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Additional efficacy and safety from the DESTINY-Breast05 study of trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients with high-risk human epidermal growth factor receptor 2–positive (HER2+) primary early breast cancer with residual invasive disease after neoadjuvant therapy

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On behalf of the DESTINY-Breast05 investigators

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DESTINY Breast05

Declaration of interests

Dr Loibl reports:

- Grants and/or honorarium for advisory boards and/or contracts from AstraZeneca, AbbVie, Agendia, Amgen, BionTech, Celgene, Bristol Meyers Squibb, Daiichi Sankyo, Exact Science, Gilead, GSK, Incyte, Lilly, Medscape, Molecular Health, MSD, Novartis, Pierre Fabre, Pfizer, Relay, Roche, Sanofi, Seagen, Stemline/Menarini, Olema, Bayer, Bicycle, JAZZ Pharma, BeiGene
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- Royalties from VM Scope

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Background

- Based on the KATHERINE trial, patients with HER2+ eBC and residual invasive disease following NAT had improved outcomes with T-DM1[1,2]; however, certain subgroups derived less benefit, highlighting a persistent unmet need[3]:
    - Patients presenting with advanced locoregional disease or positive nodal status after NAT had 3-year IDFS rates of 76% and 83%, with 7-year IDFS rates of 67% and 72%, respectively[2,3]
    - 3-year IDFS was 84.7% and 7-year IDFS was 72.4% in those with **HER2 IHC 2+/ISH+** tumors[2,4]
- In DESTINY-Breast05 (NCT04622319; DCO July 2, 2025), **T-DXd demonstrated statistically significant and clinically meaningful improvement** in IDFS and DFS vs T-DM1 including patients with this unmet need,[a] and residual invasive HER2+ eBC after NAT (IDFS and DFS hazard ratio, 0.47 [95% CI, 0.34-0.66]; $P < 0.0001$)[5]
- Safety was consistent with the established safety profile of T-DXd, based on prior studies[5,6]

To further characterize the benefit–risk profile of postneoadjuvant T-DXd in this patient population, we present additional efficacy and safety data from the DESTINY-Breast05 interim analysis

DCO, data cutoff; eBC, early breast cancer; CI, confidence interval; DCO, data cut-off; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease–free survival; ILD, interstitial lung disease; NAT, neoadjuvant therapy; RT, radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; ypN, post-NAT pathologic nodal stage.

[a]cT4, N0-3, M0 or cT1-3, N2-3, M0 at presentation (before NAT) or cT1-3, N0-1, M0, with axillary node–positive disease (ypN1-3) following NAT.

1. von Minckwitz G et al. *N Engl J Med*. 2019;380(7):617-628. 2. Geyer CE et al. *N Engl J Med*. 2025;392(2):249-257. 3. Mamounas EP et al. *Ann Oncol*. 2021;32(8):1005-1014. 4. Denkert C et al. *Clin Cancer Res*, 2023;29(8):1569-1581. 5. Geyer CE, et al. Presented at European Society of Medical Oncology Congress; Berlin, Germany, October 17-20, 2025. LBA1.
6. Powell CA et al. *ESMO Open*. 2022;7(4):100554.

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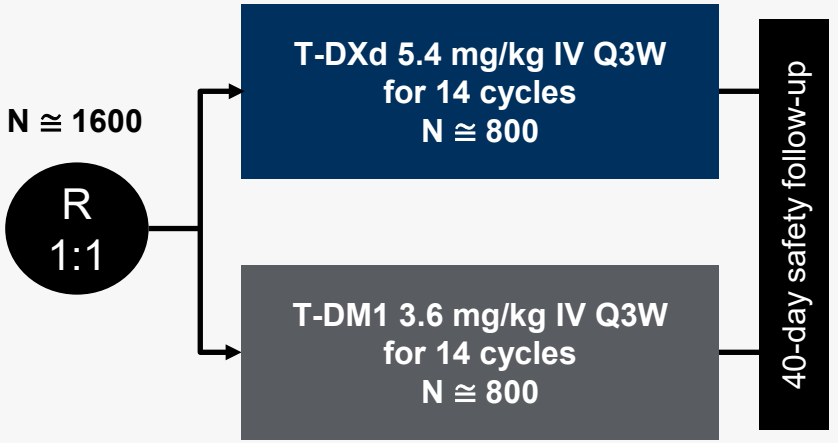
DESTINY-Breast05 study design

