SAN ANTONIO BREAST CANCER SYMPOSIUM®
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HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

DESTINY-Breast11 safety: neoadjuvant trastuzumab deruxtecan (T-DXd) alone or followed by paclitaxel + trastuzumab + pertuzumab (THP) vs dose-dense doxorubicin + cyclophosphamide followed by THP (ddAC-THP) in high-risk, HER2+ early-stage breast cancer

RF6-02
Wednesday, December 10, 2025

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On behalf of the DESTINY-Breast11 investigators

DESTINY Breast11

Disclosures

Giuseppe Curigliano

In the past 36 months:

Grants or contracts: Merck

Consulting fees: AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Ellipses Pharma, Gilead Sciences, Lilly, Menarini, Merck, Novartis, Pfizer, Roche, Seagen

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Support for attending meetings and/or travel: Daiichi Sankyo

DESTINY-Breast11 study design

A randomized, global, multicenter, open-label, Phase 3 study (NCT05113251)[1,2]

Patient population

- Previously untreated HER2+ early breast cancer
- HR-positive or HR-negative
- High risk defined as:
  - ≥cT3 and N0−3 or cT0–4 and N1−3
  - Inflammatory breast cancer

Stratification factors

- HR status: ER and/or PR-positive or negative
- HER2 status: IHC 3+, or ISH+ in the absence of IHC 3+ status

R 1:1:1

- n=321 → **T-DXd* → THP†** 4+4 cycles
- n=320 → **ddAC‡ → THP§** 4+4 cycles
- n=286 → **T-DXd*** 8 cycles

Surgery¶ + post-neoadjuvant treatment

The T-DXd alone arm closed following IDMC recommendation on March 13, 2024
The reasons were multifactorial, including a lower pCR rate, low likelihood that T-DXd alone would be superior to ddAC-THP, and the timing of surgery

Data cutoff: March 12, 2025

Primary endpoint

- pCR (ypT0/is ypN0)

Secondary endpoints include:

- pCR (ypT0 ypN0)
- Event-free survival
- Patient-reported outcomes
- Safety

Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at EOT to assess left ventricular ejection fraction

*5.4 mg/kg Q3W; †paclitaxel (80 mg/m² QW) + trastuzumab (6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ‡doxorubicin (60 mg/m² Q2W) + cyclophosphamide (600 mg/m² Q2W); §paclitaxel (80 mg/m² QW) + trastuzumab (8 mg/kg loading dose followed by 6 mg/kg Q3W) + pertuzumab (840 mg loading dose followed by 420 mg Q3W); ¶the recommended window for surgery was 3–6 weeks following administration of the last dose of neoadjuvant study treatment; ‖for patients who completed study treatment, this should take place after surgery; if all study treatments discontinued prior to completion of planned cycles, this could be prior to surgery. cT, clinical tumor stage; ddAC, dose-dense doxorubicin + cyclophosphamide; EOT, end of treatment; ER, estrogen receptor; HER2, human epidermal growth factor receptor; HER2+, HER2-positive; HR, hormone receptor; HRCT, high-resolution computed tomography; IDMC, Independent Data Monitoring Committee; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH+, in situ hybridization–positive; N, nodal stage; pCR, pathologic complete response; PR, progesterone receptor; QXW, every X weeks; R, randomized; T-DXd, trastuzumab deruxtecan; THP, paclitaxel + trastuzumab + pertuzumab; ypT0 ypN0, absence of invasive and in situ cancer in the breast and axillary nodes; ypT0/is ypN0, absence of invasive cancer in the breast and axillary nodes

1. Harbeck N, et al. Oral presentation at ESMO 2025 (Abstract 4100); 2. NCT05113251. Updated November 18, 2025. Available from: https://www.clinicaltrials.gov/study/NCT05113251 (Accessed December 1, 2025)

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Surgery¶ + post-neoadjuvant treatment

Safety follow up:
40+7 days from last dose of study treatment‖

Data cutoff: March 12, 2025

Primary endpoint

- pCR (ypT0/is ypN0)

Secondary endpoints include:

- pCR (ypT0 ypN0)
- Event-free survival
- Patient-reported outcomes
- Safety

- Chest HRCT scans were performed at screening, Q6W until EOT, at safety follow up, and if ILD/pneumonitis was suspected
  - If ILD/pneumonitis was confirmed, follow up continued until resolution; potential cases were retrospectively evaluated by an independent ILD Adjudication Committee
- Heart failure adverse events were recorded until EOT and at end of study (up to 6 years' follow up)

