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CONFERENCE REVIEW

ESMO 2025
Focus on Breast Cancer

Making Education Easy

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In this review:

Abbreviations used in this review
ADC = antibody drug conjugate
CPS = combined positive score
Dato-DXd = datopotamab deruxtecan
DFS = disease-free survival
EFS = event-free survival
ILD = interstitial lung disease
(NS)AI = (non-steroidal) aromatase inhibitor
ORR = overall response rate
OS = overall survival
pCR = complete pathological response
PFS = progression-free survival
RFS = relapse-free survival
Sac-TMT = sacituzumab tirumotecan
SG = sacituzumab govitecan
SOC = standard of care
T-DM1 = trastuzumab emtansine
T-DXd = trastuzumab deruxtecan
THP = paclitaxel-trastuzumab-pertuzumab
TNBC = triple-negative breast cancer
(TR/E)AE = (treatment-related/emergent) adverse event

Welcome to our review of the 2025 ESMO Congress held in Berlin, Germany.

This year's Congress featured a number of interesting developments in the field of breast cancer, and here I have selected 10 presentations which were particularly noteworthy. We begin with updated 5-year results from the POSITIVE trial which found that women with HR+ breast cancer who interrupted adjuvant endocrine therapy in order to get pregnant had no increased risk of breast cancer recurrence/mortality than historical controls. This is followed by the primary OS results from the monarchE trial, which showed that patients with HR+, HER2–, node-positive, high-risk early breast cancer experienced improved OS with the addition of adjuvant abemaciclib to endocrine therapy. We then review the NATALEE trial which also examined CDK4/6 inhibition in HR+, HER2– early breast cancer, with 5-year results revealing that ribociclib plus NSAI reduced the risk of invasive and distant disease recurrence versus NSAI alone. We also feature the evERA and VIKTORIA-1 trials which evaluated second-line treatment options for ER+, HER2– advanced/metastatic breast cancer following progression with CDK4/6 inhibitor therapy.

I hope you enjoy these and the other abstracts in this review, and find them informative for your clinical practice. Your feedback is appreciated – please continue to send it in. Abstracts can be located online here.

Kind regards

Dr David Okonji
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5-year follow-up results from the POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer) trial

Speaker: Fedro A Peccatori (Milan, Italy)

Summary: Previous data from the single-arm POSITIVE trial found that, with a follow-up of 41 months, a temporary interruption of adjuvant endocrine therapy during pregnancy in women with HR+ early breast cancer was not associated with increased rates of breast cancer recurrence. This session outlined the updated outcomes from a median follow-up of 71 months (n=518). Outcomes were compared with a matched external control group from the SOFT and TEXT trials (median follow-up 80 months). Overall, women in the POSITIVE trial did not have an increased 5-year cumulative incidence of breast cancer-free interval events than historical controls (2.3% vs. 13.2%, respectively; difference –0.9; 95% CI –4.2 to 2.6), and there was no between-group difference in the 5-year cumulative incidence of distant recurrence-free interval events (6.2% vs. 8.3%; difference –2.1; 95% CI –4.5 to 0.4). In the subgroup of 497 women with evaluable pregnancy outcomes, 75.8% experienced ≥1 pregnancy during the trial, and 69% had ≥1 live birth (440 newborns). At 18 months, breast cancer-free interval events were similar between women who did and did not have a pregnancy. The 5-year cumulative incidence of breast cancer-free interval events among the 36% of women who underwent embryo/oocyte cryopreservation before enrolment was 14.0% (95% CI 9.6–20.2), compared to 11.5% (95% CI 8.4–15.7) in women who did not. At 2 years, most of the evaluable women who remained disease-free had resumed the endocrine therapy protocol (n=352/429; 82%).

