Original Article

Antibody-drug conjugate monotherapy refines the oncological efficacy as compared to therapy of physicians' choices in advanced breast cancers: a systematic review and meta-analysis

Yuhua Song[1], **Yang Lv**[2]

[1]Breast Disease Center B Ward, The Affiliated Hospital of Qingdao University, Qingdao, China; [2]Department of Oncology, An Qing First People's Hospital of Anhui Medical University, Anqing, China

Contributions: (I) Conception and design: Y Song; (II) Administrative support: Y Song; (III) Provision of study materials or patients: Y Lv; (IV) Collection and assembly of data: Y Lv; (V) Data analysis and interpretation: Y Lv; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Yuhua Song, MD. Breast Disease Center B Ward, The Affiliated Hospital of Qingdao University, No.59 Haier Road, Laoshan District, Qingdao 266000, China. Email: qdsongyh@qdu.edu.cn.

Background: Antibody-drug conjugate (ADC) is an emerging therapy that bestows advanced breast tumors with encouraging clinical activity and manageable toxicity; however, the outcomes of phase 2/3 randomized controlled trials (RCTs) are heterogeneous. Our study aims to assess the clinical utilities [i.e., objective response rate (ORR), clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS)], and treatment-related adverse events (AEs) of ADC monotherapy (defined as the study cohort) versus the therapy of physician's choice (TPC) (defined as the control cohort) in participants with advanced breast tumors.

Methods: We conducted a computerized retrieval to identify RCTs from MEDLINE, Web of Science, Cochrane Library, Embase databases, and ClinicalTrials.gov until April 4th, 2023. Screening, data extraction, and quality assessment were performed in duplicate.

Results: A total of 10 RCTs were involved, with 5,089 unique patients. A binary random-effect model Mantel-Haenszel method was employed to pool data due to the considerable heterogeneity. The primary outcome measure was odds ratio (OR) with the corresponding 95% confidential interval (CI) of ORR and CBR. The secondary outcome measure represented hazard ratio (HR) of PFS and OS and OR of the frequency of any grade/grade ≥3 AEs. The pooled results showed an insignificant difference of ORR (OR =1.64; 95% CI: 0.86–3.13; P=0.136) and CBR (OR =1.43; 95% CI: 0.89–2.31; P=0.142) in the study cohort than the control cohort. The pooled effect on PFS (HR =0.62; 95% CI: 0.50–0.74; P<0.001) and on OS (HR =0.70; 95% CI: 0.57–0.83; P<0.001) both indicated a significant superiority of the study cohort. The frequency of any grade AEs (OR =1.03; 95% CI: 0.75–1.41; P=0.849) and that of grade ≥3 AEs (OR =0.83; 95% CI: 0.57–1.21; P=0.342) were both observed a nonsignificant difference between the cohorts. These domains, i.e., allocation concealment, blinding of participants and personnel, and blinding of outcome assessment, had the high risk of bias over 50%.

Conclusions: Compared to physician's choice, ADC monotherapy overall confirms a considerable refinement in survival benefits plus a similar safety profile in advanced breast tumors.

Keywords: Antibody-drug conjugate (ADC); therapy of physician's choices (TPCs); advanced breast tumors; oncological efficacy; adverse events (AEs)

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Introduction

GLOBOCAN 2020 estimates uncover 19.3 million new cancer cases and nearly 10 million cancer-related deaths in 2020; with the aging and exploding of the population, the global cancer burden is portended to be 28.4 million cases in 2040 (1). In China, solid tumors are responsible for more than 70% of all cancer-related deaths (2). Strikingly, breast cancer overcomes the lung cancer as the most newly diagnosed cancers in female populations (1). A concomitant elevation in the diagnosis and decease of advanced breast cancers in the United States is observed during the past decade (1). Advanced breast tumors are becoming an intractable problem for oncologists worldwide and have caused a resounding social-economic-psychological burden.

The management of advanced breast tumors might be optimized by developing specific targeted agents because most available drugs can only achieve an unsatisfied survival. Antibody-drug conjugate (ADC) provides a novel therapeutic paradigm, which chemically tethers a payload (i.e., cytotoxic agent) with a monoclonal antibody directed to corresponding tumor-related antigen (3), and accordingly, the cytotoxic agent can be selectively delivered into tumor cells to maximize antitumor activity and minimize toxicity. Nine ADCs have currently been approved by the Food and Drug Administration for tumor treatment in clinical settings and more than 60 ADCs are been underway to evaluate their efficacy and safety (4).

Several ADCs (e.g., sacituzumab govitecan, glembatumumab vedotin, trastuzumab emtansine; lifastuzumab vedotin, rovalpituzumab tesirine, mirvetuximab soravtansine, trastuzumab deruxtecan) have demonstrated robust antitumor activity and acceptable safety profile in many phase 1/2 clinical studies of solid tumors (5-14). Many randomized controlled trials (RCTs) and meta-analysis demonstrated the better survival outcomes of ADC monotherapy as compared to therapy of physician's choices (TPCs) in advanced solid tumor patients (15-17). Given these encouraging results, the landmark RCTs also evaluated the oncological efficacy and treatment-related adverse events (AEs) of ADC monotherapy in advanced breast tumors, with or without pretreatments (18-20). However, their conclusions are conflicting due to the administration of different ADCs and the diverse demographic characteristics of candidates. Therefore, we conducted the present meta-analysis to more precisely ascertain the role of ADC monotherapy in the treatment of patients with advanced breast tumors, regardless of the pretreating status. We present this article in accordance with the PRISMA reporting checklist (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-23-14/rc) (21,22).

Highlight box

Key findings

- Our results supported the administration of ADC monotherapy in the clinical setting of advanced breast cancers.

What is known and what is new?

- The growing appreciation of the rationality that antibody-drug conjugate (ADC) can be administrated as a single-agent regimen in patients, with a promising antitumor activity and manageable treatment-related adverse events (AEs).
- Advanced breast cancer patients administrated ADC monotherapy have an overall striking tumoricidal efficacy and tolerable toxicity when compared to TPCs. This novel therapy renders the similar tumor response, reduces disease progression, and prolongs OS; additionally, it achieves the similar frequency of any grade/grade ≥3 hematologic and non-hematologic toxicities.

What is the implication, and what should change now?

- It strictly recommends to elevate the clinical recommendations of ADC monotherapy in the treatment of advanced breast cancer patients.

