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Systematic Review

Safety profile of trastuzumab-emtansine (T-DM1) with concurrent radiation therapy: A systematic review and meta-analysis

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ABSTRACT

Background and Purpose: In recent years, the treatment landscape for breast cancer has undergone significant advancements, with the introduction of several new anticancer agents. One such agent is trastuzumab emtansine (T-DM1), an antibody drug conjugate that has shown improved outcomes in both early and advanced breast cancer. However, there is currently a lack of comprehensive evidence regarding the safety profile of combining T-DM1 with radiation therapy (RT). In this study, we aim to provide a summary of the available data on the safety of combining RT with T-DM1 in both early and metastatic breast cancer settings.

Materials and Methods: This systematic review and meta-analysis project is part of the consensus recommendations by the European Society for Radiotherapy and Oncology (ESTRO) Guidelines Committee on integrating RT with targeted treatments for breast cancer. A thorough literature search was conducted using the PUBMED/MedLine, Embase, and Cochrane databases to identify original studies focusing on the safety profile of combining T-DM1 with RT.

Results: After applying eligibility criteria, nine articles were included in the meta-analysis. Pooled data from these studies revealed a high incidence of grade 3 + radionecrosis (17%), while the rates of grade 3 + radiation-related pneumonitis (<1%) and skin toxicity (1%) were found to be very low.

Conclusion: Although there is some concern regarding a slight increase in pneumonitis when combining T-DM1 with postoperative RT, the safety profile of this combination was deemed acceptable for locoregional treatment in non-metastatic breast cancer. However, caution is advised when irradiating intracranial sites concurrently with T-DM1. There is a pressing need for international consensus guidelines regarding the safety considerations of combining T-DM1 and RT for breast cancer.

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Human Epidermal growth Receptor factor 2 (HER2) is overexpressed in 15–20% of breast cancers [1–3]. The introduction of anti-HER2 agents has improved prognosis of both early and advanced breast cancer. Trastuzumab was the first humanised monoclonal antibody targeting HER2 adopted in clinical practice [4]. The approval of a novel class of anti-cancer agents, namely the antibody–drug conjugates (ADCs), further improved HER2-positive breast cancer care [5–7]. ADCs consist of a combination of a humanised anti-HER2 monoclonal antibody linked to a specific cytotoxic payload.

Trastuzumab plus emtansine (T-DM1) was the first ADC adopted for the treatment of breast cancer. The EMILIA trial demonstrated an improved progression-free (PFS) and overall survival (OS) using T-DM1 as compared to lapatinib plus capecitabine, as second-line therapy in patients with metastatic breast cancer [8]. Similarly, the TH3RESA trial showed a survival benefit of T-DM1 when compared to treatment of physician's choice in heavily pre-treated patients with HER2-positive metastatic breast cancer [9].

In the early setting, primary systemic therapy (PST) is often applied to allow for down staging of the locoregional disease. Tumour response to PST allows to optimize postoperative systemic treatments [10]. Patients with residual invasive breast cancer after PST have a worse prognosis compared to those who achieve pathological complete response (pCR), especially in HER2-positive disease [10,11]. Therefore, treatment intensification has become the goal for these high-risk breast cancer patients. The KATHERINE trial [12], demonstrated that adjuvant T-DM1 halved the risk of recurrence of invasive breast cancer or death as compared to trastuzumab alone in patients with residual disease after PST. Thus, TDM-1 is the current standard of care for patients with non-pCR. In the KATHERINE trial, RT when prescribed, was delivered without suspension of T-DM1.

To date, there is a lack of level-1 evidence on the safety of T-DM1 in combination with different RT techniques or schedules [13–15]. There are some concerns in terms of potentially increased toxicity related to the association between T-DM1 and RT both in the early [16,17] and metastatic settings [18,19]. The purpose of this systematic review and meta-analysis is to provide an overview of available data on the safety profile of RT combined with T-DM1 in the early and advanced breast cancer settings.

Materials and methods

Literature analysis and systematic review

A systematic review was conducted to identify original studies on the safety profile of T-DM1 and RT combination. The search strategy was implemented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [20], to search PUBMED/MedLine, Embase, and Cochrane literature databases between January 2010 and September 2022 (Fig. 1).

