Breast Cancer Research Review™

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Issue 71 - 2025

In this issue:

Abbreviations used in this issue:

CR = complete response; **DFS** = disease-free survival; **HER2** = human epidermal growth factor receptor-2; **HR** = hazard ratio; **OS** = overall survival; **PFS** = progression-free survival; **RFS** = relapse-free survival.

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Welcome to issue 71 of Breast Cancer Research Review.

We begin this issue with the final analysis of invasive DFS and the second interim analysis of OS from the KATHERINE trial of adjuvant trastuzumab emtansine versus trastuzumab alone in patients with HER2-positive early breast cancer with residual invasive disease. This is followed by a phase 3 noninferiority trial of extending the postsurgical mammography interval from 1 year to 2 or 3 years for women aged ≥50 years who have had invasive or noninvasive breast cancer. There is also a real-world study assessing factors associated with patient attrition between the first and second therapy lines for metastatic breast cancer. The issue concludes with promising evaluations of a potent antibody-drug radioconjugate for treating breast cancer.

We hope you enjoy this update in breast cancer research, and we look forward to comments and feedback.

Kind Regards,

Dr Hilary Martin
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Survival with trastuzumab emtansine in residual HER2-positive breast cancer

Authors: Geyer CE Jr et al., for the KATHERINE Study Group

Summary: This report provides the prespecified final analysis of invasive DFS and second interim analysis of OS from the open-label, phase 3 KATHERINE randomised trial of adjuvant trastuzumab emtansine versus trastuzumab for 14 cycles in 1486 patients with HER2-positive early breast cancer with residual invasive disease after neoadjuvant taxane-based chemotherapy and trastuzumab. After a median 8.04 years of follow-up, trastuzumab emtansine provided a sustained improvement in invasive DFS over trastuzumab (HR 0.54 [95% CI 0.44–0.66]); the 7-year invasive DFS rate was 80.8% with trastuzumab emtansine and 67.1% with trastuzumab. Trastuzumab emtansine was associated with a lower risk of death than trastuzumab (HR 0.66 [0.51–0.87]), while 7-year OS was 89.1% vs. 84.4%. Grade ≥3 adverse events occurred in 26.1% of trastuzumab emtansine and 15.7% of trastuzumab recipients.

Comment: Previously reported data from the KATHERINE trial showing a significant improvement in risk of invasive breast cancer or death for trastuzumab emtansine compared with trastuzumab alone for those without pathological CR resulted in a shift in management of HER2-positive early breast cancer. As a direct result of this study, neoadjuvant chemotherapy has become the standard of care for patients with early HER2-positive breast cancer, other than those with small HER2-positive breast cancer tumours, to enable access to trastuzumab emtansine for those without pathological CR. This paper reports the final invasive DFS and second interim analysis of OS at a median follow-up of 8.4 years. Invasive DFS was statistically and clinically significantly improved in the trastuzumab emtansine arm. The paper also reported exploratory analyses undertaken; those with residual invasive disease of 1cm or less and negative axillary nodes had a trend towards improved invasive DFS at 85.7% for those who received trastuzumab emtansine, compared with 76.7% for those who received trastuzumab alone. This paper suggests that trastuzumab emtansine is still worthwhile using for those with smaller residual tumours. Reporting on outcome relative to percent cellularity would have been of interest. There was also a greater magnitude of benefit for trastuzumab emtansine compared with trastuzumab for those with IHC3-positive disease compared with those with IHC2-positive disease. One of the exploratory analysis updated also was for those with smaller HER2-positive, node-negative tumours at the start of neoadjuvant chemotherapy (clinical T1/clinical N0). There were 44 such patients in the trastuzumab emtansine arm and 32 in the trastuzumab group. There were no invasive disease events or deaths in the trastuzumab emtansine group and 8 (25%) reported in the trastuzumab group. Generally, outcomes are excellent for patients with smaller HER2-positive breast cancer, but this result does show that even for those with smaller tumours, if pathologic response is not achieved, trastuzumab emtansine is of benefit. Therefore, patients with smaller HER2-positive tumours should also have the option of neoadjuvant therapy considered. OS was numerically higher in the trastuzumab emtansine arm, but did not meet the prespecified boundary for statistical significance. There were no new safety concerns raised at this longer follow-up. The study supports the continued use of adjuvant trastuzumab emtansine for those without pathological CR.