Echocardiograms or multigated acquisition scans were performed during screening (<28 days prior to randomization), during treatment (<3 days before Cycle 5), and at EOT to assess left ventricular ejection fraction

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DESTINY-Breast11 primary results

- **T-DXd-THP** demonstrated **statistically significant and clinically meaningful improvement in pCR rate** vs **ddAC-THP** in patients with high-risk HER2+ eBC
- The **safety profile of T-DXd-THP was favorable** vs **ddAC-THP**, and there were **no new safety signals** for T-DXd-containing regimens
- In the **T-DXd-THP** and **T-DXd** arms, there were **lower rates of**:

%	T-DXd-THP	ddAC-THP	T-DXd
Grade ≥3 AEs	37.5	55.8	22.6
Serious AEs	10.6	20.2	10.2
AEs leading to treatment interruptions	37.8	54.5	18.0
Left ventricular dysfunction	1.3	6.1	0.7
Grade ≥3	0.3	1.9	0
Fatigue	41.3	54.8	42.4

T-DXd-THP pCR rate

67.3%

ΔpCR vs ddAC-THP: 11.2% (95% CI 4.0, 18.3)

HR-positive: **61.4%**
HR-negative: **83.1%**

- **ILD/pneumonitis rates were low and similar** across all arms (**4.4%** vs **5.1%** vs **4.9%**)

We report additional safety data for AESIs (ILD/pneumonitis and left ventricular dysfunction) and clinically relevant AEs (nausea, vomiting, neutropenia, and peripheral neuropathy) in the T-DXd-THP, ddAC-THP, and T-DXd arms

Median (range) duration of treatment was 24.1 (3.0–39.7) weeks for T-DXd-THP, 21.0 (2.0–30.9) weeks for ddAC-THP, and 24.0 (3.0–32.1) weeks for T-DXd
AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; eBC, early breast cancer
Harbeck N, et al. *Ann Oncol*. 2025;doi 10.1016/j.annonc.2025.10.019: Oct 21 [Epub ahead of print]

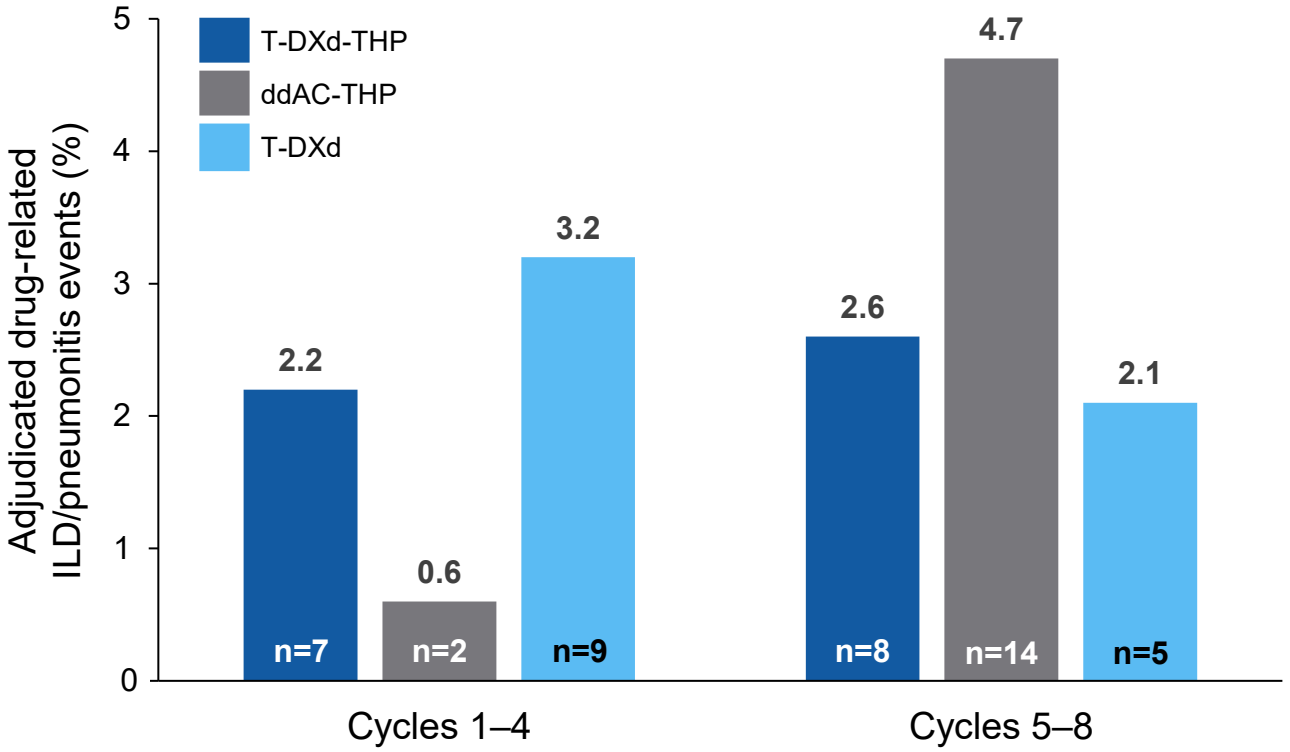
Adjudicated drug-related ILD/pneumonitis: events by cycle

