A RESEARCH REVIEW™
CONFERENCE REVIEW

ASCO 2025
Focus on Breast Cancer

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30 May – 3 June 2025; Chicago, USA

In this review:

Abbreviations used in this review
CKD = cyclin-dependent kinase
ctDNA = circulating tumour DNA
ER = estrogen receptor
HER2 = human epidermal growth factor receptor 2
ILD = interstitial lung disease
P13K = phosphoinositide 3-kinase
PFS = progression-free survival
OFS = ovarian function suppression
OS = overall survival
PROTAC = proteolysis targeting chimera
SERD = selective ER degrader
TNBC = triple-negative breast cancer
VMS = vasomotor symptoms

Welcome to this review of the American Society of Clinical Oncology (ASCO) Annual Meeting 2025, with a focus on Breast Cancer.

The conference attracted thousands of people engaged in cancer research and care. I have selected and reviewed a number of interesting presentations that focused on breast cancer research. All of the selected studies have since been published in the *Journal of Clinical Oncology*.

I hope you find the Conference Review interesting and look forward to your feedback.

Kind regards

Dr Sheridan Wilson
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Treatment rechallenge after trastuzumab deruxtecan-related interstitial lung disease: A multi-institution cohort study

Authors: Natsuhara KH et al.

Summary: In this multi-institution cohort study, trastuzumab deruxtecan (T-DXd) rechallenge was safe and provided a long duration of clinical benefit in patients with breast cancer who developed grade 1 interstitial lung disease (ILD) during initial treatment. Patients treated with steroids had faster radiographic ILD improvement, and median time to rechallenge was 42 days after the last T-DXd dose. In 38 patients with grade 1 ILD who were rechallenged (61% with a lower dose), 26% developed recurrent ILD grade 1–3 after a median 211 days. Of the nine patients rechallenged after grade 2 ILD, two (22%) developed recurrent grade 2/3 ILD. No grade 5 toxicity was seen after rechallenge.

Comment: T-DXd was approved in NZ for use as second-line treatment of advanced HER2-positive breast cancer in Jan 2025. This highly effective antibody-drug conjugate represents a significant step change in the management of HER2-positive breast cancer. Toxicity data from the DESTINY suite of studies, which investigate T-DXd in HER2-positive and HER2-low early and advanced breast cancer, alerted clinicians to the important risk of ILD. ILD is experienced in 10–15% of patients treated with T-DXd. If identified at an early, asymptomatic stage, this side effect can typically be managed with steroids, however ILD can be severe and fatal in a small number of cases. Regular monitoring for radiological changes of ILD, before symptoms develop, is an accepted component of T-DXd protocols since re-treatment upon resolution of the changes is permissible. In this abstract, the real-world experience of patients rechallenged with T-DXd is presented. The findings suggest that, with careful patient selection and close monitoring, some patients can be safely rechallenged, often achieving a further extended period of treatment in the post ILD phase. The abstract doesn't tell us about the characteristics of the patients who were not selected for rechallenge. Whilst approximately a quarter of those rechallenged experienced further ILD, there were no cases of fatal ILD. The study emphasises the importance of early detection and use of steroids in the management of ILD, and the potential to continue HER2-targeted therapy in some cases. As access to HER2-targeted therapies expands in NZ, managing toxicities like ILD becomes crucial. Resource constraints can make accessing timely radiology a challenge but developing protocols for ILD surveillance and safe rechallenge could enhance treatment continuity, which is particularly valuable given limited second-line options in this country.

Reference: J Clin Oncol. 2025;43(16 suppl):1015

Abstract

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Vepdegestrant, a PROTAC estrogen receptor (ER) degrader, vs fulvestrant in ER-positive/human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer: Results of the global, randomized, phase 3 VERITAC-2 study

Authors: Hamilton EP et al.

Summary: The results of the phase 3 VERITAC-2 study support the use of vepdegestrant as a potential oral treatment option for previously treated patients with *ESR1* mutation (*ESR1*m) ER-positive/HER2-negative advanced breast cancer. A total of 624 patients (median age 60 years) with ER-positive/HER2-negative advanced breast cancer, who had had one prior line of a CKD 4/6 inhibitor plus endocrine therapy and ≤1 additional line of endocrine therapy were randomised 1:1 to vepdegestrant 200mg orally once daily continuously or fulvestrant 500mg intramuscularly (days 1 and 15 of cycle 1, then day 1 of subsequent cycles). The primary end-point was PFS in patients with *ESR1*m and in all patients. PFS was significantly longer with vepdegestrant than fulvestrant in patients with *ESR1*m (median 5.0 vs 2.1 months) but did not differ significantly between groups in all patients (median 3.7 vs 3.6 months). Treatment-emergent adverse events were mostly grade 1–2, and the most common event in the vepdegestrant arm was fatigue (26.6% vs 15.6% with fulvestrant).