Reference: N Engl J Med 2025;392:249–57
Abstract

Annual versus less frequent mammographic surveillance in people with breast cancer aged 50 years and older in the UK (Mammo-50)

Authors: Dunn JA et al.

Summary: Women aged ≥50 years at initial diagnosis of invasive or noninvasive breast cancer and who were recurrence-free 3 years after curative surgery were randomised to mammography every year (n=2618) or 2-yearly after conservation surgery or 3-yearly after a mastectomy (n=2617) and were followed for 6 years in this phase 3 noninferiority trial. There was no significant difference between the annual versus less frequent mammography arms for 5-year breast cancer-specific survival rate (98.1% vs. 98.3% [p<0.0001 for noninferiority]), 5-year recurrence-free interval (94.1% vs. 94.5%) or 5-year OS rate (94.7% vs. 94.5%). Among the 345 breast cancer events recorded, 61.7% and 68.2% from the respective annual and less frequent mammography arms were from emergency admissions or symptomatic hospital referrals.

Comment: This was a large study of 5235 women over 50 years of age with a history of invasive or noninvasive breast cancer with no recurrence 3 years after initial diagnosis, examining annual mammogram surveillance compared with 2-yearly for patients with breast conserving surgery and 3-yearly for those with mastectomy. Thus for those with mastectomy in the less frequent arm, mammography was undertaken less frequently than recommended by BreastScreen Australia for patients without a breast cancer history of every 2 years from age 50–74 years. The majority of patients in the study (87.4%) had invasive disease. The median follow-up for the study was 5.7 years, which would have meant a median only 1–2 mammograms in the less frequent mammogram arm. The rationale for the study was based partly on reduced locoregional recurrence rates over time from 30% in studies from 1990s to 15% in studies from 2011. The paper also quotes data showing local recurrence rates to be lower in older women. The study found breast cancer-specific survival, RFS and OS to be the same between the groups. However, it should be noted that follow-up for the study was a median of 5.7 years. Generally at this duration of follow-up, a screen-detected primary breast cancer would not be anticipated to cause death, and in most cases, even if metastatic disease were present, similarly most patients would still be alive, particularly those with oestrogen receptor-positive and HER2-positive disease. Therefore, the OS and breast cancer-specific survival data are too early to be properly assessed at this timepoint. RFS is an interesting assessment, as at this median follow-up there will have been less mammograms in the 3-yearly mammogram arm performed, and hence potentially less recurrences detected. The results of the study confirm there were fewer recurrences detected in the 3-yearly mammogram arm. Longer follow-up is required to assess whether the extended time interval between mammograms is truly noninferior in this population.

Reference: Lancet 2025;405:396–407
Abstract

A phase III trial of adjuvant ribociclib plus endocrine therapy versus endocrine therapy alone in patients with HR-positive/HER2-negative early breast cancer

Authors: Hortobagyi GN et al.

Summary: This article reported the final invasive DFS results from the NATALEE trial, in which men and pre- or postmenopausal women with stage IIA, IIB or III hormone receptor-positive/HER2-negative early breast cancer had been randomised to receive letrozole 2.5 mg/day or anastrozole 1 mg/day for 60 months with (n=2549) or without (n=2552) ribociclib 400 mg/day on a 3 weeks on, 1 week off schedule for 36 months; the participants also received goserelin 3.6mg once every 28 days; at data cutoff, 78.3% of participants assigned to ribociclib had discontinued this agent with 42.8% completing 3 years. Compared with letrozole or anastrozole alone, the addition of ribociclib was associated with a significant benefit for invasive DFS (HR 0.749 [95% CI 0.628–0.892]), with a greater 3-year invasive DFS rate (90.7% vs. 87.6%) and consistency of benefit seen across prespecified subgroups, including disease stage and nodal status. The addition of ribociclib was also associated with improvements in distant DFS and RFS; OS data were immature. There were no new safety signals detected.

Comment: This paper is topical, with a positive PBAC (Pharmaceutical Benefits Advisory Committee) recommendation in November for adjuvant ribociclib, and recent approval by TGA for this indication. The updated paper provides data at a median of 33.3 months of follow-up. These results confirm the earlier positive signal for the use of adjuvant ribociclib, with a 3-year invasive DFS rate of 90.7% in the ribociclib plus nonsteroidal aromatase inhibitor arm compared with 87.6% in the non-steroidal aromatase inhibitor alone arm. Benefit was confirmed for subgroups of stage II disease, stage III disease, node-positive disease and node-negative disease. The paper did report the OS rates, with no notable difference between arms; however, much longer follow-up is required to examine OS for hormone receptor-positive breast cancer. In terms of safety, this was as expected; however, the study did run during the COVID-19 pandemic, with six COVID-19-related deaths in the ribociclib arm compared with only one COVID-19-related death in the nonsteroidal aromatase inhibitor alone arm. The data support the use of adjuvant ribociclib for the patient cohorts eligible for the trial.

