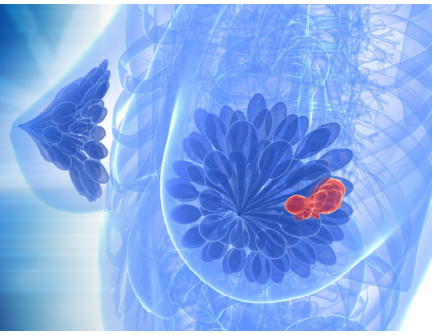
Breast Cancer Research Review™



Making Education Easy

Issue 79 - 2026

In this issue:

- Trastuzumab deruxtecan in HER2-low metastatic breast cancer
- First-line ribociclib 600 vs. 400mg in hormone receptor+, HER2– advanced breast cancer
- Adjuvant carboplatin-intensified chemotherapy in high-risk, early-stage, triple-negative breast cancer
- Outcomes of anastrozole, letrozole and exemestane in postmenopausal breast cancer
- Adjuvant chemotherapy for hormone receptor+, HER2– breast cancer
- Fear and medical misinformation in breast cancer
- Pembrolizumab extended-interval dosing in breast cancer
- First-line ribociclib + letrozole in elderly hormone receptor+, HER2– advanced breast cancer
- Predicting heart failure and cardiomyopathy after breast cancer treatment
- ARX788 for HER2+ breast cancer and brain metastases

Abbreviations used in this issue:

ADC = antibody-drug conjugate; **AUC** = area under the curve; **DFS** = disease-free survival; **HER2** = human epidermal growth factor receptor-2; **HR** = hazard ratio; **ILD** = interstitial lung disease; **ORR** = overall response rate; **OS** = overall survival; **PFS** = progression-free survival; **RCT** = randomised controlled trial.

Welcome to issue 79 of Breast Cancer Research Review.

The DESTINY-Breast04 trial previously demonstrated improved OS and PFS with trastuzumab deruxtecan versus chemotherapy of physician's choice in patients with HER2-low metastatic breast cancer – we begin this issue with outcomes from this trial after a median 32 months of follow-up. There is also research comparing third-generation aromatase inhibitors, namely anastrozole, letrozole and exemestane, for survival outcomes in postmenopausal women with hormone receptor-positive early-stage breast cancer. Other included research has reported on the impact that extending dosing intervals for pembrolizumab for breast cancer has on immune-related adverse events and clinical outcomes. We conclude the issue with the phase 2 ACE-Breast-06 study of the next-generation ADC ARX7888 in patients with HER2-positive breast cancer with active brain metastases, since patients with brain metastases were excluded from the previous ACE-Breast-02 trial.

We hope you find the selected papers provide you with some valuable take-home messages to reflect on. Remember, we always enjoy receiving your comments and feedback.

Kind Regards,

Dr Hilary Martin
hilary.martin@researchreview.com.au

Trastuzumab deruxtecan in HER2-low metastatic breast cancer

Authors: Modi S et al.

Summary: This paper reported long-term survival for participants from the phase 3 DESTINY-Breast04 trial comparing trastuzumab deruxtecan with physician's choice of chemotherapy for patients with HER2-low metastatic breast cancer; improved OS and PFS in the trial's trastuzumab deruxtecan arm has been previously reported. The present analysis after a median 32.0 months of follow-up reported continued longer median OS duration in the trastuzumab deruxtecan arm than the chemotherapy arm (22.9 vs. 16.8 months; HR 0.69 [95% CI 0.55–0.86]), including in participants with hormone receptor-positive disease (23.9 vs. 17.6 months; 0.69 [0.55–0.87]) and, in exploratory analyses, in the subgroups of participants with hormone receptor-negative and oestrogen receptor immunohistochemistry 1–10% and >10% disease. Trastuzumab deruxtecan had an overall safety profile that was generally manageable and considered acceptable.

