Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. A detailed description of the eligibility and exclusion criteria

Eligibility criteria

Participants: the patient was diagnosed with a malignant cancer that met the criteria of international guidelines. We did not limit the age, sex, number of lines of treatment, stage of the cancer, and other primary demographic characteristics of the patients with the cancer.

Intervention and Comparators: the intervention group was any of the rituximab biosimilars, trastuzumab biosimilars, and bevacizumab biosimilars (As of February 2023, only these three therapeutic cancer biosimilars have been approved in China). The comparators were their reference drug. We did not have any restrictions on dosage, treatment duration, treatment regimen, or number of patients included.

Study designs: we included randomized controlled trials (RCT) and cohort studies (comparative studies of biosimilars and originator drugs). The RCT was limited to explicit pre-specification for a non-inferiority or equivalence trial design. In addition, the primary endpoints of randomized controlled trials should include at least one of the efficacy endpoints. For the cohort studies, we did not restrict the study design (equipotent or noninferiority) and did not set out to have at least one primary efficacy endpoint, considering the evidence from the cohort studies as complementary evidence to the RCT.

Exclusion criteria

(1) Non-comparative studies (e.g., reviews, expert commentaries, editorials, and clinical guidelines);

(2) Studies without comparators;

(3) The primary endpoints of the randomized controlled trials were pharmacokinetic parameters or safety;

(4) The data for the cohort study design were derived from survey research.

eAppendix 2. Evidence sources and search strategy.

We conducted a systematic search based on PICO items in Embase, PubMed, Cochrane Library and ClinicalTrials.gov from database inception to February 1, 2023. XXL and XD were responsible for screening documents independently that met the inclusion criteria by title, abstract, and full text. If there was an inconsistency, it is resolved by the third reviewer.

Participants: Carcinoma or cancer or adenocarcinoma or tumor or oncology or neoplasm or malignant or lymphoma.

Intervention: biosimilar or 'follow-on biologic' or 'subsequent-entry biologic' or 'similar biologic' or 'highly similar' OR 'biologic copy' or 'subsequent-entry biological' or 'subsequent-entry biologic' or 'subsequent entry biologic' or 'subsequent entry biological' or 'biosimilarity' or Riabni or Ruxience or Truxima or rituximab-arrx or rituximab-pvvr or rituximab-abbs or Herzuma or trastuzumab-pkrb or Kanjinti ortrastuzumab-anns or Ogivri or trastuzumab-dkst or Ontruzant or trastuzumab-dttb or Trazimera or trastuzumab-qyyp or Mvasi or bevacizumab-awwb or Zirabev or bevacizumab-bvzr.

Comparators: Avastin or bevacizumab or Herceptin or trastuzumab or Rituxan or Rituximab or reference or originator or brand name or brand-name.

Study designs: Compared or comparison or compare or contrast or versus or equivalence or switching or equivalent or equivalence or equivalence or comparing.

The research strategy was similar to the previous study [JAMA Oncol. 2022;8(4):537-545] and the search strategy in this study as follow:

Search strategy of PubMed	
#1	Carcinoma[Title/Abstract] OR cancer[Title/Abstract] OR adenocarcinoma[Title/Abstract] OR tumor[Title/Abstract] OR oncology[Title/Abstract] OR neoplasm[Title/Abstract] OR malignant[Title/Abstract] OR lymphoma[Title/Abstract]
#2	biosimilar[Title/Abstract] OR 'follow-on biologic'[Title/Abstract] OR 'subsequent-entrybiologic'[Title/Abstract] OR 'similar biologic'[Title/Abstract] OR 'highly similar'[Title/Abstract] OR 'biologic copy'[Title/Abstract] OR 'subsequent-entry biological'[Title/Abstract] OR 'subsequent-entry biologic'[Title/Abstract] OR 'subsequent entry biologic'[Title/Abstract] OR 'subsequent entry biological'[Title/Abstract] OR 'biosimilarity'[Title/Abstract] OR Riabni[Title/Abstract] OR Ruxience[Title/Abstract] OR Truxima[Title/Abstract] OR rituximab-arrx[Title/Abstract] OR rituximab-pvvr[Title/Abstract] OR rituximab-abbs[Title/Abstract] OR Herzuma[Title/Abstract] OR trastuzumab-pkrb[Title/Abstract] OR Kanjinti ortrastuzumab-anns[Title/Abstract] OR Ogivri[Title/Abstract] OR trastuzumab-dkst[Title/Abstract] OR Ontruzant[Title/Abstract] OR trastuzumab-dttb[Title/Abstract] OR Trazimera[Title/Abstract] OR trastuzumab-qyyp[Title/Abstract] OR Mvasi[Title/Abstract] OR bevacizumab-awwb[Title/Abstract] OR Zirabev[Title/Abstract] OR bevacizumab-bvzr[Title/Abstract]
#3	Avastin[Title/Abstract] OR bevacizumab[Title/Abstract] OR Herceptin[Title/Abstract] OR trastuzumab[Title/Abstract] OR Rituxan[Title/Abstract] OR Rituximab[Title/Abstract] OR reference[Title/Abstract] OR originator[Title/Abstract] OR brand name[Title/Abstract] OR brand-name[Title/Abstract]
#4	Compared[Title/Abstract] OR comparison[Title/Abstract] OR compare[Title/Abstract] OR contrast[Title/Abstract] OR versus[Title/Abstract] OR equivalence[Title/Abstract] OR switching[Title/Abstract] OR equivalent[Title/Abstract] OR equivalence[Title/Abstract] OR equivalence[Title/Abstract] OR comparing[Title/Abstract]
#5	#1 and #2 and #3 and #4
Search strategy of Embase	