Comment: It is pleasing to see new ER-targeting agents progressing through clinical trials. Vepdegestrant, a novel PROTAC-based ER degrader, demonstrated promising activity compared to fulvestrant in endocrine-resistant ER-positive/HER2-negative disease. Endocrine therapy remains a cornerstone for those with ER-positive advanced breast cancer, integrating newer agents, and more potent ER-targeting may translate into more effective management of resistant disease. Whilst the vepdegestrant data are positive, absolute improvements appear modest with a PFS of just 5 months. The very short 2.1-month PFS seen in the fulvestrant arm is in keeping with that seen in other later-line endocrine therapy trials using fulvestrant as a single agent comparator. This observation is helpful for clinicians considering the position of fulvestrant in the treatment algorithm for ER-positive advanced breast cancer. Acknowledging that the majority of advanced breast cancer is ER-positive, expanding well tolerated, targeted treatment options is key to improving outcomes. Ongoing efforts to find effective agents for use in later lines of endocrine therapy are warranted.

Reference: J Clin Oncol. 2025;43(17 suppl):LBA1000
Abstract

INAVO120: Phase III trial final overall survival (OS) analysis of first-line inavolisib (INAVO)/placebo (PBO) + palbociclib (PALBO) + fulvestrant (FULV) in patients (pts) with *PIK3CA*-mutated, hormone receptor-positive (HR+), HER2-negative (HER2–), endocrine-resistant advanced breast cancer (aBC)

Authors: Turner NC et al.

Summary: Combination therapy with inavolisib + palbociclib + fulvestrant has a significant OS benefit in patients with *PIK3CA*-mutated, hormone receptor (HR)-positive/HER2-negative, endocrine-resistant advanced breast cancer according to the final OS analysis of the INAVO120 study. Patients were randomised to receive placebo or inavolisib (9mg orally once daily on days 1–28 of each 28-day cycle) + palbociclib (125mg orally once daily on days 1–21 of each cycle) + fulvestrant (500mg intramuscularly on days 1 and 15 in cycle 1 then every ~4 weeks). Median OS was 34.0 months in the inavolisib arm and 27.0 months in the placebo arm (stratified hazard ratio 0.67, 95% CI 0.48–0.94; p=0.019). Median time to chemotherapy was 35.6 and 12.6 months in the inavolisib and placebo arms, respectively (stratified hazard ratio 0.43; 95% CI 0.30–0.60). No new safety signals were reported.

Comment: *PIK3CA* mutations are found in 40% of ER-positive advanced breast cancers and are associated with inferior prognosis. Agents that target the PI3K/AKT/mTOR pathway have been of interest in breast cancer for more than a decade however challenging toxicity profiles restricted the use of the earlier non-selective PI3K inhibitors. With more selective PI3K inhibition, improved tolerability can be achieved. In the INAVO120 study, combining a selective oral PI3Ka inhibitor (inavolisib) with palbociclib and fulvestrant improved PFS compared with placebo plus palbociclib and fulvestrant as first-line treatment for *PIK3CA*-mutated advanced breast cancer that had relapsed on or shortly after concluding adjuvant endocrine therapy. The final OS analysis of INAVO120 confirms the benefit of adding inavolisib, with a 7-month improvement in OS (median OS 34 months) and a significant extension of the time to first subsequent chemotherapy. Whilst more toxicity was observed in the inavolisib arm, the adverse events were in keeping with those expected of the agents in use. Hyperglycaemia was a particular issue, experienced in 40% of patients (patients with diabetes were not eligible for this trial). It is noteworthy that this patient population were all endocrine resistant (either primary or secondary) and had visceral disease, thus representing a group of patients who often experience a steeper and shorter disease trajectory. In the first-line treatment of ER-positive advanced breast cancer, clinicians have a number of treatment strategies to choose from and prefer to adjust their recommendations on the basis of trial data, disease distribution, time to relapse, patient preference and comorbidities. A question that will have increasing relevance is how to apply these data to the patient population who relapse following receipt of a CDK 4/6 inhibitor in the adjuvant setting. The INAVO120 results represent the first trial data to show an improvement in OS with a PI3K pathway-targeted drug. Thus, the INAVO120 regimen provides a new combinatorial strategy for treatment in the first-line setting for a highly-selected group of patients, and underscores the growing importance of molecular profiling to guide targeted therapy for breast cancer.

Reference: J Clin Oncol. 2025;43(16 suppl):1003
Abstract

[†]Data are from the second interim analysis of OS in DESTINY-Breast03 (DCO July 2022) and update the registration data from the PFS interim analysis.[1-3] PFS assessed by BICR; primary endpoint. [‡]At the second interim analysis, the median OS was not reached in either treatment group. 95% CI: 40.5 months-NE with ENHERTU vs 34.0 months–NE with T-DM1; secondary endpoint.

