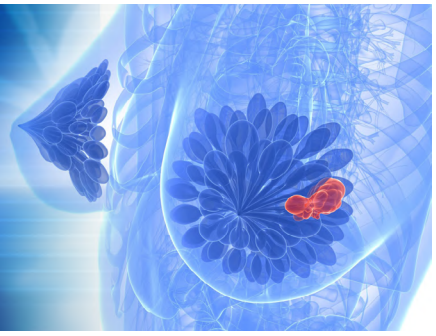
ASCO 2025
Conference Review™
Focus on Breast Cancer



Making Education Easy

20 May to 3 June, 2025

In this review:

Abbreviations used in this review:

CDK4/6(i) = cyclin-dependent kinase 4/6 (inhibitor); **ctDNA** = circulating tumour DNA; **DFS** = disease-free survival; **ER** = oestrogen receptor; **HER2** = human epidermal growth factor receptor 2; **HR** = hazard ratio; **HR+** = hormone receptor-positive; **ILD** = interstitial lung disease; **ITT** = intention-to-treat; **OR** = odds ratio; **OS** = overall survival; **pCR** = pathological complete response; **PFS** = progression-free survival; **SERD** = selective ER degrader; **T-DXd** = trastuzumab deruxtecan; **(TE)AE** = (treatment-emergent) adverse event; **(T)HP** = (taxane,) trastuzumab, pertuzumab; **TNBC** = triple-negative breast cancer.

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Independent commentary by Dr Nick Zdenkowski

Nick is a medical oncologist whose practice and research focusses on breast cancer. His clinical practice is based in Newcastle, NSW. He also works as Scientific Advisory Committee Chair and Medical Advisor for Breast Cancer Trials, based at the headquarters in Newcastle. His research interest is in neoadjuvant systemic therapy and shared decision-making for patients with breast cancer.

Welcome to our review of the 2025 ASCO Annual Meeting held in Chicago, USA.

This year ASCO welcomed more than 45,000 professionals from 100 countries worldwide. There was a rich programme of abstracts dedicated to all aspects of cancer research, and here I have discussed 10 presentations which were particularly noteworthy in the field of breast cancer. One of the highlights was the first interim analysis of the DESTINY-Breast09 trial, which demonstrated substantially improved PFS with first-line T-DXd plus pertuzumab versus taxane, trastuzumab and pertuzumab (THP) in patients with HER2+ advanced/metastatic breast cancer. This is followed by the FINER study which found that the addition of ipatasertib to fulvestrant significantly prolonged PFS in patients with HER2-/ER+ metastatic breast cancer after progression on first-line CDK4/6i plus aromatase inhibitor. Other abstracts of interest report on the real-world outcomes of patients rechallenged after T-DXd-related ILD, the final 15-year results of the pivotal TEXT/SOFT trials, and the promising efficacy of a novel oral PROTAC ER degrader for patients with *ESR1*-mutated ER+/HER2- advanced breast cancer.

I hope you find this review valuable for your clinical practice and the lives of your patients. Full abstracts are available online here.

Kind regards,

Dr Nicholas Zdenkowski
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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

Speaker: Sara Tolaney (Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA)

Summary: The global, phase 3 DESTINY-Breast09 trial randomly assigned eligible patients (n=1157) with HER2+ advanced/metastatic breast cancer 1:1:1 to first-line T-DXd plus pertuzumab (n=383), taxane, trastuzumab and pertuzumab (THP; n=387) or T-DXd plus placebo. Sara Tolaney presented the interim analysis of results from the T-DXd plus pertuzumab and THP arms. At a median follow-up of 20 months (38% mature for PFS), patients who received T-DXd plus pertuzumab showed significantly longer PFS versus THP (40.7 vs. 26.9 months; HR 0.56; 95% CI 0.44–0.71; p<0.00001), and this PFS benefit was observed in all subgroups. Patients in the T-DXd plus pertuzumab arm achieved a median response duration of more than 3 years (39.2 months; 95% CI 35.1–not calculable). At the time of data cut-off, OS data were not yet mature. Grade ≥3 TEAEs were experienced by 63.5% and 62.3% of patients in the T-DXd plus pertuzumab and THP arms, respectively, while 27.0% and 25.1% experienced serious TEAEs; adjudicated drug-related ILD/pneumonitis was reported in 12.1% (primarily grade 1-2; 0.5% grade 5) and 1.0% (all grade 1-2).