#1	carcinoma:ab,ti OR cancer:ab,ti OR adenocarcinoma:ab,ti OR tumor:ab,ti OR oncology:ab,ti OR neoplasm:ab,ti OR malignant:ab,ti OR lymphoma:ab,ti
#2	biosimilar:ab,ti OR 'follow-on biologic':ab,ti OR 'subsequent-entrybiologic':ab,ti OR 'similar biologic':ab,ti OR 'highly similar':ab,ti OR 'biologic copy':ab,ti OR 'subsequent-entry biological':ab,ti OR 'subsequent-entry biologic':ab,ti OR 'subsequent entry biologic':ab,ti OR 'subsequent entry biological':ab,ti OR 'biosimilarity':ab,ti OR riabni:ab,ti OR ruxience:ab,ti OR truxima:ab,ti OR 'rituximab arrx':ab,ti OR 'rituximab pvvr':ab,ti OR 'rituximab abbs':ab,ti OR herzuma:ab,ti OR 'trastuzumab pkrb':ab,ti OR 'kanjinti ortrastuzumab-anns':ab,ti OR ogivri:ab,ti OR 'trastuzumab dkst':ab,ti OR ontruzant:ab,ti OR 'trastuzumab dttb':ab,ti OR trazimera:ab,ti OR 'trastuzumab qyyp':ab,ti OR mvasi:ab,ti OR 'bevacizumab awwb':ab,ti OR zirabev:ab,ti OR 'bevacizumab bvzr':ab,ti
#3	avastin:ab,ti OR bevacizumab:ab,ti OR herceptin:ab,ti OR trastuzumab:ab,ti OR rituxan:ab,ti OR rituximab:ab,ti OR reference:ab,ti OR originator:ab,ti OR 'brand name':ab,ti
#4	compared:ab,ti OR comparison:ab,ti OR compare:ab,ti OR contrast:ab,ti OR versus:ab,ti OR switching:ab,ti OR equivalent:ab,ti OR equivalence:ab,ti OR comparing:ab,ti
#5	#1 and #2 and #3 and #4
Cochrane library	
#1	(Carcinoma or cancer or adenocarcinoma or adenocarcinoma or malignancy or tumor or oncology or neoplasm or malignant or malignant or lymphoma):ti,ab,kw
#2	(biosimilar or 'follow-on biologic' or 'subsequent-entrybiologic' or 'similar biologic' or 'highly similar' OR 'biologic copy' or 'subsequent-entry biological' or 'subsequent-entry biologic' or 'subsequent entry biologic' or 'subsequent entry biological' or 'biosimilarity' or Riabni or Ruxience or Truxima or rituximab-arrx or rituximab-pvvr or rituximab-abbs or Herzuma or trastuzumab-pkrb or Kanjinti ortrastuzumab-anns or Ogivri or trastuzumab-dkst or Ontruzant or trastuzumab-dttb or Trazimera or trastuzumab-qyyp or Mvasi or bevacizumab-awwb or Zirabev or bevacizumab-bvzr):ti
#3	(Avastin or bevacizumab or Herceptin or trastuzumab or Rituxan or Rituximab or reference or originator or brand name or brand-name):ti
#4	(Carcinoma or cancer or adenocarcinoma or adenocarcinoma or malignancy or tumor or oncology or neoplasm or malignant or malignant or lymphoma):ti,ab,kw
#5	#1 and #2 and #3 and #4
Search strategy of Clinicaltrials.gov	

#1	(Rituximab OR Trastuzumab OR Bevacizumab) AND Biosimilar AND ("compared" OR "comparison" OR "compare" OR "contrast" OR "versus" OR "equivalence" OR "switching" OR "equivalent" OR "equivalence" OR "bioequivalence" OR "comparing") | Completed WITH RESULTS

eAppendix 3. Price and uptake of biosimilar and reference drugs.

The Chinese healthcare system is established under a multi-tiered governance structure, involving the central, provincial, regional, and county governments[1,2]. The majority of drug procurement occurs through centralized bidding at the provincial or city level, which may result in regional variations[1]. Therefore, XXL and XD extracted the winning prices of each biosimilar and originator drug between 2015-2022 from different provinces or cities and calculated the weighted average price of the drug using the number of population as weights. The exchange rate of the U.S. dollar to the Chinese yuan was 6.9. Similar to the previous study[1], we adjusted the price of biosimilars and their reference drug based on the annual consumption index published by the National Bureau of Statistics of China given the effect of inflation.