BEFORE PRESCRIBING ENHERTU, PLEASE CLICK HERE TO READ THE MANUFACTURER'S DATA SHEET.

ENHERTU is funded for the treatment of eligible patients with HER2+ metastatic breast cancer under Special Authority criteria. ENHERTU is unfunded for all other indications; a prescription charge will apply. Please refer to the Pharmaceutical Schedule.

ENHERTU® (trastuzumab deruxtecan) powder for concentrate for solution for infusion 100mg vial (20mg/ml 5mL solution). Prescription Medicine. **Indication: Breast Cancer, HER2-Positive:** Monotherapy treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who previously received: trastuzumab and a taxane for metastatic disease, or one prior anti-HER2-based regimen and developed disease recurrence during or within six months of completing neo-adjuvant or adjuvant therapy. **Breast Cancer, HER2-Low:** Treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISHnegative) breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients with hormone receptor positive (HR+) breast cancer should additionally have received or be ineligible for endocrine therapy. **Unresectable or Metastatic Non-small Cell Lung Cancer:** ENHERTU as monotherapy is indicated for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy. Select patients for treatment of unresectable or metastatic HER2-low breast cancer based on IHC 1+ or IHC 2+/ISH tumour status, and for NSCLC based on the presence of activating HER2 (ERBB2) mutations detected by a validated test. **Dosage and Administration: IMPORTANT - Do not substitute ENHERTU for or with trastuzumab or trastuzumab emtansine.** To prevent medication errors, check vial labels to ensure the medicine being prepared and administered is ENHERTU (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine. Recommended dose 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Administer initial dose as 90-minute intravenous infusion. If tolerated, subsequent doses may be administered over 30 minutes. Management of infusion-related symptoms may include slowing or interruption of infusion rate or treatment discontinuation. Refer to Data Sheet for further information. ***Premedication:*** ENHERTU is emetogenic. See Data Sheet for full information on premedication for prevention of chemotherapy-induced nausea and vomiting. ***Dose modifications:*** Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation. Refer to Data Sheet for full information. ENHERTU dose should not be re-escalated after a dose reduction is made. No dosage adjustment required in patients aged ≥65 years. The safety and efficacy of ENHERTU in children and adolescents below 18 years of age have not been established, no data are available. Mild or moderate renal impairment or mild hepatic impairment. Insufficient data for dosage adjustment in moderate hepatic impairment. No data available in patients with severe hepatic impairment. Limited data available in severe renal impairment. Higher incidence of Grade 1 and 2 ILD/pneumonitis leading to increase in discontinuation of therapy observed in patients with moderate renal impairment. ENHERTU must be reconstituted with sterile water for injection and diluted in 5% dextrose solution prior to administration as an intravenous infusion. ENHERTU must not be administered as intravenous push or bolus. See Data Sheet for full information on reconstitution, dilution, and administration. **Contraindications:** Hypersensitivity to active substance or to any of excipients. **Special Warnings and Precautions for Use:** ***Interstitial Lung Disease (ILD)/Pneumonitis:*** cases of ILD and/or pneumonitis have been reported with ENHERTU, with fatal outcomes observed. Monitor patients for signs and symptoms of ILD/pneumonitis. Advise patients to immediately report cough, dyspnoea, fever, and/or any new or worsening respiratory symptoms. Evidence of ILD/pneumonitis should be promptly investigated. See full Data Sheet for further information on evaluation and management. Withhold ENHERTU for asymptomatic (Grade 1) ILD/pneumonitis until recovery to Grade 0. ENHERTU should be permanently discontinued in patients diagnosed with symptomatic (≥Grade 2) ILD/pneumonitis. Patients with a history of ILD/pneumonitis or with moderate or severe renal impairment may be at increased risk of developing ILD/pneumonitis; monitor carefully. ***Neutropenia:*** including cases of febrile neutropenia have been reported with ENHERTU. Dose interruption or reduction may be required. Refer to Data Sheet for monitoring and management information. ***Left Ventricular Ejection Fraction (LVEF):*** decrease has been observed with anti-HER2 therapies. See full Data Sheet for information on monitoring and management. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure or if LVEF less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Treatment with ENHERTU has not been studied in patients with LVEF less than 50% prior to initiation of treatment ***Embryo Foetal Toxicity:*** ENHERTU can cause embryo-foetal and foetal harm when administered to a pregnant woman. Pregnancy status of females of reproductive potential should be verified prior to initiation of ENHERTU. ***Use in pregnancy:*** **Category D.** Effective contraception should be used by women of reproductive potential during treatment with ENHERTU and for at least 7 months following last dose, and for men with female partners of childbearing potential during ENHERTU treatment and for at least 4 months following last dose. Administration of ENHERTU to pregnant women is not recommended, and patients should be informed of potential risks to foetus before they become pregnant. If women become pregnant during treatment or within 7 months following last dose, close monitoring is recommended. Male patients must not freeze or donate sperm during treatment and for at least 4 months after final dose of ENHERTU. ***Use during lactation:*** discontinue breastfeeding prior to starting treatment with ENHERTU. Breastfeeding may begin 7 months after concluding treatment. ***Fertility:*** animal toxicity studies suggest potential for impairment of male reproductive function and fertility. Advise male patients to seek counselling on sperm storage before starting treatment with ENHERTU. ***Effects on ability to drive and use machines:*** patients who experience adverse reactions such as fatigue, headache and dizziness should observe caution when driving or using machinery. Refer to full Data Sheet for further information. **Adverse Effects: Breast Cancer Pooled Analysis** *Very common (≥10%):* anaemia, leukopenia, neutropenia, lymphopenia, and thrombocytopenia; nausea, vomiting, constipation, diarrhoea, abdominal pain, stomatitis, dyspepsia; fatigue, pyrexia; transaminases increased; upper respiratory tract infection; weight decreased; decreased appetite, hypokalaemia; musculoskeletal pain; headache, dizziness; cough, interstitial lung disease, epistaxis, dyspnea; alopecia, rash. *Common (≥1% - <10%):* dry eye, vision blurred; abdominal distention, gastritis, flatulence; infusion related reaction; increase of blood alkaline phosphatase, bilirubin or creatinine; dehydration; dysgeusia; pruritis, skin hyperpigmentation. **NSCLC:** *Very common (≥10%):* neutropenia, anaemia, leukopenia, thrombocytopenia, nausea, constipation, vomiting, diarrhoea, stomatitis, fatigue, transaminases increased, decreased appetite, hypokalaemia, interstitial lung disease, alopecia. *Common (≥1% - <10%):* lymphopenia, abdominal pain, upper respiratory tract infection, headache, dyspnoea, epistaxis, rash. Refer to Data Sheet for full list of adverse effects.