Comment: Trastuzumab deruxtecan is currently available via the PBS within Australia for HER2-low disease that has progressed on at least one line of previous chemotherapy in the advanced setting. This paper reports on the data from DESTINY-Breast04, which is the study on which the approval for HER2-low disease in Australia is based, examining patients who had HER2-low disease and 1–2 previous lines of chemotherapy. This paper reports updated OS at a median of 32.0 months follow-up. The study confirms the earlier reported finding of significant benefit in the trastuzumab deruxtecan arm compared with the treatment of physician's choice arm with median OS in the trastuzumab deruxtecan arm just over 6 months longer than the median OS in the treatment of physician's choice arm. The OS difference is both clinically and statistically significant. Analyses were undertaken for the hormone receptor-positive cohort and the triple-negative cohort. The difference in OS for the hormone receptor-positive cohort was similar to the overall cohort with statistically significant benefit for those who received trastuzumab deruxtecan. The triple-negative cohort analysis had a substantial numerical difference in median OS between the groups at 17.1 months compared with 8.3 months in the treatment of physician's choice group, so almost 9 months longer in the trastuzumab deruxtecan arm; however, this difference was not statistically significant with an HR of 0.58 (95% CI 0.31–1.08). There was only a reasonably small number of patients in this triple-negative cohort, with 40 patients in the trastuzumab deruxtecan arm and only 18 in the treatment of physician's choice, which has likely contributed to the lack of statistical significance. In contrast there were 331 patients treated with trastuzumab deruxtecan in the hormone receptor-positive cohort and 163 with treatment of physician's choice. There were no additional safety signals and no additional events of ILD and/or pneumonitis during the additional follow-up period covered by this paper beyond those reported in the primary analysis. The study supports the use of trastuzumab deruxtecan for HER2-low breast cancer patients.

Reference: Nat Med 2025;31:4205–13
Abstract

600- vs 400-mg first-line ribociclib in hormone receptor-positive/*ERBB2*-negative advanced breast cancer

Authors: Cardoso F et al.

Summary: The phase 2 AMALEE study examined whether a lowered ribociclib starting dose (400 vs. 600mg) could reduce the incidence of adverse events while maintaining efficacy in 376 patients with hormone receptor-positive, HER2-negative advanced breast cancer. After a median follow-up of 53.5 months, the absolute ORR difference between ribociclib 400mg and 600mg was –7.2% (ORR ratio 0.87 [90% CI 0.74–1.03]), median PFS was 26.9 vs. 25.1 months, the median duration of response was 26.5 vs. 28.8 months, and the time to response was 13.1 vs. 9.0 months. Maximal plasma concentration was 28.0% lower and 24-hour AUC was 42.7% lower with ribociclib 400mg than with 600mg. Ribociclib 400mg was associated with a shorter Fridericia-corrected QT interval (12.5 vs. 19.7 milliseconds), a lower grade 3–4 neutropenia rate (41.0% vs. 58.5%), and a lower rate of dose reductions due to adverse events (15.4% vs. 36.9%). Liver-related adverse events, kidney toxic effects, ILD/pneumonitis and adverse event-prompted discontinuation rates did not differ between doses.

Comment: While the metastatic breast cancer studies used ribociclib 600mg as the commencing dose for patients, the adjuvant study NATALEE utilised only ribociclib 400mg. The rationale for the ribociclib 400mg dose, as per the recent publication in JAMA by Fasching et al. of updated 4-year outcomes, was to "*improve safety and adherence while maintaining efficacy*". The efficacy of the reduced dose seems to be based on data supporting efficacy of lower dose ribociclib in the metastatic setting for those who had undergone a dose reduction. The use of the 400mg dose in the early setting and potentially similar efficacy to the 600mg dosing has raised the question of whether the initial dosing used in the metastatic setting should be 400mg also. This paper reports on the AMALEE trial, which was a phase 2 trial designed to examine noninferiority of the 400mg dosing of ribociclib compared with the 600mg dose in the metastatic setting. This study was requested by the US FDA to determine whether the lower dose was equivalent efficacy wise and would reduce QT prolongation rates. While grade 3 and 4 neutropenia rates, QT interval length at cycle 1 day 15 and dose reductions were lower in the 400mg arm, other toxicities such as liver-related adverse events and adverse event-related treatment discontinuations were similar in both arms. For ORR noninferiority of ribociclib 400mg compared with 600mg, the lower limit of the 90% CI of the ORR ratio of 400mg ribociclib compared with 600mg ribociclib needed to be greater than the noninferiority margin of 0.814. The ORR for the study for those treated as per protocol was 48.9% for the 400mg dose and 56.1% for the 500mg dose with a ratio of 0.87, with a 90% CI of 0.74–1.03. This lower limit of 0.74 was below the prespecified required margin of 0.814 for noninferiority. Results were similar when repeated with the intention to treat population. The study was not powered to examine differences in PFS between the treatment doses. Based on the results of this study in the metastatic/advanced setting, 600mg should be continued to be the standard commencement dose for ribociclib.

Reference: JAMA Oncol 2025;11:1356–63
Abstract

Effect of adjuvant carboplatin intensified chemotherapy versus standard chemotherapy on survival in women with high risk, early stage, triple negative breast cancer (CITRINE)

Authors: Liu Y et al.

