations used in this issue**
**CNS** = central nervous system
**CT** = computed tomography
**DFS** = disease-free survival
**FDA** = Food and Drug Administration
**HER2+** = human epidermal growth factor receptor 2–positive
**HR** = hazard ratio
**HRT** = hormone replacement therapy
**mBC** = metastatic breast cancer
**ORR** = overall response rate
**OS** = overall survival
**pCR** = pathological complete response
**PFS** = progression-free survival
**RRSO**= risk-reducing salpingo-oophorectomy
**TKI** = tyrosine kinase inhibitor
**TNBC** = triple receptor–negative breast cancer



# Welcome to this issue of Breast Cancer Research Review

The COVID-19 pandemic has compounded the challenge of providing timely treatment to achieve the best outcomes for patients with breast cancer. A study on key performance indicators reviewed in this issue reports that rates of care in Australia and New Zealand prior to the pandemic were lower than international standards. Other studies reviewed in this issue assess different treatment options and their impact on survival outcomes.

We hope you enjoy our selection for this issue and welcome your comments and feedback.

Kind regards,

**Dr David Okonji**
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## Risk-reducing salpingo-oophorectomy, natural menopause, and breast cancer risk

**Authors:** Mavaddat N, et al.


**Summary:** The association between risk-reducing salpingo-oophorectomy (RRSO) and breast cancer risk was explored in a multicentre prospective cohort of BRCA1 (n=2272) and BRCA2 (n=1605) mutation carriers with a mean follow-up of 5.4 years and 4.9 years, respectively. No evidence of risk reduction with RRSO was evident for BRCA1 mutation carriers (HR 1.23; 95% CI 0.94–1.61). A potentially beneficial effect was observed for BRCA2 mutation carriers for RRSO carried out before age 45 years (HR 0.68; 95% CI 0.40–1.15) compared with after age 45 years (HR 1.07; 95% CI 0.69–1.64). Increased risk reduction was also evident in BRCA2 carriers with ≥5 years elapsed since RRSO (HR 0.51; 95% CI 0.26–0.99). Effects in premenopausal and postmenopausal women were similar.


**Comment (EWK):** This is the largest multicentre, prospective cohort study of 3,877 women who carry a pathological variant of either BRCA1/2 genes to examine the role of RRSO in breast cancer risk-reduction. It showed there was no association between RRSO and breast cancer for BRCA1 pathological variant carriers, and a very modest risk reduction for BRCA2 after more than 5 years since the surgery. This is very valuable information for our consenting process as there is a perception amongst clinicians and patients that a RRSO will reduce ovarian cancer and breast cancer such that only one risk-reducing operation may be required. Effective pharmaceutical ovarian suppression is available to treat breast cancers and RRSO should occur for ovarian risk-reduction only. The timing of this needs to be balanced with the comorbidities associated with early oophorectomy including reduced quality of life, cardiovascular disease, and osteoporosis. Patients need to be aware that they require continued breast surveillance following RRSO if they do not opt for risk-reducing mastectomy. Further work is required with longer follow-up particularly in younger women and the association between HRT use and breast cancer risk following RRSO in gene carriers.


***Reference: Breast Cancer Res. 2020;22(1):8.***

Abstract

## What are the appropriate thresholds for high quality performance indicators for breast surgery in Australia and New Zealand?

**Authors:** Salindera S, et al.

**Summary:** Thresholds for compliance with high quality performance indicators to improve patient care were evaluated using BreastSurgANZ Quality Audit data from 2012–2016 and 2018. Using thresholds comparable with globally accepted standards: a threshold of ≥40% for immediate breast reconstruction in 3761 patients undergoing mastectomy for in situ disease would be achieved by 30% of all members and 78% of very high-volume surgeons; a threshold of ≥70% for breast conservation in 31,698 patients with invasive tumours ≤2 cm would be achieved by 64% of all surgeons. Using thresholds lower than globally accepted standards: a threshold of ≥20% for immediate breast reconstruction in 26,007 patients undergoing mastectomy would be achieved by 28% of all members and 78% of very high-volume surgeons; a threshold of ≥15% for neoadjuvant chemotherapy in 1382 patients aged ≤50 years would be achieved by 36% of all surgeons.