Methods

This meta-analysis has been registered on PROSPERO (ID: CRD42023432893). There was no need for Ethical or Institutional Review Board Approval for the study design due to the nature of our work.

Literature search

A computerized literature retrieval was performed in the MEDLINE, Web of Science, Cochrane Library, Embase databases, and ClinicalTrials.gov to identify English published articles up to April 4th, 2023. The following terms were used: ((“cancer”[MesH] OR cancer OR tumor OR tumour OR carcinoma) AND (advanced OR metastatic)) AND (antibody-drug conjugate) AND (ORR OR (objective response) OR (overall response) OR PFS OR OS OR (progression-free survival) OR (overall survival)) AND (randomized controlled trials).

Inclusion and exclusion criteria

RCTs comparing the oncological efficacy and/or safety between advanced breast cancer patients received ADC monotherapy (categorized as the study cohort) and those received physician's choice (categorized as the control cohort) were in full consideration for inclusion. Moreover, potential RCTs needed to meet the following inclusion criteria: (I) populations—advanced or metastatic breast carcinoma patients; (II) treatment strategy—single agent of approved ADC administrated in the study cohort and TPCs in the control cohort; and (III) endpoints—reported at least one of the following outcomes: objective response rate (ORR), clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), and/or any grade AEs. Besides, it needed to remove the citations with any of the following conditions: (I) article type—reviews, case reports, prospective studies, retrospective studies, editorials, letters, comments, study protocols, and conference papers; (II) treatment strategy—other therapies combined in the study cohort, or ADC encompassed in the control cohort; and (III) overlapping study populations.

Data extraction and quality assessment

We extracted the following data from the included RCTs by using a standardized form: (I) study characteristics—clinical trial information, publication year, original nation, study phase, ADCs, and sample size of enrollment; (II) demographic characteristics—median age, primary tumor site, and race; and (III) outcome characteristics—the event number of ORR and CBR, the frequency of any grade/grade ≥3 AEs and the hazard ratio (HR) of PFS and OS. ORR was the accumulation of complete response and partial response according to Response Evaluation Criteria in Solid Tumors (RECIST), regardless of the version. CBR was defined as the percentage of patients who achieved complete response, partial response, or at least six months of stable disease. PFS was defined as the time from randomization to the time of first radiologic progression according to RECIST, or the date of death from any causes. OS was defined as the time from diagnosis to last follow-up or time of death. AEs were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, regardless of the version. Quality assessment of all RCTs was judged by the Cochrane risk of bias tool with Review Manager 5.4 (https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman). Two co-authors (Dr. Yuhua Song and Dr. Yang lv) independently executed the literature search, study selection, and data extraction. If there were any inconsistencies, they were resolved by discussion.

Data synthesis and statistical analysis

The primary outcome measure was odds ratio (OR) with the corresponding 95% confidential interval (CI) of ORR and CBR. The secondary outcome measure represented HR with 95% CI of PFS and OS and OR with 95% CI of the frequency of any grade/grade ≥3 AEs. The crude ORs were separately calculated and the crude HRs were extracted from the included articles. The number of events when was not provided in the papers was computed based on the endpoint percentage or other relevant information (e.g., the percentage of events and the total number). The heterogenicity that implicated the degree of variability in results across the analyzed studies was assessed by Cochran's Q test and Higgins I^2 statistic test (23); P<0.10 suggested significant heterogeneity, and different cutoff intervals of I^2 values at 0–25%, 26–50%, 51–75%, and 76–100% mapped to nonsignificant, moderate, substantial, and considerable heterogeneity, respectively. A binary fixed-effect model, Mantel-Haenszel method or a binary random-effect model, Mantel-Haenszel method was used to pool the crude HRs or ORs in light of the heterogeneity test, namely the former for the meta-analysis with no significant heterogeneity (P≥0.10) and the latter for the meta-analysis with significant heterogeneity (24). We also conducted subgroup analysis of all the outcomes to explore possible causes of heterogeneity among study results. The publication bias was evaluated by an Egger's test with a significant level of P<0.05. All statistical analysis was performed by the software StateSE, version 12.0 (https://www.stata.com/). The results of syntheses were visually displayed by the forest plots and those of the subgroup analyses were present by tables. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Data were collected from randomized clinical trials, those trials have been approved by institutional review boards. Under this circumstance, the Affiliated Hospital of Qingdao University waived the requirement of ethical approval.

Results

Literature search

A PRISMA flow diagram of the literature screening selection was outlined in *Figure 1*. The study strategy yielded a total of 2,690 citations, and 309 reduplications,

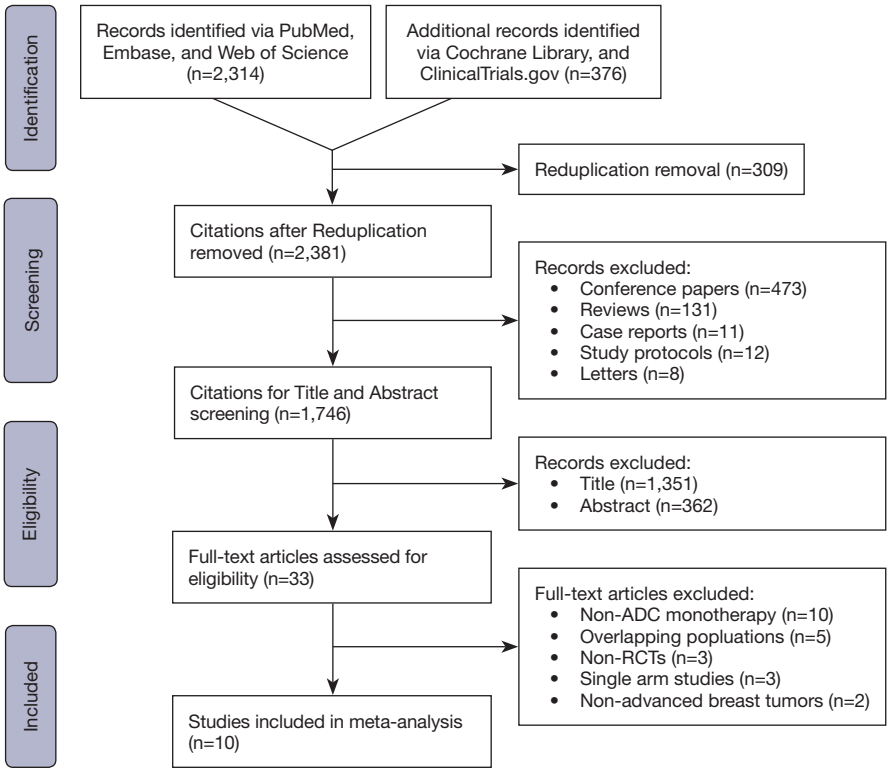

Figure 1 PRISMA flow diagram of study selection. ADC, antibody-drug conjugate; RCTs, randomized controlled trials.