Summary: In this open-label phase 3 trial, 808 women with operable high risk triple-negative breast cancer who had undergone definitive surgery were evenly randomised to receive an investigational regimen of four cycles of epirubicin and cyclophosphamide every 2 weeks followed by four cycles of paclitaxel and carboplatin every week or a control regimen of four cycles of epirubicin and cyclophosphamide every 2 or 3 weeks followed by four cycles of paclitaxel every week. Median follow-up was 44.7 months. Compared with the control regimen, the investigational (carboplatin-containing) regimen was associated with a higher estimated 3-year DFS rate (primary endpoint; 92.3% vs. 85.8%; HR 0.64 [95% CI 0.43–0.95]); however, violation of the proportional hazards assumption was detected (p=0.02). A piecewise hazard model revealed that the HR increased from 0.31 (95% CI 0.13–0.73) for 0–12 months, to 0.65 (0.39–1.09) for 12–36 months, and to 1.98 (0.69–5.69) for >36 months. The investigational regimen was also found to be superior to the control regimen for the secondary endpoints of 3-year recurrence-free survival (93.8% vs. 88.3% [p=0.02]), 3-year distant DFS (94.8% vs. 89.8% [p=0.04]) and 3-year OS (98.0% vs. 94.0% [p=0.01]). The incidences of grade 3–4 treatment related adverse events in the respective investigational and control arms were 66.7% and 55.0%; there were no treatment-related deaths recorded.

Comment: This is yet another study examining the role of carboplatin for the treatment of triple-negative breast cancer. In this study, the use of adjuvant epirubicin-cyclophosphamide 2-weekly followed by weekly paclitaxel was compared with treatment with adjuvant epirubicin-cyclophosphamide followed by weekly paclitaxel combined with carboplatin. Patients enrolled on the study required either node-positive disease or if node-negative, Ki67 of at least 50%. There were 404 patients in each of the study arms. At a median follow-up of 44.7 months, the estimated percentage of patients disease free at 3 years was higher in the carboplatin arm at 92.3% compared with 85.8%. Three-year OS was also higher in the carboplatin group at 98% compared with 94%. Exploratory subgroup analysis found DFS to favour the carboplatin group for all subgroups examined. There was a higher rate of adverse events in the carboplatin group. Currently the standard of care for most triple-negative breast cancer patients is neoadjuvant rather than adjuvant therapy, with inclusion of immunotherapy. This study does support the use of carboplatin for those treated in the adjuvant setting.

Reference: BMJ 2025;391:e085457
Abstract

Earn CPD

Royal Australasian College of Physicians (RACP) MyCPD participants can claim the time spent reading and evaluating research reviews as CPD in the online MyCPD program. Please contact MyCPD@racp.edu.au for any assistance.

Royal Australian & New Zealand College of Radiologists (RANZCR) members can claim reading related to their practice as a CPD activity under the category 'journal reading and web based no certificate *reflection required'. More info.

CPD Home. Subscribers can claim the time spent reading and evaluating research reviews as an Educational Activity: Professional Reading in the CPD Tracker. Please Contact Us for support.

Nursing and Midwifery Board of Australia (NMBA) Journal reading and watching videos (including Research Reviews') may be considered a self-directed activity set out in the NMBA Registration Standard: Continuing Professional Development. One hour of active learning will equal one hour of CPD. Details at NMBA CPD page.

Breast Cancer Research Review™

Independent commentary by Dr Hilary Martin

Dr Hilary Martin is a medical oncologist at Fiona Stanley Hospital Perth subspecialising in breast cancer. Her initial oncology training was undertaken in South Australia. She subsequently worked as a breast unit fellow at the Royal Marsden Hospital, London, and also as a clinical fellow at Royal Perth Hospital. She has a Masters of Public Health through the University of Sydney and a PhD through the University of Western Australia. Her research interests include mammographic breast density, survivorship, CTDNA, and lobular breast cancer.

Outcomes of anastrozole, letrozole, and exemestane in patients with postmenopausal breast cancer

Authors: Dumas E et al.

Summary: This study of 148,436 women with postmenopausal hormone receptor-positive early-stage breast cancer compared those who initiated adjuvant anastrozole (38.5%), letrozole (52.9%) or exemestane (8.5%) for the outcomes of DFS and OS. After a median 63 months of follow-up and evaluated under natural persistence, the estimated 8-year DFS rate was lower for exemestane recipients than for anastrozole or letrozole recipients (79.1% vs. 81.0% and 81.1%, respectively), as was the 8-year OS rate (88.8% vs. 90.5% and 89.9%), with exemestane recipients more likely to discontinue treatment within 5 years (39.3% vs. 35.1% and 35.0%); the lower survival outcomes were also seen under perfect persistence.