2L+: second and later lines; BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; HER2+: human epidermal growth factor receptor 2-positive; HR: hazard ratio; ILD: interstitial lung disease; NCCN: National Comprehensive Cancer Network® (NCCN®); NE: not estimable; mBC: metastatic breast cancer; OS: overall survival; mPFS: median progression-free survival; T-DM1: trastuzumab emtansine.

References: 1. ENHERTU (trastuzumab deruxtecan) Data Sheet. **2.** Hurvitz SA *et al. Lancet* 2023;401:105-17. **3.** Cortes J *et al. N Engl J Med* 2022;386:1143-54. **4.** Gennari A *et al. Ann Oncol* 2021; 32:1475-1495. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V1.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed August 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **6.** Cancer Institute NSW, eviQ Cancer Treatments Online, Protocol ID 4150 v1.0: Breast Metastatic Trastuzumab Deruxtecan. Available at https://www.eviq.org.au/medical-oncology/breast/metastatic/4150-breast-metastatic-trastuzumab-deruxtecan. Accessed June 2025. **7.** Rugo H *et al. ESMO Open* 2022;7(4):100553.

A double-blind placebo controlled randomized phase III trial of fulvestrant and ipatasertib as treatment for advanced HER2-negative and estrogen receptor positive (ER+) breast cancer following progression on first line CDK 4/6 inhibitor and aromatase inhibitor: The CCTG/BCT MA.40/FINER study (NCT04650581)

Authors: Chia SKL et al.

Summary: Ipatasertib + fulvestrant significantly prolongs PFS compared to placebo + fulvestrant in patients with ER-positive/HER2-negative metastatic breast cancer after progression on first-line CDK 4/6 inhibitor + aromatase inhibitor treatment, according to the results of the MA.40/FINER study. The study evaluated whether adding ipatasertib to standard therapy (fulvestrant) could slow the progression of advanced ER-positive/HER2-negative breast cancer when initiated immediately post progression on a first-line CDK 4/6 inhibitor + aromatase inhibitor. A total of 250 pre/peri/postmenopausal women and men with ER-positive/HER2-negative metastatic breast cancer were randomised 1:1 to receive ipatasertib + fulvestrant versus placebo + fulvestrant. Median follow-up was 15.2 months. In the intent-to-treat analysis, PFS (primary outcome) was 5.32 months in the ipatasertib arm and 1.94 months in the placebo arm (hazard ratio 0.61, 95% CI 0.46–0.81; p=0.0007). Treatment discontinuation due to adverse events was reported in 6.5% and 0.8% of patients in the respective arms.