**Comment (EWK):** A good reminder to us all on the importance of standards, measuring them and reflecting on them to improve patient outcome and care. It is not surprising to see that higher volume surgeons are more compliant with the standards however the curves are not so far apart as one would expect. The usual themes of under-resourcing and access will be contributing to this; however surgeon preference does have an impact and we have to be mindful of offering all the options available. Some of the key performance indicators measured do relate to patient survival and in our current environment of rapidly increasing costs of cancer treatments and diagnostics, it is important to remember that there is plenty of room for survival gains in maximising what we do have: mammogram screening, multidisciplinary teams and use of the available, and sometimes very cheap, adjuvant therapies. The additional measure of the use of neoadjuvant chemotherapy for under 50s is timely following the Create-X and Katherine trials which show a survival benefit using adaptive therapy in some groups who do not achieve pCR. Neoadjuvant chemotherapy in these groups is no longer a 'nice to have' to allow surgical planning and genetic testing but offers an improved outcome. It is important that the audit captures the patient choice as a reason for non-compliance as increasingly we are competing with a world of limitless information and the option of alternative treatments. Lastly, there is the issue of 'outlier surgeons' and how best to work to improve compliance and patient outcome which is a further goal of BreastSurgANZ.

***Reference: Breast. 2020;51:94-101.***
Abstract



## Dietary supplement use during chemotherapy and survival outcomes of patients with breast cancer enrolled in a cooperative group clinical trial (SWOG S0221)

**Authors:** Ambrosone CB, et al.

**Summary:** Associations between breast cancer outcomes and supplement use were evaluated in a prospective study ancillary to a therapeutic trial in 1134 patients randomised to receive cyclophosphamide, doxorubicin and paclitaxel. Use of vitamin B12 was associated with worse DFS (HR 1.83; 95% CI 1.15–2.92; p<0.01) and OS (HR 2.04; 95% CI 1.22–3.40; p<0.01). Breast cancer recurrence was significantly associated with iron supplementation (HR 1.79; 95% CI 1.20–2.67; p<0.01) and use of antioxidant supplements such as vitamins A, C, E; carotenoids and coenzyme Q10 (HR 1.41; 95% CI 0.98–2.04; p=0.06). Small numbers limited evaluation of relationships between survival outcomes and individual antioxidants. There was no association between survival outcomes and use of multivitamins.

***Reference: J Clin Oncol. 2020;38(8):804-814.***
Abstract

## Complementary and alternative medicine and musculoskeletal pain in the first year of adjuvant aromatase inhibitor treatment in early breast cancer patients

**Authors:** Hack CC, et al.

**Summary:** Use of complementary and alternative medicine (CAM) did not prevent or improve the development of aromatase inhibitor-induced musculoskeletal syndrome in a phase 4 study in 1396 postmenopausal patients receiving letrozole for hormone receptor–positive early breast cancer. CAM included vitamins, high-dose vitamin C, food supplements, mistletoe, enzymes, acupuncture, homeopathy, Chinese herbs, mushrooms, meditation, prayer, relaxation, yoga, tai chi, qigong, and bioresonance. The majority of patients (64.5%) had a history of CAM use prior to initiation of aromatase inhibitor treatment and these patients had higher pain scores for muscle or joint pain than CAM non-users. Both users and non-users of CAM experienced significant increases in pain over time, particularly during the first 6 months of aromatase inhibitor therapy.