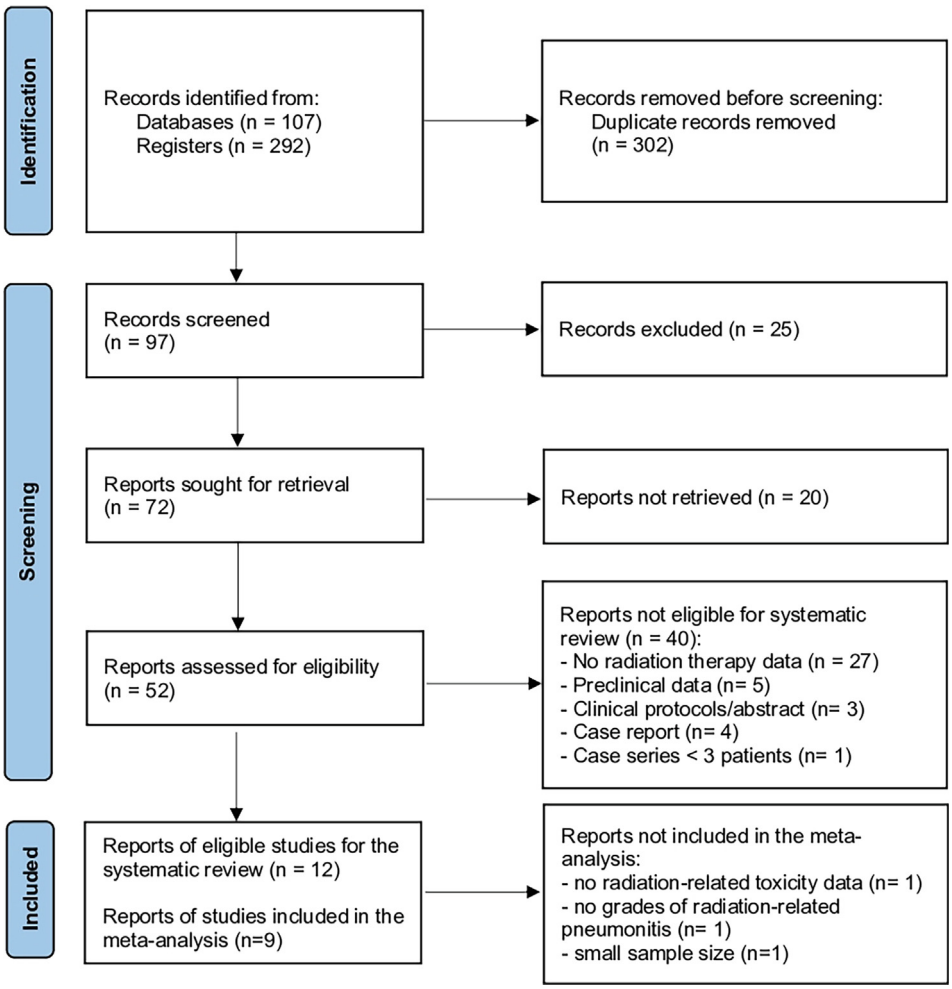

Fig. 1. PRISMA flow diagram depicting the search strategy in the systematic review literature search.

A specific research string based on the following keywords was developed: "breast" OR "mammary" OR "breast cancer" OR "breast neoplas*", "radiotherapy", "irradiation", "radiation", "radiotherapy", "concurrent*", "concomitant*", "combin*", "associat*", "simultaneous*", "Trastuzumab DM1", "T-DM1", "trastuzumab emtansine", "Trastuzumab-DM1", "huN901-DM1", "huN901 DM1", "huN901DM1".

Studies that met the following inclusion criteria were considered for the meta-analysis: (1) investigated cohorts of breast cancer patients (more than 5 patients) who received T-DM1 in combination with (2) palliative or (3) ablative RT for (4) intracranial or (5) extracranial disease in the (6) early or (7) metastatic setting. To ensure consistency and accuracy, two independent reviewers (VS and KK) completed the data extraction process. In case of any disagreements, a third author (IM) resolved the discrepancies, ensuring the reliability of the extracted data.