A global, multicenter, randomized, open-label, phase 3 trial (NCT04622319)

Key Eligibility Criteria

- **Residual invasive disease in the breast and/or axillary lymph nodes** after neoadjuvant chemotherapy with HER2-directed therapy (NAT)[a]
- **High-risk defined as presentation prior to NAT with:**
  - **Inoperable eBC (cT4, N0-3,** M0 **or cT1-3, N2-3,** M0**) OR**
  - **Operable eBC (cT1-3, N0-1,** M0**) with axillary node–positive disease (ypN1-3) after NAT**
- **Centrally confirmed HER2+** (IHC 3+ or ISH+) eBC
- ECOG PS 0 or 1

Stratification factors
- Extent of disease at presentation (inoperable, operable)
- HER2-targeted NAT (single, dual)
- Hormone receptor status (positive, negative)
- Post-NAT pathologic nodal status (positive, negative)



Primary endpoint
- IDFS

Key secondary endpoint
- DFS

Other secondary endpoints
- OS
- DRFI
- BMFI
- Safety

- **Concomitant adjuvant ET was allowed per local practices**
- **If administered, RT could be initiated concurrently with study therapy or completed prior to initiation of study therapy (sequential) per investigator**
- **ILD monitoring program for patients treated with RT**
  - All patients had baseline non-contrast, low dose (LD) chest CT during screening
  - All RT patients (concurrent and sequential) had LD chest CT 6 weeks after start of study therapy, then every 12 weeks while on therapy, and at 40-day follow-up
  - Sequential RT patients had additional LD chest CT after completion of RT prior to start of study therapy

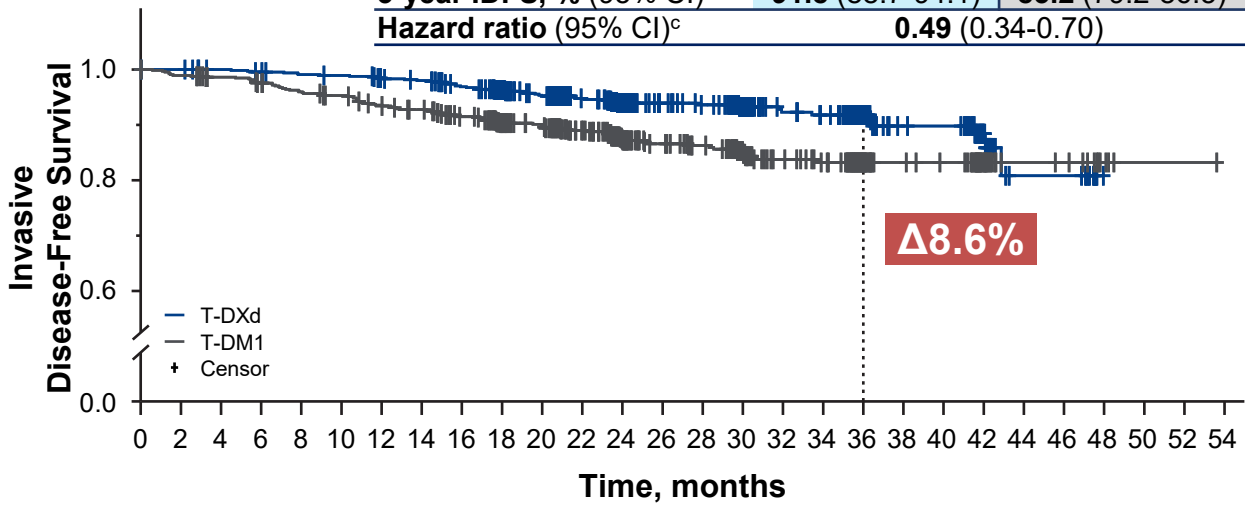
BMFI, brain metastasis–free interval; CT, computed tomography; eBC, early breast cancer; DCO, data cutoff; DFS, disease-free survival; DRFI, distant recurrence–free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; IV, intravenous; NAT, neoadjuvant therapy; OS, overall survival; Q3W, every 3 weeks; R, randomization; RT, radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; ypN, post-NAT pathologic nodal stage.