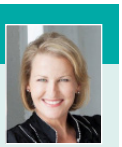
***Reference: Breast. 2020;50:11-18.***
Abstract

**Comment (EWK):** Two interesting and timely papers measuring the outcome of commonly used CAM. CAM can be divided into a few groups including those focusing on the mind, body, manipulation and exercise, however a number of cancer patients also use ingestible CAM during and after their treatment. Many of these come accompanied with strong claims of improving cancer survival and with no side effects, which can be difficult to compete with when conventional medicine can offer an intention-to-cure with side effects. As these products are over-the-counter, there is also a belief that they are harmless.

Ambrosone et al. demonstrate that these products are far from harmless and cause an increase in breast cancer recurrence and to a lesser extent, death. This included antioxidants, and non-oxidants such as B12 and iron. It remains unclear whether supplements exert a direct or indirect stimulatory effect on cancer cells or if they interfere with the chemotherapy pharmacokinetics/pharmacodynamics. Either way, they do lead to a poorer outcome whilst multivitamins showed no benefit either way, which suggests they are unnecessary.

Hack et al. look at the use of CAM in relation to aromatase inhibitor-associated musculoskeletal pain: it did not prevent or reduce the pain, in fact the CAM users reported higher pain scores. A large 64% of patients in this study reported use of CAM at the time of diagnosis and therefore before the start of aromatase inhibitor treatment. This group also reported a higher baseline pain which needs to be investigated – do they have a higher susceptibility to pain? Is there a specific character profile or personality that is more liable to use CAM to improve their quality of life? There are issues with this paper; whilst a large study there were patients excluded, use of analgesics was not measured and the patients were enrolled in 2009–2010. However, the conclusions do fit with the Australian paper by Lombard et al. which also failed to find a significant benefit of CAM in this setting. As 35% of New Zealanders regularly take a health supplement, it is important our patients understand that over-the-counter products are not without their risks, and importantly, unlikely to benefit as well. Good luck with that conversation… it is not always well received.

### Independent commentary by Erica Whineray Kelly



Erica is a breast cancer surgeon and advocate based in Auckland, New Zealand. Erica co-founded and is the managing director of both Auckland Breast Centre (ABC) and Focus Radiotherapy. Erica is also a consultant for the national breast screening programme, a member of New Zealand Global Women, Australasian and European breast cancer organisations, is a Be. Accessible Fab 50 leader as an advocate in the accessibility space, and was a founding Chair of the advisory board of the InZone Girls project. Outside this, Erica is a mentor to a number of students, and is married with two children.

## Late effects of adjuvant chemotherapy adumbrate dormancy complexity in breast cancer

**Authors:** Demicheli R, et al.

**Summary:** Adjuvant chemotherapy reduced the rate of early and intermediate relapses in an analysis of 1518 premenopausal patients with node-positive breast cancer. Patients were enrolled in a series of randomised clinical trials on early breast cancer and underwent surgery only (n=397) or surgery + adjuvant chemotherapy (n=1121). After follow-up of ≥15 years, adjuvant chemotherapy reduced the rate of distant metastases changing the pattern from two early sharp peaks at 9 months and 33 months with surgery only to a residual peak at 18 months. With adjuvant therapy, the wide intermediate peak spanning from 50 months to 90 months in patients who underwent surgery only changed to two small peaks at 50 months and 80 months. The late peak at 115–120 months was unchanged by adjuvant therapy.

**Comment (EWK):** A very interesting look at older data from randomised trials from between 1972–1987 in Milan and Belgium to observe the hazard ratios for distant recurrence in premenopausal women. These patients were treated with either surgery or surgery and chemotherapy with a minimum follow up of 15 years. The aim was to assess the relapse peaks following primary surgical removal. It is known that there is a dormancy in breast cancer and that surgery to remove the primary tumour can terminate this dormancy and induce early relapse. The paper described the four peaks of distant metastases at 1, 3, 6 and 10 years but also that adjuvant chemotherapy reduced the size of the peaks at 1, 3 and 6 years. However, chemotherapy did not alter the size of the 10-year peak. This supports the paradigm of breast cancer development including tumour homeostasis, parallel tumour development, the role of the microenvironment, and surgical acceleration of the metastatic process. The chemoresistant nature of the micrometastatic cells that induce the 10-year relapse suggest a parallel/different biology. This suggests a multiplicity of dormant nanometastases parallel in development and unique in sensitivity to treatments. What would add to this is long-term data on the role of endocrine treatment on relapse which was not given in these patients. The key to improving survival for these late relapses will be understanding the mechanisms around tumour dormancy.