473 conference papers, 131 reviews, 11 case reports, 12 study protocols, and eight letters were excluded. The remaining 1,746 potential citations were assessed by title and abstract screening, and 1,713 of them were removed; fundamental characteristics of the abstracts were judged with respect to the inclusion and exclusion criteria, and 33 full-length articles were obtained. After full-text scrutinization, 23 of them were further omitted by the following reasons: (I) non-ADC monotherapy in the study cohort (n=10); (II) overlapping study populations (n=5); (III) non-RCTs (n=3); (IV) single-arm trial (n=3); and (V) non-advanced solid tumor (n=2). Ultimately, 10 eligible RCTs (9,18-20,25-30) with 5,089 advanced breast tumor participants were involved in this meta-analysis.

Characteristics of the studies included for meta-analysis

Characteristics of the 10 included RCTs in the "study-level" analysis were shown in *Table 1*, and those in the "patient-level" analysis were summarized in *Table 2*. Phase 3 RCTs accounted for 80% of all studies; the publication year ranged from 2013 to 2023 (median: 2019); the median age in the study cohort and the control cohort both was 55 years old; the largest subset of original countries was the USA (n=9); trastuzumab emtansine ranked first for therapy in the study cohort (n=4); and five RCTs described patients with human epidermal growth receptor 2 (HER2)-positive breast cancer. Additionally, *Table 1* provided the study names, the ClinicalTrials.gov identifiers, study phases, molecular subtypes, regimens for both cohorts, the numbers concerning events versus totals in the cohorts of ORR and CBR, and the crude HRs with 95% CIs of PFS and OS.

ORR and CBR

Overall, six RCTs with 2,808 unique participants provided available data for the assessment of tumor response (i.e., six for the analysis of ORR and four for that of CBR). The pooled effect on ORR was not statistically significant (OR =1.64; 95% CI: 0.86–3.13; P=0.136) (*Figure 2A*). With regard to the subgroup analysis of ADCs, ORR was significantly improved in sacituzumab govitecan, whereas the results in glembatumumab vedotin, and trastuzumab emtansine were nonsignificant (*Table 3*). Finally, no

Table 1 Characteristics of included studies in the "study-level" analysis

Study (NCT#)	Phase	Subtypes	Regimen of study group	Regimen of control group	Total samples	e/T of ORR (n/T)		e/T of CBR (n/T)		Hazard ratio (95% CI)	
						Study cohort	Control cohort	Study cohort	Control cohort	PFS	OS
ASCENT (NCT02574455)	3	TNBC	Sacituzumab govitecan	TPCs	468	82/235	11/233	163/235	73/233	0.41 (0.32–0.52)	0.48 (0.38–0.59)
EMERGE (NCT01156753)	2	NA	Glembatumumab vedotin	TPCs	124	10/83	5/41	51/83	24/41	1.19 (0.78–1.79)	1.37 (0.85–2.17)
EMILIA (NCT00829166)	3	HER2$^+$	Trastuzumab emtansine	Capecitabine and lapatinib	991	173/397	120/389	NA	NA	0.65 (0.55–0.77)	0.68 (0.55–0.85)
METRIC (NCT01997333)	2	TNBC	Glembatumumab vedotin	Capecitabine	327	29/218	15/109	112/218	42/109	0.95 (0.71–1.29)	1.06 (0.78–1.43)
MARIANNE (NCT01120184)	3	HER2$^+$	Trastuzumab emtansine	Trastuzumab and taxane	732	181/303	195/287	256/303	253/287	0.91 (0.73–1.13)	0.86 (0.64–1.16)
TDM4450g (NCT00679341)	2	HER2$^+$	Trastuzumab emtansine	Trastuzumab and docetaxel	137	42/67	41/70	NA	NA	0.59 (0.36–0.97)	1.06 (0.48–2.35)
TH3RESA (NCT01419197)	3	HER2$^+$	Trastuzumab emtansine	TPCs	602	NA	NA	NA	NA	0.53 (0.42–0.66)	0.55 (0.37–0.83)
DESTINY-Breast02 (NCT03523585)	3	HER2$^+$	Trastuzumab deruxtecan	TPCs	608	NA	NA	NA	NA	0.36 (0.28–0.45)	0.66 (0.50–0.86)
TROPiCS-02 (NCT03901339)	3	Luminal HER2$^-$	Sacituzumab govitecan	Chemotherapy	543	NA	NA	NA	NA	0.66 (0.53–0.83)	NA
DESTINY-Breast04 (NCT03734029)	3	HER2 low	Trastuzumab deruxtecan	TPCs	557	NA	NA	NA	NA	0.50 (0.40–0.63)	0.64 (0.49–0.84)

NCT, normolized controlled trials; e/T, event/Toal; ORR, objective response rate; CBR, clinical benefit rate; CI, confidential interval; PFS, progression-free survival; OS, overall survival; TNBC, triple-negative breast cancer; NA, not available; HER2$^{+/-}$, human epidermal growth receptor 2-positive/negative; TPC, treatment of physician's choice.

significantly improved ORR was observed in both phase 2 and 3 RCTs (*Table 3*).

The pooled result of CBR indicated no significant difference between the cohorts (OR =1.43; 95% CI: 0.89–2.31; P=0.142) (*Figure 2B*). As seen in *Table 3*, a significantly better outcome with CBR for the study cohort over the control cohort was observed in the subgroup analysis of sacituzumab govitecan and glembatumumab vedotin, but not in that of trastuzumab emtansine (*Table 3*). Moreover, phase 2 RCTs showed a significantly higher CBR in the study cohort than the control cohort, although no significant difference was observed in phase 3 RCTs (*Table 3*).

PFS and OS

Overall, all RCTs were included for the evaluation of survival (i.e., 10 for the analysis of PFS and 9 for that of OS). The pooled results showed a significant superiority in PFS of the study cohort relative to the control cohort (HR =0.62; 95% CI: 0.50–0.74; P<0.001) (*Figure 3A*). The subgroup analyses of ADCs in sacituzumab govitecan, trastuzumab emtansine, and trastuzumab deruxtecan revealed a significantly better PFS in the study cohort than the control cohort (*Table 4*). Moreover, PFS was significantly improved in phase 2 RCTs but marginally improved in phase 3 RCTs (*Table 4*).