n (%)	T-DXd-THP (N=320)	ddAC-THP (N=312)	T-DXd (N=283)
All grade	14 (4.4)	16 (5.1)	14 (4.9)
Grade 1	4 (1.3)	4 (1.3)	2 (0.7)
Grade 2	8 (2.5)	6 (1.9)	12 (4.2)
Grade 3	1 (0.3)	5 (1.6)	0
Grade 4	0	0	0
Grade 5	1 (0.3)	1 (0.3)	0
Grade ≥3	2 (0.6)	6 (1.9)	0

Median (range) time to onset:

- **82.5 (32–184) days** (T-DXd-THP; n=14)*
- **77.0 (41–149) days** (ddAC-THP; n=16)†
- **78.0 (25–155) days** (T-DXd; n=14)

Adjudicated drug-related ILD/pneumonitis by cycle of onset‡



All-grade adjudicated drug-related ILD/pneumonitis rates were low and similar across all arms, and Grade ≥3 events were most frequent with ddAC-THP

Rates remained stable (T-DXd-THP) and were higher (ddAC-THP) in the THP phase (Cycles 5–8) vs Cycles 1–4

Safety analyses included all patients who received at least one dose of any study treatment
*Q3W schedule; †Q2W schedule; ‡percentages are calculated using the number of patients at risk at any point in the cycle window as the denominator, and patients may be counted twice if they had multiple events in different cycles

Adjudicated drug-related ILD/pneumonitis: treatment discontinuations, interruptions, reductions, and SAEs

Adjudicated drug-related ILD/pneumonitis, n (%)	T-DXd-THP (N=320)	ddAC-THP (N=312)	T-DXd (N=283)
Leading to treatment discontinuation	6 (1.9)	7 (2.2)	9 (3.2)
Grade 1	0	0	2 (0.7)
Grade 2	5 (1.6)	4 (1.3)	7 (2.5)
Grade 3	0	3 (1.0)	0
Grade 5	1 (0.3)	0*	0
Leading to treatment interruption	3 (0.9)	6 (1.9)	3 (1.1)
Grade 1	1 (0.3)	2 (0.6)	0
Grade 2	1 (0.3)	0	3 (1.1)
Grade 3	1 (0.3)	4 (1.3)	0
Leading to dose reduction	0	0	0
SAE	2 (0.6)	9 (2.9)	1 (0.4)

The incidence of treatment discontinuations and interruptions due to ILD/pneumonitis were low across treatments, with no dose reductions, and there were more SAEs in the ddAC-THP arm compared with T-DXd-THP and T-DXd arms

Safety analyses included all patients who received at least one dose of any study treatment
*One Grade 5 event in ddAC-THP arm; however, the patient died prior to decision to discontinue treatment
SAE, serious adverse event

Adjudicated drug-related ILD/pneumonitis: steroid use and outcome

Per the protocol, systemic steroids could be considered for Grade 1 suspected ILD/pneumonitis that occurred during treatment with T-DXd and were recommended for Grade ≥2 suspected events*

Adjudicated drug-related ILD/pneumonitis	T-DXd-THP (N=320)	ddAC-THP (N=312)	T-DXd (N=283)
Treated with steroids, n treated / total events (%)†			
Grade 1	4/8 (50.0)	1/6 (16.7)	4/7 (57.1)
Grade 2	4/5 (80.0)	5/6 (83.3)	6/7 (85.7)
Grade 3	0/0 (0)	2/3 (66.7)	0/0 (0)
Grade 5	1/1 (100)	1/1 (100)	0/0 (0)
Grade ≥3	1/1 (100)	3/4 (75.0)	0/0 (0)
Outcome of worst event, n with outcome / total events (%)			
Recovered or resolved	10/14 (71.4)	13/16 (81.3)	8/14 (57.1)
Recovering or resolving	0/14 (0)	1/16 (6.3)	1/14 (7.1)
Recovered or resolved with sequelae	1/14 (7.1)	0/16 (0)	1/14 (7.1)
Not recovered or not resolved	2/14 (14.3)	1/16 (6.3)	4/14 (28.6)
Fatal	1/14 (7.1)	1/16 (6.3)	0/14 (0)
Median duration of first event, days (95% CI)	45 (35, 126)	43 (22, 61)	60 (25, 105)