***Reference: Breast. 2020 May 8. doi.org/10.1016/j.breast.2020.05.002. [Epub ahead of print]***
Abstract



## Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer

**Authors:** Murthy RK, et al.

**Summary:** The addition of oral tucatinib, a highly selective inhibitor of HER2 tyrosine kinase, to trastuzumab and capecitabine treatment significantly improved survival outcomes in a randomised, placebo-controlled study of 612 women with heavily pre-treated HER2+ mBC. Rates of PFS at 1 year were 33.1% in patients treated with tucatinib and 12.3% in patients who received placebo (HR 0.54; 95% CI 0.42–0.71; p<0.001). PFS rates in patients with brain metastases were 24.9% and 0%, respectively (HR 0.48; 95% CI 0.34–0.69; p<0.001). Median duration of PFS was 7.8 months with tucatinib (7.6 months for patients with brain metastases) and 5.6 months with placebo (5.4 months for patients with brain metastases). Rates of OS at 2 years were 44.9% in patients treated with tucatinib and 26.6% in patients who received placebo (HR 0.66; 95% CI 0.50–0.88; p=0.005). Median OS was 21.9 months and 17.4 months, respectively. Adverse events that occurred more commonly with addition of tucatinib compared with placebo included diarrhoea and elevated aminotransferase levels.

**Comment (DO):** There has been near tripling in OS from a median survival of 2 years to now approximately 6 years, due to therapeutic advances in HER2+ mBC in the last 20 years. Despite this, 40–50% of patients with this metastatic disease subtype will subsequently develop CNS metastases at some point in their disease course, eventually succumbing to them. The HER2CLIMB study addresses this unmet need, becoming the first randomised control trial in HER2+ mBC to include patients with untreated and/or progressive brain metastases. Tucatinib, the investigational product in question, is a small molecule TKI that is more selective in its HER2-receptor targeting, unlike the other two approved TKIs for treating HER2+ mBC, lapatinib (approved in 2007 and targeting HER1 and HER2) and neratinib (approved in 2020 and targeting HER1, 3 and 4). In this study, combination tucatinib, trastuzumab and capecitabine doubled the ORR in the overall population compared to the control, thereby reducing the risk of progressive disease by half in a population that had previously progressed on trastuzumab, pertuzumab and T-DM1 in the metastatic setting. On the strength of these results, tucatinib received full FDA approval in April 2020, becoming the 7th US FDA approved anti-HER2 therapy. It is, arguably, the new standard of care in the third-line metastatic setting in HER2+ mBC. Of particular note, and with the caveat that we must not make cross-trial comparisons, combination lapatinib and capecitabine (pooled meta-analysis)[1] and neratinib and capecitabine (smaller phase 2 study)[2] registered a CNS ORR of 29% and 49%, respectively, in the same disease subtype and setting. However, the CNS ORR of combination tucatinib, trastuzumab and capecitabine was not reported in this publication; as such, it will be intriguing to know (when undoubtedly this is subsequently reported) whether the CNS ORR of tucatinib, trastuzumab and capecitabine not only reflects that seen in its preceding non-randomised phase 1 study (40%),[3] but also how it matches up to its other TKI competitors in this space and setting. Either way, what is clear and unanimous is that even in the face of theoretical/preclinical concerns regarding evolving tumour-related anti-HER2 therapy resistance, the HER2 receptor remains an active and important target even in heavily pre-treated HER2+ mBC. On the other hand, what is less clear and remains to be answered, is whether capecitabine could be omitted in long-term responders while maintaining a backbone of maintenance tucatinib and trastuzumab in a bid to avoid the untoward fluoropyrimidine-related side effects of diarrhoea, palmar-plantar erythrodysesthesia, fatigue and nausea. Finally how relevant are these data in New Zealand breast oncology practice? Firstly, there are no publicly funded treatment options beyond trastuzumab, pertuzumab and T-DM1 (i.e. first- and second-line therapies, respectively); furthermore, in contrast to jurisdictions in both Europe and the USA, the practice of continuing trastuzumab post-progression, while switching chemotherapy partners is not expressly permitted. Therefore, even the control arm of the HER2CLIMB study, which is likely to fare better than best supportive care is (strictly speaking) not available in New Zealand as a third-line treatment option.