Comment: In clinical practice, in the absence of head-to-head studies thus far, the three aromatase inhibitors letrozole, anastrazole and exemestane are expected to have similar efficacy and in the adjuvant setting have similar approved indications, although ribociclib can only be prescribed in combination with anastrazole or letrozole. If patients develop toxicity on one agent, clinicians will consider switching to a different agent. Notably the SOFT and TEXT trials of adjuvant endocrine therapy utilised exemestane with ovarian suppression rather than letrozole or anastrazole as the aromatase inhibitor option. Three previously conducted RCTs comparing either all three agents, anastrazole with letrozole or exemestane with letrozole have not shown strong evidence of risk of recurrence being greater with any one of these agents. This study retrospectively examined data from a national database that included 148,438 postmenopausal women in France treated with aromatase inhibitor therapy as adjuvant therapy between Jan 2011 and Dec 2020, with data analysis between Nov 2024 and May 2025. The rationale from the investigators was that it was thought that the RCTs may have been too small to detect small differences between the agents. The primary endpoints examined were DFS and OS. Letrozole was the most commonly used initial endocrine therapy, with 52.9% receiving this agent, while 38.5% received anastrazole and only a very small proportion of patients received exemestane at only 8.5%. The study found that exemestane was associated with slightly lower DFS and OS after 8 years of therapy compared with anastrazole and letrozole. However, these results need to be interpreted with caution, as there were differences among the cohorts that may have contributed to these differences, other than differences in efficacy of agents. We do not know why exemestane was chosen compared with the other agents for the small proportion who received this agent. This may have factored into the differences in outcome. There was a lower proportion of those receiving exemestane being managed at a comprehensive cancer centre (17.7% compared with 27.5% and 24.5% for those treated with letrozole and anastrazole, respectively) and a greater proportion being treated in for-profit private hospitals at 52% compared with 38.3% and 41.8%, respectively, for those treated with letrozole and anastrazole. There may therefore have been other differences in care and management across the centres or in individual patient characteristics that led to the selection of treatment site that may have contributed to these differences seen in outcomes. Also, endocrine discontinuation rates were highest in the exemestane cohort at 39.3% compared with 35.1% and 35.0% in the anastrazole and letrozole groups, respectively. While further endocrine therapy was trialled by a higher proportion of those treated with exemestane at 28.9% compared with 25.4 and 27.7% of those treated with anastrazole and letrozole, respectively, there was a greater proportion of patients who were not receiving any endocrine therapy after initial therapy who trialled endocrine therapy in the exemestane arm. There was also a greater proportion of patients who received tamoxifen as next-line therapy rather than another aromatase inhibitor in the exemestane arm compared with the other two arms, which has been proven to be less effective in RCTs in this setting compared with aromatase inhibitor therapy. While perfect persistence analysis was undertaken to try to account for confounding bias due to choice of aromatase inhibitor at bias and for selection bias due to censoring at endocrine therapy discontinuation, this may not have successfully accounted for all differences between the groups other than treatment selection. This paper does not seem sufficient to strongly base an endocrine therapy decision upon. However, as there are sometimes later-line studies that require patients to have received or progressed on a nonsteroidal aromatase inhibitor, and the requirement for ribociclib to be given with a nonsteroidal aromatase inhibitor, in clinical practice using letrozole or anastrazole as the first-line endocrine therapy preference is my usual approach.

Reference: JAMA Netw Open 2025;8:e2550842
Abstract

Adjuvant chemotherapy use for hormone receptor-positive, *ERBB2*-negative breast cancer after RxPONDER trial

Authors: Freeman JQ et al.

Summary: Temporal patterns of and disparities in adjuvant chemotherapy use were reported according to age, genomic risk and nodal involvement for a retrospective cohort of 504,937 endocrine therapy-eligible women with stage I–III hormone receptor-positive, HER2-negative breast cancer who had undergone lumpectomy or mastectomy. For premenopausal women with node-negative tumours, those with a low genomic risk had a decrease in adjuvant chemotherapy from 6.5% in 2010 to 0.9% in 2022, and those with intermediate genomic risk had a decrease from 29.6% to 11.1% over the same time period. Meanwhile, premenopausal women with node-positive disease and low genomic risk had a decrease in chemotherapy use from 33.3% in 2010 to 12.7% in 2019, followed by an increase to 25.7% in 2022; similarly for those with intermediate genomic risk, there was a decrease from 55.8% in 2010 to 38.1% in 2019 followed by an increase to 48.9% in 2022. For postmenopausal women with low to intermediate genomic risk, decreases in chemotherapy use were seen from 2010 to 2022 for those with node-negative and those with node-positive disease. Chemotherapy use was lower for Black women with high genomic risk than their White counterparts, irrespective of menopausal and nodal status (adjusted odds ratio 0.84 [95% CI 0.78–0.90]), and also for premenopausal Black versus White women with low to intermediate genomic risk, irrespective of nodal status (0.85 [0.77–0.94]).