Most patients with Grade ≥2 events received steroid treatment, and the majority (~65–85%) of cases were resolved, or resolving, by data cutoff

Safety analyses included all patients who received at least one dose of any study treatment
*Other immunosuppressants could also be considered for Grade ≥3 events; †investigator-reported grade for patients with adjudicated drug-related ILD/pneumonitis

Left ventricular dysfunction

n (%)	T-DXd-THP (N=320)	ddAC-THP (N=312)	T-DXd (N=283)
Left ventricular dysfunction	4 (1.3)	19 (6.1)	2 (0.7)
Grade 1	0	3 (1.0)	0
Grade 2	3 (0.9)	10 (3.2)	2 (0.7)
Grade 3	1 (0.3)	6 (1.9)	0
Grade ≥3	1 (0.3)	6 (1.9)	0
Ejection fraction decreased	4 (1.3)	15 (4.8)	2 (0.7)
Grade 2	3 (0.9)	9 (2.9)	2 (0.7)
Grade 3	1 (0.3)	6 (1.9)	0
Grade ≥3	1 (0.3)	6 (1.9)	0
Cardiac failure	0	4 (1.3)	0
Grade 1	0	3 (1.0)	0
Grade 2	0	1 (0.3)	0

Rates of all-grade and Grade ≥3 left ventricular dysfunction were higher with ddAC-THP vs T-DXd-THP and T-DXd, and there were no events of cardiac failure in the T-DXd-containing arms

Safety analyses included all patients who received at least one dose of any study treatment

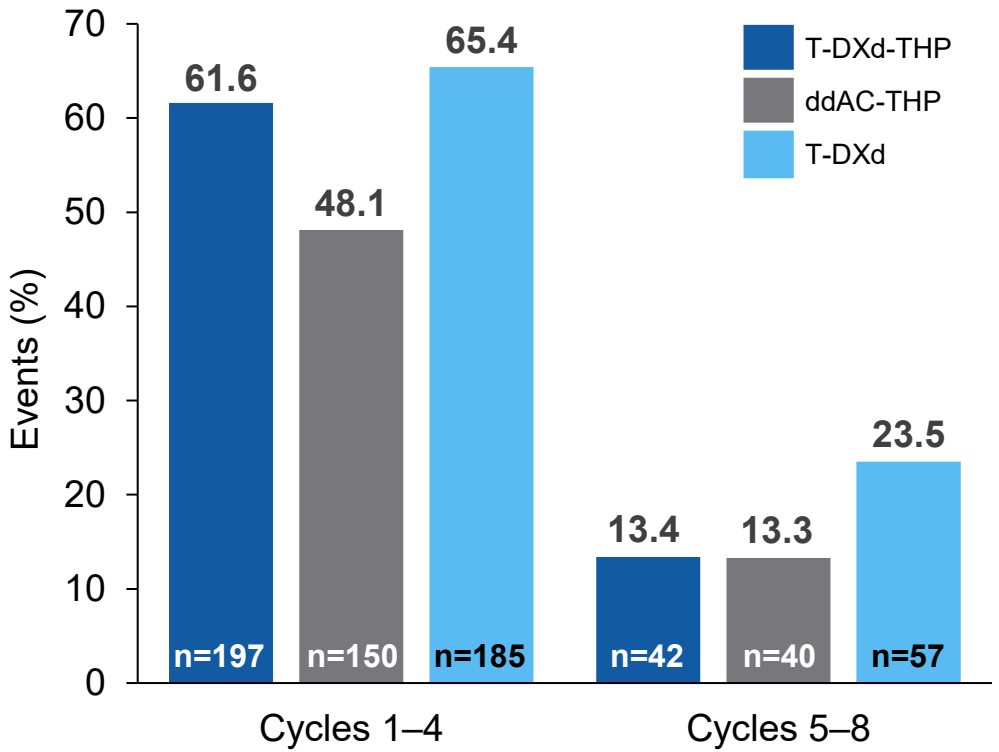
Nausea and vomiting: events by cycle and antiemetic use

n (%)	T-DXd-THP (N=320)	ddAC-THP (N=312)	T-DXd (N=283)
All-grade nausea	207 (64.7)	161 (51.6)	193 (68.2)
Grade ≥3	6 (1.9)	1 (0.3)	3 (1.1)
All-grade vomiting	92 (28.8)	66 (21.2)	88 (31.1)
Grade ≥3	3 (0.9)	2 (0.6)	3 (1.1)

