The Breast 85 (2026) 104691

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Concomitant radiation therapy and trastuzumab deruxtecan in metastatic breast cancer: feasibility, safety, and outcomes from a real-life multicentre international cohort

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ARTICLE INFO

Keywords:
Metastatic breast cancer
Trastuzumab deruxtecan
Radiotherapy
Concomitant therapy
Adverse events
Brain metastases

ABSTRACT

Background and purpose: Radiation therapy (RT) remains a cornerstone of management for metastatic breast cancer (mBC), though systemic therapy drives overall disease control. Administering RT concomitantly with systemic treatment may raise concerns regarding toxicity. This multicentre retrospective study evaluated the safety of trastuzumab deruxtecan (T-DXd), an antibody–drug conjugate, when delivered alongside RT.

Materials and methods: Data from six European centres were analysed. Concomitancy was defined as RT administered during T-DXd or within 10 days of a treatment cycle. The primary endpoint was the incidence of grade ≥3 adverse events (AEs). Exploratory endpoints included progression-free survival (PFS) and overall survival (OS).

Results: A total of 147 patients were included; 67 received concomitant RT (71 courses) and 80 received T-DXd alone. Median age was 49 years (range 25–85). The central nervous system was the most frequent RT site (54.9 %). Grade ≥3 AEs occurred in 24 patients (16.3 %), with no significant difference between RT and no-RT cohorts (11.9 % vs 20.0 %; p = 0.30). Permanent T-DXd discontinuation due to toxicity occurred in 19 patients (12.9 %), with similar rates in the RT and no-RT groups (11.9 % vs 13.8 %). One case of symptomatic radionecrosis was observed after intracranial RT. Exploratory analyses showed no adverse effect of concomitant RT on PFS or OS.

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https://doi.org/10.1016/j.breast.2026.104691
Received 7 November 2025; Accepted 2 January 2026
Available online 2 January 2026
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Conclusion: Concomitant administration of T-DXd and RT appears feasible and well tolerated, without increased risk of severe or treatment-limiting toxicity. These real-world findings support the safety of this combination and warrant confirmation in prospective studies.

1. Introduction

Trastuzumab deruxtecan (T-DXd) is a potent antibody-drug conjugate (ADC) composed of trastuzumab linked to deruxtecan, a topoisomerase I inhibitor payload [1]. It has become a key therapeutic option for patients with metastatic HER2-positive breast cancer following the superiority demonstrated over trastuzumab emtansine (T-DM1) in the DESTINY-Breast03 trial [2,3]. Preliminary results from DESTINY-Breast09 further suggest a potential role in the first-line setting [4]. T-DXd shows a manageable safety profile, with gastrointestinal and haematological adverse events (AEs) being the most frequent [5], while interstitial lung disease (ILD) represents the main serious toxicity requiring careful monitoring [1–3]. The therapeutic spectrum has expanded to include tumours with low HER2 expression, defined as immunohistochemistry (IHC) 1+ or 2+ without in situ hybridisation (ISH) amplification [6–8].

Radiation therapy (RT) remains an essential component in the multidisciplinary management of metastatic breast cancer (mBC), delivered for palliation or with ablative intent in selected oligometastatic or oligoprogressive cases [9,10]. Although combining RT with T-DXd may offer synergy, evidence on safety and feasibility is limited. In DESTINY-Breast03, palliative RT (excluding thoracic fields) was permitted during T-DXd without an apparent increase in ILD [2,3]; however, the safety of true concomitant delivery remains largely unexplored.

This multicentre international study aimed to evaluate the safety and efficacy of concomitant T-DXd and RT in patients with mBC, comparing outcomes and treatment-related toxicity with those not receiving RT.

2. Materials and methods

2.1. Patient population

We conducted a retrospective analysis of patients with metastatic HER2-positive or low HER2 expression breast cancer treated at six academic centres across four European countries (Italy, Slovenia, Austria, Sweden). Eligible patients were treated with T-DXd between May 2021 and May 2024, with some receiving concomitant RT and others not, according to physician's choice. Baseline variables included age, ECOG performance status, prior thoracic RT, smoking history, pre-existing lung disease/ILD, autoimmune disorders, and other major comorbidities (reported in Table 1). Clinical data were collected from institutional electronic medical records, including information on metastatic disease diagnosis, T-DXd treatment, RT characteristics, AEs, survival outcomes, and biological features of both primary tumours and metastases, where available. Patients received T-DXd as first-line through ≥ fourth-line systemic therapy.