[a]NAT is defined as ≥16 weeks' NAT with ≥9 weeks trastuzumab ± pertuzumab and ≥9 weeks taxane-based chemotherapy.

IDFS subgroup analysis: HER2 status[a]

HER2 IHC 3+

	T-DXd n = 676	T-DM1 n = 670
Patients with events, n (%)	**46** (6.8)	**86** (12.8)
3-year IDFS, % (95% CI)	**91.8** (88.7-94.1)	**83.2** (79.2-86.5)
Hazard ratio (95% CI)[c]	**0.49** (0.34-0.70)	

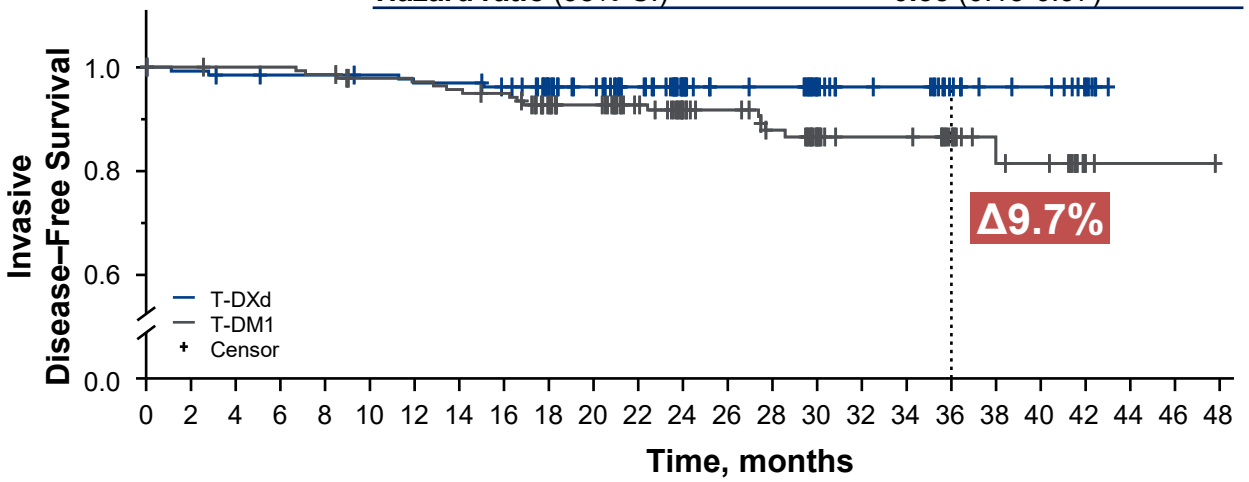


Number at risk

T-DXd	676	655	650	646	641	639	631	626	607	570	532	458	376	329	320	239	239	184	110	80	79	40	14	14	0	0	0	0
T-DM1	670	640	629	620	607	600	586	577	558	515	491	433	339	282	271	189	189	144	97	67	64	34	13	12	4	1	1	0

HER2 ISH+[b]

	T-DXd n = 140	T-DM1 n = 147
Patients with events, n (%)	**5** (3.6)	**16** (10.9)
3-year IDFS, % (95% CI)	**96.2** (91.0-98.4)	**86.5** (78.1-91.8)
Hazard ratio (95% CI)[c]	**0.35** (0.13-0.97)	



Number at risk

T-DXd	140	131	129	128	128	127	125	125	122	112	100	84	62	51	50	36	29	28	19	12	11	6	0	0	0
T-DM1	147	141	140	140	138	134	133	131	129	117	108	94	78	73	66	44	33	33	23	17	15	4	1	1	0

T-DXd demonstrated IDFS benefit over T-DM1 in both the HER2 IHC 3+ and HER2 ISH+ groups

HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; IHC, immunohistochemistry; ISH, in situ hybridization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]By central test from pre-neoadjuvant core sample or surgical specimen. [b]ISH+ included centrally assessed HER2 IHC 1+ (T-DXd n = 11; T-DM1 n = 14) and IHC 2+ (T-DXd n = 129; T-DM1 n = 133). Two patients were IHC2+/ISH− and not included. [c]Hazard ratio and 95% CI from unstratified Cox proportional hazards model.