Comment: This study examined the use of chemotherapy following the availability of data from the TAILORx and RxPONDER trials. The TAILORx trial showed that for postmenopausal women with node-negative breast cancer, chemotherapy could be omitted for those with a low Oncotype DX® recurrence risk score (below 26) as no additional benefit was seen for this group with the addition of chemotherapy. Similarly in the RxPONDER trial for postmenopausal women with between 1–3 lymph nodes involved, there was no benefit seen for those with a recurrence score of below 26. Thus chemotherapy could be omitted from this cohort's treatment. For premenopausal women, however, the TAILORx trial showed a low-risk group with recurrence score below 11, with no significant benefit from chemotherapy for whom chemotherapy could be omitted, and an intermediate risk group with some benefit from chemotherapy with the benefit increasing as the score increased from 11-25, and then a high-risk group with score of 26 and above for whom chemotherapy was recommended. Analysis of the data from RxPONDER showed benefit for all premenopausal women with 1–3 lymph nodes involved, including the low- and intermediate-risk groups. Whether this benefit for the low- and intermediate-risk groups was due to chemotherapy entirely or whether the ovarian suppression resulting from chemotherapy is unknown. The study retrospectively analysed data from the 2010–2022 US National Cancer Database. In total, 504,937 women were included. As expected, chemotherapy use decreased for node-negative premenopausal patients with low genomic risk over time from 6.5% to 0.9%, and for those with intermediate genomic risk from 29.6% to 11.1% by 2022. TAILORx was published in 2018. It is unclear whether the patients who had genomic testing available prior to the publication had testing undertaken as part of the TAILORx study, or whether the testing was undertaken privately. For the premenopausal cohort with 1–3 lymph nodes involved, chemotherapy use declined between 2010–2019 for the low and intermediate genomic risk groups but increased in 2022 for the low and intermediate genomic risk groups following publication of RxPONDER in 2021. For postmenopausal women for the low- and intermediate-risk groups, adjuvant chemotherapy use reduced for node negative and node positive patients. In the Australian context Oncotype DX testing is not funded and thus only those able to self-fund are able to undertake testing. The pattern of change in chemotherapy receipt is as would be anticipated with the TAILORx and RxPONDER data. The results of the OFSET trial, which is evaluating the addition of adjuvant chemotherapy to ovarian function suppression plus endocrine therapy in premenopausal patients with pN0-1 oestrogen receptor-positive, HER2-negative breast cancer and an Oncotype DX recurrence score below 25, are awaited to determine whether there is a further subset of the premenopausal women for whom chemotherapy can be omitted.

Reference: JAMA Netw Open 2025;8:e2549109
Abstract

Fear and medical misinformation regarding risk of progression or recurrence among patients with breast cancer

Authors: Miller DG et al.

Summary: These researchers reported on exposure to misinformation among 997 adult survey respondents with a history of breast cancer, 52% of whom were receiving active treatment. Exposure to misinformation on breast cancer was reported by 76% of respondents, with 65% reporting misinformation about factors that increase cancer progression or recurrence risk, and 54% reporting misinformation regarding factors that decrease such risk. The respondents reported a median score of 19 on a 0- to 36-point scale, with 38% of participants reporting clinically significant fear (score ≥22). The self-reported treatment adherence rate was 76%. There was no significant association reported between exposure to misinformation and either clinically significant fear of recurrence or treatment nonadherence. Misinformation exposure was more likely among patients of Hispanic ethnicity (adjusted odds ratio 2.96 [95% CI 1.15–10.05]), although statistical significance was lost for this association after adjusting for fear of recurrence and treatment adherence.