***Reference: N Engl J Med. 2020;382(7):597-609.***
Abstract

## Trastuzumab deruxtecan in previously treated HER2-positive breast cancer

**Authors:** Modi S, et al.

**Summary:** The efficacy of trastuzumab deruxtecan was evaluated in an open-label, single-group, multicentre, phase 2 study in 184 patients with HER2+ mBC who had received previous treatment with trastuzumab emtansine. The recommended dose of trastuzumab deruxtecan was established as 5.4 mg/kg. ORR was 60.9% (95% CI 53.4–68.0), median duration of response was 14.8 months (95% CI 13.8–16.9) and median PFS was 16.4 months (95% CI 12.7–not reached). Common grade ≥3 adverse events included decreased neutrophil count (20.7%), anaemia (8.7%) and nausea (7.6%). Interstitial lung disease was observed in 13.6% of patients and indicated a need for careful monitoring of pulmonary symptoms.

**Comment (DO):** Standard chemotherapy agents often have narrow therapeutic indices with low specificity resulting in early, intermediate and late toxicities. Furthermore, they are vulnerable to the development of early tumour resistance resulting in short progression-free intervals. Antibody drug conjugates (ADCs) are therefore a result of a collective desire in both patients and their oncologists to access therapies with wider therapeutic index, which avoid unnecessary toxicity without compromising outcomes. For the last 7 years in the USA (and less than 6 months in New Zealand), there was only one ADC (T-DM1) approved for treating mBC. In the last 4 months, two new ADCs received accelerated US FDA approval for the treatment of mBC: trastuzumab deruxtecan (December 2019) and sacituzumab govitecan-hziy (April 2020) for metastatic HER2+ and triple receptor–negative disease, respectively. Trastuzumab deruxtecan is an ADC consisting of a humanised HER2 antibody attached to chemotherapy. In this study, DESTINY-Breast01, a heavily pre-treated population with HER2+ mBC (who received a median of 6 lines of therapy in the metastatic setting, including pertuzumab, trastuzumab and T-DM1 itself) registered an astonishing 97.3% disease control rate while on trastuzumab deruxtecan. What's more, the ORR seen in this phase 2 study was not only deep and prolonged, but was also surprisingly identical to that reported in its preceding phase 1 counterpart (60% vs 59.5%, respectively).[4] Allowing for the vagaries of cross-trial comparisons, T-DM1, when evaluated in a phase 3 trial setting in a less pre-treated population (1–5 lines), who had not previously received pertuzumab, only managed an ORR of 31–43%; furthermore, the PFS with T-DM1 was 6–9 months,[5,6] while that seen with trastuzumab deruxtecan was 16.4 months. Potential explanations for the augmented potency of this drug appear to be firstly its payload: unlike T-DM1 in which the payload is a tubulin inhibitor, trastuzumab deruxtecan contains a topoisomerase I inhibitor, a chemotherapy agent that is not traditionally used in breast cancer and so less likely to confer cross-resistance. Secondly, is its higher chemotherapy drug to antibody ratio: 7–8 chemotherapy drug molecules per antibody versus T-DM1's 3–4 per antibody. Thirdly, it is highly membrane permeable, thus exhibiting a "bystander effect", meaning it may also have cytotoxic properties on tumour cells not expressing the HER2 receptor; therefore, it may be effective in disease demonstrating tumour heterogeneity. A going concern, however, is the small but not insignificant risk of drug-related interstitial pneumonitis (13.6% incidence, 2.2% mortality) with a median onset of 6–7 months; this clearly requires clinical vigilance, a low threshold for investigation with a high resolution CT chest, prompt drug discontinuation and high-dose glucocorticoid therapy if confirmed. Finally, it must be borne in mind that the DESTINY-Breast01 study was an open-label, single-arm phase 2 dose-registration study and so the results of the confirmatory phase 3 DESTINY-Breast02 trial in the T-DM1 refractory setting are eagerly awaited.