The pooled result of OS indicated a significant improvement in the study cohort (HR =0.70; 95% CI: 0.57–0.83; P<0.001) (*Figure 3B*). Consistent to the subgroup analysis of PFS, the significant better results were observed in sacituzumab govitecan, trastuzumab emtansine, and trastuzumab deruxtecan (*Table 4*). The subgroup analysis of phase 2 RCTs was also statistically significant (*Table 4*).

Frequency of any grade/grade ≥3 AEs

Overall, nine included RCTs provided data for analyzing frequency of AEs, with 4,481 unique participants. The

Table 2 Characteristics of included studies in the "patient-level" analysis

Characteristics	Study (N=10), No. [%]	Analyzed participants (N=5,089), No. [%]
Study type		
Phase 2 RCTs	2 [20]	588 [12]
Phase 3 RCTs	8 [80]	4,501 [88]
Publication year, median [range]	2019 [2013–2023]	NA
Median age, median [range], years		
Study cohort	54 [52–65]	NA
Control cohort	54 [52–66]	NA
Original nation		
USA	9 [90]	4,098 [81]
Germany	1 [10]	991 [19]
Antibody-drug conjugate		
Sacituzumab govitecan	2 [20]	1,011 [20]
Glembatumumab vedotin	2 [20]	451 [9]
Trastuzumab emtansine	4 [40]	2,462 [48]
Trastuzumab deruxtecan	2 [20]	1,165 [23]
Molecular subtypes		
Triple-negative breast cancer	2 [20]	795 [16]
$HER2^+$ breast cancer	5 [50]	3,070 [60]
HER2 low breast cancer	1 [10]	557 [11]
Luminal $HER2^-$ BC	1 [10]	543 [11]
Unclassified	1 [10]	124 [2]

The calculation of median value is based on the provided data from included studies. RCT, randomized controlled trial; y, year; $HER2^{+/-}$, human epidermal growth receptor 2-positive/negative; BC, breast cancer.

pooled OR suggested that the frequency of any grade AEs (OR =1.03; 95% CI: 0.75–1.41; P=0.849) and that of grade ≥3 AEs (OR =0.83; 95% CI: 0.57–1.21; P=0.342) was both not significantly different between the cohorts (*Figure 4A*,*4B*).

We further performed a subgroup analysis of ADCs according to hematologic and non-hematologic toxicity, respectively (Table S1). A significantly higher frequency of any grade hematologic toxicity was observed in sacituzumab govitecan but in glembatumumab vedotin and trastuzumab emtansine. The frequency of any grade non-hematologic toxicity was significantly increased in sacituzumab govitecan and glembatumumab vedotin, but significantly decreased in trastuzumab emtansine. Furthermore, sacituzumab govitecan was more frequent to develop grade ≥3 hematologic toxicities than TPCs. Finally, a significantly greater frequency of grade ≥3 non-hematologic toxicity was observed in sacituzumab govitecan and glembatumumab vedotin.

Publication bias and sensitivity analysis

The publication bias of all meta-analyses in terms of the P value (ranging from 0.137 to 0.704) was statistically nonsignificant (Figure S1, Table S2), indicating no existence of publication bias. Sensitivity analysis was utilized for selecting appropriate studies in the individual meta-analysis (Figures S2-S7) (31).

Quality appraisal and evidence level

The high risk of bias was over 50% in the domains including allocation concealment, blinding of participants

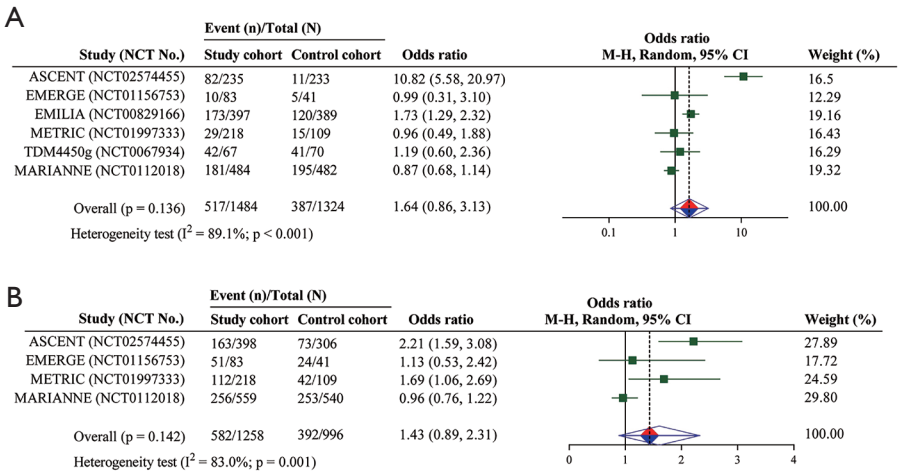

Figure 2 Pooled forest plot for comparison of objective response rate and clinical benefit rate between the ADC-monotherapy cohort and the physician's choice cohort. (A) The pooled forest plot for comparison of objective response rate, and (B) the pooled forest plot for comparison of clinical benefit rate. M-H, Mantel-Haenszel; CI, confidence interval; ADC, antibody-drug conjugate.

Table 3 Subgroup analysis of objective response rate and clinical benefit rate

Subgroup analyses	No. of RCTs	Statistical results			Heterogeneity test	
		Pooled OR (95% CI)	Pooled P value	Weight (%)	I^2	P value
Objective response rate						
ADCs						
SG	1	10.82 (5.58–20.97)	<0.001	16.50	NA	NA
GV	2	0.97 (0.54–1.73)	0.912	28.72	0.0	0.970
TE	3	1.22 (0.74–2.02)	0.444	54.78	82.7	0.003
Phase						
III	3	2.41 (0.85–6.84)	0.097	54.99	96.1	<0.001
II	3	1.05 (0.68–1.64)	0.816	45.01	0.0	0.904
Overall	6	1.64 (0.86–3.13)	0.136	100.00	90.6	<0.001
Clinical benefit rate						
ADCs						
SG	1	2.21 (1.59–3.08)	<0.001	27.89	NA	NA
GV	2	1.51 (1.01–2.25)	0.043	42.32	0.0	0.380
TE	1	0.96 (0.76–1.21)	0.726	29.80	NA	NA
Phase						
III	2	1.44 (0.64–3.28)	0.379	57.68	93.9	<0.001
II	2	1.51 (1.01–2.25)	0.043	42.32	0.0	0.380
Overall	4	1.62 (0.79–3.34)	0.142	100.00	83.0	0.001

RCT, randomized controlled trial; OR, odds ratio; CI, confidence interval; ADC, antibody-drug conjugate; SG, sacituzumab govitecan; GV, glembatumumab vedotin; TE, trastuzumab emtansine; NA, not available.

