

## **SUPPLEMENTARY MATERIAL**

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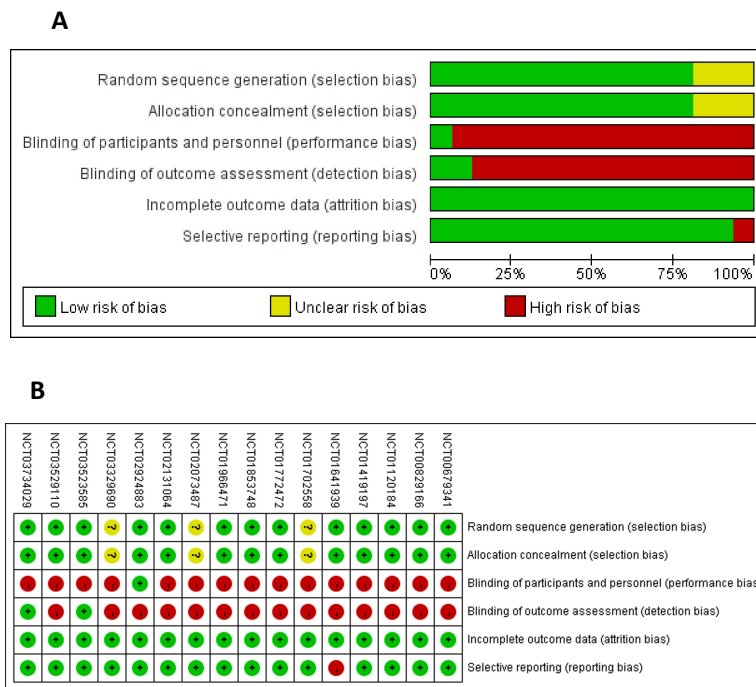


Figure S1. Risk of bias assessment for RCT according to RoB tool. (A) Risk of bias graph; (B) Risk of bias summary.

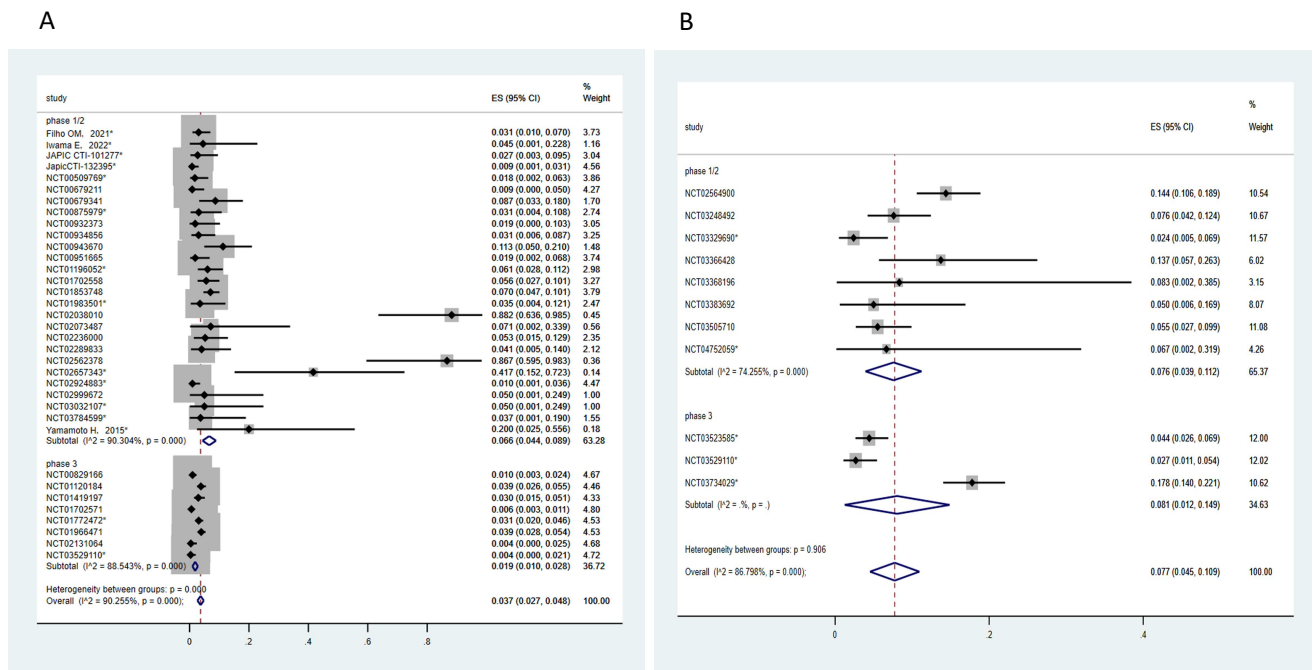


Figure S2. The incidence of all grade cardiac toxicity between phase I/II trials and phase III trials in different drug subgroups. (A) The incidence of all-grade cardiac toxicity between phase I/II trials and phase III trials in T-DM1 treatment. (B) The incidence of all-grade cardiac toxicity between phase I/II trials and phase III trials in T-DXd treatment.