Comment: This proffered paper was presented as a late-breaking abstract. It was a global, collaborative, academic, single-arm, prospective trial of >500 patients recruited between Dec 2014 to Dec 2019. After an initial period of at least 18 months, patients were allowed to temporarily interrupt adjuvant endocrine therapy in order to get pregnant. This was truly an altruistic trial of Herculean proportions and implications: after 71 months of follow-up, despite 91% safely registering a live birth and only 82% resuming endocrine therapy, there was no increased risk of breast cancer recurrence or mortality compared to bootstrapped/matched historical controls from the previously published adjuvant prospective SOFT/TEXT endocrine therapy studies. A word of caution though: firstly, these results appear most applicable to those with low- to moderate-risk disease, but not those with high-risk disease (i.e. 4–9 lymph nodes involved or with tumour sizes of >5cm), because they were under-represented in this study (4–5% patients). Secondly, the risk of late relapse (beyond 5 years) is yet to be determined.

Presentation LBA12
Abstract

monarchE: primary overall survival (OS) results of adjuvant abemaciclib + endocrine therapy (ET) for HR+, HER2-, high-risk early breast cancer (EBC)

Speaker: Stephen R Johnston (London, UK)

Summary: The open-label, randomised, phase 3 monarchE trial demonstrated that patients with HR+, HER2–, node-positive, high-risk early breast cancer achieved improvements in invasive DFS and distant RFS with adjuvant abemaciclib plus endocrine therapy (intervention), versus endocrine therapy alone (control). Here, Stephen Johnston presented updated invasive DFS and distant RFS data, alongside primary OS results (secondary endpoint). At a median follow-up of 6.3 years in the ITT population, 301 and 360 patients in the intervention and control arms had died, respectively. Patients who received adjuvant abemaciclib plus endocrine therapy experienced a 15.8% reduction in risk of death versus controls (HR 0.84; 95% CI 0.72–0.98; p=0.027), and this benefit in OS was consistent across subgroups. The benefit in invasive DFS with adjuvant abemaciclib plus endocrine therapy persisted for up to 7 years (77.4% vs. 70.9%; HR 0.73; 95% CI 0.66–0.82), as did the benefit in distant RFS (80.0% vs. 74.9%; HR 0.75; 95% CI 0.66–0.84). In the metastatic setting, fewer patients in the intervention arm received subsequent CDK4/6 inhibitors versus controls (34% vs. 52%). No late toxicities were observed.

Presentation LBA13

Abstract

Adjuvant ribociclib (RIB) plus nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+/HER2– early breast cancer (EBC): NATALEE 5-year outcomes

Speaker: John P Crown (Dublin, Ireland)

Summary: In NATALEE, patients with stage II/III HR+/HER2– early breast cancer achieved significant benefits in invasive DFS with the addition of adjuvant ribociclib to a non-steroidal aromatase inhibitor (NSAI). In this session, John Crown shared results from the 5-year protocol-specified efficacy analysis, with a median follow-up of ~2 years following completion of ribociclib. At the time of data cut-off (28 May, 2025), none of the patients were still on ribociclib, and 5 years of NSAI treatment had been completed by similar proportions of patients in the ribociclib plus NSAI arm (36.5%) and the NSAI arm (34.4%). At a median follow-up of 55.4 months, patients in the ribociclib plus NSAI arm continued to experience a benefit in invasive DFS versus NSAI alone (HR 0.716; 95% CI 0.618–0.829; p<0.0001); the absolute invasive DFS rates at 3, 4 and 5 years were 90.8% versus 88.0%, 88.3% versus 83.9% and 85.5% versus 81.0%, respectively. The benefit in invasive DFS was consistent across patient subgroups, including those with N0 disease (HR 0.606; 95% CI 0.372–0.986). Patients in the ribociclib plus NSAI also continued to experience benefits in distant RFS (HR 0.699; 95% CI 0.594–0.824) and distant DFS (HR 0.709; 95% CI 0.608–0.827). There was an OS trend in favour of ribociclib plus NSAI (HR 0.80; 95% CI 0.637–1.003; p=0.026). No unexpected safety signals were reported.