Comment: This trial was given its own special time slot as a late-breaking abstract, and was presented to a packed hall at 7.30am on Monday morning. The CLEOPATRA regimen of THP has been the standard of care for first-line treatment of metastatic breast cancer for over a decade. This interim analysis of DESTINY-Breast09 triggered the threshold for reporting of the comparison of THP with T-DXd plus pertuzumab. The T-DXd monotherapy arm is yet to be reported. A clinically and statistically significant 13.8-month PFS benefit was seen, extending PFS to over 40 months in the T-DXd plus pertuzumab arm. Around one-third of patients never receive second-line treatment for HER2+ metastatic breast cancer, underscoring the benefits of giving the most active agent up-front. Half of patients had *de novo* disease and half were ER+; however, fewer than 10% had received prior pertuzumab. Endocrine therapy was permitted, although only small numbers actually received it. There were five treatment-related deaths with T-DXd plus pertuzumab (two from ILD) and one with THP. OS data are immature, and relatively few patients in the control arm received T-DXd after progression. This regimen can be considered a new standard of care, with caveats. It is a long time on a more intensive regimen that is not without side effects. Could an induction regimen be used followed by maintenance HP? How could the PATINA data be integrated into this? Are there biomarkers or clinical predictors of poor prognosis, or of greater need for first-line T-DXd, such as heavy burden of disease, brain metastases, rapid progressors or *PIK3CA* mutation?

Abstract #LBA1008
Abstract

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

Speaker: Stephen Chia (BC Cancer Agency, Vancouver, Canada)

Summary: PI3K/AKT pathway alterations are a known mechanism of resistance to endocrine therapy. The objective of the double-blind, phase 3 MA.40/FINER trial was to assess the efficacy and safety of ipatasertib (AKT inhibitor) in advanced HER2-/ER+ breast cancer immediately after progression with first-line CDK4/6 inhibitor (CDK4/6i) plus aromatase inhibitor. A total of 250 patients (247 females) across Australia, NZ and Canada were randomised 1:1 to ipatasertib plus fulvestrant, or placebo plus fulvestrant. At a median follow-up of 15.2 months, 21.0% and 11.3% of patients in the ipatasertib and placebo arms were still receiving protocol treatment. Treatment with ipatasertib was associated with significantly longer PFS versus placebo in the ITT population (5.32 vs. 1.94 months, respectively; HR 0.61; 95% CI 0.46–0.81; p=0.0007), and in the cohort of patients with AKT pathway alterations (5.45 vs. 1.91 months; HR 0.47; 95% CI 0.31–0.72; p=0.0005). Grade ≥3 AEs occurred in 37.1% and 27.4% of patients in the ipatasertib and placebo arms, respectively. There were higher rates of diarrhoea (16% vs. 0%), fatigue (3% vs. 0%), vomiting (2% vs. 0%) and rash (2% vs. 0%) in the ipatasertib arm versus placebo, and 6.5% and 0.8% of patients had AE-related discontinuations.

Comment: FINER was a collaboration between the Canadian Clinical Trials Group and Breast Cancer Trials (ANZ) investigating second-line fulvestrant and ipatasertib/placebo. A significant benefit was seen with ipatasertib, and interestingly, this was independent of AKT pathway alterations, despite ipatasertib's mechanism of action as an AKT inhibitor. All patients had received a CDK4/6i and endocrine therapy in the first-line treatment of ER+ /HER2- breast cancer. Whilst the discussant suggested single-agent fulvestrant is no longer standard of care, we do not yet have ready access to the targeted agents in Australia that can be combined with a SERD. We also do not yet have access to oral SERDs such as elacestrant. All patients received the results of the Foundation Medicine Liquid testing that was done in screening for this trial: 44% of patients had an AKT pathway alteration and 50% had an *ESR1* mutation. Whilst diarrhoea, nausea and anorexia were higher in the ipatasertib arm, there was a low discontinuation rate. It remains to be seen how these targeted agents will be integrated with the oral SERDs, including the need for biomarker testing to determine which patients are candidates for which treatments.