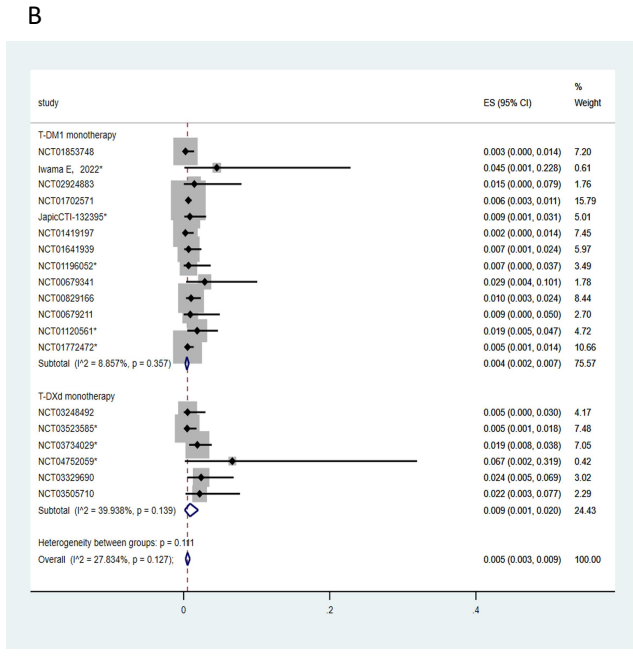
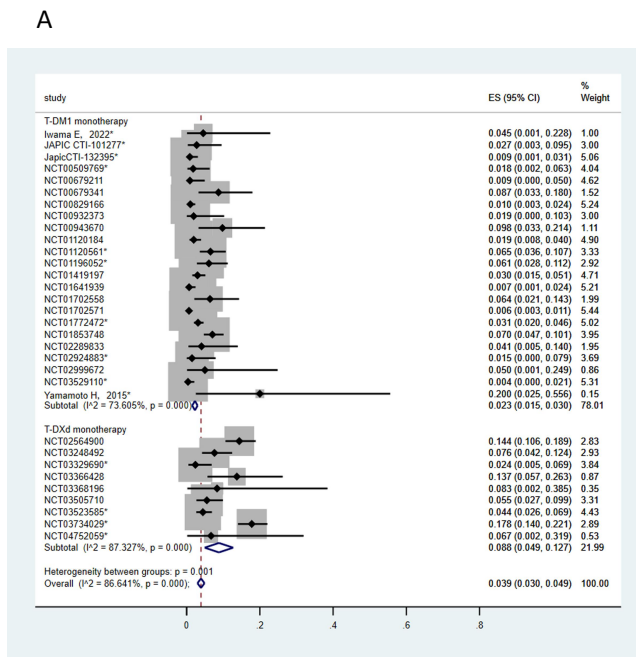


Figure S3. The incidence of cardiac toxicity between T-DM1 and T-DXd in monotherapy treatment. (A) The incidence of all-grade cardiac toxicity between T-DM1 and T-DXd in monotherapy treatment. (B) The incidence of  $\geq 3$ /serious grades cardiac toxicity between T-DM1 and T-DXd in monotherapy treatment.