The study-specific group of patients developing grade equal or greater than 2 or 3 (grade 2 + or 3 +) radionecrosis, radiation pneumonitis, and skin toxicity were pooled into summary proportions using the *metaprop* command in Stata Software (StataCorp LLC, Texas, USA), with prior Freeman-Tukey double arcsine transformation of proportions (and subsequent back-transformation of the pooled estimate) and use of the exact method to calculate the corresponding 95% confidence intervals (95%CI) [21]. By means of this approach, proportions close or equal to 0% can be accommodated. The heterogeneity across studies was quantified using the I^2 statistics, which can be interpreted as the proportion of the total variability of study estimates that is due to actual heterogeneity rather than mere chance.

Using the Cochrane risk-of-bias tool for randomised trials [22] and non-randomised studies (ROBINS-I) [23], the risk-of-bias of each study was assessed by two independent reviewers (VS and KK). Certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria [24]. Toxicity had to be either graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), or properly described. In few series toxicity was not graded according to the CTCAE scale. PROSPERO registration number: CRD42023399005.

Consensus development process

This systematic review and meta-analysis project is an integral component of the ESTRO Guidelines Committee's efforts to provide recommendations on the integration of radiotherapy (RT) with targeted treatments for breast cancer. The initiative is led by a multidisciplinary Core Group and Expert Panel comprising medical and clinical oncologists, radiation oncologists, preclinical scientists, and patient advocates. This diverse collaboration ensures a comprehensive and well-rounded approach to developing evidence-based guidelines that incorporate the perspectives and expertise of various stakeholders in the field of breast cancer treatment.

Results

The systematic literature search identified a total of 399 articles (Fig. 1). After removing duplicates, 97 articles were screened, and 72 full texts were reviewed. Among them, twelve articles met all the eligibility criteria for systematic review [16,17,25–34]. Finally, nine articles were included in the meta-analysis [16,17,25,27–30,32,33]. Eight retrospective studies [25–31,33], two phase 2 [17,34], and two phase 3 trials [16,34] were included in the systematic review. Seven [25–31] and five studies [16,17,32–34] focused on palliative treatment for metastatic disease and adjuvant treatment for locoregional disease, respectively. Two studies were not included in the meta-analysis due to the lack of radiation-related toxicity data and grades of radiation-related pneumonitis [26,34] and one was excluded due to the small sample size (three patients) [31]. Main studies characteristics are summarized in Table 1, including sequencing of TDM1 with RT and site of RT [16,17,25–34]. Except for the study conducted by Bellon et al. [17], detailed information regarding radiation therapy dose, fractionation, and treatment volumes was not available in the included studies.

A total of 1813 patients were included in the evaluation, with a median age ranging from 35 to 56 years and a follow-up period ranging from 3 to 57 months. Among the included studies, only six provided information on the total fractionated dose and number of fractions used for RT [25,28–31,33], while no data on the RT schedules were reported in six studies [16,17,26,27,32,34].

Risk of Bias and GRADE assessments of trials included in the meta-analysis were conducted to evaluate the quality of the included studies. Based on the domains of the risk-of-bias tools for non-randomized and randomized trials, four studies were considered to be at low risk of bias [16,17,32,33], while five studies were assessed to be at moderate risk of bias [25,27–30]. The overall assessment is presented in Table 2. The GRADE Working Group grades of evidence are described in the **Supplemental** Table 1.

Five retrospective mono-institutional articles were included in the analysis, reporting on treatment-related toxicity for intracranial irradiation [25,27–30]. The number of patients per study ranged from seven to 28, with a median of 16 patients. Three studies were conducted in the USA [25,28,29], while one study each was conducted in France [27] and Canada [30]. The timing of brain stereotactic radiosurgery (SRS) and T-DM1 administration was categorized as sequential or concomitant in all studies, and the use of whole-brain radiation therapy (WBRT) was specified in three studies [27,28,30]. The diagnosis of radionecrosis was determined either pathologically or radiologically, although this information was not available in some studies [25,27]. Two studies compared the incidence of radionecrosis based on the timing between RT and T-DM1 administration [25,27]. While the grade of radionecrosis was not specified according to the CTCAE, cases requiring treatment or hospitalization were scored as grade 2 or 3, respectively. The pooled incidence of grade 2 + and 3 + radionecrosis was 37% and 17%, respectively (Fig. 2**a-b**), with a significant heterogeneity between the studies (I^2 72.9%).