Abstract #LBA1005
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

Speaker: Nicholas Turner (Royal Marsden Hospital, London, UK)

Summary: The SERENA-6 trial examined whether a ctDNA-guided approach could be used to inform a switch in treatment before disease progression in patients with HR+/HER2- advanced breast cancer, by identifying emergent *ESR1* mutations during first-line treatment with aromatase inhibitor (anastrozole/letrozole) plus CDK4/6i (abemaciclib/palbociclib/ribociclib). A total of 3256 eligible patients underwent ctDNA testing for *ESR1* mutations every 2–3 months, until 315 patients with detected *ESR1* mutations (without evidence of disease progression) were randomly assigned 1:1 to either switch to camizestrant or to continue with the aromatase inhibitor. All patients continued their CDK4/6i type and dose. The first ctDNA test detected *ESR1* mutations in approximately half of all patients. At the time of data cut-off, patients who switched to camizestrant showed prolonged PFS (16.0 vs. 9.2 months; HR 0.44; 95% CI 0.31–0.60; p<0.00001), and this was consistent across patient subgroups. At 12 months, the PFS rates with camizestrant versus continued aromatase inhibitor were 60.7% versus 33.4%, and the 24-month PFS rates were 29.7% versus 5.4%. With maturity at 27%, the hazard ratio for PFS2 was 0.52 (95% CI 0.33–0.81). There were no unexpected safety signals, and the rates of discontinuations due to AEs were 1.3% with camizestrant and 1.9% with continued aromatase inhibitor.

Comment: This plenary presentation stimulated extensive discussion on the clinical utility of ctDNA in identifying molecular progression in the absence of clinical/imaging progression. Over 3000 patients were recruited to the trial, who were on first-line endocrine therapy and CDK4/6i for metastatic breast cancer. The Guardant360 ctDNA assay was run at the same time as restaging imaging every 2–3 months. The 315 patients with emergence of an *ESR1* mutation without anatomic progression were randomised, and a PFS benefit was seen in the camizestrant group. PFS2 and OS were immature. Time to quality of life deterioration was 17 months longer in the camizestrant group. Crossover was not allowed. Questions were raised about the potential anxiety associated with additional tests during screening and the impact of post-progression therapy. Challenges will remain in the interpretation of PFS2 due to imbalance in the number of agents received across study arms. Is there a lead time bias in the experimental arm? Nonetheless, this is an important trial which was published simultaneously in the New England Journal of Medicine, and has led to camizestrant being granted breakthrough status by the FDA.

Abstract #LBA4
Abstract

De-escalated neoadjuvant taxane plus trastuzumab and pertuzumab with or without carboplatin in HER2-positive early breast cancer (neoCARHP)

Speaker: Hong-Fei Gao (Guangdong Provincial People's Hospital, Southern Medical University, Guangzhou, China)

Summary: The neoCARHP investigators examined the efficacy and safety of de-escalated neoadjuvant THP with or without carboplatin in patients with untreated stage II–III invasive HER2+ breast cancer. Eligible patients (n=774) across 15 hospitals in China were randomly assigned 1:1 to receive 6 cycles of 3-weekly investigator-selected THP with carboplatin (TCbHP; n=384) or without carboplatin (THP; n=382). The THP regimen was non-inferior to TCbHP with regard to pCR (primary endpoint; 64.1% vs. 65.9%; OR 0.93; 95% CI 0.69–1.25; p=0.0089). There were lower rates of grade 3–4 AEs with THP versus TCbHP (20.7% vs. 34.6%), and lower rates of serious AEs (1.3% vs. 4.7%). The most frequent grade 3-4 AEs observed with THP versus TCbHP were neutropenia (6.8% vs. 16.4%), leukopenia (5.5% vs. 14.8%) and diarrhoea (2.6% vs. 4.2%).