The healthcare facilities are categorized into primary healthcare facilities, first, second and third level hospitals in China. Usually, a higher level means a greater level of treatment. In this study, we used the national hospital sales volume from Pharnexcloud databse module[3], which covered the sales volume of cancer biosimilars in secondary and higher hospitals across the country, as no public database of drug sales volume was available. XXL and XD extracted the sales volume of each cancer biosimilar and originator drugs for each quarter since the biosimilar was introduced to the market. For multiple biosimilars that were approved (e.g. eight bevacizumab biosimilars were approved in China), we aggregated the sales volume of these biosimilars. The annual uptake rate for biosimilars is calculated by dividing the one-year sales of biosimilars by the one-year sales of their reference drugs.

The cut-off date for price uptake rates of biosimilars was December 31, 2022.

eTable 1. Comparison of regulatory factors for biosimilar oncology drugs in the NMPA, FDA, EMA, and PMDA.

Items	NMPA	FDA	EMA	PMDA
Key patent expiration of Bevacizumab	2018	2017	2018	2017
Key patent expiration of Rituximab	2013	2018	2013	NA
Key patent expiration of Trastuzumab	NA	2019	2014	NA
Patent challenges	Rarely occur	Either formal litigation in court or administrative challenges (inter partes reviews) occur for 56% of approved oncology biosimilars	Rarely occur	In January, 2019, Celltrion won two appeal cases claiming that Roche's patent for trastuzumab for the treatment of HER2-positive breast cancer was invalid;Tokyo District Court dismissed Genentech's claim against Sandoz-Kirin to prohibit the marketing of a rituximab biosimilar
Indication extrapolation	Primary consideration is given to core patents, with more limited impact of patents on indications; Exclusivity periods have not been established	Impact of core and indication patents; Impact of exclusivity period (especially for 7-year orphan drug designation)	Impact of core and indication patents; Impact of exclusivity period	Impact of core and indication patents; Impact of exclusivity period.
Reimbursement policy	Determined by China National Healthcare Security Administration	Determined by individual insurers	Determined by national authorities	Determined centrally by Japan's Central Social Medical Insurance Council of the Ministry of Health, Labour, and Welfare
Switching of patients from a reference biologic to a biosimilar	No regulatory designation for interchangeability	Not permitted unless the biosimilar has been formally designated as interchange-able by FDA	No regulatory designation for interchangeability	Permitted under the PMDA's Guideline for the quality, safety, and efficacy assurance of follow-on biologics (revised Feb 2, 2020)

Pharmacist substitution of a reference biologic with a biosimilar	Not permitted	Not permitted unless FDA has designated the biosimilar as interchangeable with the reference biologic, and even if it has 45 US states do not permit substitution unless patient consent, doctor consent, or both have been documented	Permitted in several EU countries	Not permitted
Price	Price competition; Price discounts of biosimilars in China range from 10-31% in 2022 (the data derived from eTable 14 of this study)	Price competition; Price discounts of biosimilars in the USA range from 10% to 33%; Impact of pay for delaying agreements between biosimilars and originator drugs	Price competition; European price discounts for biosimilars average 30%	The Japanese Ministry of Health, Labour, and Welfare sets prices for biosimilars at a 30% discount in principle, and at 40% if the biosimilar has ten or more approved indications

Items of FDA, EMA, and PMDA derived from published literature (Lancet Oncol. 2020;21(12):e575-e588).
Abbreviations: NA, not applicable; FDA, US Food and Drug Administration; EMA, European Medicines Agency; PMDA, Japanese Pharmaceuticals and Medical Devices Agency; NMPA, National Medical Products Administration.

eTable 2. Individual biosimilar guidelines issued by the NMPA in China(n=10).

Initiation date	Guidelines	Biosimilar approval or not
2020-05-28	Clinical trial design guidelines for liraglutide injection biosimilars	No
2020-07-20	Guidelines for clinical trials of rituximab injection biosimilars	Yes
2020-07-20	Guidelines for clinical trials of trastuzumab biosimilars for injection	Yes
2020-08-03	Clinical trial guidelines for adalimumab injection biosimilars	Yes
2020-08-03	Clinical trial guidelines for bevacizumab injection biosimilars	Yes
2021-02-04	Guidelines for clinical trials of omalizumab biosimilars for injection	No
2021-04-22	Guidelines for clinical trials of tolimumab injection biosimilars	Yes
2021-04-22	Guidelines for clinical trials of patalizumab injection biosimilars	No
2022-01-20	Clinical trial design guidelines for cetuximab injection biosimilars	No
2022-01-26	Guidelines for clinical trial design of teriparatide injection biosimilars	Yes

eTable 3. The cancer biosimilars approved by the FDA, EMA, PMDA, and NMPA (as of February 1, 2023).