Regarding toxicity related to radiation for extracranial disease, there was only one case-series study that assessed palliative RT and concurrent T-DM1 toxicity in three patients with bone metastases [31]. The patients received RT to the thoracic vertebrae, sacrum, and shoulder, with dose-fractionation schedules of 15 Gy in five fractions for two patients and 8 Gy in one fraction for one patient. All patients experienced good pain relief, and no side effects related to the concomitant use of RT and T-DM1 were reported.

In the adjuvant setting, three articles reported on radiation pneumonitis. These included one phase 2 single-arm study with 116 patients [32], one phase 2 randomized study with 239 patients [17], and one phase 3 randomized trial with 624 patients [16]. The pooled incidence of grade 2 + and grade 3 + radiation-related pneumonitis was 1% and less than 1%, respectively (Fig. 2**c-d**), with very low heterogeneity (I^2 0%).

Regarding radiation-related skin toxicity, three articles were analysed, which included one retrospective observational study with 14 patients [33], one phase 2 randomized study with 239 patients [17], and one phase 3 randomized trial with 624 patients [16]. The pooled incidence of grade 2 + and grade 3 + radiation-related skin toxicity was 32% and 1%, respectively (Fig. 2**e-f**), with a low level of heterogeneity (I^2 0%).

Table 1
Main characteristics of studies included in the systematic review.

Author	Year	Type of study	Patients, n	RT site	Treated sites, n	Timing of T-DM1 administration *	Median follow up, months (range)	Median dose (range)/ fraction	TRAE	Overall TRAE events, n
Metastatic setting										
Carlson et al. [27]	2014	Retrospective	7	Brain	22	Sequential (post-RT)	24 (NR)	20 Gy (16–24) in 1 fraction	Radionecrosis	4
Jacot et al. ** [26]	2016	Retrospective	36	Brain	NR	Sequential (pre-RT)	8.1 (1.4–39.6)	NR	Hematologic toxicity, emesis, fatigue, mucositis	48
Géraud et al. ** [31]	2016	Retrospective	3	Bone	3	Concomitant	9 (3–12)	8 Gy in 1 fraction; 15 Gy in 5 fractions	NR	0
Géraud et al. [27]	2017	Retrospective	12	Brain	18	Concomitant or sequential (pre-RT)	NR	NR	Radionecrosis, neurological symptoms, alopecia	14
Stumpf et al. [28]	2019	Retrospective	23	Brain	5 #	Concomitant or sequential (pre-RT or post-RT)	NR	20 Gy (18–25) in 1–5 fractions	Radionecrosis	9
Mills et al. [29]	2021	Retrospective	16	Brain	40	Concomitant or sequential (pre-RT or post-RT)	13.2 (0.1–55.5)	21 Gy (14–24) in 1 fraction; 25 Gy (20–30) in 3–5 fractions	Radionecrosis, neurological symptoms	9
Id Said et al. [30]	2022	Retrospective	28	Brain	NR	Sequential (pre-RT or post-RT)	15.6 (NR)	15–24 Gy in 1 fraction; 24–32 Gy in 3–5 fractions	Radionecrosis	13
Adjuvant setting										
Krop et al. [32]	2015	Phase II (single arm)	116 ***	Breast/ chest wall	116	Concomitant or sequential (pre-op and post-RT)	24.6 (0.2–29)	NR	Radiation pneumonitis	3
von Minckwitz et al. [16]	2018	Phase III	624 ***	Breast/ chest wall	624	Concomitant	41.4 (0.1–62.6)	NR	Radiation pneumonitis, skin reactions	199
Zolcsak et al. [33]	2020	Retrospective	14	Breast/ chest wall	14	Concomitant	3 (NR)	50 Gy in 25 fractions +/- tumour bed boost	Skin reactions	17
Krop et al. ** [34]	2022	Phase III	695	Breast/ chest wall	695	Concomitant °	57 (NR)	NR	Radiation pneumonitis	21
Bellon et al. [17]	2022	Phase II (randomised)	239 ***	Breast/ chest wall	239	Concomitant	46.8 (NR)	NR	Radiation pneumonitis, skin reactions	213

Abbreviations: RT, radiation therapy; fr, fraction; NR, not reported; TRAE, treatment-related adverse event.
* According to the definition/description of each paper.
** Not included in the meta-analysis.
*** Patients treated with T-DM1 and RT.
° Concomitant with T-DM1 and pertuzumab.
Median number of lesions treated per patient (with or without T-DM1).