Presentation LBA14

Abstract

Comment: Both monarchE and NATALEE were large adjuvant CDK4/6 inhibitor studies in early high-risk breast cancer, deploying abemaciclib and ribociclib, respectively. As such, they have been coupled in this commentary. The former was more mature at the time of these presentations, reporting its primary OS results (after median 6.3 years follow-up): all those on abemaciclib were off treatment for a median of 4 years. On the other hand, NATALEE read out its 5-year outcomes, with all those on ribociclib being off treatment for a median of 2 years. Both studies were simultaneously published online, with the more significant results of monarchE published in a higher Impact Factor journal, Annals of Oncology (65.4), compared to NATALEE (ESMO Open, Impact Factor 8.3). monarchE met its primary endpoint, exhibiting a statistically significant, albeit modest 1.8% OS benefit (HR 0.84); although not yet mature, NATALEE's 5-year absolute OS benefit was comparable (at 1.6%) with a very similar hazard ratio (of 0.80). This is quite notable for the fact that NATALEE, unlike monarchE, recruited lower clinical-risk patients with stage IIA (node-negative) and IIB disease (albeit of high genomic risk by Oncotype DX score or Ki-67 status). It is likely that both of these studies will define a new SOC: the future use of adjuvant CDK4/6 inhibitor + endocrine therapy is likely to become commonplace in HR+, HER2–, high-risk early breast cancer. In which case, it will become increasingly important not only to be able to identify those in whom we can safely omit adjuvant CDK4/6 inhibitor therapy, but also to become adept at managing side effects of the same in those who warrant it.

Sacituzumab tirumotecan (sac-TMT) vs investigator's choice of chemotherapy (ICC) in previously treated locally advanced or metastatic hormone receptor-positive, HER2-negative (HR+/HER2-) breast cancer (BC): results from the randomized, multi-centre phase III OptiTROP-Breast02 study

Speaker: Man Li (Dalian, China)

Summary: In the OptiTROP-Breast02 trial, eligible pre-treated patients with HR+, HER2– metastatic breast cancer (n=399; median age 54 yrs; 57% with ≥2 prior lines) have been randomly assigned to receive sacituzumab tirumotecan (sac-TMT; n=100) or investigator's choice of chemotherapy (n=199). At the time of data cut-off (22 January, 2025), 113 and 61 patients in the sac-TMT and chemotherapy arms, respectively, were still on treatment. Patients administered sac-TMT achieved significantly longer PFS versus chemotherapy (8.3 vs. 4.1 months; HR 0.35; 95% CI 0.26–0.48; p<0.0001), with 6-month PFS rates of 61.4% and 25.7%, respectively. The PFS benefit with sac-TMT was consistent regardless of HER2 expression (HER2-zero HR 0.39; 95% CI 0.26–0.57; HER2-low HR 0.31; 95% CI 0.20–0.48). Patients in the sac-TMT arm also achieved improvements in ORRs (41.5% vs. 24.1%). With 7.4 months of median follow-up, OS data remained immature, however there was a trend in favour of sac-TMT (HR 0.33; 95% CI 0.18–0.61). Man Li stated that sac-TMT had a manageable safety profile. The rates of grade ≥3 TRAEs with sac-TMT and chemotherapy were 62.0% versus 64.8%, respectively, and the most frequent TRAEs were reduced neutrophil counts (44.5% vs. 51.5%) and reduced white blood cell counts (31.0% vs. 31.6%); pneumonitis was recorded in 1.5% versus 1.0%, with discontinuations due to TRAEs in 0% versus 0.5%, respectively.