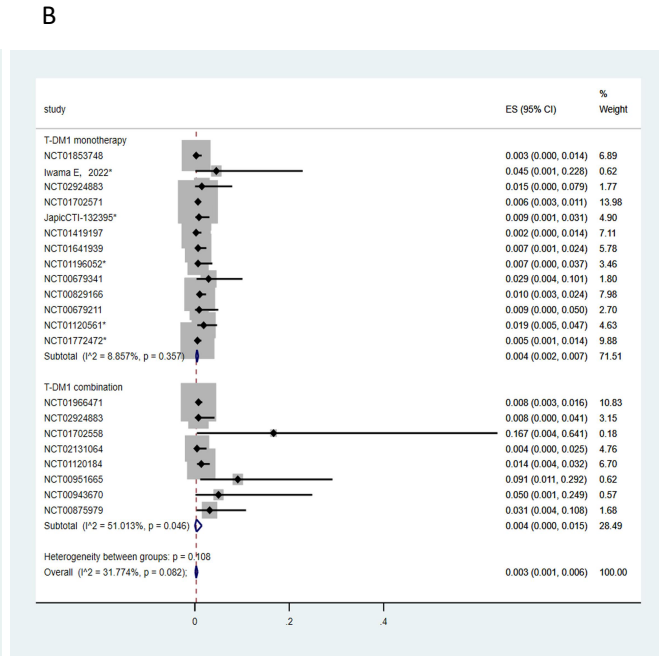
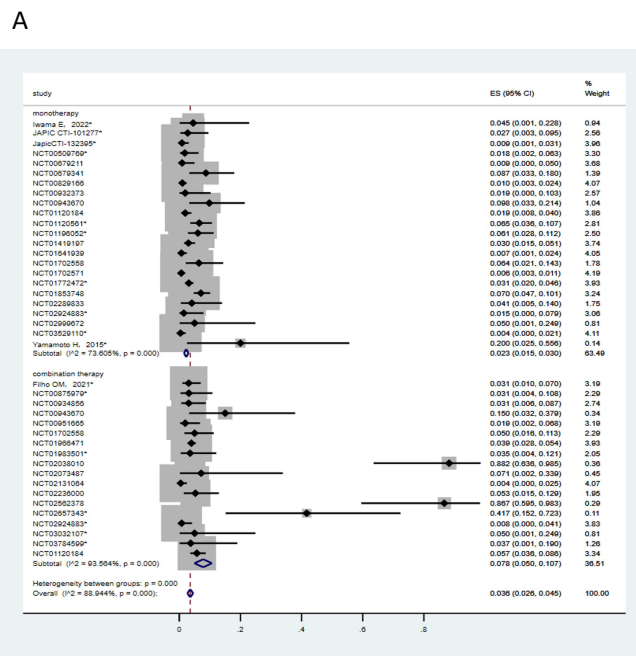


Figure S4. The incidence of cardiac toxicity of T-DM1 in monotherapy and combination therapy. (A) The incidence of all-grade cardiac toxicity induced by T-DM1 in monotherapy and combination therapy. (B) The incidence of cardiac toxicity with  $\geq 3$ /serious grades induced by T-DM1 in monotherapy and combination therapy.

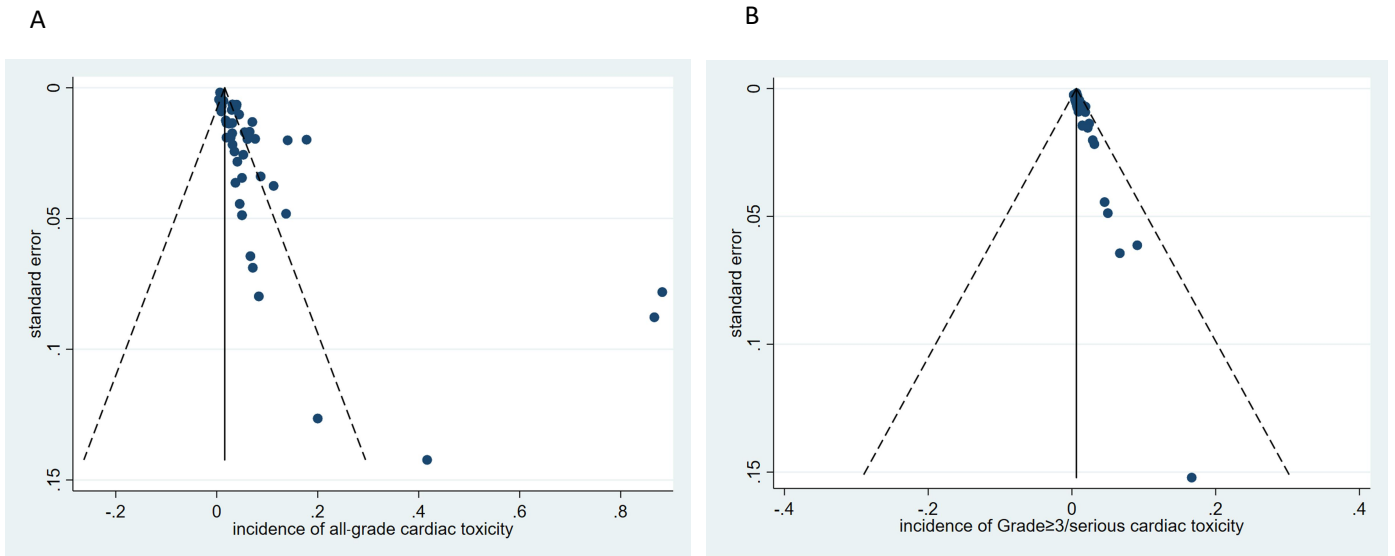


Figure S5. Funnel plots of the incidence of cardiotoxicity for all grades (A) and  $\geq 3$ /serious grades (B).

