# Breast Cancer Research Review™

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Issue 65 - 2024


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**Abbreviations used in this issue:**

**CR** = complete response; **DFS** = disease-free survival; **ER/PR** = oestrogen/progesterone receptor; **HER2** = human epidermal growth factor receptor-2; **HR** = hazard ratio; **IDC/ILC** = invasive ductal/lobular carcinoma; **MTD** = maximum tolerated dosage; **OS** = overall survival; **PFS** = progression-free survival; **RFS** = relapse-free survival; **SUV** = standardised uptake value; **TNBC** = triple-negative breast cancer.

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## Welcome to issue 65 of Breast Cancer Research Review.

We begin this issue with research from Sweden, which retained the ER positivity threshold of ≥10%, reporting real-world characteristics, treatment patterns and survival for patients with ER-negative/low, HER2-negative breast cancer treated as TNBC. Other real-world data included this month provide insights into the long-term outcomes for high-risk ILC versus IDC, according to the MonarchE trial inclusion criteria, in a cohort of patients who underwent surgery for first primary, nonmetastatic, hormone receptor-positive, HER2-negative breast cancer. There is also a subgroup analysis of premenopausal participants from the PENELOPE-B trial, which had previously reported that adding postneoadjuvant palbociclib to endocrine therapy provided no benefit over placebo in terms of invasive DFS in patients with hormone receptor-positive, HER2-negative breast cancer at high risk of relapse. The issue concludes with research evaluating $^{18}$F-FES ($^{18}$F-fluoro-oestradiol) PET-CT as a tool for predicting response to endocrine therapy in patients with ER-positive, HER2-negative metastatic breast cancer.

Thank you for your comments and feedback – they are always appreciated.

Kind Regards,


**Dr Hilary Martin**
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## Real-world overall survival and characteristics of patients with ER-zero and ER-low HER2-negative breast cancer treated as triple-negative breast cancer

**Authors:** Acs B et al.

**Summary:** Patient and tumour characteristics, treatment patterns and OS were reported for a Swedish population-based cohort of patients with HER2-negative breast cancer treated as TNBC. For the 90.1% and 9.9% tumours that were ER-negative and ER-low, respectively, the pathological CR rates were 25.1% and 28.1%, with ER-low tumours having a trend for better OS than ER-negative tumours (HR 0.84 [95% CI 0.71–1.00]). ER status had no significant impact on OS or distant DFS on multivariate analysis, nor was there any impact of pathological CR on OS after preoperative treatment according to ER status.

**Comment:** ER and PR positivity had previously been considered positive for ≥10% for each to be considered hormone receptor-positive. However, this threshold for positivity was lowered to ≥1% in 2010 by ASCO and the College of American Pathologists. Most of the world adopted this new threshold and definition; however, the Swedish Breast Cancer Group did not alter their definition based on their interpretation of the data at the time, and continued to include patients with ER/PR status of 1–10% as hormone-negative, and therefore considered those with ER/PR 1–10% and HER2-negative (defined as IHC 0, 1+ or 2+ with negative ISH) as TNBC. At the time of the change, the shift expanded the patient cohort who were recommended treatment with adjuvant endocrine therapy. However, it has narrowed the cohort that would be considered triple-negative, and thus excluded those with ER/PR 1–10% from the triple-negative trials, including those of immunotherapy. This subgroup of 1–10% ER/PR-negative and HER2-negative formed 10% of the total triple-negative cohort within Sweden. In total, a cohort of 7958 women were identified, of whom 5928 women considered triple-negative with available percentage ER status were identified who were treated between 2008 and 2020. The purpose was to determine whether the patients with low ER positivity behaved similarly to those with <1% ER positivity. On multivariate analysis, there was a difference in OS between those with ER <1% and those with ER 1–10%. There was also no difference when the small proportion of the cohort who received adjuvant endocrine therapy or had missing endocrine therapy data were excluded. Pathological CR rates were also similar between the two groups. The data from this study showing similar clinical outcomes for ER-low disease as for <1% disease are not unexpected, given the similarities on gene expression studies of ER-low and <1% disease, as well as the molecular data that show, like <1% disease, ER-low disease is predominantly of a basal molecular phenotype. Given these similarities in biology and clinical outcomes, the study supports consideration of extending the definition and inclusion for studies of TNBC to include this reasonably small cohort of patients to ensure this subgroup are not denied access and consideration of access to treatments they may also benefit from.