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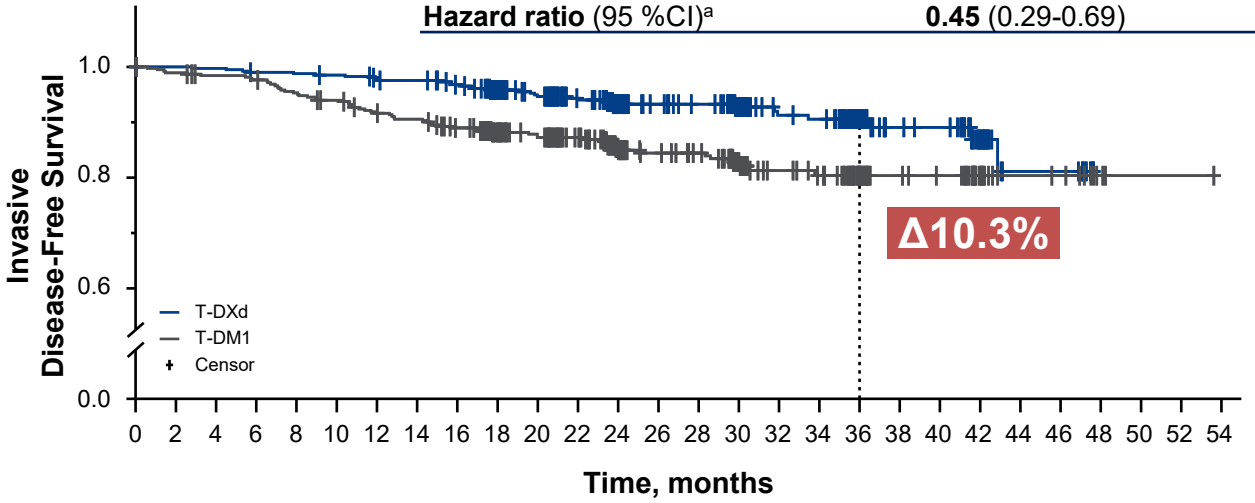
IDFS subgroup analysis: Prior neoadjuvant chemotherapy

Prior anthracyclines

	T-DXd n = 423	T-DM1 n = 399
Patients with events, n (%)	**32** (7.6)	**61** (15.3)
3-year IDFS, % (95% CI)	**90.6** (86.1-93.6)	**80.3** (74.8-84.8)
Hazard ratio (95 %CI)[a]	**0.45** (0.29-0.69)	