Product	NMPA		EMA		FDA		PMDA	
INN	Reference	Biosimilars	Reference	Biosimilars	Reference	Biosimilars	Reference	Biosimilars
Bevacizumab	Avastin (2010)	Ankeda (2019) Dayoutong (2020) Boyounuo (2021) Airuituo (2021) Pubeixi (2021) Beianting (2021) Puxinting (2021) Hanbeitai (2021)	Avastin (2005)	Mvasi (2018) Zirabev (2019) Aybintio (2020) Alymsys (2021) Oyavas (2021) Abevmy (2021) Vegzelma (2022)	Avastin (2004)	Mvasi (2017) Zirabev (2019) Alymsys (2022) Vegzelma (2022)	Avastin (2007)	Bevacizumab(Pfizer) (2019) Bevacizumab (Daiichi Sankyo) (2019) Bevacizumab (Nichiiko) (2021) Bevacizumab (CTNK) (2022)
Rituximab	Mabthera (2000)	Hanlikang (2019) Dabohua (2020)	Mabthera (1998)	Truxima (2017) Rixathon (2017) Ruxience (2020)	Rituxan (1997)	Truxima (2018) Ruxience (2019) Riabni (2020)	Rituxan (2001)	Rituximab (KHK) (2017) Rituximab (Pfizer) (2019)
Trastuzumab	Herceptin (2002)	Hanyouqu (2020)	Herceptin (1998)	Ontruzant (2017) Herzuma (2018) Kanjinti (2018) Trazimera (2018) Ogivri (2018) Zercepac (2020)	Herceptin (1998)	Ogivri (2017) Herzuma (2018) Ontruzant (2019) Trazimera (2019) Kanjinti (2019)	Herceptin (2001)	Trastuzumab (NK/CTH) (2017) Trastuzumab (Daiichi Sankyo) (2018) Trastuzumab (Pfizer) (2018)

The reference products and biosimilars are expressed as trade names. The bracketed content indicates the year of approval.
Abbreviations: INN, International Nonproprietary Names. FDA, US Food and Drug Administration. EMA, European Medicines Agency. PMDA, Japanese Pharmaceuticals and Medical Devices Agency. NMPA, National Medical Products Administration.

eTable 4. Biosimilar products approved in China (n=23).

Numbers	Biosimilars		Reference drugs		Time difference[a]
	Names	Approval date	Names	Approval date	
1	Rituximab-HLX01	2019-02-22	Rituximab	2000-03-15	19.0
2	Rituximab-IBI301	2020-09-30			
3	Teriparatide-SAL001	2019-09-29	Teriparatide	2011-03-04	8.6
4	Adalimumab-BAT1406	2019-11-04	Adalimumab	2010-02-26	9.7
5	Adalimumab-HS016	2019-12-06			
6	Adalimumab-IBI303	2020-09-02			
7	Adalimumab-HLX03	2020-12-02			
8	Adalimumab-TQZ2301	2022-01-18			
9	Adalimumab-UBP1211	2022-03-01			
10	Bevacizumab-QL1101	2019-12-06	Bevacizumab	2010-02-26	9.8
11	Bevacizumab-IBI305	2020-06-17			
12	Bevacizumab-LY01008	2021-04-30			
13	Bevacizumab-BP102	2021-06-22			
14	Bevacizumab-BAT1706	2021-11-17			
15	Bevacizumab-MIL60	2021-11-24			
16	Bevacizumab-TAB008	2021-11-30			
17	Bevacizumab-HLX04	2021-11-30			
18	Trastuzumab-HL02	2020-08-12	Trastuzumab	2002-09-05	17.9
19	Infliximab-CMAB008	2021-07-12	Infliximab	2006-05-17	15.2
20	Infliximab-HS626	2021-09-24			
21	Infliximab-GB242	2022-02-23			
22	Insulin aspart-HS005	2021-09-13	Insulin aspart	2002-08-16	19.1
23	Denosumab-LY06006	2022-11-08	Denosumab	2019-05-21	3.5

[a]Time difference is defined as the duration between the first approved biosimilar and the reference drug.

eTable 5. The number of approved and in-development oncology biosimilars products in China (As of February 1, 2023)

Biosimilars	I phase	III phase	NDA review	Approved
Bevacizumab	5	9	2	8
Rituximab	2	5	2	2
Trastuzumab	2	7	3	1

eTable 6. Demographic and clinical characteristics of the included RCTs (n=39).