Reference: Ann Oncol 2025;36:149–57
Abstract

HER2DX in HER2-positive inflammatory breast cancer: correlative insights and comparative analysis with noninflammatory breast cancers

Authors: Lynce F et al.

Summary: The accuracy of HER2DX for predicting pathological CR was compared between 23 participants with stage III HER2-positive inflammatory breast cancer (from a phase 2 trial of neoadjuvant trastuzumab, pertuzumab and paclitaxel) and 156 patients with stage III HER2-positive noninflammatory breast cancer (from four different cohorts). Compared with patients with noninflammatory breast cancer, those with inflammatory breast cancer differed in terms of clinicopathological characteristics, including greater use of pertuzumab and chemotherapy and lower axillary burden. Both HER2DX pathological CR score and pertuzumab use were significant predictors of pathological CR, but not of inflammatory breast cancer status. Recipients of trastuzumab-based chemotherapy from the respective HER2DX pathological CR-high, -medium and -low subgroups had pathological CR rates of 68.9%, 58.5% and 16.3%. There were minor differences noted between the inflammatory and non-inflammatory breast cancer groups on comparative gene expression analysis for individual HER2, immune and proliferation genes.

Comment: The HER2DX assay utilises tumour size, nodal status and expression of 27 genes covering four signatures (immune infiltration, tumour cell proliferation, luminal differentiation and HER2 expression) to give three scores: i) the HER2DX risk score, which predicts long-term prognosis; ii) the HER2DX pathological CR score, which predicts likelihood of achieving a pathological CR; and iii) the ERBB2 score, which reflects *ERBB2* mRNA expression levels. The assay has been previously examined in early HER2-positive breast cancer. This reported study examines the utility of the assay for stage III HER2-positive inflammatory breast cancer treated with neoadjuvant trastuzumab, pertuzumab and paclitaxel, compared with scores for stage III HER2-positive non-inflammatory breast cancer treated with neoadjuvant trastuzumab-based treatment from four cohorts. The study found that inflammatory breast cancer patients with a high HER2DX pathological CR score had a higher rate of pathological CR, and the authors concluded this may ultimately allow de-escalation. HER2DX pathological CR score was the best predictor of pathological CR, compared with other variables such as hormone receptor status, tumour size and nodal status. The study did have only 23 patients with inflammatory breast cancer included. Larger studies are needed to validate these findings and determine whether HER2DX assay results can be safely used to guide de-escalation of therapy, such as enabling omission of anthracycline therapy.

Reference: ESMO Open 2025;10:104100
Abstract

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Factors associated with first-to-second-line attrition among patients with metastatic breast cancer in the real world

Authors: Blondeaux E et al.

Summary: First- to second-line attrition was reported for an ambispective real-world observational cohort of 3109 patients with metastatic breast cancer enrolled in the Gruppo Italiano Mammella-14/BIO-META study; failure to first-line treatment was recorded for 2498 of the cohort. The first- to second-line attrition rate was 9.0%, with similar rates for those with hormone receptor-positive, HER2-negative disease (8.5%) and those with HER2-positive disease (7.1%), but the highest rate (13.0%) was seen for those with triple-negative disease. Independent predictors of first- to second-line attrition were age, menopausal status, disease-free interval from primary tumour diagnosis, type of metastatic spread and tumour subtype.

Comment: This was a large study of 2398 patients who completed at least first-line therapy for metastatic breast cancer within the GIM14/BIO-META observational study, run by the Gruppo Italiano Mamella. This paper focussed on attrition between first- and second-line therapy. Breast cancer has multiple lines of available therapy, and thus attrition in this setting is not due to availability of treatment options, but rather either toxicity or cancer progression, such that further systemic therapy is not a feasible option, or patient decision not to undertake further treatment. Of the cohort, 66.0% had hormone receptor-positive, HER2-negative disease, 24.9% HER2-positive and only 7.1% triple-negative breast cancer. Interestingly, over half the patients (52.0%) had only one metastatic site. For most of the study period, CDK inhibitors were not available, and hence only 14.2% of those with hormone receptor-positive, HER2-negative disease received a CDK inhibitor. Nine percent did not receive a second-line therapy, with those with triple-negative breast cancer having the highest rate of failure to receive a second line of therapy at 13.0%. On multivariate analysis, older age, postmenopausal status, shorter disease-free interval from initial early breast cancer and triple negative breast cancer subtype and visceral metastases were associated with higher rates of attrition. Patients with *de novo* stage IV disease also had a higher rate of attrition. The study notes data regarding comorbidities, and the reason for discontinuation and failure to progress to a second line of therapy was not obtained. It would be useful to obtain these data to better understand the reasons for early cessation of treatment.