Comment: There has never been such a breadth of access to information accessible as there is for patients currently undergoing treatment. Unfortunately there is a substantial amount of misinformation available, particularly through social media and online platforms. This study examined the impact of exposure to misinformation about cancer recurrence or progression on recurrence fears and treatment adherence. An anonymous online survey was undertaken between Jul and Aug 2023 through Breastcancer.org, with US residents aged 18 years and over and with a breast cancer diagnosis within the past 10 years eligible. The survey asked whether they had encountered information regarding certain factors, such as sugar consumption increasing the risk of recurrence or progression, or other factors, such as cleanses for reducing the risk of recurrence or progression. The survey also included the nine-question validated Fear of Cancer Recurrence Inventory-Short form to assess the level of fear of recurrence or progression. In total, 997 patients answered at least some survey questions and were eligible. There was a 99% completion rate of all the misinformation questions, with those not responding to the questions assumed not to have been exposed to misinformation. The majority of participants had encountered misinformation about factors related to cancer progression or recurrence risk, with information about sugar increasing risk the most frequently encountered misinformation. A reasonably high proportion of participants reported clinically significant fear of cancer recurrence at 38%. The study hypothesis had been that misinformation exposure would lead to higher fear of recurrence or progression and greater likelihood of treatment nonadherence; however, this was not the case, with no association seen with either of these factors in this survey. The lack of association between exposure to misinformation and fear of recurrence or nonadherence is not necessarily surprising. The study did not assess participants' health beliefs and whether they acted on the misinformation. Participants may have been exposed to the information but not believed and acted on it. However, the areas of misinformation examined in the study, such as lower sugar intake reducing the risk of recurrence, would, even had the individual participant undertaken a lower sugar diet, not be expected to lead to lower treatment adherence but could have been used as an adjunct to standard therapy. Also in relation to the misinformation and fear of recurrence, the aspects examined were generally aspects that individuals could have adopted to alter their lifestyle and undertake additional interventions that the misinformation advised may reduce the risk of recurrence. The ability of some of this misinformation to provide participants with aspects to focus on, in addition to standard therapy, for some participants may have had the potential to reduce fear of recurrence, as they may believe they will have a lower risk of recurrence and thus less fear of recurrence if they undertake the measures recommended in the misinformation.

Reference: JAMA Netw Open 2025;8:e2549809
Abstract

Safety and clinical outcomes of pembrolizumab standard-interval dosing versus extended-interval dosing in patients with breast cancer

Authors: LeVee A et al.

Summary: The impact of extended pembrolizumab intervals on immune-related adverse events and clinical outcomes was explored in a retrospective cohort of 355 patients with breast cancer (71% early-stage; 92% triple-negative), among whom 17% received ≥1 cycle of extended-interval dosing and 83% received ≥1 cycle of only standard-interval dosing. Among patients who received ≥1 cycle of extended-interval pembrolizumab dosing, 45.8% initiated at 200mg and 11.9% at 400mg, 15.2% received only 400mg, and 27.1% switched between dosing schedules. For early-stage breast cancer, the any-grade immune-related adverse event rates were similar between the dosing intervals, but extended-interval dosing was associated with fewer grade ≥3 immune-related adverse events than standard-interval dosing (4% vs. 20% [p=0.01]). The two groups did not differ significantly for event-free survival and OS outcomes. For patients with metastatic breast cancer, there was no significant difference between the dosing intervals for any-grade or grade ≥3 immune-related adverse events, PFS or OS.

Comment: The KEYNOTE-522 trial examining pembrolizumab in combination with chemotherapy for early breast cancer as well as the KEYNOTE-355 trial, which examined the use of pembrolizumab in metastatic breast cancer, both utilised the standard-interval dose schedule of pembrolizumab 200mg every 3 weeks. In the US, extended-interval pembrolizumab at 400mg every 6 weeks was approved across all adult indications, including breast cancer, and for breast cancer, the PBS currently has both the 3-weekly and 6-weekly dosing schedules approved for both early and advanced triple-negative breast cancer. This was a real-world retrospective study of 355 patients treated with pembrolizumab between 2017 and 2024. Only 17% of the patients in this study received at least one cycle of extended-interval immunotherapy, with the other patients receiving only standard-interval pembrolizumab. Of patients who had at least one dose of extended-interval pembrolizumab, nine (15.2%) received only the extended-interval dosing whereas the others received some treatment at the standard interval and some at the extended interval. The rate of grade 3 or higher immune-related adverse events was lower in patients who received at least one dose of extended-interval pembrolizumab compared with those who did not; however, given the majority of patients who received extended-interval therapy had initially received standard-interval therapy without grade 3 immune-related adverse events and then changed to extended-interval therapy, this is not unexpected. For the nine patients who had only the extended-interval dosing (only 400mg 6-weekly dosing), interestingly there were no immune-related adverse events. However, it should be noted this is a very small sample of patients. Also these patients were all postmenopausal with a median age of 72.6 years. Only four patients in the early setting received extended dosing only. The number of patients in this study who only received extended-interval pembrolizumab was too small to be able to properly assess disease outcomes. Randomised controlled data are required to be able to determine whether the efficacy between the dosing schedules is equivalent. In the interim, the 6-weekly regimen can be considered, but there would need to be careful discussion with any patients wishing to undertake this schedule, given the lack of data confirming comparable efficacy, as well as limited data of immune-related events for those treated solely with this regimen in the breast cancer setting.