Comment: neoCARHP is an open-label phase 3 trial that showed 6 cycles of 3-weekly taxane (paclitaxel or docetaxel), trastuzumab and pertuzumab was non-inferior to the same regimen with the addition of carboplatin. The primary endpoint pCR was reported, but event-free survival and OS will be important. This trial was powered to show that the experimental arm was no more than 10% worse. pCR rates were similar to those seen in prior trials of the four-agent regimen, higher in ER- than ER+ tumours. There were no significant subgroup differences. The experimental regimen was less toxic, with lower rates of cytopenias, nausea and renal impairment. Note that the taxane was 3-weekly, when weekly paclitaxel tends to be better tolerated and has better efficacy than 3-weekly. The discussant suggested that this regimen could be offered in stage I-II HER2+ breast cancer.

Abstract #LBA500
Abstract

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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; NCCN: National Comprehensive Cancer Network® (NCCN®); NE: not estimable; mBC: metastatic breast cancer; OS: overall survival; mPFS: median progression-free survival; PBS: Pharmaceutical Benefits Scheme; T-DM1: trastuzumab emtansine. **References: 1.** Pharmaceutical Benefits Scheme (PBS) Schedule. Available at www.pbs.gov.au. **2.** ENHERTU (trastuzumab deruxtecan) Product Information. **3.** Hurvitz SA *et al. Lancet* 2023;401:105-17. **4.** Cortes J *et al. N Engl J Med* 2022;386:1143-54. **5.** Gennari A *et al. Ann Oncol* 2021; 32:1475-1495. **6.** 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 February 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. **7.** Cancer Institute NSW, eviQ Cancer Treatments Online, Protocol ID 4150 v4.0: Breast Metastatic Trastuzumab Deruxtecan. Available at https://www.eviq.org.au/medical-oncology/breast/metastatic/4150-breast-metastatic-trastuzumab-deruxtecan. Accessed February 2025.

Treatment rechallenge after trastuzumab-deruxtecan-related interstitial lung disease

Speaker: Hope Rugo (University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, USA)

Summary: The aim of this multicentre, retrospective cohort study was to evaluate the outcomes of a T-DXd rechallenge following ILD in diverse real-world settings. The analysis included 712 patients who received T-DXd across four centres between 2017–24, 9.1% of whom experienced ILD, and 18 patients with T-DXd-related ILD from one other centre. The median time to initial ILD after the first dose of T-DXd was 145 days. Overall, 47 patients underwent a rechallenge after grade 1 ILD (n=47; 81%) and grade 2 ILD (n=9). Patients treated with steroids showed radiographic ILD improvement sooner than those who did not receive steroids (34 vs. 82 days: p<0.01). Radiographic ILD improvement was also seen earlier among those who were rechallenged than those who were not (35 vs. 81 days; p=0.01). A total of 76% of patients with grade 1 ILD were successfully rechallenged at a median of 42 days after the last dose, and 61% of these patients underwent dose reduction. Following a rechallenge, patients were treated with T-DXd for a median of 215 days (IQR 60–334), and recurrent ILD was developed by 26% of these patients at a median of 211 days after rechallenge. Among the nine patients who were successfully rechallenged after grade 2 ILD, treatment with T-DXd was maintained for a median of 129 days (IQR 49–171), and 22% of these patients developed recurrent ILD. No deaths occurred with the rechallenge.