***Reference: Lancet Reg Health Eur 2024;40:100886***
Abstract

## Preventing alpelisib-related hyperglycaemia in HR+/HER2–/*PIK3CA*-mutated advanced breast cancer using metformin (METALLICA)

**Authors:** Llombart-Cussac A et al.

**Summary:** Adults with hormone receptor-positive, HER2-negative *PIK3CA*-mutated advanced breast cancer with normal glycaemia (cohort A; n=48) or prediabetes (cohort B; n=20) received 28-day cycles of alpelisib plus endocrine therapy after initiation of prophylactic metformin plus endocrine therapy in this phase 2 trial with median follow-up of 7.8 months. Grade 3–4 hyperglycaemia occurred during the first 8 weeks (primary endpoint) in a lower proportion of cohort A than cohort B (2.1% vs. 15.0% [p=0.016]). The incidence of serious treatment-related adverse events was 10.3%, with the most common being rash, vomiting and diarrhoea, each of which occurred in two participants (2.9%). The adverse event-associated alpelisib discontinuation rate was 13.2%, with none due to hyperglycaemia, and there had been no treatment-related deaths recorded. Median PFS duration was 7.3 months, the objective response rate was 20.6% and the clinical benefit rate was 52.9%.

**Comment:** Alpelisib is not currently funded for access in Australia for *PIK3CA*-mutated breast cancer, although there are phase 3 data supporting its use. There is a copayment access scheme that enables access for a small subgroup of those with the mutation, but at considerable cost. As a result, most oncologists in Australia will have limited experience with this agent, unless involved with recruiting for clinical trials. It would be hoped that alpelisib, or another member of this class of medication, becomes available at some point in Australia. Hyperglycaemia is a well-reported side effect of alpelisib, with grade 3–4 hyperglycaemia occurring in approximately one-third of patients in previous trials, and in my clinical experience of one patient it has been a notable treatment-related toxicity. This Spanish study examined the use of prophylactic metformin for patients planned for alpelisib. Patients were excluded if they already had a diagnosis of diabetes. There were two cohorts examined: cohort A, which comprised those with normal fasting glucose level at baseline and $HbA_{1c}$ level <5.7%; and cohort B, which comprised those with impaired fasting glucose level and/or $HbA_{1c}$ level 5.7–6.4%. Patients were commenced on metformin 1 week prior to planned commencement of alpelisib at initial dosing of 500mg twice daily, which was then escalated to 1000mg twice daily after 3 days if no GI side effects were noted. Blood glucose levels were regularly monitored and analysed over the initial 8 weeks of treatment. Rates of grade 3–4 hyperglycaemia were significantly lower than in previous studies, with only 2.1% of cohort A with grade 3 hyperglycaemia and 15% of cohort B. There were still high rates of any grade of hyperglycaemia, at 33% of cohort A and 70% of cohort B patients. No patient permanently discontinued treatment as a result of hyperglycaemia, which is an excellent result, with only 5.9% requiring a dose reduction as a result of hyperglycaemia. As expected, some patients did experience diarrhoea during the week on metformin prior to starting alpelisib (14.7% of the entire cohort) with 11.8% requiring permanent discontinuation of metformin as a result of metformin-related adverse events. This study shows prophylactic metformin use was associated with lower rates of grade 3–4 hyperglycaemia than in earlier studies without its use, although there was toxicity associated with metformin use. Discussion of the use of prophylactic metformin with patients planned for alpelisib would seem reasonable based on the results of this study, particularly for those with a prediabetic state at baseline. This, however, is not a TGA registered indication for metformin.

***Reference: eClinicalMedicine 2024;71:102520***
Abstract

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.