Comment: The TROPiCS-02 study (Lancet. 2023;402[10411]:1423–33) demonstrated a clinically meaningful and statistically significant OS benefit favouring sacituzumab govitecan (SG) over physician's choice of chemotherapy in heavily pre-treated, HR+/HER2– advanced breast cancer. This trial established SG as a SOC in those who have not only exhausted endocrine therapy treatment lines, but also received at least 2–4 previous chemotherapy regimens for metastatic HR+/HER2- advanced breast cancer (it was FDA approved for this indication in February 2023). Sac-TMT is a 'me-too' drug and OptiTROP-Breast02 is essentially a 'copy-paste' of TROPiCS-02. Like SG, sac-TMT targets the TROP2 receptor, which is ubiquitous in metastatic breast cancer. The cytotoxic payloads of both drugs belong to the topoisomerase I inhibitor class. OptiTROP-Breast02 was a positive phase 3 study exclusively conducted in China, with a clinically meaningful and statistically significant absolute PFS Δ benefit of 4.2 months. The OS data are not yet mature. Perhaps to legitimise these results in a Western population, a more global phase 3 study is currently underway: TroFuse-010 (NCT06312176). Unlike OptiTROP-Breast02, TroFuse-010 will evaluate sac-TMT in a less heavily pre-treated (only endocrine therapy as previous-line systemic therapy permitted), chemotherapy-naïve study population.

Presentation LBA23

Abstract

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Giredestrant (GIRE), an oral selective oestrogen receptor (ER) antagonist and degrader, + everolimus (E) in patients (pts) with ER-positive, HER2-negative advanced breast cancer (ER+, HER2– aBC) previously treated with a CDK4/6 inhibitor (i): primary results of the phase III evERA BC trial

Speaker: Erica Mayer (Boston, US)

Summary: The global, open-label, phase 3 evERA BC trial has enrolled patients with ER+, HER2– advanced breast cancer who experienced progression/relapse during/after CDK4/6 inhibition plus endocrine therapy. Here, Erica Mayer presented the primary results among 373 patients (~55% harbouring *ESR1* alterations) who had been randomised 1:1 to receive giredestrant plus everolimus (n=183) or standard-of-care (SOC) endocrine therapy (tamoxifen/exemestane/fulvestrant) plus everolimus (n=190). With a median follow-up of 18.6 months, patients administered giredestrant plus everolimus achieved significantly prolonged PFS versus endocrine therapy plus everolimus (ITT 8.77 vs. 5.49 months; HR 0.56; 95% CI 0.44–0.71; p<0.0001), and this PFS benefit was particularly pronounced in the subgroup of patients with *ESR1* alterations (9.99 vs. 5.45 months; HR 0.38; 95% CI 0.27–0.54; p<0.0001). With OS data maturity of 67% in the ITT population and 59% in the *ESR1*-altered population, there were trends for benefits in OS with giredestrant plus everolimus. Erica Mayer stated that this treatment combination had manageable safety, and no unexpected signals were observed.

Presentation LBA16
Abstract

Gedatolisib (geda) + fulvestrant ± palbociclib (palbo) vs fulvestrant in patients (pts) with HR+/ HER2–/*PIK3CA* wild-type (WT) advanced breast cancer (ABC): first results from VIKTORIA-1

Speaker: Sara A Hurvitz (Seattle, US)

Summary: Sara Hurvitz shared the first data from the open-label phase 3 VIKTORIA-1 trial, which enrolled patients with HR+, HER2–, *PIK3CA* wild-type advanced breast cancer that had progressed during/following treatment with CDK4/6 inhibition plus an AI. Eligible patients (n=392) were randomly assigned to gedatolisib/palbociclib/fulvestrant (triplet), gedatolisib/fulvestrant (doublet) or fulvestrant. At a follow-up of 10.1 months, patients achieved prolonged PFS with triplet therapy versus fulvestrant (9.3 vs. 2.0 months; HR, 0.24; 95% CI 0.17–0.35; p<0.0001), and prolonged PFS with doublet therapy versus fulvestrant (7.4 vs. 2.0 months; HR 0.33; 95% CI 0.24–0.48; p<0.0001); these PFS benefits were consistent across patient subgroups. The ORRs with the triplet combination, doublet combination and fulvestrant were 32% (including one CR), 28.3% and 1%, respectively. Interim analyses of OS indicated trends in favour of the triplet (HR 0.69; 95% CI 0.43–1.12) and the doublet (HR 0.74; 95% CI 0.46–1.19). Hyperglycaemia occurred in 9.2% and 11.5% of patients in the triplet and doublet arms, respectively (grade 3 2.3% and 2.3%), and there were low rates of discontinuations due to TRAEs (2.3% and 3.1%).