Table 2
Risk of Bias assessment of studies included in the meta-analysis.

Non-randomized studies	Year	1st Author	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall Bias
	2014	Carlson JA [25]	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
	2015	Krop IE [32]	Low	Low	Low	Low	Low	Low	Low	Low
	2017	Geraud A [27]	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
	2019	Stumpf PK [28]	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
	2020	Zolcsak Z [33]	Moderate	Low	Low	Low	Low	Low	Low	Low
	2021	Mills MN [29]	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
	2022	Id Said B [30]	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Randomized studies	**Year**	**1st Author**	**Selection bias Random sequence generation**	**Selection bias Allocation concealment**	**Reporting bias Selective reporting**	**Other sources of bias**	**Performance bias Blinding (participants and personnel**	**Detection bias Blinding (outcome assessment)**	**Attrition bias Incomplete outcome data**	**Overall Bias**
	2019	von Minckwitz G [16]	Low	Low	Low	Low	High	High	Low	Low
	2022	Bellon JR [17]	Low	Low	Low	Low	High	High	Low	Low

Discussion

T-DM1 is commonly used in both the adjuvant and metastatic settings for the treatment of HER2-positive breast cancer, as evidenced by pivotal randomized controlled trials that have demonstrated survival benefits [8,16]. However, the combination of T-DM1 with RT raises safety concerns due to the lack of level-1 evidence. Therefore, there is a need for a consensus agreement to address these uncertainties [13].

Preclinical data have indicated that T-DM1 may have a strong radiosensitizing effect on HER2-positive tumours, while HER2-negative tumours appear to be less sensitive [35]. However, contradictory findings have also been reported [36]. With regards to the toxic effects of combination therapy, conflicting results have emerged over time, creating uncertainties regarding the overall safety of combining T-DM1 with RT. In this context, we present the first systematic review and meta-analysis that investigates the concurrent use of T-DM1 and RT in breast cancer.

For patients with intracranial metastatic disease, there are concerns regarding the elevated risk of radionecrosis when combining brain SRS with T-DM1 [19,37]. In our study, we found a pooled incidence of Grade 3 + radionecrosis of 17%, which is higher than the reported incidence of 6 to 11% after brain SRS alone [37,38]. This highlights the potential increased risk associated with the combination therapy.

Case series reported by Carlson and colleagues [25], showed that four out of seven patients receiving SRS followed by T-DM1 developed symptomatic radionecrosis, and three of them permanently suspended systemic treatment. Thereafter, several case reports noted conflicting findings, although the clinical frameworks were extremely heterogeneous in terms of RT type (SRS or WBRT), sequencing, and treatment intervals between RT and T-DM1 administration [19,39,40]. Jacot and colleagues [26], conducted an analysis of 39 patients who received T-DM1 for brain metastases. While the majority of patients (n = 36) received WBRT, only one patient underwent SRS. However, the study did not provide specific information on radiation-related toxic effects, and as a result, it was not included in the meta-analysis.

In the study by Geraud and colleagues [27], it was observed that the rate of radionecrosis was higher in patients who received SRS concomitantly with T-DM1 (2 out of 4 treatments; 50%) compared to those who received sequential treatment (4 out of 14 treatments; 28.6%). Sequential treatment was defined as a discontinuation of T-DM1 for one week or longer before SRS. Although the number of patients with symptomatic radionecrosis was not specified, none of the patients suspended T-DM1. On the other hand, Mills and colleagues [29], reported a low rate of radionecrosis even after concurrent administration of RT and T-DM1. They analysed 16 patients with 40 lesions who received SRS and T-DM1, with 19 lesions treated concurrently. Only one case of symptomatic radionecrosis (3%) was reported after concomitant SRS and T-DM1. It is worth noting that all the patients in these reports were treated with T-DM1, and thus the extent of the impact of T-DM1 on the increased risk of radionecrosis remains unclear.