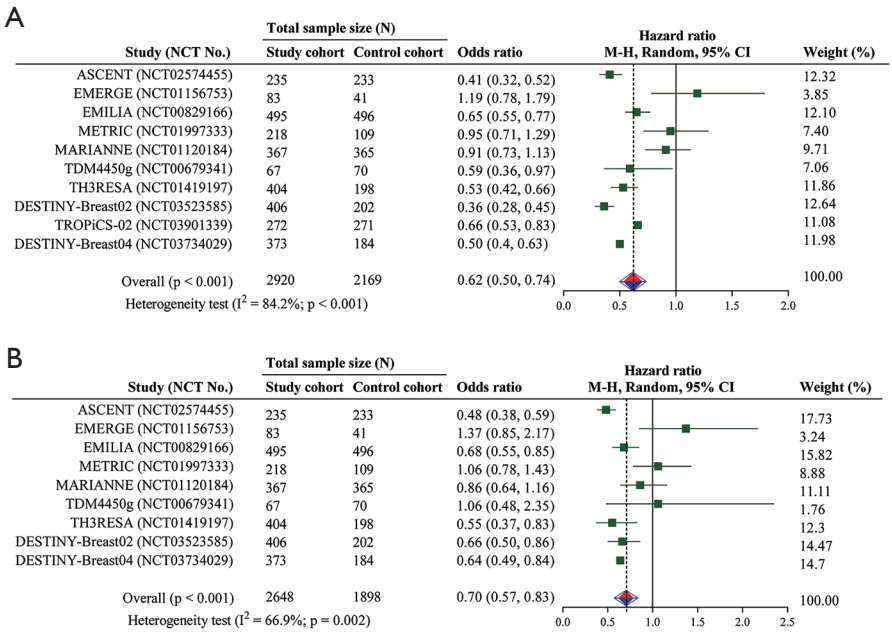

Figure 3 Pooled forest plot for comparison of progression-free survival and overall survival between the ADC-monotherapy cohort and the physician's choice cohort. (A) The pooled forest plot for comparison of progression-free survival, and (B) the pooled forest plot for comparison of overall survival. M-H, Mantel-Haenszel; CI, confidence interval; ADC, antibody-drug conjugate.

and personnel, and blinding of outcome assessment, whereas no high risk of bias was observed in the following domains, random sequence generation, incomplete outcome data, selective reporting, and other bias (Table S3). Finally, all analyses only showed a moderate level of evidence (Grade evidence by GRADEpro system, Figure S8).

Discussion

The present study included 10 phase 2/3 RCTs of ADC monotherapy for patients with advanced breast tumors, wherein the control arms comprised of mono-chemotherapy, polychemotherapy, and dual-targeted therapy; our results reflected the oncological efficacy and safety profile of ADC monotherapy versus the most common physician's choice in relevant advanced solid tumors. The meta-analysis demonstrates the significant correlation between ADC monotherapy and the refined oncological efficacy, with an overall decrement of 22% in the instantaneous risk of disease progression and that of 36% in the risk of survival threat in this clinical setting. In addition, ADC monotherapy appears an overall alike frequency of any grade treatment-related AEs and grade ≥3 AEs to the standard-of-care in advanced cancer tumors.

As a steeply evolving therapeutic modality, ADC harbors the monoclonal antibody that functions as a vehicle directly carrying the payload to tumors, which theoretically experiences a stronger anticancer activity and achieves more tumor shrinkage. Results from our study did not show the significant difference of ORR and CBR between ADC monotherapy and TPCs in patients with advanced breast tumors. By contrast, when changing regimens of the control cohort from capecitabine plus lapatinib towards trastuzumab plus taxane, the inferiority of ADC monotherapy in HER2-positive breast cancer arises, yet the CBR is still not significantly different (19). These interesting findings contribute to the phase 3 MARIANNE study (ClinicalTrials.gov identifier NCT01120184) (19) further investigating tumor response between ADC (i.e., trastuzumab emtansine) combined with targeted therapy (i.e., pertuzumab) and trastuzumab combined with taxane in advanced HER2-positive breast cancers. Although ORR in the trastuzumab emtansine plus pertuzumab arm does not outnumber the trastuzumab plus taxane arm (64.2% *vs.* 67.9%), the median duration of response (DoR) in the former is significantly higher than the latter (21.2 *vs.* 12.5 months); furthermore, single-agent of trastuzumab emtansine fulfills a discernable increment of median DoR as compared to trastuzumab

Table 4 Subgroup analysis of progression-free survival and overall survival

Subgroup analyses	No. of RCTs	Statistical results			Heterogeneity test	
		Pooled HR (95% CI)	Pooled P value	Weight (%)	I^2	P value
Progression-free survival						
ADCs						
SG	2	0.53 (0.28–0.77)	<0.001	23.40	86.5	0.007
GV	2	1.01 (0.76–1.26)	0.930	11.26	0.0	0.419
TE	4	0.66 (0.51–0.81)	<0.001	40.98	71.0	0.016
TD	2	0.47 (0.27–0.67)	<0.001	10.10	0	0.876
Phase						
III	7	0.56 (0.44–0.68)	<0.001	81.68	85.5	<0.001
II	3	0.87 (0.55–1.19)	0.384	18.32	59.8	0.083
Overall	10	0.62 (0.50–0.73)	<0.001	100.00	84.2	<0.001
Overall survival						
ADCs						
SG	2	0.55 (0.38–0.73)	<0.001	32.20	65.1	0.090
GV	2	1.12 (0.83–1.41)	0.335	12.12	0.0	0.409
TE	4	0.69 (0.56–0.83)	<0.001	40.98	18.5	0.298
TD	1	0.64 (0.47–0.81)	<0.001	14.70	NA	NA
Phase						
III	6	0.62 (0.52–0.73)	<0.001	86.13	53.4	0.057
II	3	1.12 (0.84–1.39)	0.304	13.87	0.0	0.706
Overall	9	0.70 (0.57–0.83)	<0.001	100.00	66.9	0.002

RCT, randomized controlled trial; HR, hazard ratio; CI, confidence interval; ADC, antibody-drug conjugate; SG, sacituzumab govitecan; GV, glembatumumab vedotin; TE, trastuzumab emtansine; TD, trastuzumab deruxtecan; NA, not available.

plus taxane. A drawback of our study was that the analysis of DoR between the cohorts was not conducted due to the insufficient data from included RCTs.