Presentation LBA17
Abstract

Comment: There is now a hectic profusion of potential second-line treatment options for ER+, HER2– advanced breast cancer post-progression following first-line CDK4/6 inhibitor endocrine therapy. Although none of these are PHARMAC-funded in NZ, other global jurisdictions have approved some of these, with the tacit understanding that all of them, so far, require specific biomarker pre-selection; these include: fulvestrant + alpelisib (*PIK3CA* mutations; Lancet Oncol. 2024;25[12]:e629–38), fulvestrant + capivasertib (AKT pathway-altered; N Engl J Med. 2023;388[22]:2058–70), elacestrant (Clin Cancer Res. 2024;30[19]:4299–309) and imlunestrant + abemaciclib (*ESR1* mutations; N Engl J Med. 2025;392[12]:1189–202). Well, this space is poised to get even more crowded with the recent presentation of the evERA and VIKTORIA-1 phase 3 randomised controlled studies at ESMO 2025.

evERA showcased the second-line combination of giredestrant, an oral, next-generation selective oestrogen receptor degrader (SERD) in combination with everolimus, versus SOC endocrine therapy + everolimus in all-comers. The co-primary endpoints were PFS in those with *ESR1* mutations and the ITT population; however, a predicated statistically significant PFS in the *ESR1*-mutated subpopulation was first required before hierarchical testing allowed for split alpha spending to ascertain PFS in the ITT population. On the other hand, VIKTORIA-1 was a 2-part, three-arm study. Part 1 of the study evaluated gedatolisib (an intravenous selective PIK3CA/AKT/mToR – PAM inhibitor) in combination with palbociclib + fulvestrant (arm A) or fulvestrant (arm B) or fulvestrant alone (arm C) in 'all-comers'. Part 2 of the study was exclusive to patients with *PIK3CA*-mutation-positive disease. Only part 1 of the study was reported in ESMO 2025.

Both evERA and VIKTORIA-1 met their primary endpoints. Of note, in evERA, the PFS benefit was statistically significant and clinically meaningful in the ITT population (Δ 3.3 months); however, it was more pronounced in the *ESR1*-mutated sub-population (Δ 5 months), suggesting that most of the PFS benefit in the study arm was driven by the *ESR1*-altered sub-population of patients, and not those with *ESR1*-wild type mutations. Likewise, for part 1 of VIKTORIA-1, looking specifically at gedatolisib + palbociclib + fulvestrant (arm A) versus fulvestrant alone (arm C), the primary endpoint was met, with an even more impressive absolute PFS benefit (Δ 7.3 months). Therefore, with this triplet combination, the VIKTORIA-1 investigators effectively re-sensitised patients to a re-challenge with a CDK 4/6 inhibitor, and in so doing, upended previous conventional dogma suggesting that such an approach is an exercise in futility.

Finally, OS data are not yet mature for either study. Furthermore, in VIKTORIA-1, 58% of the control arm crossed over to receive treatment with gedatolisib-containing combinations at disease progression. Be that as it may, I suspect that the active arm regimens in both of these studies will probably be approved by the USA regulatory body, the FDA, in due course – thus further crowding the second-line ER+, HER2– advanced breast cancer space even more. Nonetheless, the fact that 'all-comers' derived a PFS benefit irrespective of biomarker selection makes either of these study options quite attractive in jurisdictions such as NZ, where genomic sequencing assays of metastatic breast cancer to identify 'actionable' genetic mutations that can be targeted with specific therapies are not easily available, or are prohibitively expensive.