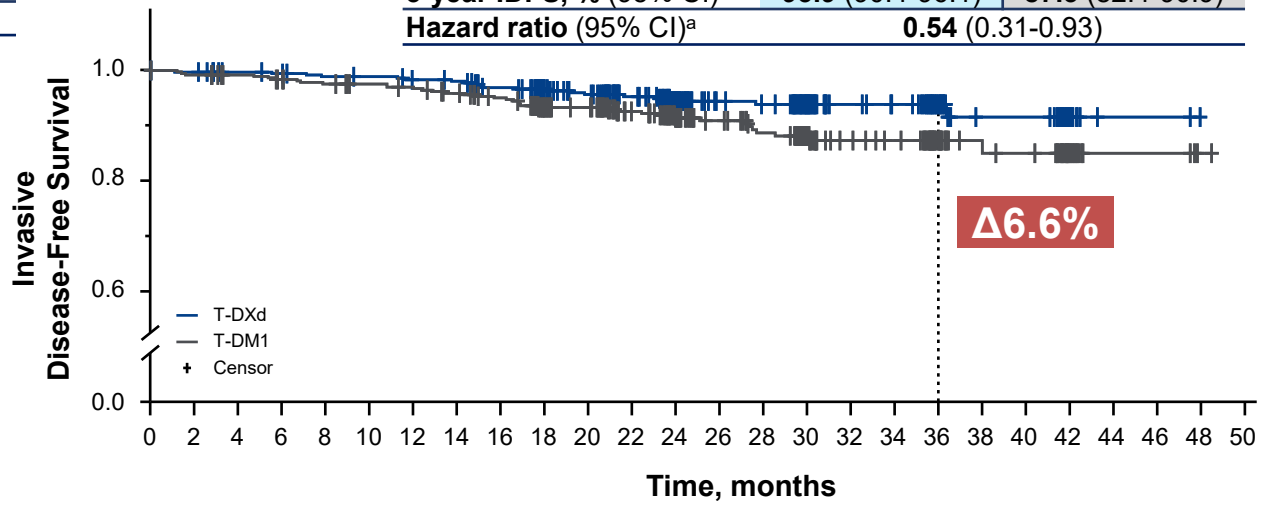


Number at risk

T-DXd	423	412	411	407	406	404	399	397	388	358	334	288	233	211	205	155	124	122	74	55	53	31	12	12	0	0	0	0
T-DM1	399	383	378	375	365	358	347	342	330	304	286	256	196	169	162	117	92	86	61	45	42	21	10	9	3	1	1	0

Prior platinum-based therapy

	T-DXd n = 386	T-DM1 n = 392
Patients with events, n (%)	**20** (5.2)	**37** (9.4)
3-year IDFS, % (95% CI)	**93.9** (90.4-96.1)	**87.3** (82.4-90.9)
Hazard ratio (95% CI)[a]	**0.54** (0.31-0.93)	



Number at risk

T-DXd	386	366	360	358	354	353	349	347	336	316	291	248	198	161	158	115	89	85	51	34	34	14	2	2	0	0	
T-DM1	392	371	365	360	355	351	348	341	332	304	291	253	206	172	161	106	86	82	54	38	36	17	4	5	1	0	

IDFS benefit was observed with T-DXd compared to T-DM1 regardless of prior NAT used

IDFS, invasive disease–free survival; NAT, neoadjuvant therapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Some patients with prior anthracycline use may also have received platinum-based therapy, and vice versa.
[a]Hazard ratio and 95% CI from unstratified Cox proportional hazards model.

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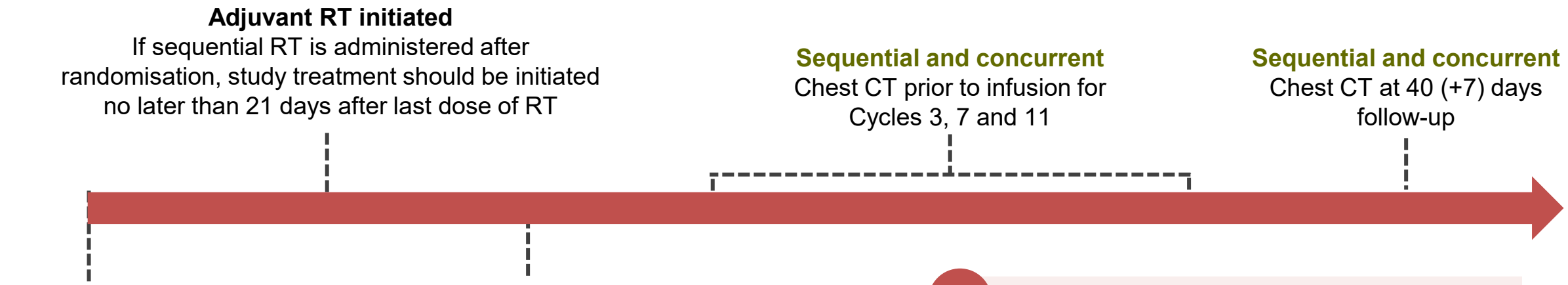
CT requirements for identifying ILD and radiation pneumonitis, as per protocol

Low-dose, non-contrast CT requirements:



! If any signs or symptoms of radiation-induced pneumonitis or drug-related ILD appeared, additional chest CT were recommended

CT, computed tomography; ILD; interstitial lung disease; RT, radiotherapy.