The primary endpoint was the association between concomitant RT administration and AEs greater or equal to grade 3 (≥G3). Secondary endpoints included the association between RT and any-grade AEs, PFS, overall survival (OS), T-DXd discontinuation, and the impact of RT-related features on acute and late AEs.

AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Radiation-related AEs were additionally scored using the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) criteria [11]. Acute toxicity was defined as any AE occurring within 90 days of RT completion. Patients were clinically evaluated every 21 days during T-DXd therapy and at the beginning and end of RT, or during RT if clinically indicated (RT cohort only). RT was stratified by intent (palliative vs ablative).

Ablative RT was defined as a biological effective dose ≥50 Gy equivalent dose in 2-Gy fractions (EQD2 [10]) delivered in ≤12

Table 1
Clinical and pathological characteristics of the study population overall and according to radiation therapy administration.

Features	No RT cohort (n = 80)	RT cohort (n = 67)	Whole series (n = 147)	p-value[a]
Median age, years (range)	53 (26–85)	45 (25–75)	49 (25–85)	**0.001**
Age at T-DXd initiation, n (%)				**<0.001**
<50 years	8 (10.0)	27 (40.3)	35 (23.8)	
≥50 years	72 (90.0)	40 (59.7)	112 (76.2)	
De novo stage IV, n (%)				0.86
No	51 (63.8)	44 (65.7)	95 (64.6)	
Yes	29 (36.2)	23 (34.3)	52 (35.4)	
Neoadjuvant chemotherapy, n (%)				0.58
No	59 (73.8)	46 (68.7)	105 (71.4)	
Yes	21 (26.2)	21 (31.3)	42 (28.6)	
Adjuvant chemotherapy, n (%)				0.48
No	51 (63.8)	47 (70.1)	98 (66.7)	
Yes	29 (36.2)	20 (29.9)	49 (33.3)	
ER at BC diagnosis, n (%)				0.42
<10 %	22 (27.5)	23 (34.3)	45 (30.6)	
≥10 %	56 (70.0)	41 (61.2)	97 (66.0)	
NA	2 (2.5)	3 (4.5)	5 (3.4)	
PgR at BC diagnosis, n (%)				0.43
<10 %	37 (46.3)	35 (52.2)	72 (49.0)	
≥10 %	40 (50.0)	29 (43.3)	69 (46.9)	
NA	3 (3.8)	3 (4.5)	6 (4.1)	
HER2 at BC diagnosis, n (%)				0.72
Negative (Score 0)	2 (2.5)	2 (3.0)	4 (2.7)	
Low expression (Score 1+ or Score 2+ not ISH amplified)	14 (17.5)	13 (19.4)	27 (18.4)	
Positive (Score 3+ or 2+ ISH amplified)	57 (71.2)	49 (73.1)	106 (72.1)	
NA	7 (8.8)	3 (4.5)	10 (6.8)	
ER at metastatic biopsy, n (%)				0.95
<10 %	18 (22.5)	16 (23.9)	34 (23.1)	
≥10 %	23 (28.8)	21 (31.3)	44 (29.9)	
NA	1 (1.3)	1 (1.5)	2 (1.4)	
Biopsy not performed	38 (47.5)	29 (43.3)	67 (45.6)	
PgR at metastatic biopsy, n (%)				0.75
<10 %	25 (31.2)	23 (34.3)	48 (32.7)	
≥10 %	14 (17.5)	15 (22.4)	29 (19.7)	
NA	3 (3.8)	0 (0)	3 (2.0)	
Biopsy not performed	38 (47.5)	29 (43.3)	67 (45.6)	
HER2 at metastatic biopsy, n (%)				0.059
Negative (Score 0)	2 (2.5)	0 (0)	2 (1.4)	
Low expression (Score 1+ or 2+ ISH not amplified)	23 (28.8)	12 (17.9)	35 (23.8)	
Positive (Score 3+ or 2+ ISH amplified)	17 (21.2)	26 (38.8)	43 (29.3)	
Biopsy not performed	38 (47.5)	29 (43.3)	67 (45.6)	
Distribution of metastases, n (%)				0.76
Bone only	7 (8.8)	8 (11.9)	15 (10.2)	