Number	First Author	Year	Clinical trial number	Sponsor	Country	Study design	MRCT	Cancer types	Biosimilar	Originator	Sex (M/F)	No. Patients in biosimilar	No. Patients in originator	Primary efficacy endpoints (Times)	study duration[a] (month)
Bevacizumab biosimilars vs Bevacizumab															
1	Stroyakovskiy et al.[1]	2022	NCT01763645	Biocad	Russian	equivalence	Yes	advanced non-squamous NSCLC	BCD-021	bevacizumab	230/110	212	145	ORR (18w)	25.37
2	Thatcher et al.[2]	2019	NCT01966003	Amgen	US	equivalence	Yes	advanced nonsquamous NSCLC	ABP215	bevacizumab	NA	328	314	ORR (25w)	20.63
3	Reinmuth et al.[3]	2019	NCT02364999	Pfizer	US	equivalence	Yes	newly diagnosed Stage IIIB or IV NSCLC	PF-06439535	bevacizumab	467/252	358	361	ORR (19w)	25.37
4	Reck et al.[4]	2020	NCT02754882	Samsung	Korea	equivalence	Yes	metastatic or recurrent NSCLC	SB8	bevacizumab	508/255	379	384	ORR (24w)	18.93
5	Yang et al.[5]	2019	NCT02954172	Innovent	China	equivalence	No	metastatic or recurrent non-squamous NSCLC	IBI305	bevacizumab	279/162	224	226	ORR (18w)	23.00
6	Trukhin et al.[6]	2021	NCT03296163	mAbxience	Spain	equivalence	Yes	stage IIIB/IV non-squamous NSCLC	MB02	bevacizumab	383/244	315	312	ORR (18w)	17.07
7	Rezvani et al.[7]	2020	NCT03288987	AryoGen	Iran	noninferiority	No	metastatic CRC	BE1040V	bevacizumab	91/35	82	42	PFS (NA)	22.13
8	Qin et al.[8]	2021	NCT03511963	Henlius	China	equivalence	No	metastatic CRC	HLX04	bevacizumab	404/271	340	337	PFSR (36w)	24.57
9	Shi et al.[9]	2021	NCT03533127	Luye	China	equivalence	No	unresectable, metastatic, or recurrent non-squamous NSCLC	LY01008	bevacizumab	352/237	324	325	ORR (18w)	31.47
10	Chu et al[10]	2021	NCT03169335	Qilu	China	equivalence	No	untreated advanced non-squamous NSCLC	QL1101	bevacizumab	318/217	269	266	ORR (18w)	15.07
11	Hengrui[11] (Sponsor)	2022	NCT05169801	HengRui	China	equivalence	No	metastatic or recurrent non-squamous NSCLC	BP102	bevacizumab	NA	262	255	ORR (18w)	21.13
12	Wan et al.[12]	2021	NCT03196986	Mabworks	China	equivalence	No	metastatic or recurrent non-squamous NSCLC	MIL60	bevacizumab	325/183	257	260	ORR (12w)	23.87
13	Syrigos et al.[13]	2021	NCT02810457	Centus	UK	equivalence	Yes	advanced/recurrent non-squamous NSCLC	FKB238	bevacizumab	483/248	364	367	ORR (30m)	28.97
14	Kim et al.[14]	2022	NCT02272413	Boehringer Ingelheim	Germany	equivalence	Yes	recurrent or metastatic (stage IV) NSCLC	BI695502	bevacizumab	417/246	338	333	ORR (18w)	24.10

Number	First Author	Year	Clinical trial number	Sponsor	Country	Study design	MRCT	Cancer types	Biosimilar	Originator	Sex (M/F)	No. Patients in biosimilar	No. Patients in originator	Primary efficacy endpoints (Times)	study duration[a] (month)
15	Socinski et al.[15]	2021	EudraCT no. 2015-005141-32	Mylan GmbH	US	equivalence	Yes	IV unresectable, recurrent, or metastatic NSCLC	MYL-14020	bevacizumab	424/247	337	334	ORR (18w)	28.83
16	Chen et al.[16]	2022	NCT03329911	Bio-Thera	China	equivalence	Yes	advanced nonsquamous NSCLC	BAT1706	bevacizumab	NA	325	326	ORR (18w)	24.87
17	Lu et al.[17]	2023	NCT05427305	TOT	China	equivalence	No	metastatic EGFR wild-type non-squamous NSCLC	TAB 008	bevacizumab	457/194	277	272	ORR (18w)	29.53
18	Verschraegen et al.[18]	2022	NCT03676192	Celltrion	Korea	equivalence	No	metastatic or recurrent non-squamous NSCLC.	CT-P16	bevacizumab	397/149	342	347	ORR (21w)	28.50
Rituximab biosimilars vs Rituximab															
1	Kaplanov et al.[19]	2014	NA	Biocad	Russia	noninferiority	Yes	B-Cell Non-Hodgkin's Lymphoma/follicular non-Hodgkin's lymphoma	BCD-020	rituximab	NA	46	46	ORR (NA)	23.73
2	Toogeh et al.[20]	2018	IRCT201305296302N5	AryoGen	Iran	noninferiority	No	untreated or recurrent B-CLL	Zytux	rituximab	57/13	35	35	ORR (NA)	8.00
3	Jurczak et al.[21]	2017	NCT01419665	Sandoz	Switzerland	equivalence	Yes	untreated, advanced stage (Ann Arbor stage III or IV) follicular lymphoma	GP2013	rituximab	277/350	314	315	ORR (21w)	43.90
4	Kim et al.[22]	2017	NCT02162771	Celltrion	Korea	noninferiority	No	newly diagnosed advancedstage follicular lymphoma	CT-P10	rituximab	63/77	70	70	ORR (24w)	18.23
5	Ogura et al.[23]	2018	NCT02260804	Celltrion	Korea	equivalence	No	untreated low-tumour-burden follicular lymphoma	CT-P10	rituximab	123/145	130	128	ORR (7m)	26.23
6	Poddunaya et al.[24]	2020	NCT01701232	Biocad	Russia	equivalence	Yes	indolent non-Hodgkin lymphomas	BCD-020	rituximab	84/90	89	85	ORR (4w)	64.97