Treatment management guidelines for drug-related ILD and radiation pneumonitis, as per protocol

	GRADE 1 (ASYMPTOMATIC)	GRADE 2 (SYMPTOMATIC)	GRADE 3–4
Dose modification guidelines for drug-related ILD	Interrupt T-DXd, systemic steroids (eg, prednisone 0.5 mg/kg/day or equivalent) can be considered; T-DXd can be restarted only if the event is fully resolved to Grade 0[a]	**Grade ≥2 (symptomatic[b]):** Permanently discontinue patient from T-DXd treatment, promptly initiate steroids (eg, prednisone 1.0 mg/kg/day or equivalent)	
Dose modification guidelines for radiation-related pulmonary toxicity	**Maintain** dose and schedule	• **Interrupt** until recovered to baseline or Grade ≤1 • Manage per SoC (eg, steroids) • Relationship to radiotherapy should be determined on the basis of timing and location of radiographic abnormalities relative to the radiation treatment	**Discontinue** from study treatment

ILD, interstitial lung disease; SoC, standard of care; T-DXd, trastuzumab deruxtecan.
[a]If resolved in ≤28 days from day of onset, maintain dose. If resolved in >28 days from day of onset, reduce dose 1 level. However, if the event grade 1 ILD/pneumonitis has not resolved within 126 days from the last infusion, T-DXd should be discontinued. [b]Develops an acute onset of new/worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever.
Clinical Study Protocol. DESTINY-Breast05. Protocol DS8201-A-U305. Version 3.0, 22 Nov 2020.

Adjudicated drug-related ILD by adjuvant RT

	T-DXd (n = 806)[a]			T-DM1 (n = 801)[a]		
Adjudicated drug-related ILD, any grade, overall, n (%)	77 (9.6)			13 (1.6)		
Adjudicated drug-related ILD, by adjuvant RT, n (%)	**Sequential (n = 319)**	**Concurrent (n = 438)**	**Sequential or concurrent (n = 757)**	**Sequential (n = 270)**	**Concurrent (n = 480)**	**Sequential or concurrent (n = 750)**
Any grade	34 (10.7)	42 (9.6)	76 (10.0)	7 (2.6)	5 (1.0)	12 (1.6)
Grade 1	6 (1.9)	10 (2.3)	16 (2.1)	4 (1.5)	3 (0.6)	7 (0.9)
Grade 2	24 (7.5)	27 (6.2)	51 (6.7)	3 (1.1)	2 (0.4)	5 (0.7)
Grade 3	3 (0.9)	4 (0.9)	7 (0.9)	0	0	0
Grade 4	0	0	0	0	0	0
Grade 5[b]	1 (0.3)	1 (0.2)	2 (0.3)	0	0	0
Grade ≥3	4 (1.3)	5 (1.1)	9 (1.2)	0	0	0
Time to onset, median (range), days[c]	122.0 (36-350)	124.5 (37-326)	123.5 (36-350)	79.0 (36-142)	121.0 (78-130)	121.0 (36-142)
Duration, median (95% CI), days[d,e]	77.0 (41-114)	67.0 (43-107)	74.0 (46-106)	114.0 (22-NE)	142.0 (51-NE)	114.0 (51-235)

- Timing of adjuvant RT did not impact incidence or severity of adjudicated drug-related ILD in either arm
- In the T-DXd arm, adjuvant RT timing had no effect on time to onset or duration of adjudicated drug-related ILD
- Most patients with drug-related ILD had recovered or were recovering at the data cutoff; in the T-DXd arm, the proportion of patients who had recovered from ILD was higher among those who received concurrent RT compared with sequential RT (69.0% vs 58.8%)

ILD, interstitial lung disease; RT, radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]All patients who received at least one dose of study treatment. [b]Grade 5 adjudicated drug-related ILD was reported in 2 patients (0.2%) in the T-DXd arm, one at cycle 6 and one at cycle 7. In these 2 patients, treatment management guidelines were not appropriately followed, emphasizing the importance of appropriate identification of and adherence to guidelines. [c]Time to first adjudicated ILD onset = onset date of first ILD adjudicated as drug-related - first dose date + 1. [d]Median is based on Kaplan-Meier Estimate. CIs were computed using the Brookmeyer-Crowley method. [e]Duration of first ILD = investigator reported end date - investigator reported onset date + 1. End date will be censored for ongoing ILDs.