The ultimate goal of clinical treatment is to lengthen the duration of survival. The survival benefits are not observed in all ADCs; specifically, the administrations of trastuzumab emtansine in HER2-positive breast cancers and sacituzumab govitecan in triple-negative breast cancer (TNBC) all benefit the improvements in PFS and OS (*Figure 3A*,*3B*). Despite that the overall ameliorated PFS and OS of ADC monotherapy in advanced breast tumors is demonstrated by our study, we should perceive the dramatically different situations caused by the diversity of tumor ecosystem and ADCs.

Our results implicate the overall similar frequency of any grade/grade ≥3 AEs between ADC monotherapy and physician's choice. Furthermore, with reference to the overall frequency of any grade/grade ≥3 hematologic and non-hematologic toxicity, there is still no significant difference between the cohorts. In fact, as the crude OR values are shown in *Figure 4A*,*4B*, the frequency comparison of any grade AEs or grade ≥3 AEs between the cohorts in per-RCTs is discordant due to the diversity of ADC in the study cohort and the regimens in the control cohort.

The majority of four included RCTs (9,20,26), excepting the phase 3 MARIANNE study (19), collectively denote the significantly lower frequency of any grade/grade ≥3 AEs in advanced HER2-positive breast cancer patients treated with trastuzumab emtansine monotherapy than those treated with physician's choice. In TNBC, the occurrence of low-

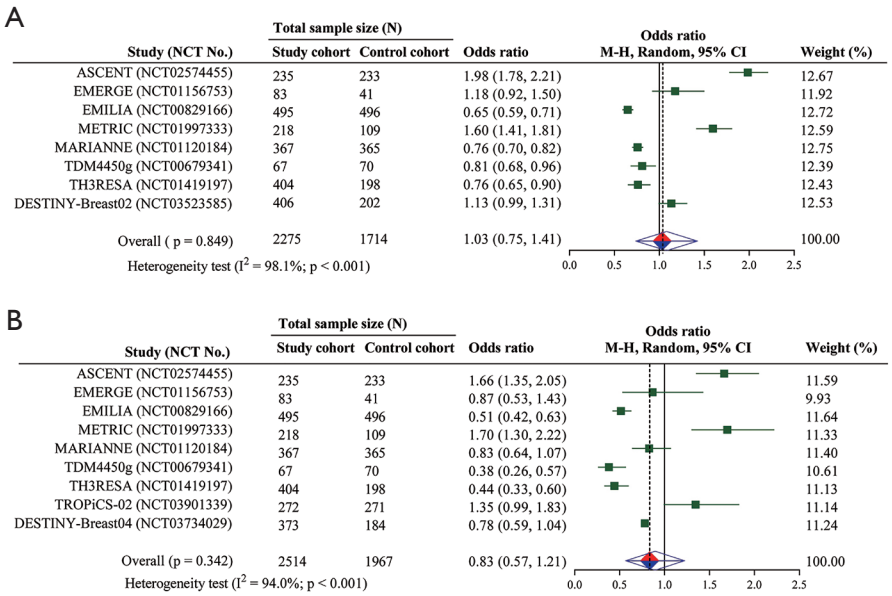

Figure 4 Pooled forest plot for comparison of treatment-related adverse events between the ADC-monotherapy cohort and the physician's choice cohort. (A) The pooled forest plot for comparing the frequency of any grade adverse events, and (B) the pooled forest plot for comparing the frequency of grade ≥3 adverse events. M-H, Mantel-Haenszel; CI, confidence interval; ADC, antibody-drug conjugate.

grade/grade ≥3 AEs of two ADCs (sacituzumab govitecan, and glembatumumab vedotin) is more frequent than physician's choice; the most clinically noteworthy AEs in sacituzumab govitecan are neutropenia and diarrhea and in glembatumumab vedotin are rash, peripheral neuropathy and alopecia (25,27). Importantly, the frequency of any grade AEs in advanced ovarian cancer patients undergoing mirvetuximab soravtansine is significantly higher than those undergoing physician's choice, whilst that of grade ≥3 AEs is lower in the mirvetuximab soravtansine arm.

There are some limitations in this first meta-analysis regarding ADC monotherapy in advanced solid tumors. The first limitation of our study is that all pooled results are calculated by a random effect model and are manifested with considerable heterogeneity; however, the leave-one-out sensitivity analyses guarantee the reasonable inclusion of studies for individual meta-analyses. The heterogeneity was likely correlated to the design of the study itself because RCTs with different phases, therapy lines, ADCs, agents in TPCs, and molecular subtypes were involved for analysis. Second, subgroup analysis is neither conducted in terms of treatment lines nor with or without the previous chemotherapy, which is attributive to the inadequate information provided from partially analyzed RCTs.

Conclusions

ADC monotherapy demonstrates the overall improvements in survival benefits plus the overall comparable frequency of AEs in advanced breast tumors when compared to TPCs. However, we could not use an 'one-size-fits-all' management approach to supersede physician's choice by ADC monotherapy in all patients of advanced breast tumor, because these clinical benefits and similar safety profiles between the two arms experienced dramatically different results across all analyzed RCTs.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-23-14/rc

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Conflicts of Interest: Both authors have completed the

ICMJE uniform disclosure form (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-23-14/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Data were collected from randomized clinical trials, those trials have been approved by institutional review boards. Under this circumstance, the Affiliated Hospital of Qingdao University waived the requirement of ethical approval.