Number	First Author	Year	Clinical trial number	Sponsor	Country	Study design	MRCT	Cancer types	Biosimilar	Originator	Sex (M/F)	No. Patients in biosimilar	No. Patients in originator	Primary efficacy endpoints (Times)	study duration[a] (month)
7	Candelaria et al.[25]	2019	NCT02268045	mAbxience	Spain	noninferiority	Yes	DLBCL with untreated CD20þ, at stage I (only with bulky disease) or stages II to IV disease	RTXM83	rituximab	155/117	136	136	ORR (18w)	36.53
8	Sharman et al.[26]	2020	NCT02213263	Pfizer	US	equivalence	Yes	Low Tumor Burden, Follicular Lymphoma	PF-05280586	rituximab	178/216	196	198	ORR (26w)	37.30
9	Niederwieser et al.[27]	2020	NCT02747043	Amgen	US	equivalence	Yes	Follicular Lymphoma	ABP 798	rituximab	130/126	128	128	ORR (28w)	37.63
10	Archigen[28] (Sponor)	2020	NCT02809053	Archigen	Korea	equivalence	Yes	patients with low Tumor Burden Follicular lymphoma	SAIT101	rituximab	141/174	157	158	ORR (28w)	30.33
11	Shi et al.[29]	2020	NCT02787239; CTR20150583	Henlius	China	equivalence	No	treatment-naïve, CD20-positive DLBCL	HLX01	rituximab	220/182	201	206	ORR (18w)	31.43
12	Song et al.[30]	2021	NCT02867566	Innovent	China	equivalence	No	untreated CD20 DLBCL	IBI301	rituximab	214/202	209	210	ORR (18w)	36.97
Trastuzumab biosimilars vs Trastuzumab															
1	Stebbing et al.[31]	2017	NCT02162667	Celltrion	Korea	equivalence	Yes	neoadjuvant treatment of HER2-positive early-stage breast cancer.	CT-P6	trastuzumab	0/549	271	278	pCR (30w)	24.17
2	Rugo et al.[32]	2017	NCT02472964	Mylan Inc.	UK	equivalence	Yes	ERBB2 (HER2)–Positive Metastatic Breast Cancer	MYL-14010	trastuzumab	0/528	250	250	ORR (24w)	44.63
3	Von Minckwitz et al.[33]	2018	NCT01901146/CT 2012-004319-29	Amgen	US	equivalent	Yes	Early BC	ABP 980	trastuzumab	0/725	364	361	pCR (7w)	36.73
4	Pivot et al.[34]	2018	NCT02149524	Samsung	Korea	equivalence	No	Early BC	SB3	trastuzumab	0/875	437	438	pCR (24w)	23.33
5	Pegram et al.[35]	2019	NCT01989676	Pfizer	US	equivalence	Yes	HER2-positive metastatic breast cancer	PF-05280014	trastuzumab	0/707	352	355	ORR (25w)	30.40

Number	First Author	Year	Clinical trial number	Sponsor	Country	Study design	MRCT	Cancer types	Biosimilar	Originator	Sex (M/F)	No. Patients in biosimilar	No. Patients in originator	Primary efficacy endpoints (Times)	study duration[a] (month)
6	Pivot et al.[36]	2022	NCT03013504	Prestige	Singapore	equivalence	Yes	ERBB2-positive early breast cancer	HD201	trastuzumab	0/502	251	251	pCR (24w)	14.13
7	Alexeev et al.[37]	2020	NCT01764022	Biocad	Russian	equivalence	Yes	metastatic HER2(+) breast cancer	BCD-022	trastuzumab	0/225	115	110	ORR (18w)	29.37
8	Xu et al.[38]	2021	NCT03084237; EudraCT 2016-000206-10; CTR20160526	Henlius	China	equivalence	Yes	Recurrent or Metastatic HER2-Positive breast cancer	HLX02	trastuzumab	0/649	324	325	ORR (24w)	24.17
9	Nodehi et al.[39]	2022	NCT03425656	AryoGen	Iran	noninferiority	No	HER2-positive early-stage breast cancer patients	TA4415V	trastuzumab	0/92	48	44	pCR (23w)	20.17

[a]Study duration is defined as the period from the date of first enrolled patient to cut-off date of primary analysis. The median duration for assessing the primary efficacy endpoints of bevacizumab biosimilars, rituximab biosimilars, and trastuzumab biosimilars was 18 weeks, 23 weeks, and 24 weeks, respectively.
Abbreviations: NA, not available; ORR, objective response rate; pCR, pathologic complete response; PFS, progression-free survival; PFSR, progression-free survival rate; MRCT, multi-regional clinical trial; Early BC, early breast cancer; w, week.

eTable 7. Demographic and clinical characteristics of the included cohort studies (n=10).