Comment: The MA.40/FINER study investigates the concept of targeting the PI3K/AKT/mTOR pathway post progression on endocrine and CDK 4/6 inhibitor. Specifically, this phase 3 trial examines the efficacy of adding ipatasertib, an AKT inhibitor, to fulvestrant compared with placebo + fulvestrant. Second-line treatment in ER-positive advanced breast cancer is a crowded space however few studies have specifically explored second-line treatments after front-line CDK 4/6 inhibitor use. In this study, median PFS in the AKT pathway-altered population (as determined by FoundationOne cfDNA testing) was significantly improved with the addition of ipatasertib. As seen in other studies, fulvestrant alone does not provide meaningful disease control in later lines of endocrine therapy for ER-positive advanced breast cancer and its use as a single agent in the second-line setting needs to be considered in this context. The ipatasertib + fulvestrant combination was generally tolerable with no unexpected safety signals. Hyperglycaemia is an adverse event of special interest in agents that act on the PI3K/AKT/mTOR pathway. Hyperglycaemia rates with ipatasertib are lower than with PI3K inhibitors. The OS data from MA.40 are immature and will be of interest in later trial updates. This study further highlights the role of cell-free DNA for biomarker-guided treatment selection and shows that targeting the AKT pathway can improve PFS.

Reference: J Clin Oncol. 2025;43(17 suppl):LBA1005
Abstract

INDEPENDENT COMMENTARY BY
Dr Sheridan Wilson MB ChB FRACP

Dr Sheridan Wilson is a Medical Oncologist specialising in the treatment of breast cancer. Sheridan graduated from the Auckland University School of Medicine in 2003 and became a Fellow of the Royal Australasian College of Physicians in 2012. Between 2013 and 2014, Sheridan completed a clinical research fellowship in breast cancer at The British Columbia Cancer Agency, Vancouver, Canada. Since her return to New Zealand, Sheridan has maintained an interest in translational research and is an active participant in the Breast Cancer Special Interest Group of New Zealand. Sheridan works at Auckland City Hospital where she currently holds the position of Clinical Lead for the breast team in Medical Oncology.

Sacituzumab govitecan (SG) + pembrolizumab (pembro) vs chemotherapy (chemo) + pembro in previously untreated PD-L1–positive advanced triple-negative breast cancer (TNBC): Primary results from the randomized phase 3 ASCENT-04/KEYNOTE-D19 study

Authors: Tolaney SM et al.

Summary: The findings of the ASCENT-04/KEYNOTE-D19 study support the use of sacituzumab govitecan + pembrolizumab as a potential new standard of care treatment in patients with previously untreated PD-L1-positive advanced triple-negative breast cancer (TNBC). A total of 443 patients were randomised 1:1 to sacituzumab govitecan (10 mg/kg intravenously, day 1 and 8) + pembrolizumab (200mg, day 1 for a maximum 35 cycles) in 21-day cycles or chemotherapy (gemcitabine + carboplatin, paclitaxel, nab-paclitaxel) + pembrolizumab until disease progression or unacceptable toxicity. Median follow-up was 14 months. Sacituzumab govitecan + pembrolizumab significantly improved PFS versus chemotherapy + pembrolizumab (hazard ratio 0.65, 95% CI 0.51–0.84; p=0.0009). Median duration of response was 16.5 and 9.2 months in the respective groups. The most frequent grade ≥3 treatment-emergent adverse events with sacituzumab govitecan + pembrolizumab were neutropenia (43%) and diarrhoea (10%).

Comment: The ASCENT-04 study investigates sacituzumab govitecan partnered with pembrolizumab in the first-line treatment of PD-L1-positive, advanced TNBC. Despite advances in treatment options for TNBC, less than half of patients with this diagnosis receive second-line treatment. This speaks to the relative treatment resistance and heavy disease burden often seen in this patient population and there remains high unmet need for treatment options in advanced TNBC. Efficacy data for sacituzumab govitecan in later line treatment for TNBC and research suggesting synergy between antibody drug conjugates and immune checkpoint inhibitors, suggests this combination may offer benefit in first-line treatment. The ASCENT-04 study is an international phase 3 study that recruited 443 patients. The results from this phase 3 trial show that substituting chemotherapy with sacituzumab govitecan plus pembrolizumab significantly improves PFS. There was also a higher overall response rate and more durable responses seen in the sacituzumab govitecan arm. There were no new safety signals or increased immune-mediated adverse events in the investigational arm. In this study a small number of participants (approximately 5%) had received immunotherapy in the neoadjuvant setting. In subgroup analysis, the benefit of sacituzumab govitecan was not clear for this group, however with such small numbers no firm conclusions can be made. It is likely that over time, the proportion of patients who have received immunotherapy in the neoadjuvant setting will increase and it will be impossible to know how this data applies to that patient population. OS data are immature, a high number of patients in the chemotherapy group went on to receive sacituzumab govitecan in the second-line setting, despite this, the early OS results are encouraging. The results from ASCENT-04 make a case for not saving the best for last and support using sacituzumab govitecan in the first-line setting.