Reference: Oncologist 2025;30:oyaf371
Abstract

A phase IV prospective study of efficacy and safety of ribociclib and letrozole as first-line therapy in older women (≥70 years) with hormone receptor-positive HER2-negative advanced breast cancer

Authors: Van Houdt M et al.

Summary: Seventy women aged ≥70 years, 45 of whom were frail at study entry, with hormone receptor-positive, HER2-negative advanced breast cancer received ribociclib 600mg 3 out of every 4 weeks along with letrozole as first-line therapy in the phase 4 RibOB study. After a median 30.5 months of follow-up, the median PFS duration was 36 months, the respective 24- and 36-month breast cancer-specific survival rates were 82% and 75%, median OS duration had not been reached, and the median time to treatment failure was 14.6 months, with no significant differences between fit and frail participants. The grade ≥3 adverse event rate was 67%, most commonly neutropenia (47%), the grade ≥3 liver toxicity rate was 3%, and the grade ≥3 QT prolongation rate was 4%. Ribociclib discontinuation prior to progression was recorded for 43% of participants, and 57% and 23% needed their dose reduced to 400mg and 200mg, respectively, with 20% continuing the full 600mg dose until study end, disease progression or death. There were no significant changes in quality of life over time.

Comment: This is a reasonably small single-arm study of 70 women aged 70 years or over treated with ribociclib plus letrozole in the metastatic setting. The rationale for this study was the under-representation of older patients and frailer patients in clinical trials. The standard metastatic dosing of 600mg was utilised. Thirty percent of the patients were aged 80 years or over. Frailty was assessed using the G8 score with more than half of the population (45/70) assessed as frail, defined as a G8 score less than 14. Twenty percent of the population had possible cognitive impairment based on mini-COG score at baseline, and 8.7% were malnourished at baseline. Treatment appeared effective with a median PFS duration of 36.5 months at median follow-up of 30.5 months. This is much longer than the median PFS duration of 25.3 months in the MONALEESA-2 trial for the overall group treated with ribociclib plus nonsteroidal aromatase inhibitor. There was no statistically significant difference in PFS between fit and frail patients or other measures of efficacy assessed. There was also a similar rate of grade 3 or higher adverse events between the frail and fit patients. Rates of discontinuation of ribociclib prior to disease progression were high in this cohort overall at 43%. Only 20% continued the full dose until the end of study, disease progression or death. Frail patients were more likely to require a dose reduction, with 47% of frail patients requiring dose reduction compared with 28% of fit patients. Quality of life and functional status were generally stable during the study. The trial confirms the safety and efficacy of this combination in the metastatic setting for older patients, although discontinuation rates for reasons other than progression were high.

Reference: ESMO Open 2026;11:105896
Abstract

Risk prediction model for development of heart failure or cardiomyopathy after breast cancer treatment

Authors: Barac A et al.

Summary: These researchers reported on their development and validation of a model for predicting the 10-year risk of developing heart failure or cardiomyopathy during systemic treatment for invasive early-stage breast cancer. They used a longitudinal cohort of 26,044 women aged 18–79 years with newly diagnosed invasive local or regional breast cancer, with a median 5.2 years of follow-up, with 60% randomised to a derivation cohort and the rest to a validation cohort. The resulting risk model provided high accuracy with good calibration for predicting heart failure or cardiomyopathy risk across three subgroups; the heart failure or cardiomyopathy risk in the validation cohort matched the estimates from the derivation cohort for classifying 1.7% of women as low risk and 19.4% as high risk for experiencing heart failure or cardiomyopathy over 10 years. The model exhibited good discriminatory ability, with a time-dependent AUC of 0.79 at 10 years in the validation cohort.