DESTINY-Breast11: neoadjuvant trastuzumab deruxtecan alone (T-DXd) or followed by paclitaxel + trastuzumab + pertuzumab (T-DXd-THP) vs SOC for high-risk HER2+ early breast cancer (eBC)

Speaker: Nadia Harbeck (Munich, Germany)

Summary: The multicentre, open-label DESTINY-Breast11 trial randomly assigned eligible patients with untreated high-risk, HER2+ early breast cancer to receive neoadjuvant trastuzumab deruxtecan alone (T-DXd), T-DXd plus paclitaxel-trastuzumab-pertuzumab (T-DXd-THP) or SOC dose-dense doxorubicin plus cyclophosphamide plus THP. The Independent Data Monitoring Committee advised that the T-DXd alone arm be closed. Thus, Nadia Harbeck presented results from patients randomised to T-DXd-THP (n=321) or SOC (n=320). At the time of data cut-off (12 March, 2025), patients administered T-DXd-THP showed significantly higher pCR rates versus SOC (67.3% vs. 56.3%; difference 11.2; 95% CI 4.0–18.3; p=0.003), and pCR benefits were seen across patients with HR+ disease (61.4% vs. 52.3%) and HR– disease (83.1% vs. 67.1%). There was an early EFS trend in favour of T-DXd-THP (HR 0.56; 95% CI 0.26–1.17). Rates of grade ≥3 AEs were lower with T-DXd-THP than with SOC (37.5% vs. 55.8%), and AEs of interest were less frequent in the T-DXd-THP arm (left ventricular dysfunction 1.9% vs. 9.0%; ILD/pneumonitis 4.4% vs. 5.1%).

Presentation 291O

Abstract

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INDEPENDENT COMMENTARY BY

Dr David Okonji

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Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients (pts) with high-risk human epidermal growth factor receptor 2–positive (HER2+) primary breast cancer (BC) with residual invasive disease after neoadjuvant therapy (tx): interim analysis of DESTINY-Breast05

Speaker: Charles E Geyer (Pittsburgh, US)

Summary: In the open-label phase 3 DESTINY-Breast05 trial, 1635 patients with residual, high-risk, invasive HER2+ breast cancer after neoadjuvant treatment were randomly assigned 1:1 to T-DXd (n=818) or trastuzumab emtansine (T-DM1; n=817). Here, Charles Geyer shared the interim results from a median follow-up of 29.9 months in the T-DXd arm and 29.7 months in the T-DM1 arm. Patients administered T-DXd achieved significant benefits in invasive DFS (HR 0.47; 95% CI 0.34–0.66; p<0.0001) and DFS (HR 0.47; 95% CI 0.34–0.66; p<0.0001), with a numerical improvement in brain metastasis-free interval (HR 0.64; 95% CI 0.35–1.17). Grade ≥3 TEAEs were observed in 50.6% versus 51.9% of patients administered T-DXd and T-DM1, respectively, with ILD in 9.6% (grade 5 n=2) versus 1.6%, and TEAE-related deaths in 0.4% (n=3) versus 0.6% (n=5).

Presentation LBA1

Abstract

Comment: The current SOC for treating ≥T2 size or node-positive HER2-positive early breast cancer is anti-HER2 antibody-containing neoadjuvant chemotherapy. In this context, a pCR is associated with improved survival. We also know without a shadow of doubt that T-DXd is effective in improving survival in the HER2+ metastatic breast cancer setting; however, it is associated with a 10–15% risk of ILD, 2% of which can be fatal. Bearing in mind the potential survival benefit, and with one eye on potential side effects, both of these large trials (of >1000 patients each) couldn't be any more perfectly poised and powered to evaluate this ADC in early disease.