## Safety and efficacy of anlotinib combined with taxane and lobaplatin in neoadjuvant treatment of clinical stage II/III triple-negative breast cancer in China (the neoALTAL trial)

**Authors:** Liang Y et al.

**Summary:** Forty-five patients with stage II–III TNBC (71% with nodal involvement; 20% stage III) received five 3-week cycles of anlotinib 12mg on days 1–14 plus six cycles of taxanes and lobaplatin followed by surgery in this phase 2 trial. The pathological CR rate (primary endpoint) was 57.8%, with respective breast and axillary pathological CR rates of 64.4% and 71.9%, and the proportion who achieved residual cancer burden class 0–I was 86.7%, with no recurrences or metastases during short-term follow-up. The pathological CR rates for the respective immunomodulatory, basal-like immune-suppressed and luminal androgen receptor subtypes were 68.8%, 58.3% and 33.3%, for *MYC*-amplified and wild-type patients they were 77% and 50%, and for g*BRCA*1/2-mutated and wild-type patients they were 78% and 53%. After a median 14.9 months of follow-up, there were no disease progression events and no deaths during neoadjuvant therapy or during postoperative follow-up. The grade 3–4 treatment emergent adverse event rate was 64%, with the most common being neutropenia, leucopenia, thrombocytopenia, anaemia and hypertension.

**Comment:** This study examined the use of anlotinib, which is a tyrosine kinase inhibitor against vascular endothelial growth factor receptors 1/2/3, platelet-derived growth factor-α/β receptors and fibroblast growth factor receptors 1–4 and c-Kit. While this is the investigational agent for this study, the protocol also included another agent that is not available to my knowledge in the Australian setting – lobaplatin. This is a platinum-based agent, similar to carboplatin and cisplatin, which has phase 2 data in the setting of neoadjuvant pathological CR rates for TNBC from a study undertaken by the Chinese group that have also undertaken this currently reported study. This was a single-arm study of neoadjuvant anlotinib plus taxane plus lobaplatin for patients with stage II–III TNBC, with the primary outcome of pathological CR. The study enrolled a total of 45 patients, and showed a 57.8% pathological CR rate. Treatment was reasonably well tolerated, with the most frequent adverse event of hypertension at 89%, with cytopenias the next most common side effects, and 58% experiencing hand-foot syndrome. Reassuringly, there were no treatment-related deaths, and 91% of patients completed the planned treatment. The pathological CR rate with this combination is reasonably high, and similar to the NeoPACT study with pembrolizumab plus platinum plus taxane at 58% pathological CR. The authors have noted that the LAR subtype had 33% pathological CR rate, which is higher than previous studies at 10%. This was a small nonrandomised study. Further research with a larger randomised cohort, and utilising standard of care therapy, is required to determine whether there is a role for this agent. The regimen utilised without anthracycline inclusion, with lobaplatin use, and without immunotherapy is not the current standard of care for TNBC. This study does show safety of the combination is present, but substantial further research is required to determine the place if any for anlotinib.

***Reference: eClinicalMedicine 2024;71:102585***
Abstract

## Comparison of long-term outcome between clinically high risk lobular versus ductal breast cancer

**Authors:** Magnoni F et al.

**Summary:** Long-term outcomes were reported comparing high-risk ILC versus IDC for a propensity score-matched Italian cohort of patients who underwent surgery for first primary, nonmetastatic, hormone receptor-positive, HER2-negative breast cancer; there were 322 matched clinically high-risk patients from each of the IDC and ILC groups. After a median 13.2 years of follow-up, there was no significant difference between the IDC versus ILC group for the respective 5- or 10-year invasive DFS rates (77.7% vs. 75.5% and 57.3% vs. 50.7%), the 5- and 10-year distant RFS rates (80% vs. 78.7% and 65.3% vs. 61.5%) or OS. Axillary recurrence was seen in 17 ILC patients and ten IDC patients. Predictors of unfavourable invasive DFS and OS were age <35 years, pT2–3 and axillary involvement with >10 positive axillary nodes.