Comment: This study investigated a cohort of women with first primary invasive breast cancer diagnosed between 2008 and 2020 to try to develop a model for predicting risk of heart failure or cardiomyopathy after breast cancer treatment. Sixty percent of the cohort were selected randomly to form the derivation cohort for the model. Potential predictors were assessed in the derivation model, and then examined in the cross-validation cohort formed by the other 40% of patients. The final model for the risk score incorporated breast cancer treatment, cardiovascular risk factors and sociodemographic factors. The model did not examine biomarkers or cardiac imaging results, which may further strengthen a model. The final model was able to prospectively identify those at risk of heart failure/cardiomyopathy over a 10-year period based on breast cancer risk, with the high-risk group having an estimated risk of heart failure or cardiomyopathy at 10 years of 19.4% compared with only 1.7% in the low-risk group for the validation cohort.

Reference: JAMA Oncol 2025;11:1479–87
Abstract

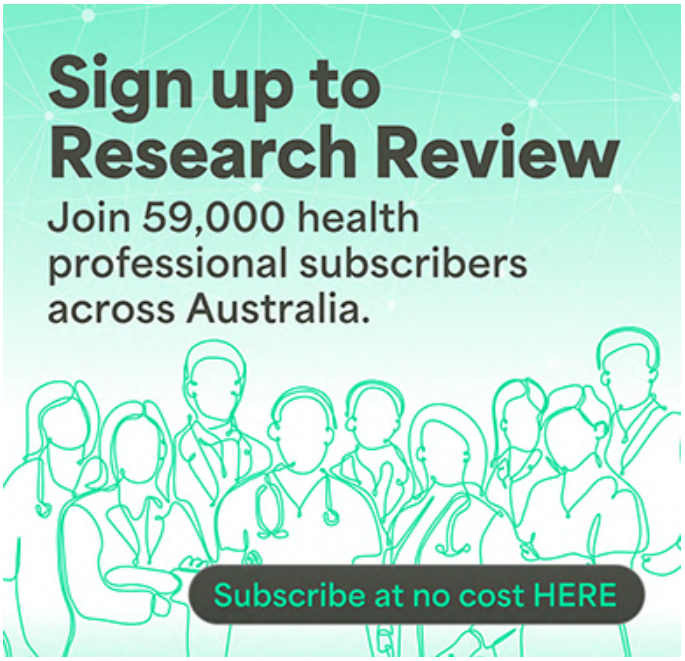
Efficacy and safety of ARX788 for individuals with HER2-positive breast cancer and brain metastases (ACE-Breast-06)

Authors: Li T et al.

Summary: Thirty-two patients aged 18–75 years with HER2-positive breast cancer who had received trastuzumab, taxane and a tyrosine kinase inhibitor, and with ≥1 measurable active brain metastatic lesion measuring ≥1cm, were treated with intravenous ARX788 (a next-generation ADC) 1.5 mg/kg every 3 weeks until progression or unacceptable toxicity in this phase 2 trial from China. Median follow-up was 15.0 months, and at final data cutoff, two participants were still receiving ARX788. The CNS clinical benefit rate (primary endpoint) was 34.4%, the confirmed CNS ORR was 25.0%, median CNS PFS duration was 5.6 months and median PFS duration was 5.5 months; OS data were immature. Extracranial progression alone was recorded for 8.3% of participants, while 70.8% had intracranial progression alone, and 20.8% had both. The grade ≥3 treatment-related adverse event rate was 12.5%, the most common of which were blurred vision (9.4%), ILD/pneumonitis (6.3%), keratopathy (6.3%), dry eyes (3.1%) and thrombocytopenia (3.1%); the grade ≥3 gastrointestinal toxicity rate was <1%. There was one case of grade 5 ILD/pneumonitis recorded.

Comment: This study examined the use of ARX788, which is an ADC with an anti-HER2 monoclonal antibody linked via para-acetylphenylalanine to Amberstatin269 (the payload). The previous study, ACE-Breast-02, showed that ARX788 increased PFS in HER2-positive advanced breast cancer compared with lapatinib plus capecitabine; however, patients with brain metastases were excluded from that study. This paper reports on the phase 2 ACE-Breast-06 study, which examined the efficacy and safety of ARX788 in patients with advanced HER2-positive breast cancer and active brain metastases. While brain metastases were included, patients with leptomeningeal metastases or cystic brain metastases were excluded, as were those with previous trastuzumab emtansine exposure, other anti-HER2 ADC therapy and those with brain metastases requiring urgent local therapy. The median brain PFS duration was 5.6 months, with a response rate of 25% and a clinical benefit rate of 34.4%. The most common treatment-related adverse events at grade 3 or above were blurred vision, keratopathy, dry eyes, thrombocytopenia and ILD. This study does confirm brain activity, and the treatment could be considered for use in patients with HER2-positive disease and active brain metastases.

Reference: eClinicalMedicine 2025;90:103614
Abstract



Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.