Comment: T-DXd has become established as a key breast cancer treatment option. As an offset to its remarkable efficacy, pneumonitis is a problem that we are all likely to have to grapple with. It is seen in about 12% of patients, and tends to occur early in the treatment course. It can be life-threatening, but tends to respond to early steroid treatment. These retrospective data show that patients with grade 1 pneumonitis, and even a selection of those with grade 2, can be successfully retreated with T-DXd after recovery of the pneumonitis. The median treatment duration after retreatment was 215 days, meaning that patients who cease treatment after grade 1 pneumonitis may miss out on many additional months of disease control. One-quarter of patients experienced a second episode of pneumonitis and many of these were able to have a successful second rechallenge. The presenter, Hope Rugo, indicated that the interval between chest scans could be stretched out after the first couple of 6-weekly scans, assuming that the patient did not have any concerning symptoms. Therefore, rechallenge of T-DXd is appropriate after resolution of grade 1, and potentially grade 2 pneumonitis.

Abstract #1015
Abstract

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

Speaker: Fatima Cardoso (ABC Global Alliance, Lisbon, Portugal)

Summary: The OASIS 4 researchers assessed the safety and efficacy of elinzanetant (dual neurokinin-1 and -3 receptor antagonist) for vasomotor symptoms associated with adjuvant endocrine therapy among women aged 18–70 years who were at high risk of developing, or had been diagnosed with, HR+ breast cancer. Eligible women with ≥35 moderate-to-severe vasomotor symptoms per week were randomly assigned 2:1 to either elinzanetant for 52 weeks (n=316) or placebo for 12 weeks before elinzanetant for 40 weeks (n=157). With regard to the primary outcome, patients in the 52-week elinzanetant arm experienced a significantly greater reduction in vasomotor symptom frequency versus placebo at week 4 (-6.5 vs. -3.0, respectively; p<0.0001) and week 12 (-7.8 vs. -4.2; p<0.0001); improvements in symptom frequency were seen as early as week 1 (-4.0 vs. -1.8). Patients in the 52-week elinzanetant arm also achieved greater reductions in vasomotor symptom severity at week 4 (-0.7 vs. -0.4) and week 12 (-1.0 vs. -0.5). Throughout the 12-week placebo-controlled period, TEAEs were reported by 69.8% and 62.0% of the 52-week elinzanetant and placebo arms, respectively. Between weeks 13–52, both arms reported fewer TEAEs.

Comment: Hot flushes and insomnia are major drawbacks of endocrine therapy for breast cancer. This class of drug also includes fezolinetant which is available in Australia. It is a neurokinin-1 and -3 antagonist, reducing hyperactivity of the KNDy neurons in the hypothalamus that cause vasomotor symptoms. The non-hormonal mechanism is considered safe in ER+ breast cancer, as opposed to menopausal hormonal therapy, which is contraindicated due to the increased recurrence risk. This study was placebo-controlled until 12 weeks, at which time all patients were put on the active agent. The frequency and severity of hot flushes improved within a week of starting treatment, and the reduction was substantial and sustained. There was a placebo effect seen. It would have been interesting to compare it to other available non-hormonal agents such as oxybutynin or venlafaxine. 90% of patients chose to continue treatment in an optional 2-year extension. This treatment had few side effects: 10% reported fatigue/somnolence and 5% had diarrhoea. Liver dysfunction is not an issue with this agent, whereas liver function test monitoring is required with fezolinetant due to the rare risk of significant liver dysfunction. This trial is reassuring about the effectiveness of this class of drug in breast cancer as another option for vasomotor symptoms. Reducing the toxicity of endocrine therapy gives a greater chance of persistence and benefit.

Abstract #508
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

Speaker: Prudence Francis (Peter MacCallum Cancer Centre, Melbourne, Australia)