**Comment:** Comparisons between ductal and lobular cancer for both the optimal treatment approach as well as treatment-related outcomes remain a challenge. While there are certain features that are clearly shown in the literature, such as lower pathological CRs to chemotherapy, a higher propensity to unusual sites of metastases, and greater difficulty in accurately assessing disease with standard imaging modalities for lobular compared with ductal carcinoma, whether outcomes were better for lobular or ductal cancers when matched on other histopathologic features had not been clearly examined. This study retrospectively analysed data from the MonarchE trial, which was the study of adjuvant abemaciclib for high-risk breast cancer. For analysis, the researchers examined group 1 (patients with at least 4 axillary lymph nodes or 1–3 positive lymph nodes and grade 3 tumour or tumour at least 5cm in size) and group 2 (which was patients with 1–3 positive axillary lymph nodes and Ki-67 of at least 20%, G1–2 tumour and size <5cm). In total there were 2511 high-risk patients with IDC identified and 361 high-risk patients with ILC identified. Median follow-up at time of analysis was 8.2 years for events and 13.2 years for survival. There was no statistical difference in events at 10 years between the two subsets when propensity score matched between high-risk ILC and IDC. There was a statistically nonsignificant higher rate of axillary recurrence in the ILC cohort compared with the IDC cohort. There was also no statistically significant difference in 5- and 10-year invasive DFS between the groups, nor for distant RFS, nor for OS. This analysis supports the use of abemaciclib for both lobular and ductal breast cancer high-risk adjuvant patients given the similar outcomes between the two groups.

***Reference: eClinicalMedicine 2024;71:102552***
Abstract

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## Aspirin vs placebo as adjuvant therapy for breast cancer

**Authors:** Chen WY et al.

**Summary:** This randomised, placebo-controlled phase 3 trial assessed whether aspirin decreased the risk of invasive cancer events among 3020 patients with high-risk nonmetastatic breast cancer. The study was stopped early, at an interim analysis point, for futility. After a median 33.8 months follow-up, 253 invasive DFS events had occurred (141 with aspirin and 112 with placebo; HR 1.27 [95% CI 0.99–1.63]). All invasive DFS events, including death, distant and locoregional invasive progression, and new primary events were more common in the aspirin group, and there was no difference in OS (HR 1.19 [95% CI 0.82–1.72]). Grade 3–4 adverse event rates did not differ between groups.

**Comment:** Aspirin is a widely available medication, with previous observational studies showing reduced death rates in breast cancer survivors who had regularly utilised aspirin, as well as data from vascular disease prevention studies showing a reduced risk of cancer with metastatic disease for patients treated with aspirin, as well as other studies showing a reduced risk of metastatic cancer for patients receiving aspirin. There is a plausible mechanism for anticancer effect from aspirin through both an antiplatelet effect as well as an anti-inflammatory effect. This current study appears to be the first randomised controlled study investigating the use of aspirin as part of adjuvant therapy for breast cancer. Patients were required to have HER2-negative disease for study enrolment, and were randomised either to aspirin 300mg daily or placebo, and were required to be within 18 months of diagnosis. However, as a result of slow accrual for hormone receptor-positive disease, eligibility was extended to allow patients up to 10 years postdiagnosis. Patients were required to be considered high risk for enrolment, defined either as node-positive disease for hormone receptor-positive disease or either node-positive or tumour greater than 2cm for hormone receptor-negative disease; 1510 were randomised to aspirin and 1510 to placebo. Almost 90% of the cohort had hormone receptor-positive disease. At a median follow-up of 33.8 months, there was no statistically significant difference between the groups, although numerically there was a greater rate of death in the aspirin group, as well as higher rates of invasive progression and new primary events. Adverse event rates were similar between the two arms. The study was ceased early as the futility boundary was crossed. Therefore, follow-up was only reasonably short. For hormone receptor-positive breast cancer, recurrences can occur late. Most of the cohort were within 18 months of diagnosis at the time of recruitment. Therefore, a benefit for late recurrence may be occurring, but not captured within these data. Furthermore, it may be that even the window of commencement 18 months from diagnosis is too long for benefit. Studies indicate that the benefit of other adjuvant therapies, such as localised radiotherapy, endocrine therapy and chemotherapy, is greatest if instituted early postdiagnosis. This broader eligibility window for enrolment was pragmatic to enable more rapid enrolment, but may have compromised the results for the study. Based on the results of this study, use of aspirin as adjuvant therapy in breast cancer is not supported. In the paper discussion, the authors advise and intention to pool the data from this study with those of the Add-Aspirin trial to investigate breast cancer subtypes. Analysis at longer follow-up would be of interest also; however, this does not appear to be planned.