Reference: ESMO Open 2025;10:104125
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.

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Trastuzumab duocarmazine in pretreated human epidermal growth factor receptor 2-positive advanced or metastatic breast cancer

Authors: Turner N et al., on behalf of the TULIP Trial Investigators

Summary: Patients with unresectable locally advanced or metastatic HER2-positive breast cancer who had progressed during or after ≥2 HER2-targeted therapies or after trastuzumab emtansine were randomised to trastuzumab duocarmazine (n=291) or physician's choice of therapy (n=146) in the open-label phase 3 TULIP trial; 93.6% of participants had metastatic disease. Compared with physician's choice therapy, trastuzumab duocarmazine recipients had a significantly longer median PFS duration (primary endpoint; 7.0 vs. 4.9 months [p=0.002]), with the benefit consistent across most predefined subgroups, as well as a numerically longer median OS duration at first analysis (20.4 vs. 16.3 months [p=0.153]) and tendencies for better clinical benefit rate, duration of response and reduction in target lesion measurement; however, objective response rates were similar (27.8% vs. 29.5%). The grade ≥3 treatment-emergent adverse event rates in the respective trastuzumab duocarmazine and physician's choice arms were 52.8% and 48.2%.

Comment: Trastuzumab duocarmazine is another HER2 targeted antibody drug conjugate, combining trastuzumab and the cytotoxic agent duocarmycin, which alkylates DNA. This phase 3 study randomised patients to either trastuzumab duocarmazine or treatment of physicians choice (lapatinib-capecitabine, trastuzumab-capecitabine, trastuzumab-vinorelbine or trastuzumab-eribulin). Only a very small proportion of patients in the study had received previous trastuzumab deruxtecan (eight patients in total of the 437 patients treated on trial). The majority of patients had received trastuzumab emtansine. There was a significant improvement in median PFS in the trastuzumab duocarmazine arm compared with treatment of physician's choice at 7.0 months compared with 4.9 months. Preliminary OS assessment favoured trastuzumab duocarmazine, although the confidence interval crossed 1. Interestingly the overall response rates were similar between trastuzumab duocarmazine and treatment of physicians choice at 27.8% and 29.5%, respectively; however, the median duration of response was longer in the trastuzumab duocarmazine arm at 15.1 months compared with 4.6 months in the treatment of physician's choice arm. Ocular toxicity was a significant issue in the trastuzumab duocarmazine arm, with 78.1% of patients experiencing at least one ocular treatment-related adverse event, and 20% of the patients in the trastuzumab duocarmazine arm ceasing treatment as a result of ocular toxicity. There were two pneumonitis-related deaths in the study. While promising in terms of PFS, there was a high discontinuation rate due to ocular toxicity. In an increasingly busy HER2-positive metastatic cancer space, it is uncertain whether this agent will, though effective, progress as a result of toxicity, as well as the fact that given only a very small proportion of patients had received trastuzumab deruxtecan prior, it has not been tested following trastuzumab deruxtecan therapy, which would usually be used as second-line anti-HER2 therapy.

Reference: J Clin Oncol 2025;43:513–23
Abstract

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Outcomes and treatment patterns for stage I human epidermal growth factor receptor 2-positive breast cancer in the Surveillance, Epidemiology, and End Results database, 2010–2019

Authors: Waks AG et al.