(*continued on next page*)

Table 1 (*continued*)

Features	No RT cohort (n = 80)	RT cohort (n = 67)	Whole series (n = 147)	p-value[a]
Visceral only	37 (46.2)	28 (41.8)	65 (44.2)	
Both	36 (45.0)	31 (46.3)	67 (45.6)	
Metastatic site, n (%)				**0.004**
Bone	43/80 (53.8)	39/67 (58.2)	82/147 (55.8)	
Lung	33/80 (41.3)	14/67 (20.9)	47/147 (32.0)	
Liver	30/80 (37.5)	23/67 (34.3)	53/147 (36.1)	
Lymph nodes	28/80 (35.0)	27/67 (40.3)	55/147 (37.4)	
Central nervous system	18/80 (22.5)	37/67 (55.2)	55/147 (37.4)	
Other	21/80 (26.3)	9/67 (13.4)	30/147 (20.4)	
T-DXd treatment line, n (%)				**0.047**
1st line	3 (3.7)	3 (4.5)	6 (4.1)	
2nd line	9 (11.3)	16 (23.9)	25 (17.0)	
3rd line	18 (22.5)	21 (31.3)	39 (26.5)	
≥4th line	50 (62.5)	27 (40.3)	77 (52.4)	

Abbreviations: BC = breast cancer; NA = not available; ISH = in situ hybridisation; ER = oestrogen receptor; PgR = progesterone receptor; T-DXd = trastuzumab deruxtecan.

[a] Chi-square or Fisher's exact test was used for categorical variables; Mann–Whitney *U* test was used for continuous variables, as appropriate. Percentages may not total 100 % due to rounding.

fractions, irrespective of technique, in line with EORTC/ESTRO OligoCare definitions (EORTC-1822-RP), part of the EORTC-E^2-RADIatE platform [12]. Concomitant RT (primary definition) was RT delivered during T-DXd or within ≤10 days of the first T-DXd dose (elimination half-life of T-DXd ~7 days). Intracranial cases were classified as intact lesions or postoperative cavities; all cases in this cohort involved intact lesions.

Tumour assessments were performed using computed tomography, positron emission tomography, or magnetic resonance imaging at baseline and every 3–4 cycles, or earlier in the event of suspected progression, according to institutional practice. This retrospective study was approved by the institutional review boards of all participating centres; the requirement for informed consent was waived in accordance with national regulations.

2.2. Statistical analysis

Baseline patient characteristics were compared according to RT use with the chi-square or Mann–Whitney test, as appropriate. The association between individual characteristics and selected toxicities was initially assessed with chi-square tests. All analyses were performed on the entire cohort. Survival outcomes were analysed for OS and PFS. OS was defined as the interval from initiation of T-DXd to death from any cause or last follow-up. PFS was defined as the interval from initiation of T-DXd to first disease progression at any site or death, whichever occurred first. Survival analyses (PFS/OS) were considered exploratory. Patients who died before experiencing disease progression were censored at the date of death. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HRs) with 95 % CIs were calculated using univariate Cox proportional hazards models. All tests were two-sided, and p-values <0.05 were considered statistically significant. Analyses were conducted using SPSS Statistics software, version 22 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient characteristics

A total of 147 consecutive patients treated with T-DXd, with or without concomitant RT, were retrospectively evaluated. Sixty-seven patients received RT immediately before or during T-DXd administration, accounting for 71 courses of concomitant RT, while 80 patients did not receive RT. Median age was 49 years (range 25–85): 45 years (range 25–75) in the RT cohort and 53 years (range 26–85) in the non-RT cohort (p = 0.001). The median follow-up from T-DXd initiation was 9 months (range 0.5–46) for the entire cohort.