First Author	Year	Trial design	Country	Sex(M/F)	Cancer types	Biosimilar	Originator	No. Patients in biosimilar	No. Patients in originator	Primary efficacy endpoints	study duration[a] (month)
Rituximab											
Roy et al.[40]	2013	retrospective analysis	India	156/67	diffuse large B-cEll lymphoma	Reditux	Rituximab	72	101	NA	79.07
Bankar et al.[41]	2020	retrospective analysis	India	111/41	diffuse large B-cEll lymphoma	Reditux	Rituximab	92	60	NA	48.67
Deng et al.[42]	2022	retrospective analysis	China	20/13	diffuse large B-cEll lymphoma	HLX-01	Rituximab	15	18	NA	26.30
Bevacizumab											
Zhao et al.[43]	2022	retrospective analysis	China	533/413	advanced non-small-cell lung cancer	QL1101	Bevacizumab	551	395	ORR	35.47
Trastuzumab											
Bae et al.[44]	2021	retrospective analysis	Korea	NA	Early-stage and metastatic breast cancer	CT-P6	Trastuzumab	125	129	pCR & PFS	69.00
Park et al.[45]	2022	retrospective analysis	Korea	NA	advanced gastric Cancer	CT-P6	Trastuzumab	30	72	NA	120.70
Yang et al.[46]	2022	retrospective analysis	Canada	20/13	early breast cancer w/ neoadjuvant chemotherapy	MYL-1401 O	Trastuzumab	59	77	pCR	12.13
Bernat-Peguer a et al.[47]	2022	retrospective analysis	Spain	NA	early breast cancer	CT-P6	Trastuzumab	20	24	NA	48.67
Eser et al.[48]	2023	real-world use/ retrospective analysis	Turkey	NA	early and metastatic breast cancer	MYL-1401 O	Trastuzumab	25	28	pCR and PFS	42.53
Liu et al.[49]	2022	retrospective analysis	China	105/0	early breast cancer	HLX02	Trastuzumab	65	40	NA	9.07

[a]Study duration is defined as the period from the period of participants will be followed and observed to assess the occurrence of specific outcomes.
Abbreviations: NA, not available; ORR, objective response rate; pCR, pathologic complete response; PFS, progression-free survival.

eTable 8. The results of the risk of bias assessment of the RCTs based on the Cochrane Collaboration's tools.

First Author	Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessors (performance bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Other potential bias	Overall assessment: risk of bias
Bevacizumab biosimilars vs Bevacizumab									
Stroyakovskiy et al.[1]	2022	+	+	+	+	+	+	+	low
Thatcher et al.[2]	2019	+	+	+	+	+	+	+	low
Reinmuth et al.[3]	2019	+	+	+	—	+	+	+	low
Reck et al.[4]	2020	+	+	+	+	—	+	+	low
Yang et al.[5]	2019	+	+	+	+	+	+	+	low
Trukhin et al.[6]	2021	+	+	+	+	+	+	+	low
Rezvani et al.[7]	2020	+	+	+	+	+	+	+	low
Qin et al.[8]	2021	+	+	+	+	+	+	+	low
Shi et al.[9]	2021	+	+	+	—	+	+	+	low
Chu et al[10]	2021	+	+	+	?	—	+	+	unclear
Hengrui[11] (Sponsor)	2022	?	+	+	+	+	+	+	low
Wan et al.[12]	2021	+	+	+	+	+	+	+	low
Syrigos et al.[13]	2021	+	+	+	+	+	+	+	low
Kim et al.[14]	2021	+	+	+	+	—	+	+	low
Socinski et al.[15]	2021	?	?	+	+	+	+	+	unclear
Chen et al.[16]	2022	?	+	+	?	+	+	+	unclear

First Author	Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessors (performance bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Other potential bias	Overall assessment: risk of bias
Lu et al.[17]	2023	+	+	+	+	—	+	+	low
Verschraegen et al.[18]	2022	+	+	+	+	+	+	+	low
Rituximab biosimilars vs Rituximab									
Kaplanov et al.[19]	2014	+	+	—	—	—	+	+	high
Toogeh et al.[20]	2018	+	+	+	+	+	+	+	low
Jurczak et al.[21]	2017	+	+	+	+	+	+	+	low
Kim et al.[22]	2017	+	+	+	+	+	+	+	low
Ogura et al.[23]	2018	+	+	+	+	+	+	+	low
Poddunaya et al.[24]	2020	+	+	—	—	+	+	+	high
Candelaria et al.[25]	2019	+	+	+	+	+	+	+	low
Sharman et al.[26]	2020	+	+	+	?	+	+	+	low
Niederwieser et al.[27]	2020	+	+	+	+	+	+	+	low
Archigen[28] (Sponor)	2020	?	+	+	+	+	+	+	low
Shi et al.[29]	2020	?	+	+	?	+	+	+	unclear
Song et al.[30]	2021	+	+	+	+	+	+	+	low
Trastuzumab biosimilars vs Trastuzumab									
Stebbing et al.[31]	2017	+	+	+	+	+	+	+	low