T-DM1 has been found to cross the blood–brain barrier, potentially leading to a synergistic effect with brain RT [18,41]. Stumpf et al. [28], provided a possible explanation for the development of brain oedema and radionecrosis following T-DM1 and RT. They demonstrated that T-DM1 enhanced the radiation-induced upregulation of AQP4 (aquaporin-4), a water transporter, in astrocytes. This resulted in astrocytic swelling and an increase in astrocytic cell size at a high radiation dose of 8 Gy/1 fraction, which was significantly larger than the effect induced by radiation and trastuzumab. The study also reported an incidence of symptomatic radionecrosis after SRS with or without WBRT. The incidence was 39.1% (1 out of 23 patients) with concurrent or sequential T-DM1 and 4.5% (1 out of 22 patients) without T-DM1, indicating a 13.5-fold increased risk of radionecrosis with

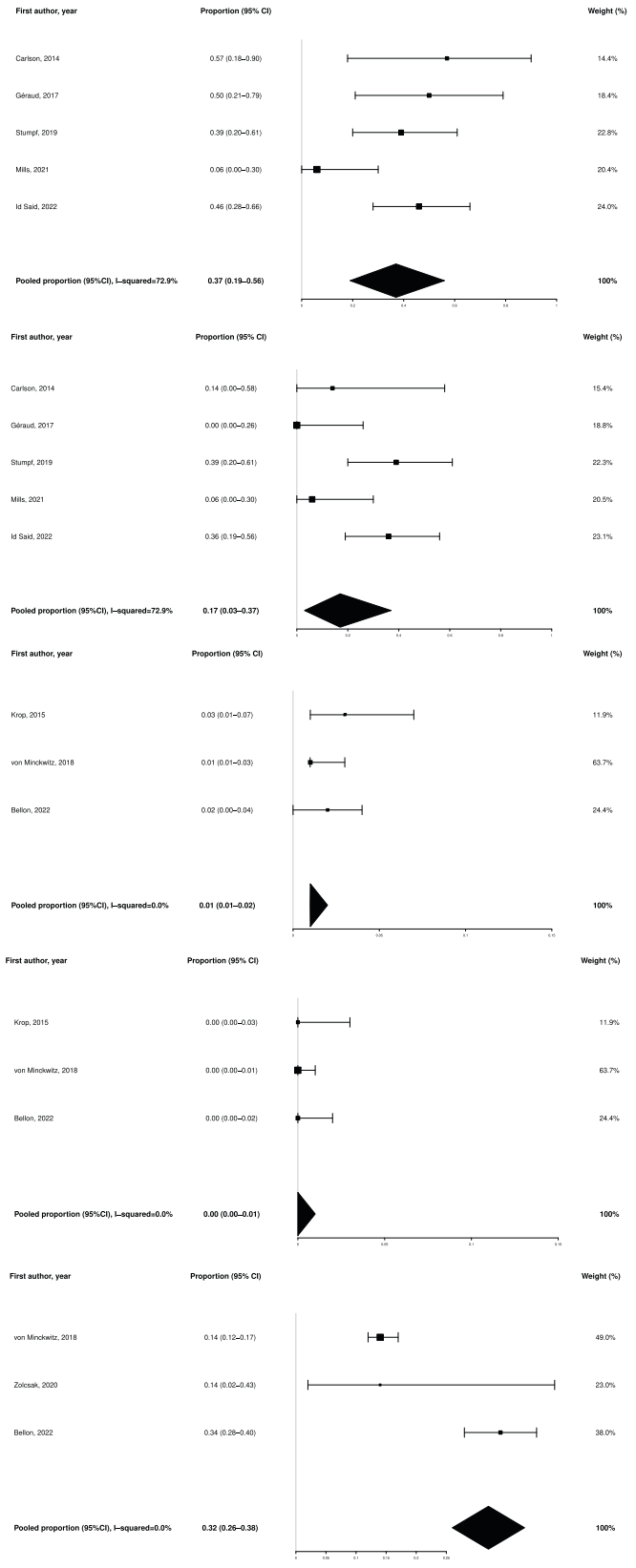

Fig. 2. Meta-analysis results concerning radionecrosis of grade 2+ (**a**) and grade 3+ (**b**); radiation pneumonitis of grade 2+ (**c**) and grade 3+ (**d**), and skin toxicity of grade 2+ (**e**) and grade 3+ (**f**).

T-DM1. Among the nine patients who experienced radionecrosis after SRS and T-DM1, six patients received concurrent treatment. The definition of sequential T-DM1 administration varied among studies: the time range was 77 to 131 days if T-DM1 was administered prior to SRS, and 420 to 1426 days if T-DM1 was administered after SRS.