***Reference: JAMA 2024;331:1714–21***
Abstract

## Phase Ib dose-escalation trial of taselisib (GDC-0032) in combination with HER2-directed therapies in patients with advanced HER2+ breast cancer

**Authors:** Grinshpun A et al

**Summary:** Sixty-eight patients with advanced HER2-positive breast cancer received taselisib added to trastuzumab emtansine, or to trastuzumab plus pertuzumab with or without paclitaxel or fulvestrant, in this dose-escalation phase 1b study. The MTD for taselisib was established as 4mg once daily. Grade ≥3 adverse events attributed to taselisib occurred in 34 participants, and the most common any-grade adverse events were diarrhoea, fatigue and oral mucositis. At the MTD and after a median 43.8 months of follow-up, the median PFS duration when taselisib was added to trastuzumab emtansine was 6.3 months (10.4 months for participants with prior trastuzumab emtansine use), and the respective median PFS durations for taselisib added to trastuzumab-pertuzumab and trastuzumab-pertuzumab-fulvestrant were 1.7 and 10.6 months.

**Comment:** This is the second study selected this month examining PIK3CA targeting agents, in this case taselisib, an α-selective PIK3CA inhibitor, in combination with various anti-HER2 therapies. This was a phase 1b study, therefore primarily investigating the MTD of taselisib with four different treatment combinations: i) with trastuzumab emtansine; ii) with trastuzumab and pertuzumab; iii) with trastuzumab, pertuzumab and paclitaxel; and iv) with trastuzumab, pertuzumab and fulvestrant. Patients were required to have metastatic or inoperable locally advanced or inoperable locally recurrent HER2-positive breast cancer with no standard therapy available, and having failed all standard available therapies. Patients were allowed to have used trastuzumab, pertuzumab, lapatinib or trastuzumab emtansine previously. Taselisib 4mg was found to be the MTD for the nonchemotherapy arms and 2mg the maximum for the paclitaxel-containing arm. Dose-limiting toxicities included thrombocytopenia, diarrhoea and liver function test derangement. The most frequent adverse events attributed to taselisib were diarrhoea, fatigue, oral mucositis, anorexia, nausea and thrombocytopenia. Median PFS for those who had used trastuzumab emtansine previously in the arm with taselisib added to this agent was 10.4 months, and 6.3 months for those who had not used trastuzumab emtansine previously. Interestingly, those with *PIK3CA* wild-type had better responses, with the fraction of patients with baseline ctDNA mutation 30% of those with a CR or partial response, 41% in those with stable disease, and 71% in patients with progressive disease. There were eight patients who cleared the *PIK3CA* mutation. Seven of eight of these patients had a median mean allele frequency of <5. Those who cleared the mutation had longer PFS. This study is reasonably small. Further investigation of the potential role of taselisib for HER2-positive disease could be considered. It should be noted that this study was undertaken prior to the availability of trastuzumab deruxtecan. The efficacy and role after trastuzumab deruxtecan therefore has not been investigated. Nonetheless, there may be a subset of patients for whom taselisib may have benefit. Research investigating the role in CNS disease would be of particular interest.

***Reference: ESMO Open 2024;9:103465***
Abstract



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## Palbociclib combined with endocrine treatment in hormone receptor-positive, HER2-negative breast cancer patients with high relapse risk after neoadjuvant chemotherapy