Patients' characteristics are summarised in Table 1. Most patients received T-DXd as fourth or later line of systemic therapy (52.4 %, n = 77/147). Over 60 % of patients had previously received neoadjuvant (28.6 %) or adjuvant (33.3 %) chemotherapy. De novo metastatic disease was observed in 52 patients (35.4 %), with similar distribution across groups (36.2 % in no RT vs 34.3 % in RT group).

At primary BC diagnosis, HER2 status was positive in 106/147 patients (72.1 %), low HER2 expression (1+ or 2+ ISH non-amplified) in 27 (18.4 %), and score 0 in four (2.7 %), with missing data in 10 cases (6.8 %). At metastatic recurrence, among the 80 patients with available re-biopsy data, HER2 was positive in 43 (29.3 %), low expression in 35 (23.8 %), and score 0 in two (1.4 %). Biopsy of metastatic sites was not performed in 67 patients (45.6 %). Among the 71 patients with paired HER2 data at both primary and metastatic timepoints, concordance was observed in 47 (66.2 %) and discordance in 24 (33.8 %), including four cases shifting from score 0 to low expression, seven from low expression to HER2-positive, and one from low expression to score 0.

Visceral metastases were present in 132/147 patients (89.8 %), with similar distribution across the RT and no-RT groups (94.0 % and 91.2 %,

Table 2
Treatment details of RT courses.[a]

Features	n (%)
Sites of RT treated metastases (n = 71)	
Central nervous system	39 (54.9)
Bone	21 (29.6)
Lymph nodes	3 (4.2)
Liver	1 (1.4)
Other	7 (9.9)
Number of treated metastases (n = 71)	
1–5	55 (77.5)
>5	13 (18.3)
NA	3 (4.2)
RT intent (n = 67 patients)	
Ablative	36 (53.7)
Palliative	31 (46.3)
RT technique (n = 71)	
3D-CRT	7 (9.9)
IMRT-VMAT	37 (52.1)
CyberKnife	7 (9.9)
Gamma Knife	4 (5.6)
Not reported	16 (22.5)
EQD2 (n = 71)	
<50Gy	53 (74.6)
≥50Gy	11 (15.5)
NA	7 (9.9)
BED (n = 71)	
<50Gy	41 (57.7)
≥50Gy	23 (32.4)
NA	7 (9.9)

Abbreviations: RT, radiation therapy; 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy; EQD2, equivalent dose in 2Gy fractions; Gy, Gray; BED, biologically effective dose; NA, not available.

[a] A total of 71 RT courses were delivered to 67 patients; four patients received two courses. Data are presented per course unless otherwise stated.

respectively). The most common metastatic sites were bone (82/147, 55.8 %), liver (53/147, 36.1 %), and lung (47/147, 32.0 %). Brain metastases (BM) were reported in 55/147 patients (37.4 %), with a higher incidence in the RT cohort (37/67, 55.2 %) compared to the no-RT group (18/80, 22.5 %). Distribution of metastatic sites significantly differed between groups (p = 0.004), mainly due to a higher proportion of CNS metastases in the RT cohort.

3.2. Radiation therapy features

Following our study definition, all patients treated with RT in the metastatic setting received concomitant RT with T-DXd. A total of 71 RT courses were delivered to 67 patients, as detailed in Table 2. The median prescribed dose was 44 Gy (range 8–48), delivered over a median of four fractions (range 1–20). The median EQD_2 and BED were 45 Gy (range 12–104) and 55 Gy (range 14–125), respectively.

The most frequent treatment site was the CNS (54.9 %; n = 39/71), followed by bone (29.6 %; n = 21/71). Ablative RT was used in 36 (53.7 %) and palliative RT in 31 cases (46.3 %). IMRT/VMAT accounted for 52.1 % of courses; 3D-CRT and CyberKnife each 9.9 %, Gamma Knife 5.6 %. EQD2 ≥ 50 Gy was delivered in 15.5 % of cases; BED >50 Gy in 32.4 %.