Reference: J Clin Oncol. 2025;43(17 suppl):LBA109
Abstract

Trastuzumab deruxtecan (T-DXd) + pertuzumab (P) vs taxane + trastuzumab + pertuzumab (THP) for first-line (1L) treatment of patients (pts) with human epidermal growth factor receptor 2–positive (HER2+) advanced/metastatic breast cancer (a/mBC): Interim results from DESTINY-Breast09

Authors: Tolaney SM et al.

Summary: Trastuzumab deruxtecan (T-DXd) + pertuzumab may represent a new first-line standard of care in patients with HER2-positive advanced/metastatic breast cancer, according to the findings of the DESTINY-Breast09 study. Eligible patients had HER2-positive advanced/metastatic breast cancer and no prior chemotherapy or HER2-directed therapy for advanced/metastatic breast cancer. Patients were randomised 1:1:1 to T-DXd 5.4 mg/kg + placebo, T-DXd + pertuzumab, or taxane + trastuzumab + pertuzumab (THP); 52% of patients had de-novo disease. This planned interim analysis presented data for the T-DXd + pertuzumab (n=383) and THP (n=387) arms. At the interim data cutoff (median follow up 29 months), T-DXd + pertuzumab significantly improved PFS compared with THP (hazard ratio 0.56, 95% CI 0.44–0.71; p<0.00001). Median response duration with T-DXd + pertuzumab exceeded 3 years. Drug-related ILD/pneumonitis occurred in 12.1% of patients in the T-DXd + pertuzumab group and 1.0% in the THP group.

Comment: Have we found a new standard of care in first-line treatment for metastatic HER2-positive breast cancer? If we were making decisions based on PFS data the answer would be a clear 'yes'. However, there are some important limitations and unanswered questions to consider. In DESTINY-Breast09, a multicentre, open-label study, patients were randomised to either T-DXd, T-DXd + pertuzumab or the control arm of a taxane + THP. The control arm has been a firmly entrenched standard of care following the CLEOPATRA study data, which read out more than 10 years ago. In the current abstract, interim analysis results for T-DXd + pertuzumab versus THP are presented showing a PFS benefit in favour of the T-DXd + pertuzumab arm (40.7 months vs 26.9 months); this is a clinically and statistically significant result. Response rates and duration of response were both significantly improved with T-DXd. OS data are immature but there is an early trend favouring the T-DXd arm. It is noteworthy that approximately 50% of the trial participants had de novo metastatic cancer, a higher proportion than would be expected in the real-world setting.

Taken at face value, the toxicity data suggest that treatment-emergent serious events occurred in a similar number in each arm. However, there were 13 deaths in the T-DXd + pertuzumab arm and just three in the THP arm. Furthermore, >70% of those receiving T-DXd reported nausea compared with <30% in the THP arm. Nausea with THP is likely to be restricted to the first 6–8 cycles, which are inclusive of taxane-based chemotherapy, and would not be expected during the pertuzumab + trastuzumab (HP) maintenance phase. The practical implication is that patients receiving T-DXd might experience many more months of nausea compared with THP. Vomiting, fatigue, poor appetite, weight loss and bowel disturbance also occurred more frequently with T-DXd. As trial populations are generally restricted to those with few comorbidities and good performance status, the reality of these side effects may be different in a real-world population.

T-DXd is a drug that keeps on giving, and this is true both in terms of efficacy results in various settings and in terms of potential side effects. In contrast, side effects incurred with THP are likely to be present during the chemotherapy-containing phase of treatment and abate in the HP maintenance phase. Treatment costs, both financial and in terms of quality of life are particularly important in the context of treatments that may be administered for years (median duration of treatment with T-DXd was 21 months). Patient-reported outcomes from this study will be important in understanding the quality-of-life implications of long-term treatment with T-DXd.

Whilst DESTINY-Breast09 undoubtedly reinforces the impressive activity of T-DXd, it creates more questions about the optimal sequencing of HER2-directed therapy. Having a biomarker to identify patients who may obtain durable control on a THP regimen could be a way to avoid the long term burden of T-DXd. Similarly an induction approach, comprising T-DXd followed by maintenance HP might be a way to get the best of both worlds. Real-world data and ongoing correlative science endeavours within the DESTINY-Breast09 study will be needed to explore these ideas.

Reference: J Clin Oncol. 2025;43(17 suppl):LBA1008
Abstract

15-year outcomes for women with premenopausal hormone receptor-positive early breast cancer (BC) in the SOFT and TEXT trials assessing benefits from adjuvant exemestane (E) + ovarian function suppression (OFS) or tamoxifen (T) + OFS

Authors: Francis PA et al.