Per the protocol, prophylaxis with 2–3 antiemetics* prior to each dose of T-DXd was recommended, but not mandated

Protocol-recommended antiemetics on or prior to Cycle 1 Day 1*			
3-antiemetic regimen	54 (16.9)	124 (39.7)	40 (14.1)
2-antiemetic regimen	183 (57.2)	126 (40.4)	157 (55.5)
All antiemetics on or prior to Cycle 1 Day 1	284 (88.5)	282 (88.1)	240 (83.9)
≥3-antiemetic regimen	105 (32.8)	174 (55.8)	77 (27.2)

Nausea events by cycle of onset†



Vomiting events occurred with a similar trend by cycle of onset

Nausea and vomiting events were generally low grade, and rates decreased substantially after Cycles 1–4; use of ≥3 antiemetics was much greater with ddAC-THP than with T-DXd-THP and T-DXd

Safety analyses included all patients who received at least one dose of any study treatment
*Use of 2 or 3 of the following was recommended by the protocol: a glucocorticoid, serotonin (5-HT3) receptor antagonist, and a neurokinin-1 receptor antagonist; †percentages are calculated using the number of patients at risk at any point in the cycle window as the denominator; if a patient has occurrences in different cycles, the patient may be counted in multiple cycles

Neutropenia (grouped term*): events by grade and GCSF use

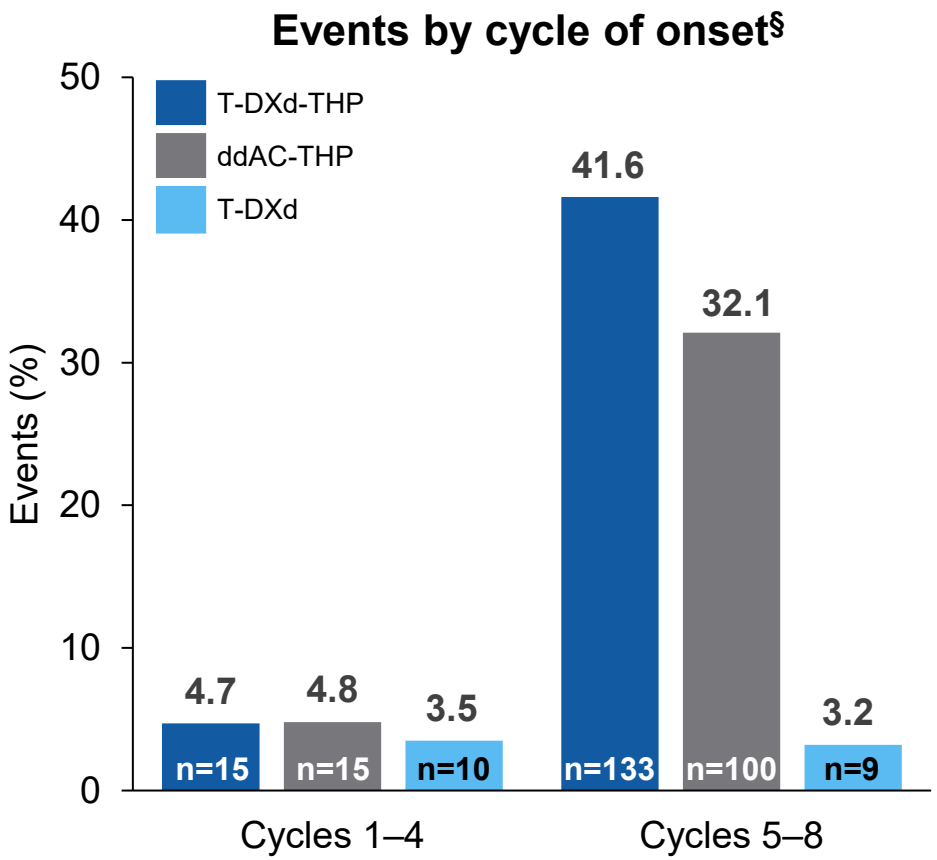
n (%)	T-DXd-THP (N=320)	ddAC-THP (N=312)	T-DXd (N=283)
All-grade neutropenia*	93 (29.1)	138 (44.2)	61 (21.6)
Grade 1	14 (4.4)	7 (2.2)	12 (4.2)
Grade 2	35 (10.9)	23 (7.4)	29 (10.2)
Grade 3	33 (10.3)	47 (15.1)	18 (6.4)
Grade 4	11 (3.4)	61 (19.6)	2 (0.7)
Grade ≥3	44 (13.8)	108 (34.6)	20 (7.1)
Per the protocol, hematopoietic growth factors may have been used for prophylaxis or treatment based on the clinical judgment of the investigator (T-DXd/T-DXd-THP), or per local prescribing information and guidelines (ddAC-THP)			
GCSF use			
At any time†	73 (22.7)	279 (87.2)	46 (16.1)
Within 28 days after onset of neutropenia*	38 (11.9)	101 (32.4)	26 (9.2)
Including febrile neutropenia	40 (12.5)	102 (32.7)	26 (9.2)