3.3. Adverse events

Permanent discontinuation of T-DXd due to toxicity occurred in 19 patients: 8 (11.9 %) in the RT group and 11 (13.8 %) in the no-RT group. Overall, 24/147 patients (16.3 %) experienced ≥ G3 AEs, with no significant difference between the no RT (16/80, 20.0 %) and RT (8/67, 11.9 %) cohorts (p = 0.30). When analysing acute AEs separately, ≥G3 toxicity occurred in 13/80 patients (16.2 %) in the no RT group and 7/67 (10.4 %) in the RT group (p = 0.31). Late ≥ G3 AEs were observed in 8/80 (10.0 %) and 5/67 (7.5 %) patients, respectively (p = 0.59). No significant association was found between concomitant RT and overall (p = 0.30), acute (p = 0.31), or late (p = 0.59) severe AEs.

EQD2 (<50 Gy vs ≥ 50 Gy) and BED (<50Gy vs ≥ 50 Gy) were not associated with acute or late toxicity of any grade (p = 0.75 and p = 1.0, respectively). Age ≥50 years was the only factor significantly associated with an increased risk of acute toxicity (p = 0.035).

ILD (any grade) occurred in 7/67 patients (10.4 %) in the RT cohort and 7/80 (8.8 %) in the no RT cohort. Among the 47 patients reporting lung as site of metastases (33/80 no RT cohort vs 14/67 RT cohort), no one received irradiation of lung metastases. Nausea was reported in 27/67 irradiated patients (40.3 %; all G1–2) and 39/80 non-irradiated patients (48.8 %; including two G3 cases). Neutropenia occurred in 15/80 patients (18.8 %) in the no RT group and 3/67 (4.5 %) in the RT group; all ≥ G3 events occurred in the no RT cohort.

Among patients with BM in the RT cohort (37/67; 55.2 %), 32/37 (86.5 %) received intracranial irradiation (39 lesions). Intracranial RT was not associated with ≥G3 acute (p = 0.69), ≥G3 late (p = 1.00), any-grade acute (p = 0.32), or late AEs (p = 0.27). One case of symptomatic radionecrosis (SRN) was reported after fractionated stereotactic RT (fSRT; 25 Gy in 5 fractions to >5 lesions), at a median follow-up of 11 months. CNS techniques included whole-brain RT (WBRT, n = 12/39; 30.7 %), fSRT, (n = 20/39; 51.3 %), and stereotactic radiosurgery (SRS, n = 7/39; 18.0 %). All patients were treated for intact brain metastases; none underwent surgery followed by RT to the surgical cavity. The distribution of haematologic and non-haematologic AEs was comparable between cohorts, with no unexpected safety signals from concomitant T-DXd and RT (Table 3).

3.4. Survival outcomes

PFS and OS analyses were exploratory and are reported to contextualise the cohort. Median PFS was 8.2 months (mean 9.0, SD 6.1) for the overall cohort (HR 0.97, 95 % CI 0.53–1.79), and median OS was 9.3 months (mean 12.1, SD 9.4). Concomitant RT was not significantly associated with either PFS (log-rank p = 0.92) or OS (log-rank p = 0.34). At 12 and 24 months, OS was 90.1 % (95 % CI 82.5–94.0) and 65.4 % (95 % CI 45.0–75.8) in the no RT cohort, and 85.1 % (95 % CI 76.1–89.7) and 62.7 % (95 % CI 46.4–71.0) in the RT cohort. PFS rates at 12 and 24 months were 71.7 % (95 % CI 59.4–78.0) and 37.2 % (95 % CI 12.5–49.8) in the no RT group, and 66.7 % (95 % CI 51.4–74.5) and 47.8 % (95 % CI 29.6–57.1) in the RT group.

4. Discussion

RT remains a cornerstone of palliative care in metastatic disease, with a well-established safety profile across tumour types [13,14]. In selected patients with oligometastatic breast cancer, RT is increasingly used with ablative intent. Randomised data from mixed-tumour trials such as SABR-COMET support a potential improvement in local control and OS with this approach [9]. However, breast-specific studies have not consistently confirmed a survival advantage, and extrapolation from heterogeneous populations should therefore be made with caution [15–17].

T-DXd currently represents the standard of care for pretreated HER2-positive and, more recently, low HER2 expression mBC [2–4,7,8]. However, evidence on its concomitant use with RT remains limited. In DESTINY-Breast03, the incidence of grade ≥3 treatment-related AEs was higher with T-DXd than with T-DM1 (45.1 % vs 39.8 %), underscoring the need for caution when combining T-DXd with RT. Although palliative RT was permitted in the trial, excluding thoracic fields, detailed data were not reported.