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Supplementary

Table S1 Subgroup analysis for frequency of treatment-related adverse events

ADCs	No. of RCTs	Statistical results			Heterogeneity test	
		Pooled OR (95% CI)	Pooled P value	Weight (%)	I^2	P value
Frequency of any grade toxicity						
SG	2	1.50 (0.87, 2.60)	0.145	25.19	97.4	<0.001
GV	2	1.40 (1.04, 1.88)	0.028	24.51	78.9	0.030
TE	4	0.73 (0.66, 0.81)	<0.001	50.29	67.7	0.026
Overall	8	1.03 (0.75, 1.41)	0.849	100.00	98.1	<0.001
Frequency of any grade hematologic toxicity						
SG	1	1.48 (1.22, 1.81)	<0.001	14.87	NA	NA
GV	2	1.20 (0.16, 9.19)	0.857	27.29	97.3	<0.001
TE	4	0.83 (0.37, 1.87)	0.653	57.84	96.6	<0.001
Overall	7	1.01 (0.58, 1.75)	0.982	100.00	95.6	<0.001
Frequency of any grade non-hematologic toxicity						
SG	1	2.23 (1.96, 2.53)	<0.001	14.44	NA	NA
GV	2	1.48 (1.31, 1.67)	<0.001	28.12	0.0	0.683
TE	4	0.74 (0.56, 0.97)	0.027	57.45	94.6	<0.001
Overall	7	1.06 (0.70, 1.61)	0.781	100.00	98.5	<0.001
Frequency of grade ≥3 toxicity						
SG	2	1.54 (1.26, 1.88)	<0.001	22.72	21.3	0.260
GV	2	1.26 (0.65, 2.42)	0.497	21.26	81.6	0.020
TE	4	0.53 (0.38, 0.72)	<0.001	44.78	81.0	0.001
TD	1	0.78 (0.59, 1.04)	0.088	11.24	NA	NA
Overall	9	0.83 (0.57, 1.21)	0.342	100.00	94.0	<0.001
Frequency of grade ≥3 hematologic toxicity						
SG	1	1.74 (1.35, 2.24)	<0.001	14.93	NA	NA
GV	2	1.50 (0.20, 11.35)	0.697	27.57	95.1	<0.001
TE	4	0.52 (0.17, 1.64)	0.266	57.50	96.4	<0.001
Overall	7	0.84 (0.38, 1.83)	0.656	100.00	95.8	<0.001
Frequency of grade ≥3 non-hematologic toxicity						
SG	1	1.63 (1.08, 2.45)	0.019	14.76	NA	NA
GV	2	1.33 (1.00, 1.77)	0.049	27.04	0.0	0.400
TE	4	0.78 (0.28, 2.14)	0.624	58.20	95.7	<0.001
Overall	7	1.04 (0.52, 2.09)	0.908	100.00	94.9	<0.001

ADC, antibody-drug conjugate; SG, sacituzumab govitecan; GV, glembatumumab vedotin; TE, trastuzumab emtansine; TD, trastuzumab deruxtecan.

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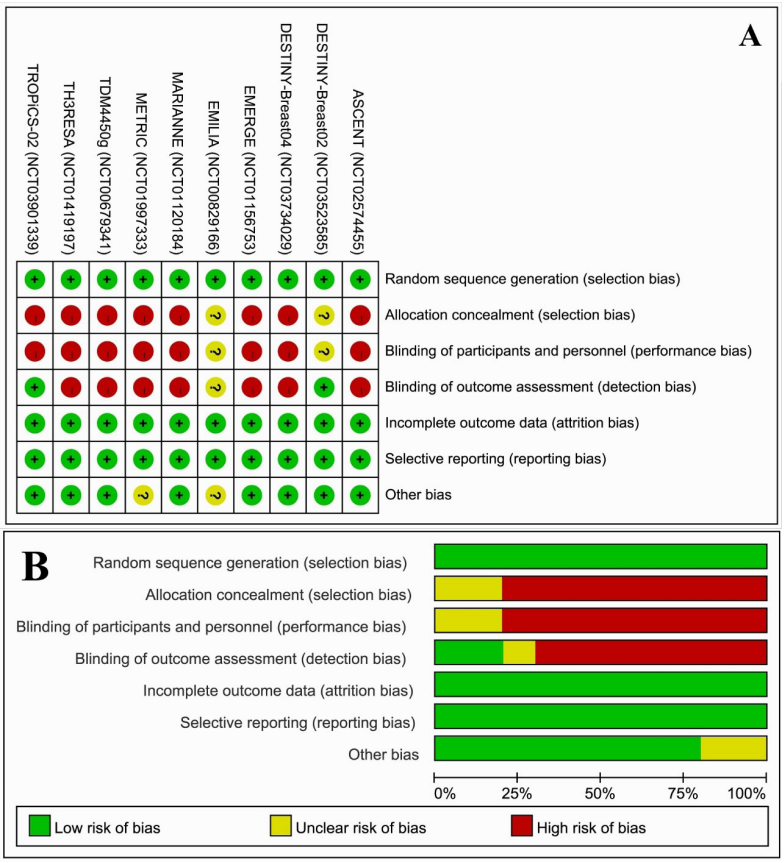

Figure S1 The judgements of risk of bias summary and risk of bias graph. (A) Shows the judgement of risk of bias summary and (B) shows the judgement of risk of bias graph.

Table S2 The funnel plot of publication bias

Analyzed label	P value*
Overall response rate	0.532
Clinical benefit rate	0.647
Progression-free survival	0.597
Overall survival	0.137
Frequency of any grade AEs	0.522
Frequency of grade ≥3 AEs	0.704

*, significant level: P<0.05.

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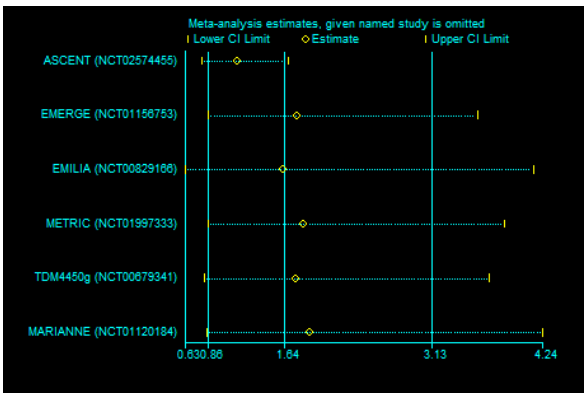

Figure S2 Sensitivity analysis for overall survival rate.

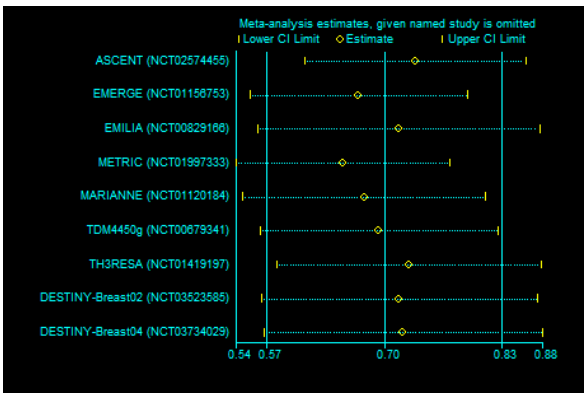

Figure S5 Sensitivity analysis for overall survival.