Summary: The 15-year results of the SOFT and TEXT trials confirm a role for ovarian function suppression (OFS) and aromatase inhibitor-containing adjuvant endocrine therapy for premenopausal women with hormone receptor-positive early breast cancer. Both trials enrolled premenopausal women with hormone receptor-positive early breast cancer from Nov 2003 to Apr 2011. The TEXT trial randomised 2660 women within 12 weeks of surgery to 5 years of exemestane + OFS versus tamoxifen + OFS; chemotherapy was optional and concurrent with OFS. The SOFT trial randomised 3047 women to 5 years of exemestane + OFS versus tamoxifen + OFS versus tamoxifen alone, within 12 weeks of surgery if no chemotherapy was planned, or within 8 months of completing neoadjuvant chemotherapy. The primary end-point in each trial was disease-free survival (DFS). For the TEXT+SOFT combined analysis, 15-year DFS was 74.9% in the exemestane + OFS arm compared with 71.2% in the tamoxifen + OFS arm (hazard ratio 0.82, 95% CI 0.73–0.92).

Comment: These pivotal trials changed the way we treat ER-positive breast cancer in young women. The extended data collection undertaken in these studies is particularly important given the long natural history of ER-positive breast cancer. Long-term follow-up from the SOFT and TEXT trials confirms sustained benefits of OFS combined with aromatase inhibitors over tamoxifen in premenopausal women with ER-positive early breast cancer. The greatest absolute gains are seen in younger women (<35 years), those with higher-grade tumours, and those who received chemotherapy. The advantage is clear in terms of improvements in DFS and distant relapse-free interval although less clear in terms of OS. The 15-year OS for lower risk cancers (mainly pT1N0, grade 1 or 2), in the SOFT study, not treated with chemotherapy, is high irrespective of endocrine therapy choice, and hence tamoxifen remains a reasonable option for this group. A challenge in the application of the SOFT/TEXT data is how to fit it into a contemporary treatment context. The trials enrolled patients between 2003–2011, before the routine use of multigene assays and adjuvant use of CDK 4/6 inhibitors. In today's climate, more nuanced decision-making may see some patients spared chemotherapy and in the future endocrine therapy backbones may be reshaped to include oral SERDs. The updated SOFT/TEXT data do not deliver any new approaches but do reinforce the importance of incorporating OFS into adjuvant therapy and support the durability of endocrine therapy and its role in reducing recurrence. The data also remind us that the risk of recurrence continues beyond 10 years, underscoring the need for long follow-up in adjuvant trials.

Reference: J Clin Oncol. 2025;43(16 suppl):505
Abstract

Efficacy and safety of elinzanetant for vasomotor symptoms associated with adjuvant endocrine therapy: Phase 3 OASIS 4 trial

Authors: Cardoso F et al.

Summary: The dual neurokinin-1 and -3 receptor antagonist elinzanetant was effective and well tolerated in women with VMS associated with adjuvant endocrine therapy (AET) participating in the OASIS 4 trial. The 52-week randomised phase 3 trial evaluated the safety and efficacy of elinzanetant in women aged 18–70 years being treated for hormone receptor-positive breast cancer who were having ≥35 moderate-to-severe VMS per week associated with AET. A total of 473 women were randomised 2:1 to receive once-daily elinzanetant 120mg for 52 weeks or placebo for 12 weeks followed by elinzanetant for 40 weeks. The primary end-points were mean change in moderate-to-severe VMS frequency from baseline to weeks 4 and 12. Mean baseline daily VMS frequency was 11.4 in the elinzanetant group and 11.5 in the placebo group. This decreased by 6.5 in the elinzanetant group and 3.0 in the placebo group at week 4 ($p<0.0001$) and by 7.8 and 4.2 in the respective groups at week 12 ($p<0.0001$). During the placebo-controlled period, somnolence, fatigue, and diarrhoea were more frequently reported with elinzanetant.

Comment: The phase 3 OASIS 4 trial represents a step change in the management of VMS, especially for women undergoing AET after breast cancer. VMS, which can include hot flushes, sweats, and disturbed sleep, significantly impair quality of life (QOL) and compromise adherence to AET. Elinzanetant, a once-daily oral dual neurokinin-1 and -3 receptor antagonist, has previously been shown to improve sleep, hot flashes and menopause-related QOL in women undergoing natural menopause. The OASIS 4 trial extended the investigation of this novel agent into the realm of VMS associated with endocrine therapy being given either as adjuvant treatment after breast cancer, or as chemoprevention in those at high risk of developing breast cancer. The 52-week duration of this trial stands out as one of the longest studies of a non-hormonal therapy for VMS in breast cancer survivors. Most prior hot flush trials, including those evaluating selective serotonin reuptake inhibitors, gabapentin, and oxybutynin, range from 4 to 12 weeks in duration. The extended timeline in OASIS 4 facilitates an assessment of efficacy beyond the initial placebo effect window and allows collection of longer term impact and safety information. A 2-year extension study is underway to collect additional data. The present results demonstrate that elinzanetant reduces both the frequency and severity of VMS compared with placebo; that it works quickly, with symptom improvement seen as early as week 1; and that it has an acceptable side effect profile (somnolence, fatigue and diarrhoea being most common). Sleep and QOL were also improved. Managing VMS in breast cancer survivors is very challenging. Elinzanetant is non-hormonal and tamoxifen-compatible. It produces rapid and durable relief of moderate-to-severe VMS in women receiving endocrine therapy and has the potential to improve adherence to endocrine therapy by reducing symptom burden. This could be a game-changer for patients struggling to stay on endocrine therapy.