***Reference: N Engl J Med. 2020;382(7):610-621.***
Abstract

## Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA)

**Authors:** Swain SM, et al.

**Summary:** Improvements in OS with pertuzumab versus placebo, in combination with trastuzumab and docetaxel, were maintained after a median of >8 years of follow-up in 808 patients with HER2+ mBC in the randomised, double-blind, placebo-controlled, phase 3 CLEOPATRA study. Median OS was 57.1 months after 99.9 months follow-up in patients treated with pertuzumab and 40.8 months after 98.7 months follow-up in patients who received placebo (HR 0.69; 95% CI 0.58–0.82). OS survival rates at 8 years were 37% and 23%, respectively. Treatment-related deaths were reported for 5 patients (1%) in the pertuzumab group and 6 patients (2%) in the placebo group. The long-term safety and cardiac safety profiles of pertuzumab, trastuzumab, and docetaxel were maintained, with two notable adverse events reported in patients who received pertuzumab since the previous analysis: congestive heart failure (n=1) and symptomatic left ventricular systolic dysfunction (n=1).

**Comment (DO):** This paper, although descriptive and exploratory, is exemplary in that it stands out as one of very few randomised controlled trials reporting a significant long-term sustained survival outcome: 8 years after a diagnosis with HER2+ mBC, over a third of patients were still alive on account of anti-HER2 therapy and chemotherapy. The authors proceed to define a clinical phenotype of "long-term responder" to be a patient with PFS not less than approximately 3 years (irrespective of which arm they were on in the study). They also have an ECOG performance status of 0, with tumours that are progestogen receptor–positive, with non-visceral involvement and median time from diagnosis with early-to-metastatic disease of approximately 2.5 years. In interpreting these astounding OS results, several key points must be borne in mind. Firstly, in stark contrast to contemporary practice, only 10% of patients in this study received adjuvant trastuzumab;[7] as such, the CLEOPTARA results are probably best applied to those with anti-HER2 therapy–naïve de novo HER2+ mBC. Secondly, those who were hormone receptor–positive were not allowed to receive endocrine therapy either during or, as is often the case in the real-world setting, as maintenance alongside anti-HER2 therapy after completing induction chemotherapy. Preclinical studies provide compelling evidence for the two-way traffic cross-interaction between the oestrogen receptor and HER2 receptor;[8] furthermore, a recent phase 2 study supports the premise that concomitant oestrogen receptor and dual anti-HER2 inhibition may provide a viable alternative to the conventional CLEOPATRA regimen, particularly in those exhibiting "a long-term responder" clinical phenotype.[9] Finally, 16% of patients were not only alive, but also remained progression free at the 8-year mark in this study. It is likely that these patients remain on a 3-weekly anti-HER2 therapy to this day; if these patients may have achieved potential cure, would it be possible at all to de-escalate/discontinue their anti-HER2 therapy altogether? Tantalising as it may sound, I suspect most breast oncologists would hesitate to do this.