Neutropenia rates were lower with T-DXd and T-DXd-THP than with ddAC-THP, and GCSF use was substantially higher with ddAC-THP

Safety analyses included all patients who received at least one dose of any study treatment
*Grouped term including the preferred terms neutropenia and neutrophil count decreased; †data reported in the full analysis set (N=321, 320, and 286 for the T-DXd-THP, ddAC-THP, and T-DXd arms, respectively)
GCSF, granulocyte colony-stimulating factor

Peripheral neuropathy*

Peripheral neuropathy, n (%)	T-DXd-THP (N=320)	ddAC-THP (N=312)	T-DXd (N=283)
All grade, n (%)	144 (45.0)	112 (35.9)	19 (6.7)
Grade 1	80 (25.0)	75 (24.0)	18 (6.4)
Grade 2	58 (18.1)	31 (9.9)	1 (0.4)
Grade 3	6 (1.9)	6 (1.9)	0
Grade ≥3	6 (1.9)	6 (1.9)	0
Possibly treatment related	137 (42.8)	105 (33.7)	16 (5.7)
SAE	0	0	0
Leading to treatment discontinuation†	7 (4.9)	7 (6.3)	0
Leading to treatment interruption†	3 (2.1)	3 (2.7)	0
Leading to dose reduction†	25 (17.4)	12 (10.7)	0
Median (range) days to first onset‡	113.0 (1–189)	89.5 (8–167)	72.0 (1–162)



Although rates of peripheral neuropathy were higher with T-DXd-THP than T-DXd and ddAC-THP, events were non-serious and generally low grade, and most occurred during the THP phase (Cycles 5–8)

Safety analyses included all patients who received at least one dose of any study treatment
*Grouped term defined using the narrow Standardised MedDRA Query 'peripheral neuropathy'; †the denominator is the number of patients with peripheral neuropathy; ‡calculated as: date of onset of the patient's first event − date of the first dose + 1; §percentages are calculated using the number of patients at risk at any point in the cycle window as the denominator; if a patient has occurrences in different cycles, the patient may be counted in multiple cycles

Conclusions

In DESTINY-Breast11, the safety profile of T-DXd-THP was manageable and less toxic than ddAC-THP

- Rates of adjudicated drug-related ILD/pneumonitis were low across arms, and there were fewer Grade ≥3 events with **T-DXd-THP** than **ddAC-THP**
  - Rates remained stable (**T-DXd-THP**) and were higher (**ddAC-THP**) in the THP phase (Cycles 5–8) vs Cycles 1–4
- Rates of overall and Grade ≥3 left ventricular dysfunction were lower with **T-DXd-THP** than **ddAC-THP**
  - There were no events of cardiac failure in the **T-DXd-containing arms**
- Rates of nausea and vomiting were higher with **T-DXd-THP** than **ddAC-THP**, highlighting the importance of following guideline recommendations for antiemetics; however, events were generally low grade
- Rates of hematologic toxicities were lower in the **T-DXd-THP** arm than the **ddAC-THP** arm
- Most peripheral neuropathy events occurred during the THP phase (Cycles 5–8) and were non-serious and generally low grade

DESTINY-Breast11 safety results support T-DXd-THP as a potential neoadjuvant treatment option for patients with high-risk HER2+ eBC

Acknowledgments

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- Presentation slides
- Plain language summary infographic

In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201)