Summary: In this presentation, Professor Prue Francis reported the final updates of the SOFT and TEXT randomised trials which enrolled premenopausal women with early HR+ breast cancer (n=2660 and n=3047, respectively); the final analyses were conducted at median follow-ups of 15 and 16.6 years, respectively. The SOFT trial found a moderate benefit in DFS (primary endpoint) with tamoxifen plus ovarian suppression versus tamoxifen alone (HR 0.85; 95% CI 0.72–1.00), and there was also a benefit in the breast cancer-free interval (HR 0.82; 95% CI 0.69–0.98). SOFT found a greater reduction in DFS events with exemestane plus ovarian suppression versus tamoxifen alone (HR 0.73; 95% CI 0.61–0.86). The 15-year EFS rates with exemestane plus ovarian suppression, tamoxifen plus ovarian suppression and tamoxifen alone were 73.5%, 70.5% and 67.0%, respectively; the 15-year OS rates were 86.9%, 86.7% and 85.3%. The combined TEXT/SOFT analyses revealed improved DFS, breast cancer-free intervals and distant recurrence-free intervals with exemestane plus ovarian suppression versus tamoxifen plus ovarian suppression; the 15-year DFS rates were 74.9% versus 71.3% (HR 0.82; 95% CI 0.73–0.92), and the 15-year OS rates were 87.8% versus 87.0% (HR 0.94; 95% CI 0.80–1.11).

Comment: The SOFT/TEXT trials, led by Professor Prue Francis and run in Australia by BCT, have been practice-changing, improving outcomes for premenopausal patients with ER+ early breast cancer. The need for long-term follow-up was shown in this presentation, with ongoing recurrences in this population out to 15 years following study enrolment. Findings from previous analyses were confirmed, in that the greatest incremental benefit in breast cancer-free interval was with the addition of exemestane to ovarian suppression, compared with tamoxifen alone or tamoxifen with ovarian suppression. The no-chemotherapy group (chemotherapy use was at the discretion of investigators), had a very good prognosis. On the contrary, the poorest prognosis and the greatest benefit of exemestane and ovarian suppression was in patients under the age of 40 or with grade 3 tumours.

Abstract #505
Abstract

Efficacy and safety of ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) in NATALEE: analysis across menopausal status and age

Speaker: Kevin Kalinsky (Winship Cancer Institute at Emory University, Atlanta, USA)

Summary: This study analysed data from patients in the NATALEE trial with high-risk, stage II/III HR+/HER2- breast cancer, to examine whether outcomes of treatment differed according to menopausal status and age. In NATALEE, women received ribociclib plus nonsteroidal aromatase inhibitor, or nonsteroidal aromatase inhibitor alone, and premenopausal women were also administered goserelin. At a median follow-up of 44.2 months, the treatment benefit with the addition of ribociclib was consistent across ages and menopausal groups. A smaller proportion of premenopausal patients discontinued ribociclib as a result of AEs compared to those who were postmenopausal (16.1% vs. 22.9%), and dose reductions due to AEs were comparable between these groups (22.4% vs. 23.6%). In both pre- and postmenopausal woman, alanine aminotransferase elevation was the most common AE leading to discontinuation (6.2% and 8.0%).

Comment: NATALEE has demonstrated a significant benefit to adjuvant ribociclib combined with an aromatase inhibitor in intermediate- to high-risk early breast cancer. This benefit has persisted after completion of the 3-year course of ribociclib, and in both stage II and III disease. A question remained about whether there was an impact of menopausal status or age on the impact of ribociclib. These results indicated that the benefits were quite stable across different age groups. Interestingly, younger patients were more likely to persist with ribociclib, possibly due to greater motivation to receive optimal treatment. Quality of life scores, using the EORTC QLQ-C30 questionnaire, were very similar across age and menopausal status.

Abstract #516
Abstract

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

Speaker: Sara Tolaney (Dana-Farber Cancer Institute and Harvard Medical School, Boston, US)

Summary: In the ASCENT-04/KEYNOTE-D19 trial, 443 patients with previously untreated, PD-L1–positive, locally advanced, unresectable or metastatic triple-negative breast cancer (TNBC) were randomly assigned 1:1 to sacituzumab govitecan plus pembrolizumab (n=221) or chemotherapy (gemcitabine + carboplatin, paclitaxel, nab-paclitaxel) plus pembrolizumab (n=222) until progression/toxicity. In this primary analysis, at a median follow-up of 14 months, patients achieved significantly longer PFS with sacituzumab govitecan plus pembrolizumab versus chemotherapy plus pembrolizumab (11.2 vs. 7.8 months; HR 0.65; 95% CI 0.51–0.84; p=0.0009), with median durations of response of 16.5 versus 9.2 months, respectively. Sara Tolaney commented that although OS data had not yet reached maturity, there was an early trend in favour of sacituzumab govitecan plus pembrolizumab. Common grade ≥3 TEAEs with sacituzumab govitecan plus pembrolizumab included neutropenia (43%) and diarrhoea (10%).