***Reference: Lancet Oncol. 2020;21(4):519-530.***
Abstract



**Independent commentary by**
**Dr David Okonji** MB BCh (UK) MRCP(UK) MRCPS(Glas) FRACP

Dr David Okonji specialises in treating breast and urogenital cancers, as well as melanoma. He has a particular focus on cancer care in the elderly. David currently practises at Wellington Regional Hospital and also undertakes private practice at Bowen Hospital, Wellington.

David is a Clinical Senior Lecturer at the University of Otago School of Medicine. He is actively involved in research as an investigator in clinical trials at Wellington Hospital. He is also an active member of the American Society of Clinical Oncology, the European Society of Medical Oncology and the Society of Geriatric Oncology.

## Pembrolizumab for early triple-negative breast cancer

**Authors:** Schmid P, et al.

**Summary:** The addition of pembrolizumab to neoadjuvant chemotherapy significantly increased the pCR rate at the first interim analysis (n=602) in a randomised phase 3 trial in patients with previously untreated stage II or III TNBC. The pCR rate was 64.8% in patients treated with pembrolizumab + chemotherapy and 51.2% in patients who received placebo + chemotherapy (difference 13.6%; 95% CI 5.4–21.8; p<0.001). The incidence of disease progression precluding definitive surgery, local or distant recurrence, a second primary tumour, or all-cause death was 7.4% in the pembrolizumab + chemotherapy group (n=784) and 11.8% in the placebo + chemotherapy group (n=390) after a median follow-up of 15.5 months (HR 0.63; 95% CI 0.43–0.93). The incidence of grade ≥3 adverse events was similar for pembrolizumab and placebo (78% vs 73%).

**Comment (DO):** pCR (defined as no evidence of tumour in the resected breast primary or associated ipsilateral axillary lymph nodes) after neoadjuvant systemic therapy is associated with an extremely favourable DFS and OS in early breast cancer. The correlation between pCR and long-term outcome is strongest for TNBC subtype.[10] However, the optimum neoadjuvant therapy for early TNBC is unknown. In this context, KEYNOTE-522 sought to evaluate the efficacy of adding immunotherapy to neoadjuvant chemotherapy; in the process though, it has brought several key discussion points to the fore. The first is the choice of chemotherapy backbone. Although carboplatin has been shown to increase absolute pCR rates by 15% (when added to standard anthracycline-taxane regimens),[11] it has resulted in conflicting survival outcomes.[12] Therefore, its inclusion in this study population where 75% of patients had moderate rather than high-risk features (stage II as opposed to stage III disease) appears difficult to justify, especially in the context of the documented increased grade 3/4 haematological toxicities associated with adding a platinum agent. Secondly, those not achieving pCR in either arm were not permitted to receive adjuvant capecitabine as per the previously published CREATE-X phase 3 trial;[13] furthermore, those receiving immunotherapy/placebo continued the said treatment in the post-surgical adjuvant setting even after achieving pCR neoadjuvantly; this seems somewhat counterintuitive to the prevailing narrative of de-escalating therapy in those with favourable prognoses. Nonetheless, the study achieved its primary endpoint of improved pCR with the addition of pembrolizumab to neoadjuvant chemotherapy. Hence, is there an expectation that neoadjuvant pembrolizumab plus anthracycline-taxane-platinum chemotherapy will become the new standard of care in early TNBC? Not just yet. We will have to wait a bit longer for the event-free survival to mature. In the meantime, adjuvant therapy in those with residual disease after neoadjuvant chemotherapy may provide a pragmatic opportunity for personalised precision medicine: to select out those who are most likely to benefit and in so doing minimise unwarranted toxicity in those who do not need it. By utilising postoperative biomarkers to further characterise "poor responders" with non-pCR disease who are at higher risk of relapse, decisions can subsequently be made on whether to consider adjuvant chemotherapy, immunotherapy or both. With this in mind, the ECOG-ACRIN 1131 study [ClinicalTrials.gov Identifier: NCT02445391] will be comparing adjuvant capecitabine versus cisplatin/carboplatin in those with residual disease after neoadjuvant chemotherapy. On the other hand, KEYNOTE 242 [ClinicalTrials.gov Identifier: NCT02954874] and A-BRAVE [ClinicalTrials.gov Identifier: NCT02926196] trials will be evaluating adjuvant pembrolizumab and avelumab, respectively, in those with high-risk TNBC (in both overall population and PD-L1-positive sub-population) who have completed (neo)adjuvant chemotherapy.