Summary: Chemotherapy use and breast cancer-specific survival were reported for 12,896 patients with stage IA HER2-positive breast cancer (74.0% hormone receptor-positive/HER2-positive and 26.0% hormone receptor-negative/HER2-positive) entered in the Surveillance, Epidemiology, and End Results database and followed for a median 46 months; 58.9% of the patients had received adjuvant chemotherapy, although utilisation of such therapy was lower for those who were older, those of Hispanic or Asian/Pacific Islander ethnicity, those who were separated, divorced or widowed, and those with a lower median household income. For pathological T1 microscopic, pathological T1a and pathological T1b tumours, the 5-year breast cancer-specific survival rates were 97.6–99.6% when there was no record of chemotherapy receipt, compared with 98.4–100.0% when chemotherapy use was recorded. For pathological T1c tumours with no record of chemotherapy receipt, the 5-year breast cancer-specific survival rates were 92.1% and 96.0% among patients with hormone receptor-negative, HER2-positive disease and those with hormone receptor-positive, HER2-positive disease, respectively; the respective rates for patients with pathological T1c tumours who had received chemotherapy were 96.7% and 98.7%.

Comment: This study examined outcomes for 12,896 patients with anatomic stage I HER2-positive breast cancer. Patients who had received neoadjuvant radiotherapy or chemotherapy were excluded from this study, as were those who did not undergo surgery. The majority of patients (58.9%) received chemotherapy, with an increase in chemotherapy use over time. For those with hormone receptor-positive, HER2-positive disease, both those who received chemotherapy and those who did not had excellent outcomes, although 5-year breast cancer-specific survival was significantly higher in the chemotherapy group at 98.7% compared with 96.0% in the no-chemotherapy or unknown group (p=0.02). Breast cancer-specific survival also favoured chemotherapy for the hormone receptor-negative, HER2-positive subgroup at 96.7%, compared with 92.1% for the n-chemotherapy or unknown group, but this was not statistically significant. The study also showed that those who received chemotherapy were more likely to be married, younger age and have a higher household income. The study did show a greater benefit for the larger stage I tumours and less benefit for smaller stage I tumours from adjuvant chemotherapy. While outcomes are excellent for the stage I tumours irrespective of chemotherapy receipt, the study supports the use of adjuvant chemotherapy for those with larger stage I tumours. Whether neoadjuvant therapy may be a preferable approach, to enable access to treatment as per the KATHERINE trial discussed in the first article reviewed, also needs to be considered.

Reference: Cancer 2025;131:e35729
Abstract

Effects of tamoxifen on cognitive function in patients with primary breast cancer

Authors: Luijendijk MJ et al.

Summary: These researchers evaluated the cognitive function of 135 women with breast cancer who had received tamoxifen for 2 years, as well as the impact of tamoxifen and endoxifen exposure on cognitive function. Results from the online neuropsychological test battery Amsterdam Cognition Scan revealed that compared with matched controls, the women had mild cognitive complaints, with worse verbal learning, processing speed, executive functioning and motor functioning. Associations of mean tamoxifen and endoxifen concentrations and tamoxifen dose with worse performance on several cognitive domains were detected after correcting for age.

Comment: Previous studies have had conflicting results relating to the effect of tamoxifen on cognition, although a large meta-analysis showed decreased verbal learning and memory, executive functioning and processing speeds for patients treated with tamoxifen or an aromatase inhibitor. The currently reported study examined whether cognitive effects from tamoxifen depend on level of exposure to tamoxifen, or its metabolites. In the study, the concentrations of the metabolite endoxifen were measured. This reported study was a substudy of the TOTAM study, which examined tamoxifen and endoxifen levels. Tamoxifen dose was increased to 30 or 40mg if endoxifen concentrations were low and could be decreased to 10mg if there were significant side effects and reasonably high endoxifen concentrations. After 2 years of treatment with tamoxifen, patients had neuropsychological testing with a battery of testing, undertaken using the validated online neuropsychological testing battery (Amsterdam Cognition Scan). Side effects of tamoxifen were also assessed using the Functional Assessment of Cancer Therapy-Endocrine Subscale. In total, 139 patients completed the Amsterdam Cognition Scan. The rate of cognitive impairment was higher in the tamoxifen arm compared with matched controls at 47% compared with 28%. In the self-reported questionnaires, patients reported mild cognitive issues and mild interference with daily activities. After adjusting for age, tamoxifen concentrations were negatively associated with two of the Amsterdam Cognition Scan outcomes. Endoxifen concentrations were also negatively associated with the same two cognition scale outcomes after adjusting for age (box tapping and fill the grid). The study showed older women were more vulnerable to cognitive effects of tamoxifen, defined as >57 years for the study. Therefore, this aspect is important to monitor for and to counsel patients regarding. Aromatase inhibitors are the more favoured agents due to greater efficacy in the postmenopausal age group. It would be useful to assess cognition with this agent using the same battery of testing to determine whether a similar effect results.