Reference: J Clin Oncol. 2025;43(16 suppl):508
Abstract

Camizestrant + CDK4/6 inhibitor (CDK4/6i) for the treatment of emergent *ESR1* mutations during first-line (1L) endocrine-based therapy (ET) and ahead of disease progression in patients (pts) with HR+/HER2– advanced breast cancer (ABC): Phase 3, double-blind ctDNA-guided SERENA-6 trial

Authors: Turner NC et al.

Summary: SERENA-6 is the first global phase 3 trial to demonstrate clinical utility of ctDNA for the detection and treatment of emerging resistance ahead of disease progression in patients with advanced breast cancer. In the study, 3256 patients with HR-positive/HER2-negative advanced breast cancer who had received at least 6 months of first-line aromatase inhibitor (AI; anastrozole or letrozole) + a CDK 4/6 inhibitor (abemaciclib, palbociclib or ribociclib) underwent ctDNA testing for emergent *ESR1* mutations every 2–3 months in conjunction with routine imaging. Upon detection of *ESR1* mutation, 315 patients without evidence of disease progression were randomised 1:1 to switch to camizestrant 75mg with continued CDK 4/6 inhibitor + placebo (for AI) versus continuing AI + CDK 4/6 inhibitor + placebo (for camizestrant). The primary end-point was investigator-assessed PFS. Median PFS was 16.0 months in patients who switched to camizestrant and 9.2 months in patients who continued with AI (hazard ratio 0.44, 95% CI 0.31–0.60; $p<0.00001$).

Comment: The SERENA-6 trial earned its place in the ASCO 2025 Plenary Session because it offers a paradigm shift in how we approach resistance in hormone receptor-positive, HER2-negative advanced breast cancer. It's not just about a new drug – it's about changing the timing and strategy of intervention using real-time molecular monitoring. SERENA-6 builds on earlier ctDNA research in metastatic breast cancer and is the first global phase 3 trial to use ctDNA surveillance to detect emergent *ESR1* mutations and guide a pre-emptive switch in endocrine therapy before radiographic progression. The goal of this approach is to extend the time on endocrine therapy in the first-line setting. The SERENA-6 results show that switching to camizestrant and continuing the CDK 4/6 inhibitor reduced the risk of progression or death by 56% compared to continuing AI + CDK 4/6 inhibitor (hazard ratio 0.44; median PFS 16.0 vs 9.2 months). A meaningful delay in time to deterioration in global health status was seen with camizestrant (23.0 vs 6.4 months) and the drug showed consistent benefit across all CDK 4/6 inhibitor and *ESR1* mutation subtypes. Does this actually change practice? Not at this stage. The investigators considered continuation of the CDK 4/6 inhibitor with switching the endocrine backbone to be maintenance of first-line therapy. Typically, a change in endocrine therapy would be considered a new line of therapy so this is somewhat inconsistent with our usual terminology. An alternative interpretation of the trial data is that changing treatment on the basis of *ESR1* mutation emergence results in earlier commencement of a second-line endocrine agent. SERENA-6 doesn't actually compare early use of the oral SERD to initiation at progression since the choice of second-line treatment in the control arm was at the discretion of the treating physician. The heterogeneity of subsequent treatment in the control arm makes it difficult to isolate the benefit of switching early.

Although the results of this study are positive, the data don't tell us if it is genuinely better in the long term to switch on the basis of a molecular marker of resistance or at the point of clinical or radiological progression. PFS 2 and OS may be helpful in understanding this but the natural history of ER-positive metastatic breast cancer and the expanding options for treatment in subsequent lines of therapy mean that these outcomes could be challenging to interpret. There is also the issue of feasibility. In SERENA-6, from a screened population of more than 3000, only 315 participants with newly detected *ESR1* mutations (but no progression) formed the randomised population. That only 10% of the screened population were eligible calls into question the scalability of this approach. High frequency liquid biopsy for molecular analysis brings an additional psychological burden for patients and carries considerable logistical and financial implications that will simply not be feasible in many settings.

SERENA-6 progresses the role of precision-guided early intervention but, in order for this strategy to move into mainstream, clinicians would need compelling OS data, accessible ctDNA testing and a favourable cost-effective analysis.

Reference: J Clin Oncol. 2025;43(17 suppl):LBA4
Abstract