Table 3
Incidence of haematologic and non-haematologic adverse events in patients treated with T-DXd with or without concurrent RT.

Adverse event[a]	No RT cohort n = 80		RT cohort n = 67		Whole series n = 147	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any Grade	Grade ≥3
Haematologic, n (%)						
Neutropenia	15 (18.8)	4 (5.0)	3 (4.5)	0 (0)	18 (12.2)	4 (2.7)
Thrombocytopenia	10 (12.5)	1 (1.3)	1 (1.5)	0 (0)	11 (7.5)	1 (0.7)
Anaemia	21 (26.3)	4 (5.0)	6 (9.0)	1 (1.5)	27 (18.4)	5 (3.4)
Non haematologic, n (%)						
Nausea	39 (48.8)	2 (2.5)	27 (40.3)	0 (0)	66 (44.9)	2 (1.4)
Diarrhoea	10 (12.5)	1 (1.3)	6 (9.0)	1 (1.5)	16 (10.9)	2 (1.4)
ILD/pneumonitis	7 (8.8)	2 (2.5)	7 (10.4)	4 (6.0)	14 (9.5)	6 (4.1)
Fatigue	47 (58.8)	6 (7.5)	29 (43.3)	5 (7.5)	76 (51.7)	11 (7.5)
Symptomatic radionecrosis	0 (0)	0 (0)	1 (1.5)	0 (0)	1 (0.7)	0 (0)
Radiation dermatitis	0 (0)	0 (0)	3 (2.0)	0 (0)	3 (2.0)	0 (0)
Total events	68 (85.0)	16 (20)	44 (65.7)	8 (11.9)	112 (76.2)	24 (16.3)

Abbreviations: ILD = interstitial lung disease; RT = radiation therapy; T-DXd = trastuzumab deruxtecan.
[a] Data are reported as number (percentage) of patients experiencing at least one event, including both acute and late phases.

Gastrointestinal toxicities were also more frequent with T-DXd across pivotal trials [2,3,7,8], prompting particular prudence when irradiating thoracic or abdominal sites. In the present study, gastrointestinal safety outcomes were reassuring. Nausea was numerically less frequent among patients receiving concomitant RT than those not receiving RT, with both grade 3 cases observed in the non-RT cohort. The overall incidence of severe nausea was low, likely reflecting the routine use of triple antiemetic prophylaxis in contemporary clinical practice.

Similarly, the rate of grade ≥2 ILD was approximately 10 % across both groups, consistent with pivotal trial data; however, in our series no patients affected by lung metastasis received lung lesion irradiation. To note, recent data from DESTINY-Breast05 (Annals of Oncology (2025) 36 (suppl_2): S1-S60. 10.1016/annonc/annonc1965), the first phase III trial to allow and prospectively monitor adjuvant RT during T-DXd therapy, provide reassuring safety signals regarding the combined approach. In the study, approximately 54 % of patients received concurrent RT, 40 % sequential RT, and 6 % no RT. The incidence of adjudicated, drug-related ILD/pneumonitis was comparable between sequential and concurrent RT delivery (10.7 % and 9.6 %, respectively), with no excess in severe or fatal events compared with T-DM1 (2.6 % and 1.0 %). These results support the feasibility of RT administered in proximity to T-DXd when appropriate pulmonary imaging and dose-modification protocols are followed, as mandated by the trial (baseline and serial chest CTs, interruption and corticosteroids for ≥ grade 2 pneumonitis).

Permanent discontinuation of T-DXd due to toxicity was uncommon, affecting <9 % of RT-treated patients. PFS and OS outcomes were consistent with real-world evidence [18–21], though shorter than those in pivotal trials [2,3,7,8]. The decision to suspend T-DXd before RT remains debated; given its ~7-day half-life [22], pausing treatment for five half-lives is clinically impractical. Accordingly, concomitancy in our study was defined as RT delivered during or within 7–10 days of T-DXd initiation to account for scheduling variability. Most patients were heavily pretreated, with over half receiving T-DXd as ≥ fourth-line therapy. RT did not significantly influence PFS or OS. The RT cohort received T-DXd earlier (23.9 % second, 31.3 % third, 40.3 % ≥ fourth vs 11.3 %, 22.5 %, and 62.5 % in no-RT), suggesting a bias toward better prognosis that may have attenuated measurable RT effects. RT patients were younger, and limited extra-cranial cases preclude site-specific lung safety conclusions. A higher proportion of HER2-positive disease in the RT group likely reflects more frequent brain-directed RT in patients with HER2-positive disease and CNS involvement.