DESTINY-Breast11 addressed the neoadjuvant question, effectively asking whether we can improve pCR rates by an adding another anti-HER2-containing therapy to the mix (T-DXd in this case), while also omitting anthracyclines from the equation. DESTINY-Breast05, on the other hand, addresses the other extreme with the more recent post-neoadjuvant question: can we grant those not achieving pCR a 'second opportunity' with a salvage therapy, thus only reserving T-DXd, a drug with recognised significant side effects, for those 'poor responders' who are at most risk of relapsed distant metastatic disease and death? As such, the conundrum that this brace of trials attempts to solve is, "*Where ought we to nest T-DXd in HER2+ early disease – in the neoadjuvant or the post-neoadjuvant setting?*"

DESTINY-Breast11 met its primary endpoint – an impressive absolute Δ 11.2% improvement in pCR favouring the T-DXd-containing neoadjuvant arm; and these were high-risk patients (node-positive 90% and T3–T4 disease 75%). Treatment in the T-DXd arm was also better tolerated than in the non-T-Dxd, anthracycline-containing control arm, which registered higher haematological toxicity. The ILD rate was low and comparable in each arm (4–5%). On a final note, it will be interesting to see how (or if) post-neoadjuvant T-DM1 (received by >50% of non-pCR patents) impacts on the currently immature secondary endpoints of EFS and OS in the long term.

DESTINY-Breast05 also met its endpoint: a spectacularly improved 3-year invasive DFS of 92.4% versus the prevailing SOC T-DM1 (83.7%) – that's an absolute improvement of Δ 8.7%, and this was despite a 20% discontinuation rate in each arm. Ominously, ILD rates were higher in the T-DXd arm compared to the T-DM1 arm; furthermore, two patients in the T-DXd arm died of a result of ILD. As with DESTINY-Breast11, the OS results for DESTINY-Breast05 are immature. For now, the jury is out as to whether the optimum approach is to 'front-load' T-DXd à la DESTINY-Breast11 (neoadjuvant), or deploy it 'out-back' as with DESTINY-Breast05 (post-neoadjuvant).

Primary results from ASCENT-03: a randomized phase III study of sacituzumab govitecan (SG) vs chemotherapy (chemo) in patients (pts) with previously untreated advanced triple-negative breast cancer (TNBC) who are unable to receive PD-(L)1 inhibitors (PD-[L]1i)

Speaker: Javier C Cortés (Barcelona, Spain)

Summary: In this proffered paper session, Javier Cortés presented the primary results from the ASCENT-03 trial, in which 588 patients with locally advanced unresectable/metastatic triple-negative breast cancer (TNBC) ineligible for PD-L1 inhibitors were randomised 1:1 to first-line sacituzumab govitecan (SG; n=279) or chemotherapy (n=279). At a median follow-up of 13.2 months, patients treated with SG achieved significantly extended PFS versus chemotherapy (9.7 vs 6.9 months; HR 0.62; 95% CI 0.50–0.78; p<0.0001), and the durations of response were 12.2 and 7.2 months, respectively. The ORR with SG was 48.4% (95% CI 42.4–54.4) versus 45.5% (95% CI 39.6–51.6) in the chemotherapy arm. The OS data were not yet mature at the time of reporting. Grade ≥3 TEAEs occurred in 66% and 62% of patients in the SG and chemotherapy arms, respectively, with 4% and 12% discontinuing treatment due to TEAEs. The most common grade ≥3 TEAE with SG was neutropenia (43%) followed by diarrhoea (9%); the most frequent grade ≥3 TEAEs with chemotherapy were neutropenia (41%) and anaemia (16%).

Presentation LBA20

Abstract

First-line (1L) datopotamab deruxtecan (Dato-DXd) vs chemotherapy in patients with locally recurrent inoperable or metastatic triple-negative breast cancer (mTNBC) for whom immunotherapy was not an option: primary results from the randomised, phase III TROPION-Breast02 trial

Speaker: Rebecca A Dent (Singapore)