Table S1. Search strategy via PubMed up to May 2023

number	Search strategy	Search results(items)
#1	(disitamab vedotin[Title/Abstract]) OR(rc 48[Title/Abstract]) OR (aidixi[Title/Abstract])	18
#2	("Ado-Trastuzumab Emtansine"[Mesh]) OR (((((((((Ado Trastuzumab Emtansine[Title/Abstract]) OR (Trastuzumab Emtansine[Title/Abstract]))) OR (Kadcyla[Title/Abstract])) OR (huN901-DM1[Title/Abstract])) OR (huN901DM1[Title/Abstract])) OR (Trastuzumab-DM1 Conjugate[Title/Abstract])) OR (Trastuzumab DM1 Conjugate[Title/Abstract])) OR (Trastuzumab-DM1[Title/Abstract]) OR (Trastuzumab DM1[Title/Abstract]))	1071
#3	(trastuzumab deruxtecan [Supplementary Concept]) OR (((((((((ds 8201[Title/Abstract])) OR (fam-trastuzumab deruxtecan-nxki[Title/Abstract])) OR (ds 8201a[Title/Abstract])) OR (ds8201[Title/Abstract])) OR (ds8201a[Title/Abstract])) OR (enhertu[Title/Abstract])) OR (fam trastuzumab deruxtecan nxki[Title/Abstract])) OR (trastuzumab deruxtecan[Title/Abstract]))	361
#4	#1 OR #2 OR #3	1354

Table S2. A list of MINORS scale scores for non-randomized controlled trials .

study	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased evaluation of endpoints	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	scores <sup>†</sup>
Iwama E, 2022	2	2	2	1	0	2	2	2	/	/	/	/	13
NCT02289833	2	2	2	1	0	2	2	2	/	/	/	/	13
NCT01702571	2	2	2	1	0	2	0	0	/	/	/	/	9
JapicCTI-132395	2	2	2	1	0	1	0	0	/	/	/	/	8
NCT01196052	2	0	2	1	0	2	2	2	/	/	/	/	11
NCT00509769	2	2	2	2	0	2	2	0	/	/	/	/	12
NCT00932373	2	1	2	1	0	1	2	0	/	/	/	/	9
NCT00679211	2	2	2	2	0	2	2	2	/	/	/	/	14
NCT02999672	1	2	2	1	0	2	2	0	/	/	/	/	10
NCT01120561	2	2	2	2	0	1	2	0	/	/	/	/	11
JAPIC CTI-10127	2	1	2	1	0	1	2	2	/	/	/	/	11
Yamamoto H,2015	2	2	2	1	0	1	2	0	/	/	/	/	10
NCT00934856	2	2	2	2	0	0	2	0	/	/	/	/	10
NCT02236000	2	2	2	1	0	1	2	0	/	/	/	/	10
NCT03784599	2	2	2	1	0	2	2	2	/	/	/	/	13
NCT00943670	2	2	2	2	0	1	2	0	/	/	/	/	11
NCT02038010	2	2	2	1	0	2	0	2	/	/	/	/	11
NCT02562378	2	2	2	2	0	2	2	0	/	/	/	/	12
NCT00875979	2	2	2	2	0	0	2	2	/	/	/	/	12
Filho OM, 2021	2	2	2	1	0	0	2	2	/	/	/	/	11
NCT00951665	1	2	2	1	0	0	2	0	/	/	/	/	8
NCT03032107	2	2	2	2	0	2	2	0	/	/	/	/	12
NCT02657343	2	2	1	1	0	1	2	0	/	/	/	/	9
NCT01983501	2	2	2	2	0	1	2	0	/	/	/	/	11
NCT03248492	2	2	2	2	0	1	2	2	/	/	/	/	11
NCT04752059	2	2	2	2	0	2	2	2	/	/	/	/	14
NCT03366428	2	2	2	2	0	2	2	2	/	/	/	/	14
NCT03368196	2	2	2	2	0	0	2	0	/	/	/	/	10
NCT02564900	2	2	2	2	0	1	2	2	/	/	/	/	13
NCT03505710	2	2	2	2	0	1	2	2	2	2	2	2	21
NCT03383692	2	2	2	2	0	1	1	2	/	/	/	/	12

MINORS: Methodological index for non-randomized studies; †The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). Item 1-8 for non-comparative studies, item 1-12 for comparative studies. The global ideal score being 16 for non-comparative studies and 24 for comparative studies.