More recently, 67 patients with 223 lesions treated with SRS with or without WBRT were analysed by Id Said and colleagues [30], reporting 35.7% symptomatic radionecrosis (10/28 patients) developed by patients receiving T-DM1 before/after SRS. Among the 39 patients not receiving T-DM1, only four patients developed radionecrosis (10.3%). Only a few studies specified the definition of concomitant administration [27,28], and the time interval between T-DM1 and RT [25,29,30].

In patients with non-metastatic disease, three studies provided rates of acute skin toxic effect after T-DM1 and concomitant breast RT. The KATHERINE trial is a phase 3 study comparing T-DM1 and trastuzumab after surgery in 1486 patients with residual disease after PST [16]. Among 1221 patients receiving RT (allowed during T-DM1 administration), grade 3 + radiation-related acute skin toxic effects were observed in 1.6% (10/624 patients) of the T-DM1 group and in 1.2% (7/597 patients) of the trastuzumab group. The low rate of severe skin toxicity reported by von Minckwitz et al. supported the safety of using both agents in combination with RT in the adjuvant setting.

In the ATEMPT phase 2 trial, which compared T-DM1 with a taxane plus trastuzumab as adjuvant systemic therapy, postoperative RT was administered concomitantly with T-DM1 after four cycles [17]. Among the 308 patients who received RT, a grade 2 or higher acute skin toxic effect was observed in 33.9% of patients in the T-DM1 group and in 23.2% of patients in the taxane plus trastuzumab group ($p = 0.11$). When skin toxicity was compared based on the fractionation of RT in patients who underwent breast-conserving surgery, a grade 2 or higher acute skin toxic effect was present in 44.7% of patients receiving daily fractionation of 2 Gy and in 17.9% of patients receiving hypofractionation (dose per fraction greater than or equal to 2.5 Gy) ($p < 0.001$). Another retrospective study conducted at Institut Curie reported a 14.3% incidence of grade 2 or higher radiation dermatitis (2 out of 14 patients) in patients receiving concurrent T-DM1 and postoperative RT [33].

In our analysis, we observed a pooled incidence of grade 2 + and 3 + skin toxic effects of 32% and 1%, respectively. These findings regarding acute skin toxic effects align with historical observations, including the observations from the START B trial [42]. The incidence rates reported in our analysis are consistent with the previously documented rates of skin toxicity associated with the combination of T-DM1 and RT. Based on the available evidence, it has been observed that the impact of the fractionation schedule used in RT has a greater influence on acute skin effects compared to the combined systemic agents, such as T-DM1 [17,43]. Therefore, moderate hypofractionation is considered a favourable option for combining postoperative breast RT with T-DM1. It is important to note that data regarding the integration of ultra-hypofractionated RT and T-DM1 are currently lacking. Therefore, further research and data are needed to evaluate the safety and efficacy of using ultra-hypofractionated RT in conjunction with T-DM1.

Three studies included in our review provided data on radiation-related pneumonitis in patients receiving T-DM1 treatment. In the KATHERINE trial, the risk of radiation-associated pneumonitis was slightly higher (1.5% vs. 0.7%) compared to the trastuzumab arm [16]. The ATEMPT trial reported a similar rate of radiation-related pneumonitis, with one patient in each arm developing grade 3 pneumonitis [17].

Another study conducted by Krop et al. [32], involved a phase 2 trial in early breast cancer patients receiving T-DM1 after anthracycline-based chemotherapy. In this study, concurrent or sequential RT was administered after four cycles of T-DM1. Two

patients experienced grade 2 radiation-related pneumonitis (one in the concurrent RT group and one in the sequential RT group), while one patient in the sequential RT group experienced grade 3 pneumonitis. In our systematic review, we found a reassuring pooled incidence of grade 2 or higher and grade 3 or higher radiation-related pneumonitis, which was 1% and less than 1%, respectively. These findings are consistent with the existing literature and provide further reassurance regarding the low incidence of radiation-related pneumonitis in patients receiving T-DM1 treatment [44].