Summary: The phase 3 TROPION-Breast02 trial enrolled 644 patients with treatment-naïve, locally recurrent, inoperable/metastatic TNBC who were ineligible for immunotherapy. Patients were randomly assigned 1:1 to datopotamab deruxtecan (Dato-DXd; n=323) or investigator's choice of chemotherapy (n=321). At a median follow-up of 27.5 months, patients administered Dato-DXd demonstrated a significant improvement in OS versus chemotherapy (23.7 vs. 18.7 months; HR 0.79; 95% CI 0.64–0.98; p=0.0291), with significantly prolonged PFS (10.8 vs. 5.6 months; HR 0.57; 95% CI 0.47–0.69; p<0.0001), a higher confirmed ORR (62.5% vs. 29.3%) and a longer median duration of response (12.3 vs. 7.1 months). Patients in the Dato-DXd arm received treatment for twice as long as those administered chemotherapy (8.5 vs. 4.1 months); however, they had similar rates of grade ≥3 TRAEs (32.2% vs. 28.8%) and fewer patients in the Dato-DXd arm discontinued treatment due to TRAEs (4.4% vs. 7.4%).

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Abstract

Comment: For longest time, first-line conventional systemic chemotherapy (either as a single agent or in combination) was the SOC for the treatment of mTNBC. This changed in November 2020, when the US FDA approved pembrolizumab + chemotherapy for mTNBC on account of its clinically meaningful OS benefit over conventional systemic chemotherapy seen in the registration phase 3 study, KEYNOTE-355 (N Engl J Med. 2022;387[3]:217–26); NZ followed suit when PHARMAC approved the same treatment for exactly the same indication 4 years later in November 2024. However, it must be borne in mind that both the survival benefit and its corresponding approved indication were exclusive to patients whose tumours expressed the PD-L1 biomarker (with a CPS cut-off of ≥10). Be that as it may, only ~40% of the ITT population in KEYNOTE-355 had a CPS of ≥10. Thus, those with mTNBC in whom immunotherapy is contraindicated because of pre-existing comorbidities or who have a CPS of <10, represent a significant majority (up to 60% of all patients with mTNBC), with an unmet need and sub-optimal survival outcomes. It is in this space that both ASCENT-03 (simultaneously published in the NEMJ on the same day as the presentation) and TROPION-Breast02 shone their light.

At the time of the ASCENT-03 presentation, the TROP2-directed ADC sacituzumab govitecan (SG) already had a proven track record as a second-line SOC systemic therapy for both mTNBC and hormone-positive HER2– breast cancer. As such, its move into the earlier (first-line) setting in mTNBC seemed the next logical step. On the other hand, TROPION-Breast02's Dato-DXd is a 'new kid on the block'. Nevertheless, like SG, it is also a TROP2-directed ADC linked to the same class of chemotherapy moiety, a topoisomerase I inhibitor.

ASCENT-03, the more immature of the two, was a positive study, reporting its primary result of a near absolute statistical improvement in a PFS benefit of ~3.0 months. OS data, immature at this time, were a secondary endpoint, showing an encouraging trend. Having said that, the trial may (in the future) struggle to realise a final OS benefit favouring SG, because the study's statistical power rests firmly with PFS as the primary outcome. Furthermore, patients in the control arm were altruistically allowed to cross-over and receive SG as second-line therapy at the time of progression. Interestingly, a descriptive PFS2 analysis presented by the investigators in ESMO 2025 appear to still favour SG over SOC chemotherapy. This suggests that SG might still come through with an OS benefit.

TROPION-Breast02 was also a positive study, reporting statistically significant PFS and OS benefits (~5 months each) favouring Dato-DXd, despite recruiting a very high-risk population – 10% had brain metastases and 15% had relapsed metastatic disease, with a disease-free interval of less than 6 months post-(neo)adjuvant chemotherapy.

Finally, despite SG and Dato-DXd targeting the same antigen (TROP2), and sharing the same chemotherapy class of payload (topoisomerase I inhibitor), their side effects couldn't be any more different. SG exhibited more haematological toxicities (requiring primary/secondary growth factor support) and diarrhoea. Dato-DXd, on the other hand, caused more ocular surface toxicity (dry eyes), stomatitis and nausea.

So, where to from here? It is likely that one (if not both) of these ADCs will be approved in the US and/or Europe in the near future for this aforementioned indication. However, with more mature OS data, Dato-DXd is likely to be the front-runner.