**Authors:** Marmé F et al.

**Summary:** This was a subgroup analysis of premenopausal PENELOPE-B trial participants; PENELOPE-B reported no improvement in invasive DFS by adding 1 year of postneoadjuvant palbociclib to endocrine therapy over placebo in patients with hormone receptor-positive, HER2-negative breast cancer at high risk of relapse. Of 616 premenopausal participants, 47.4% had ≥4 metastatic lymph nodes, 58.2% had a clinical, pathological stage, ER, grading score of ≥3, 66.1% received tamoxifen alone, and 32.9% received ovarian function suppression in addition to either tamoxifen or an aromatase inhibitor. After a median 42.8 months of follow-up, there was no significant difference in invasive DFS between the palbociclib versus placebo group (HR 0.95 [95% CI 0.69–1.30]) with only a marginally greater estimated 3-year invasive DFS rate with palbociclib (80.6% vs. 78.3%). The respective 3-year invasive DFS rates for participants receiving an aromatase inhibitor, tamoxifen plus ovarian function suppression and tamoxifen alone were 86.0%, 78.6% and 78.0%, and the rate was numerically greater in the palbociclib versus placebo arm among participants receiving tamoxifen plus ovarian function suppression (83.0% vs. 74.1%; HR 0.52 [95% CI 0.27–1.02]). Palbociclib was associated with a high rate of grade 3–4 haematological adverse events (76.1%), but did not appear to negatively impact ovarian function.

**Comment:** The PENELOPE-B study primary analysis was published in 2021, and failed to show a benefit in the use of 1 year of palbociclib following neoadjuvant chemotherapy for hormone receptor-positive breast cancer. This paper presents an exploratory subgroup analysis of the cohort of patients from this study who were premenopausal. Premenopausal status was defined as menstrual period <12 months from commencement of chemotherapy. In total, 616 of the 1250 patients in the total study cohort were considered premenopausal. Around two-thirds (66.1%) received adjuvant tamoxifen as initial endocrine therapy, 19.3% tamoxifen plus ovarian suppression and 13.6% aromatase inhibitor plus ovarian suppression. Median follow-up was 42.8 months. Consistent with the analysis of the total cohort, there was no difference in 3-year estimated invasive DFS between the palbociclib and the placebo arm for those who were premenopausal. The authors report 'numerically favourable 3-year invasive DFS' for those receiving palbociclib compared with placebo for those receiving tamoxifen plus ovarian suppression at 83.0% compared with 74.1%; however, it should be noted the study was not powered to analyse this subgroup level comparison, and numbers in this subgroup were reasonably small. Safety analysis for the premenopausal subgroup showed expected toxicity for the palbociclib arm, with higher haematological adverse events as well as hypocalcaemia, constipation, dyspnoea, fatigue, infections and stomatitis in the palbociclib arm. There was less anaemia and less thrombocytopaenia for the aromatase inhibitor plus ovarian suppression arms receiving palbociclib compared with those who received tamoxifen. Bloods to assess ovarian function of oestradiol, FSH (follicle-stimulating hormone) and AMH (anti-Müllerian hormone) were measured at baseline as well as at follow-up. Although treatment was only for 1 year of palbociclib, the study findings of no significant difference in rate of nonfertile AMH levels between the two arms provides some reassurance relating to the effect of this medication on fertility. While this is promising, specific data for ribociclib and abemaciclib are awaited to confirm whether this holds for the class of CDK4/6 inhibitors or is relevant only for palbociclib, and also whether longer duration of use of these agents results in gonadotoxicity.

***Reference: ESMO Open 2024;9:103466***
Abstract

## Ribociclib-induced cutaneous adverse events in metastatic HR+/HER2– breast cancer: incidence, multidisciplinary management, and prognostic implication

**Authors:** Borroni RG et al.

**Summary:** Cutaneous adverse events occurring during ribociclib use were reported for a retrospective cohort of 91 patients with hormone receptor-positive, HER2-negative advanced breast cancer. Thirteen of the patients developed treatment-related cutaneous adverse events within a mean of 3.9 months of starting ribociclib, with all these patients reporting itch, 53.8% reporting eczematous dermatitis and 15.4% developing maculopapular reactions. Eight of the cutaneous adverse reactions were grade 3, four were grade 2 and one was grade 1. It was found that most ribociclib discontinuations could be avoided using an integrated approach based on dose modulation and appropriate dermatological interventions. After a median 20 months of follow-up, the median PFS duration was 13 months with a significant signal of better PFS curves for patients who had experienced cutaneous adverse events.