T-DXd demonstrates significant intracranial activity, even in patients with leptomeningeal disease [23–26], as shown in trials such as DEBBRAH [26]. Although data on the timing of RT relative to T-DXd remain limited, retrospective reports suggest a potential link between ADCs and a higher risk of SRN when combined with focal brain RT. Small cohort studies [27,28], indicated higher SRN rates in patients treated with ADCs compared with non-ADC regimens, though these analyses were constrained by sample size and heterogeneity. While the SRN risk is established for T-DM1 [29,30], evidence for T-DXd is still preliminary and warrants further validation.

Only one case of SRN occurred in our series, possibly reflecting careful dose–fractionation, smaller targets, and the preferential use of fSRT/SRS over WBRT. Although limited by follow-up and sample size, our findings align with other real-world reports: Debbi et al. observed three SRN cases (5.5 %) among 54 patients receiving concomitant T-DXd and RT [31]; Bouziane et al. reported none in 13 stereotactic cases [32]; and a large multicentre analysis documented SRN in three of 287 lesions (1 %) with 97 % 12-month local control [33]. Given the high intracranial control achievable with focal RT, combining RT with brain-penetrant agents such as T-DXd may represent a valuable option for selected oligometastatic or oligoprogressive patients. Prospective studies should clarify optimal sequencing and the biological basis of RT-ADC interactions.

To our knowledge, this is the largest retrospective case–control study assessing the combination of RT and T-DXd in breast cancer, offering robust real-world evidence. However, several limitations must be acknowledged: causality cannot be established and selection bias is possible due to non-randomised treatment allocation; inter-centre heterogeneity in RT technique, dose, and supportive care may have influenced outcomes; follow-up may be insufficient for late AEs; and detailed data on concomitant medications or pharmacokinetics were unavailable. The sample size also limits analyses of rare events or subgroups. These findings underscore the need for systematic integration of RT-related parameters into future clinical trials of novel anticancer agents.

Recent ESTRO-endorsed recommendations have stressed that, even when RT is not the primary investigational modality, structured quality assurance and standardised reporting are essential to accurately interpret outcomes and avoid confounding due to underreported toxicity or missed therapeutic synergy [34]. This approach underscores the growing recognition of radiation oncology's strategic role in multimodality treatment design and the value of early collaboration with pharmaceutical partners during trial development [35].

In conclusion, our findings suggest that concomitant administration of T-DXd and RT in patients with HER2-positive or low HER2 expression mBC appears feasible and well tolerated, without a significant increase in acute or late treatment-related toxicity, even when RT is delivered with ablative intent. These observations are consistent with previous reports showing that most acute AEs are attributable to systemic therapy rather than RT [31,32]. While these real-world data support the safety of this combination in carefully selected patients, the results are hypothesis-generating and should not be interpreted as definitive. Given that patients with mBC are often heavily pre-treated and vulnerable to AEs, meticulous patient selection, individualised dosimetry, and site-specific risk assessment remain crucial. Prospective studies are warranted to better define the optimal sequencing, long-term safety, and clinical efficacy of T-DXd combined with RT, ultimately guiding its integration into standard clinical practice.