Investigator-reported radiation pneumonitis by adjuvant RT

	T-DXd[a]			T-DM1[a]		
	Sequential (n = 319)	Concurrent (n = 438)	Sequential or concurrent (n = 757)	Sequential (n = 270)	Concurrent (n = 480)	Sequential or concurrent (n = 750)
Investigator-reported RP,[b] any grade, n(%)	110 (34.5)	128 (29.2)	238 (31.4)	101 (37.4)	128 (26.7)	229 (30.5)
Grade 1	97 (30.4)	104 (23.7)	201 (26.6)	82 (30.4)	95 (19.8)	177 (23.6)
Grade 2	13 (4.1)	24 (5.5)	37 (4.9)	19 (7.0)	33 (6.9)	52 (6.9)
Grade ≥3	0	0	0	0	0	0
Time to onset, median (range), days[c]	146.5 (46-334)	123.0 (39-353)	124.0 (39-353)	110.0 (56-260)	122.5 (28-232)	120.0 (28-260)
Duration, median (95% CI), days[d,e]	411.0 (336-606)	292.0 (200-370)	352.0 (292-411)	308.0 (288-446)	297.0 (233-394)	306.0 (280-376)

- In both arms, all RP events were grade ≤2, although patients treated with sequential adjuvant RT reported higher incidences of investigator-reported RP than those treated with concurrent adjuvant RT
- Most patients with RP events had recovered or were recovering at data cutoff; rates of unrecovered/unresolved RP were higher among patients who received sequential RT in the T-DXd arm compared with the T-DM1 arm (54.5% vs 39.6%)
- In the T-DXd arm, patients receiving sequential adjuvant RT showed longer time to onset and duration of RP than those who received concurrent adjuvant RT

RP, radiation pneumonitis; RT, radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]All patients who received at least 1 dose of study treatment. [b]Grouped term. Includes the preferred terms pulmonary radiation injury, radiation alveolitis, radiation bronchitis, radiation fibrosis – lung, radiation pneumonitis. [c]Time to first investigator-reported RP onset = onset date of first investigator-reported RP – start date of radiotherapy + 1. [d]Duration of first Investigator Reported RP = investigator reported end date - investigator reported onset date + 1. End date will be censored for ongoing events.
[e]Median is based on Kaplan-Meier Estimate. CIs were computed using the Brookmeyer-Crowley method.

Conclusions

- IDFS improvement with T-DXd compared with T-DM1 was **consistent across the following subgroups**, regardless of:
  - **Prior NAT** (anthracyclines or platinum-based therapy)
  - **HER2 status** (IHC 3+ or HER2 IHC 2+/1+ and ISH+)
- Timing of adjuvant RT did not impact incidence or severity of adjudicated drug-related ILD
  - Most patients who experienced ILD had recovered or were recovering by the DCO
- Adjudicated drug-related ILD and RP events were manageable with protocol-specific management guidelines
- While differences were observed in ILD/RP time to onset, duration, and outcomes between the sequential and concurrent RT groups, further analysis is needed to assess the impact of potential confounders such as race, comorbidities, regional variability in RT, and the use of steroids for managing ILD/RP
- Overall, T-DXd demonstrated a manageable safety profile with both sequential and concurrent adjuvant RT

These additional analyses further characterize the clinical benefit and safety profile of T-DXd over T-DM1 in the post-neoadjuvant HER2+ eBC residual invasive disease setting, supporting T-DXd as a potential new standard-of-care

eBC, early breast cancer; HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; NAT, neoadjuvant therapy; RP, radiation pneumonitis; RT, radiotherapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

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