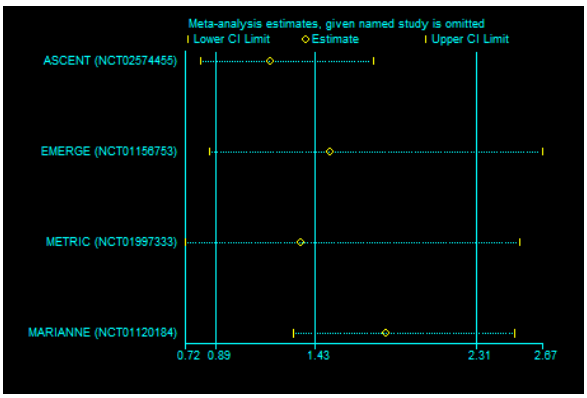

Figure S3 Sensitivity analysis for clinical benefit rate.

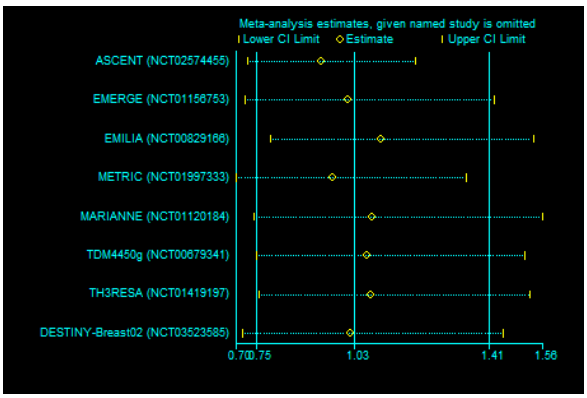

Figure S6 Sensitivity analysis for the frequency of any grade adverse events.

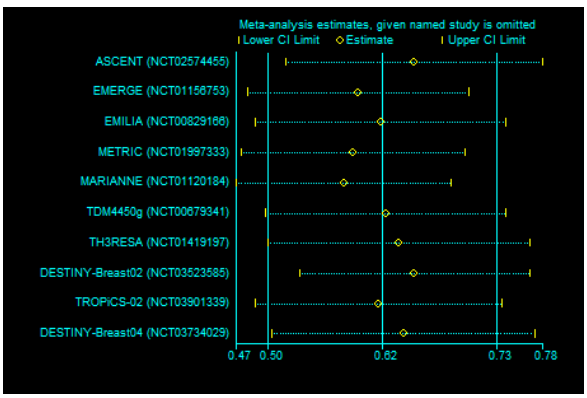

Figure S4 Sensitivity analysis for progression-free survival.

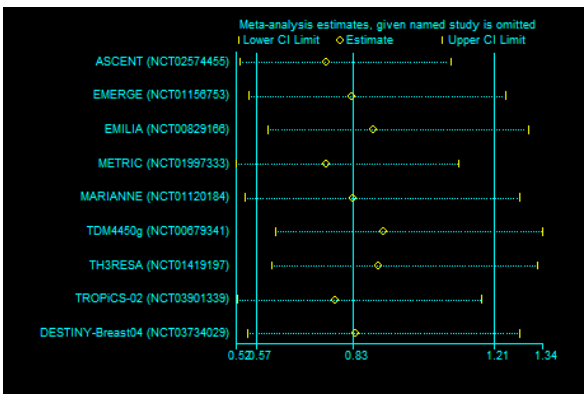

Figure S7 Sensitivity analysis for the frequency of grade ≥3 adverse events.

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Table S3 The detailed risk of bias assessments

Risk of bias	Risk of bias summary	Proportion of low risk (%)
Random sequence generation	All studies are described as randomized.	100
Allocation concealment	None of the studies have described the method of allocation concealment. Two studies do not provide sufficient information to accurately assess the method, therefore are at unclear risk of bias. The other nine studies are at high risk of bias.	0
Blinding of participants and personnel	None of the studies have described the method of allocation concealment. Two studies do not provide sufficient information to accurately assess the method, therefore are at unclear risk of bias. The other nine studies are at high risk of bias.	0
Blinding of outcome assessment	Two studies have described the method of blinding of outcome assessment. One study does not provide sufficient information to accurately assess the method, therefore is at unclear risk of bias. The other eight studies are at high risk of bias.	0–25
Incomplete outcome data	All studies are generally free of attrition bias.	100
Selective reporting	All studies are generally free of reporting bias. therefore is at unclear risk of bias.	100
Other bias	Nine studies are free of other bias, but the other two studies are at unclear risk of bias.	75–100

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ADCs	Physician's choice	Relative (95% CI)	Absolute (95% CI)		
Overall reponse rate												
10	randomised trials	not serious	very serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	691/2010 (34.4%)	443/1486 (29.8%)	**OR 1.78** (1.03 to 3.08)	**132 more per 1,000** (from 6 more to 269 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Clinical benefit rate												
6	randomised trials	not serious	very serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	788/1251 (63.0%)	483/861 (56.1%)	**OR 1.62** (0.79 to 3.34)	**113 more per 1,000** (from 59 fewer to 249 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Progression-free survival												
11	randomised trials	not serious	very serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	-/2585	-/1888	**HR 0.78** (0.61 to 0.94)	**-- per 1,000** (from -- to --)	⨁⨁⨁◯ Moderate	CRITICAL
Overall survival												
10	randomised trials	not serious	very serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	-/2538	-/1840	**HR 0.83** (0.64 to 1.02)	**-- per 1,000** (from -- to --)	⨁⨁⨁◯ Moderate	CRITICAL
Any grade adverse events												
11	randomised trials	not serious	very serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	-/2591	-/1795	**HR 1.07** (0.81 to 1.39)	**-- per 1,000** (from -- to --)	⨁⨁⨁◯ Moderate	IMPORTANT
Grade ≥ 3 adverse events												
11	randomised trials	not serious	very serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	-/2591	-/1795	**HR 0.77** (0.51 to 1.17)	**-- per 1,000** (from -- to --)	⨁⨁⨁◯ Moderate	IMPORTANT

Grade evidence by GRADEpro system.
Abbreviations: ADCs, antibody-drug conjugates; CI, confidence interval; HR, hazard Ratio; OR, odds ratio.

Figure S8 Grade evidence by GRADEpro system.

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