Reference: Br J Cancer 2025;132:180–7
Abstract

Quality-adjusted time without symptoms or toxicity analysis of trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer patients based on secondary use of the DESTINY-Breast03 trial

Authors: Dennis N et al.

Summary: This secondary DESTINY-Breast03 trial analysis evaluated treatment differences using quality-adjusted survival time without symptoms or toxicity (Q-TWiST) methods; the phase 3 DESTINY-Breast03 randomised trial compared trastuzumab deruxtecan with trastuzumab emtansine in patients with HER2-positive unresectable and/or metastatic breast cancer who progressed during or after treatment with trastuzumab plus a taxane. The participants' survival was categorised into one of the following three health states: i) time spent with grade 3–4 adverse events; ii) time without adverse events before disease progression; and iii) time from disease progression to death. It was found that compared with trastuzumab emtansine, trastuzumab deruxtecan was associated with a substantial, clinically important improvement in Q-TWiST (mean difference 3.80 months [p<0.001], with the results robust to threshold utility analysis.

Comment: Trastuzumab deruxtecan is now funded via PBS and is the preferred second-line treatment for HER2-positive breast cancer, with clearly greater efficacy with both improved PFS and OS compared with trastuzumab emtansine shown. However, it is not without side effects, including potentially fatal pulmonary toxicity. From a clinician and patient perspective, both quantity and quality of life are important. This study examined treatment differences via Q-TWiST methods, which assess quality-adjusted survival time by examining health state during: i) time with grade 3–4 adverse events; ii) time without adverse events before disease progression; and iii) time from disease progression to death. Health state was assessed using the EQ-5D-5L questionnaire. The results of the study show improved quality-adjusted survival for trastuzumab deruxtecan compared with trastuzumab emtansine. This is an important result for the study and supports the use of trastuzumab deruxtecan as the treatment of choice over trastuzumab emtansine.

Reference: Eur J Cancer 2025;217:115192
Abstract

Complete remissions of HER2-positive trastuzumab-resistant xenografts using a potent [^{225}Ac]Ac-labeled anti-HER2 antibody-drug radioconjugate

Authors: Ketchemen JP et al.

Summary: These researchers combined actinium-225 with an antibody-drug conjugate to develop an antibody-drug radioconjugate ([^{225}Ac]Ac-macropa-trastuzumab-PEG$_6$-emtansine), which they evaluated in several experiments. Stability of the antibody-drug radioconjugate was demonstrated in human serum and peripheral blood during 7-day 37°C incubation. When trastuzumab-PEG$_6$-emtansine 8 mg/kg and the antibody-drug radioconjugate 3×18 kBq were administered separately in nontumour-bearing mice 10 days apart, tolerability was good both biochemically and haematologically. MicroPET imaging and biodistribution revealed high tumour uptake. The researchers were able to conclude that their antibody-drug radioconjugate appeared more potent than antibody-drug conjugate in trastuzumab-resistant breast cancer.

Comment: Many of the newer agents in the HER2-positive area are antibody drug conjugates, such as trastuzumab deruxtecan. This xenograft study examined the use of an antibody drug radioconjugate. The agent used has ^{225}Ac as the radioisotope component. This agent is an isotope of actinium and undergoes alpha decay with a half-life of 10 days. This isotope has been investigated for use in prostate cancer, with ^{225}Ac-PSMA radioligand therapy showing promising results and it was reasonably well tolerated. In the current study, the radioisotope was linked to trastuzumab-PEG$_6$-emtansine (^{225}AC-macropa-T-PEG6-DM1), and the results were compared with standard trastuzumab emtansine. Mice with trastuzumab-resistant tumours and with trastuzumab emtansine-resistant tumours were examined. For the trastuzumab emtansine-resistant mice, tumour volumes were assessed 23 days after treatment with saline (negative control), trastuzumab emtansine, trastuzumab-PEG$_6$-emtansine and [^{225}Ac]Ac-macropa-T-PEG$_6$-DM1. Tumour volumes were substantially lower in the [^{225}Ac]Ac-macropa-T-PEG$_6$-DM1 arm, at 102.4 ±18.5 compared with 244.6 ±63 for the trastuzumab emtansine arm. Examining either this agent in humans, or potentially considering if possible the use of ^{225}Ac linked with trastuzumab deruxtecan, will be of interest.

Reference: Clin Cancer Res 2025;31:685–96
Abstract

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