Comment: Metastatic TNBC carries a substantially worse prognosis than the other major subtypes, with as many as half of those treated in the first-line never receiving second-line therapy. This emphasises the need to use the best treatment as first-line. ASCENT-04 compared the Trop-2 targeted agent sacituzumab govitecan with pembrolizumab, to chemotherapy and pembrolizumab. Tumours needed to be CPS ≥10 PD-L1-positive according to the 22C3 assay. In this poor-prognosis tumour type, the 3.4-month improvement in PFS is considered clinically meaningful. Crossover to sacituzumab was allowed post-progression, and was received by 80% of patients. OS data are awaited but may be impacted by crossover. Toxicity was as expected from the individual agents used, and discontinuation due to AEs was lower in the sacituzumab govitecan/pembrolizumab group. It should be noted that very few patients on this trial had received prior pembrolizumab in the early-stage setting, which will change now that the KEYNOTE-522 regimen has become well established. This combination has potential as a new standard of care first-line TNBC regimen.

Abstract #LBA109
Abstract

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

Speaker: Erika Hamilton (Sarah Cannon Research Institute, Nashville, Tennessee, US)

Summary: A phase 1/2 trial reported promising clinical activity with vepdegestrant, an oral PROTAC (PROteolysis TArgeting Chimera) ER degrader, in pretreated patients with advanced breast cancer. The phase 3 VERITAC-2 study randomised 624 eligible patients (median age 60 years; range 26–89) with pretreated ER+/HER2- advanced breast cancer 1:1 to either oral vepdegestrant (n=313) or intramuscular fulvestrant (n=311). Among the subgroup of patients harbouring *ESR1* mutations (43.3%), PFS was significantly longer with vepdegestrant than with fulvestrant (5.0 vs. 2.1 months; HR 0.57; 95% CI 0.42–0.77; p=0.0001), whereas there was no difference in PFS in the overall study population (3.7 vs. 3.6 months). The OS data had not yet reached maturity. Grade ≥3 TEAEs were observed in 23.4% and 17.6% of patients in the vepdegestrant and fulvestrant arms, respectively, with discontinuation due to AEs occurring in 2.9% and 0.7% of patients. TEAEs with vepdegestrant and fulvestrant included fatigue (26.6% vs. 15.6%), elevated alanine transaminase (14.4% vs. 9.8%), elevated aspartate aminotransferase (14.4% vs. 10.4%) and nausea (13.5% vs. 8.8%).

Comment: Vepdegestrant is a new anti-oestrogen in the PROTAC class. It has a potential advantage in that it acts via proteasomal ER degradation, and is recycled within the cell, allowing repeated impact against the receptors. This phase 3 trial used fulvestrant as a comparator, which may be suboptimal for the reasons outlined above. Fewer than 20% of patients had bone-only disease, indicating a poorer-prognosis group. Patients had relatively oestrogen-sensitive tumours, having experienced progression after being on first-line endocrine therapy and a CDK4/6i for at least 6 months. PFS improved by almost 3 months in the *ESR1* mutant group, with no difference in those who were *ESR1* wild-type. The AE profile was considered favourable, with fatigue as the predominant toxicity. *ESR1* mutations emerge as a resistance mechanism to aromatase inhibitor treatment, emphasising the need for mutation testing at the time of progression on first-line treatment. The efficacy and safety of combination therapy with targeted therapies is yet to be determined. This is the first phase 3 trial with this class of drug, and was published simultaneously in the New England Journal of Medicine.

Presentation #LBA1000
Abstract