***Reference: N Engl J Med. 2020;382(9):810-821.***
Abstract



## Overall survival with ribociclib plus fulvestrant in advanced breast cancer

**Authors:** Slamon DJ, et al.

**Summary:** The addition of ribociclib to fulvestrant showed a significant OS benefit in a protocol-specified second interim analysis of a randomised, placebo-controlled phase 3 trial in 726 postmenopausal patients with hormone receptor–positive, HER2-negative advanced breast cancer. OS at 42 months was 57.8% in patients treated with ribociclib + fulvestrant compared with 45.9% in patients who received placebo + fulvestrant (HR 0.72; 95% CI 0.57–0.92; p=0.00455). Median PFS was 33.6 months and 19.2 months, respectively, in a subgroup of patients receiving this treatment as their first line of therapy.

**Comment (DO):** This study, MONALEESA-3, is the third randomised controlled trial reporting on the efficacy of fulvestrant plus a CDK4/6 inhibitor versus fulvestrant plus placebo on OS.[14,15] Despite looking at different patient populations, all three trials demonstrated a clinically meaningful 6–8 month OS benefit favouring the addition of a CDK4/6 inhibitor to fulvestrant, though only two reached statistical significance (this study being one of them). Two important questions, however, arise from this and the other published papers investigating CDK4/6 inhibitor therapies in advanced breast cancer.

1) Should we add an aromatase inhibitor or fulvestrant to a CDK4/6 inhibitor in the post-menopausal endocrine therapy–naïve first-line metastatic setting? We know that fulvestrant is superior to an aromatase inhibitor in this space[16] and that aromatase inhibitor + CDK4/6 inhibitor is more efficacious than an aromatase inhibitor alone in PFS.[17–19] However, we do not know whether an aromatase inhibitor would fare better than fulvestrant when added to a CDK4/6 inhibitor in the first-line setting. Nevertheless, one can see why a proportion of patients may shy away from the latter given the inconvenience of having to attend hospital/GP surgery for monthly fulvestrant injections, which in themselves may be uncomfortable.

2) Can one continue CDK inhibition post-progression? In this study, the median time to first chemotherapy in the ribociclib/fulvestrant arm was not reached after 42 months of follow-up (56.4% patients not on chemo at time of publication of this paper), while in those on fulvestrant + placebo this was 2.5 years. So after close to 4 years on ribociclib + fulvestrant, what would be the appropriate therapy post-progression? Again, 11% of those on the ribociclib arm in this study either switched to a different CDK4/6 inhibitor or continued on the same, though it is unclear what backbone endocrine therapy they concomitantly received. Meanwhile 35% in both arms went on to receive systemic cytotoxic chemotherapy. In summary, there is no standard-of-care therapy following progression while on a CDK4/6 inhibitor and endocrine therapy. Nevertheless, the concept of continuing the CDK4/6 inhibitor backbone beyond progression and how effective this might be has become the subject of intense interest with trials such as PACE[20] (adding immunotherapy while continuing both palbociclib and fulvestrant post-progression) and TRINITI[21] (adding everolimus to ongoing ribociclib and aromatase inhibitor post-progression).

***Reference: N Engl J Med. 2020;382(6):514-524.***
Abstract

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