CRediT authorship contribution statement

Luca Visani: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Ivica Ratosa:** Conceptualization, Data curation, Writing – review & editing. **Rupert Bartsch:** Conceptualization, Data curation, Writing – review & editing. **Barbro Linderholm:** Conceptualization, Data curation, Writing – review & editing. **Gaia Griguolo:** Conceptualization, Data curation, Writing – review & editing. **Calogero Saieva:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Carlotta Becherini:** Data curation, Writing – review & editing. **Marianna Valzano:** Data curation, Writing – review & editing. **Viola Salvestrini:** Conceptualization, Writing – review & editing. **Angelika M. Starzer:** Data curation, Writing – review & editing. **Peter Kus:** Data curation, Writing – review & editing. **Niccolò Bertini:** Data curation. **Andrea Rampini:** Visualization, Writing – review & editing. **Chiara Mattioli:** Visualization, Writing – review & editing. **Domen Ribnikar:** Data curation, Writing – review & editing. **Jacopo Nori Cucchiari:** Data curation, Writing – review & editing. **Lorenzo Orzalesi:** Data curation, Writing – review & editing. **Simonetta Bianchi:** Data curation, Writing – review & editing. **Matteo Lambertini:** Data curation, Writing – review & editing. **Valentina Guarneri:** Data curation, Writing – review & editing. **Lorenzo Livi:** Conceptualization, Supervision, Writing – review & editing. **Icro Meattini:** Conceptualization, Data curation, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of generative AI and AI-assisted technologies

During the preparation of this work, the authors used text-based AI assistance for language editing only; all content was verified and approved by the authors, who take full responsibility for the final

manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

Icro Meattini reports personal fees from Eli Lilly, Novartis, Pfizer, AstraZeneca, Daiichi Sankyo, Gilead, Menarini Stemline, MSD, TEMA Sinergie, and Exact Sciences, outside the submitted work. Luca Visani reports personal fees from Daiichi Sankyo, AstraZeneca, Novartis, Eli Lilly, Menarini Stemline, and Exact Sciences, outside the submitted work. Matteo Lambertini reports advisory role for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD, Pierre Fabre, Menarini, Nordic Pharma, and Exact Sciences; receiving speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Takeda, Ipsen, Menarini, and AstraZeneca; receiving travel grants from Gilead, Roche, and Daiichi Sankyo; receiving research funding (to his institution) from Gilead; and having nonfinancial interests as a member of the national council of the Italian Association of Medical Oncology (AIOM). Angelika M. Starzer received honoraria for lectures from AstraZeneca and travel and congress registration support from PharmaMar, MSD, Lilly, AstraZeneca, and Menarini Stemline. Valentina Guarneri reports personal fees for advisory board membership for AstraZeneca, Daiichi Sankyo, Eli Lilly, Exact Sciences, Menarini Stemline, MSD, Novartis, Pfizer, Roche, Gilead, outside the submitted work, and personal fees as an invited speaker for AstraZeneca, Daiichi Sankyo, Eli Lilly, Pfizer, Exact Sciences, Gilead, Menarini Stemline, Novartis, Roche, AbbVie, outside the submitted work. Valentina Guarneri is listed as an inventor in patents “WO2022023235 – In vitro method for the prognosis of patients suffering from HER2-positive breast cancer” and “WO2023117807 – Development and validation of an in vitro method for the prognosis of patients suffering from HER2-positive breast cancer”. Gaia Griguolo reports fees for advisory role from Gilead, Seagen, Menarini Stemline, outside the submitted work, and personal fees as an invited speaker from Eli Lilly, Novartis, MSD. No other disclosures were reported.

Acknowledgments

The authors gratefully acknowledge the valuable collaboration and support of the following colleagues: Michele Aquilano, Ilaria Bonaparte, Pierluigi Bonomo, Luisa Caprara, Michela Carracino, Isacco Desideri, Giulio Francolini, Daniela Greto, Mauro Loi, Chiara Mattioli, Carolina Orsatti, Marta Pacinico, Vieri Scotti, and Gabriele Simontacchi (Radiation Oncology Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy); Lorenzo Arlia, Chiara Bellini, Giulia Bicchierai, Cecilia Boeri, Dario Cassetti, Diego De Benedetto, Federica Di Naro, Ilaria Gaggelli, Francesca Gensini, Giacomo Gigliucci, Silvia Nesi, Laura Papi, Tommaso Susini, Cinzia Tommasi, Ermanno Vanzi, Sofia Vidali, and Vania Vezzosi (Breast Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy); Giovanna Biagione, Stefania Fiaschi, Caterina Loiacono, Marta Mauro, Lisa Merlini, Costanza Priore (Centro Oncologico di Riferimento Dipartimentale, CORD, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy).

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