**Comment:** Rates of cutaneous toxicity from the metastatic ribociclib studies MONALEESA-2, -3 and -7 range from 13% to 22%. This retrospective study examined dermatological adverse events in a cohort of patients managed through a single institution receiving ribociclib plus endocrine therapy. Ninety-one patients were identified, with an incidence of cutaneous adverse events of 14.3% (13 patients). Pruritus was experienced by all patients, with cutaneous adverse events with pruritus the only cutaneous event for two patients. Eczematous dermatitis was experienced by seven patients and maculopapular reactions by two. Lichenoid reaction and urticaria were also reported. This study is useful for clinicians, as it provides specific details of the grading of presentation and management utilised. All seven patients with eczematous dermatitis required temporary cessation of ribociclib, with reintroduction at lower doses. Eczematous dermatitis was managed with topical glucocorticoids and oral antihistamines initially for all patients. The paper reports on one case for whom dupilumab 300mg subcutaneously every 2 weeks was utilised following relapse with grade 3 severity. Dupilumab is an IL-4/-13α receptor antagonist used for severe refractory atopic dermatitis. This patient was able to continue ribociclib with the use of this medication. Thus, all patients with atopic dermatitis were able to continue with ribociclib therapy. Similarly, the patient who experienced lichenoid dermatitis had recurrence of symptoms on rechallenge at the same dosage; however, at a reduced dose of 400mg, they had no further lichenoid dermatitis. In contrast, both patients with maculopapular reactions were unable to continue with ribociclib. One of these cases had ribociclib ceased following grade 2 toxicity and restarted at lower dosing, but developed grade 3 recurrence and was permanently ceased, and the other patient permanently ceased after the initial grade 3 reaction. Similarly, the patient with a grade 3 urticarial reaction had recurrence on rechallenge and ceased. This patient and one of the patients with maculopapular rash were switched to palbociclib with no recurrence of their previous cutaneous toxicity. The researchers reported a better PFS estimate for patients with cutaneous adverse events (p=0.04). However, the numbers in this study are small. Further research examining this association, as well as examining management and resolution of cutaneous toxicities, is required to better understand whether cutaneous toxicities can predict for efficacy of ribociclib, as well as to better guide management of these toxicities.

***Reference: Oncologist 2024;29:484–92***
Abstract

## Tucidinostat plus exemestane as a neoadjuvant in early-stage, hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer

**Authors:** Zhao H et al.

**Summary:** Twenty patients with stage II–III hormone receptor-positive, HER2-negative breast cancer received tucidinostat plus exemestane followed by breast-conserving surgery (n=5) or modified radical mastectomy in this phase 2 trial. Three of the participants achieved a PEPI (preoperative endocrine prognostic index) score of zero, seven experienced complete cell cycle arrest, ten achieved a radiological objective response, 20 achieved disease control, and one achieved a pathological CR. Seventeen participants showed Ki67 suppression from baseline to surgery, with a Ki67 change ratio of –73.5%. Neutropenia, leucopenia, thrombocytopenia, lymphopenia, hypoalbuminaemia, anaemia and liver enzyme level elevations constituted the reported treatment-emergent adverse events.

**Comment:** This study examined the use of tucidinostat, an oral selective HDAC (histone deacetylase) inhibitor, in combination with exemestane in the neoadjuvant setting for hormone receptor-positive, HER2-negative stage II–III breast cancer. This class of drugs regulates epigenetic changes, and generally has a reasonably low rate of side effects. The study enrolled a total of 20 patients, with patients treated with oral tucidinostat 30mg twice per week plus daily oral exemestane 25mg for up to 24 weeks. The primary endpoint examined for the study was achievement of a PEPI score of zero. The details relating to this scoring system were published previously in 2008 by Ellis et al. The system utilises prognostic factors including tumour size, lymph node status, Ki67 expression level and ER status. PEPI score was constructed for both RFS (defined as interval between treatment assignment and subsequent breast cancer event), as well as recurrent breast cancer-specific death, defined as time from treatment assignment to date of death after breast cancer relapse. Only three patients obtained a PEPI score of zero for breast cancer-specific survival and for RFS. One patient did achieve a pathological CR, and the radiological disease control rate was 100%, which included 45% with a partial radiological response and 5% with a complete radiological response. A promising finding was that for participants with a Ki67 at baseline of >20%, 81.8% achieved a reduction in Ki67 expression at follow-up. Treatment was reasonably well tolerated, as anticipated. This small study supports further investigation of tucidinostat.