Additionally, the KAITLIN phase 3 trial compared the combination of T-DM1 plus pertuzumab to trastuzumab plus pertuzumab after anthracycline-based chemotherapy following surgery [34]. Postoperative RT was initiated after four cycles of T-DM1 and administered concurrently. Among the 1399 patients who received RT, radiation-related pneumonitis was observed in 2.3% of the T-DM1-containing arm and 1.4% of the trastuzumab-containing arm. Although this study was not included in our meta-analysis due to the lack of reported grades of radiation pneumonitis, the incidence observed is consistent with contemporary data. In a recent meta-analysis, anti-HER2 ADCs including T-DM1 were associated with a 2.82 times higher risk of grade 3 + interstitial lung disease, regardless of postoperative breast RT [45].

Given the modern trend of shorter treatment durations for postoperative RT, even in early breast cancer [46], it may be reasonable to consider shortening the interval between T-DM1 cycles to avoid direct interactions. This is especially relevant considering that the half-life of T-DM1 is approximately four days.

Some limitations should be considered in our analysis findings' interpretation: (1) with the exception of randomized controlled trials for locoregional diseases, the sample sizes in the studies were generally small; (2) Only a small number of studies (between three to five) were included in the analysis for each specific endpoint; (3) all studies conducted in the metastatic setting were retrospective, introducing a high level of heterogeneity in the data; (4) the grades of radionecrosis were not consistently specified according to the CTCAE scale, which may impact the accuracy of the reported results; (5) a few studies did not clearly define the concomitant treatment and the time interval between T-DM1 and RT administration; (6) the endpoint of radiation pneumonitis may be underpowered due to the low rate of events observed in the included studies; (7) only one article provided information on the schedules and volumes of postoperative RT [17].

In conclusion, the combination of T-DM1 and brain SRS appears to have a significantly higher incidence of symptomatic radionecrosis compared to SRS alone. Therefore, caution is advised when using this combination for the treatment of intracranial disease. However, due to the lack of robust data, clear recommendations cannot be made for the treatment of extracranial metastasis. In the context of locoregional treatment for non-metastatic disease, the toxicity associated with the combination of T-DM1 and RT was found to be low, with minimal acute skin effects and radiation-related pneumonitis. There is a need for international consensus recommendations on the safety of combining T-DM1 and RT for breast cancer. Additionally, more prospective large cohorts are required to systematically report details on RT intent, volumes, doses, and techniques to further enhance our understanding of this combination treatment.

Declaration of competing interest

Maria Ekholm declares advisory board supported by Pfizer and Novartis and lecture fees supported by AstraZeneca; Tanja Skyttä declares advisory board supported by BMS, MSD, Novartis, Pierre-Fabre, and lecture fees supported by Astellas, AstraZeneca, and BMS. Matteo Lambertini received honoraria and/or participated in advisory board from Roche, Novartis, Lilly, Pfizer, AstraZeneca, Daiichi Sankyo, Gilead, SeaGen, MSD, Exact Sciences, Takeda, Ipsen, Sandoz, Libbs & Knight, a travel grant from Gilead and research support to the Institution from Gilead. Icro Meattini received honoraria for occasional attendance at advisory boards supported by Eli Lilly, Novartis, Pfizer, SeaGen, Gilead, Accuray. Philip Poortmans is medical advisor of Sordina IORT Technologies. Evandro de Azambuja disclosed honoraria and/or advisory board from Roche/GNE, Novartis, SeaGen, Zodiac, Libbs, Pierre Fabre, Lilly, AstraZeneca. Javier Cortes disclosed consulting/advisor for Roche, Celgene, Cellestia, AstraZeneca, SeaGen, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Merck Sharp & Dohme, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, Expres2ion Biotechnologies. Nadia Harbeck disclosed honoraria for lectures and/or consulting from AstraZeneca, Daiichi-Sankyo, Gilead, Lilly, MSD, Novartis, Pierre-Fabre, Pfizer, Roche, Sanofi, Sandoz, SeaGen. Hope Rugo disclosed institutional research support by Astellas Pharma Inc., AstraZeneca, Daiichi Sankyo Inc., F. Hoffmann-La Roche AG/Genentech, Inc., Gilead Sciences Inc., GlaxoSmithKline, Lilly, Merck & Co. Inc., Novartis Pharmaceuticals Corporation, OBI Pharma, Pfizer, Pionyr Immunotherapeutics, Sermonix Pharmaceuticals Inc., Taiho Oncology Inc., and Veru Inc. All the declared competing interests are outside the submitted work.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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