***Reference: Oncologist 2024;29:e763–70***
Abstract

## Early prediction of endocrine responsiveness in ER+/HER2-negative metastatic breast cancer (MBC)

**Authors:** Gennari A et al., on behalf of the ET-FES Collaborative Group

**Summary:** This pilot study evaluated $^{18}$F-FES CT-PET as a predictive tool in 147 patients with ER-positive, HER2-negative metastatic breast cancer; 117 participants with an SUV of ≥2 received single-agent endocrine therapy until disease progression, while 30 with an SUV of <2 were randomised to single-agent endocrine therapy or chemotherapy. After a median 62.4 months of follow-up, the respective disease progression and mortality rates were 73.2% and 37.3%. Among participants with an SUV of <2, the median PFS durations for the respective endocrine therapy and chemotherapy groups were 12.4 months and 23.0 months, the median OS durations were 28.2 months and 52.8 months, and the 60-month OS rates were 41.6% and 42.0%. For participants with an SUV of ≥2 (endocrine therapy), the respective median PFS and OS durations were 18.0 months and not reached, with a 60-month OS rate of 59.6%; the 60-month OS rate was significantly higher in participants treated with aromatase inhibitors than those treated with fulvestrant or tamoxifen (72.6% vs. 40.6% [p<0.005]).

**Comment:** FES-PET scans are not funded in Australia and are not readily available. The studies utilise radiolabelled oestradiol with the tracer binding to ERs. This study was a phase 2 randomised trial run across seven centres. The aim of the study was to determine whether $^{18}$F-FES CT-PET improved the ability to tailor treatment for ER-positive, HER2-negative metastatic breast cancer, and hence potentially improve disease control. Patients considered suitable for first-line endocrine therapy in the metastatic setting had baseline FES-PET along with standard imaging. Those with an SUV of ≥2 on the FES-PET were considered to have hormone-sensitive disease and managed with standard endocrine therapy, while those with low FES uptake were randomised to either arm A of single-agent endocrine therapy or arm B of chemotherapy of physician's choice. In Nov 2016, arm B was amended to either first-line chemotherapy or first-line endocrine therapy plus biological agents such as everolimus or CDK4/6 inhibitors. The study planned to enrol a total of 220 patients, with 110 endocrine-resistant patients anticipated. Enrolment commenced in Apr 2015. However, the study closed early on Dec 20, 2020 after enrolment of a total of 147 patients as a result of the coronavirus pandemic. Only 30 patients were identified with an SUV of <2, with 14 randomised to arm A of endocrine therapy alone (with one deemed ineligible subsequently) and 16 patients in the chemotherapy or endocrine therapy plus biologic agent arm (arm B). Of those in arm B, 11 received chemotherapy first line, two received endocrine therapy plus a biologic agent and three declined the assigned treatment. Median PFS of 18 months for those with SUV ≥2 is concordant with the PFS reported in the endocrine therapy-alone arms of the first-line metastatic hormone receptor-positive, HER2-negative CDK4/6 inhibitor trials such as MONALEESA-2 (16 months). The finding of >60% of patients surviving beyond 5 years, however, aligns more closely with the ribociclib plus endocrine therapy arm of the study. The median PFS for those with an SUV of <2 treated with chemotherapy (arm B) was almost double that of those treated with endocrine therapy alone (arm A) at 23 months compared with 12.4 months. The findings of this study, although with much smaller numbers than intended, indicate a role for FES in guiding treatment decisions. For patients with an FES SUV of <2, endocrine therapy alone resulted in poorer outcomes. However, the study did not investigate whether the addition of a CDK inhibitor to endocrine therapy would result in improved outcomes, or whether the use of chemotherapy is warranted for this subgroup. Further research is required to determine the optimal management for patients with low FES SUVs.

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Abstract



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