First Author	Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessors (performance bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Other potential bias	Overall assessment: risk of bias
Rugo et al.[32]	2017	+	+	+	+	+	+	+	low
von Minckwitz et al.[33]	2018	+	+	+	+	+	+	+	low
Pivot et al.[34]	2018	+	+	+	?	+	+	+	low
Pegram et al.[35]	2019	+	+	+	+	+	+	+	low
Pivot et al.[36]	2022	+	+	+	?	?	+	+	unclear
Alexeev et al.[37]	2020	+	+	+	+	+	+	+	low
Xu et al.[38]	2021	+	+	+	+	+	+	+	low
Nodehi et al.[39]	2022	?	+	+	+	+	+	+	low

The green, yellow and red color indicates low risk, unclear and high risk of bias, respectively.

eTable 9. The results of the risk of bias assessment of the cohort studies based on the Newcastle-Ottawa Risk of Bias Assessment Tool.

First Author	Year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at baseline	Comparability of cohorts on the basis of the design or analysis	Assessment of outcomes	Was follow-up long enough for outcomes occur	Adequacy of follow up of cohorts	Total scores[a] (risk of bias)
Roy et al.[40]	2013	1	1	1	1	0	1	1	1	7 (low)
Bankar et al.[41]	2020	1	1	1	1	1	1	1	0	7 (low)
Deng et al.[42]	2022	1	1	1	1	1	1	0	0	6 (high)
Zhao et al. [43]	2023	1	1	1	1	2	1	0	0	7 (low)
Bae et al.[44]	2021	1	1	1	1	2	1	1	0	8 (low)
Park et al.[45]	2022	1	1	1	1	1	1	0	0	6 (high)
Yang et al.[46]	2022	1	1	1	1	1	0	0	0	5 (high)
Bernat-Peguera et al.[47]	2022	1	1	1	1	1	1	0	0	6 (high)
Eser et al.[48]	2023	1	1	1	1	2	1	0	0	7 (low)
Liu et al.[49]	2022	1	1	1	1	2	1	0	0	7 (low)

The green, yellow and red colours indicates low risk, some concerns and high risk of bias, respectively; [a]Total scores (risk of bias): scoring from 7-9: high quality; Scoring from 4-6: high risk of bias; Scoring from 0-3: very high risk of bias.

eTable 10. Characteristics of pivotal clinical trials used to support approval of cancer biosimilars by the NMPA, FDA, EMA, and PMDA.

Regulatory Agencies	Brand name	Clinical trial number	Study design	Margin criterion	Cancer types	Biosimilar	Originator	No. Patients in biosimilar	No. Patients in originator	Primary efficacy endpoints (Times)
Bevacizumab biosimilars										
FDA/EMA/PMDA	Mvasi/Bevacizumab BS	NCT01966003	equivalence	RR=90%CI (0.67, 1.50)	NSCLC	ABP215	bevacizumab	328	314	ORR (25w)
FDA/EMA/PMDA	Zirabev/Bevacizumab BS	NCT02364999	equivalence	RR=90%CI (0.73, 1.37)	NSCLC	PF-06439535	bevacizumab	358	361	ORR (19w)
FDA/EMA/PMDA	Vegzelma/Bevacizumab BS	NCT03676192	equivalence	RR=90%CI (0.73,1.36); RD=95%CI(-12.5%, 12.5%)	NSCLC	CT-P16	bevacizumab	342	347	ORR (21w)
FDA/EMA/PMDA	Alymsys/Bevacizumab BS	NCT03296163	equivalence	RR=90%CI (0.73,1.36); RD=(-12%, 12%)	NSCLC	MB02	bevacizumab	315	312	ORR (18w)
EMA	Aybintio	NCT02754882	equivalence	RR=90%CI (0.74,1.36); RD=95%CI(-12.5%, 12.5%)	NSCLC	SB8	bevacizumab	379	384	ORR (24w)
EMA	Equidacent (withdrawal)	NCT02810457	equivalence	RR=90%CI (0.73, 1.38); RD=95%CI (-12.21%, 12.21%)	NSCLC	FKB238	bevacizumab	364	367	ORR (30m)
EMA	Abevmy	EudraCT no. 2015-005141-32	equivalence	RR=90%CI (0.73, 1.36); RD=95%CI(-12.5%, 12.5%)	NSCLC	MYL-14020	bevacizumab	337	334	ORR (18w)
NMPA	Dayoutong	NCT02954172	equivalence	RR=90%CI (0.75,1.33)	NSCLC	IBI305	bevacizumab	224	226	ORR (18w)
NMPA	Hanbeitai	NCT03511963	equivalence	RR=90%CI (0.8, 1.25); RD=95%CI (-11%, 15%)	mCRC	HLX04	bevacizumab	340	337	PFSR (36w)
NMPA	Boyounuo	NCT03533127	equivalence	RR=90%CI (0.75, 1.33)	NSCLC	LY01008	bevacizumab	324	325	ORR (18w)
NMPA	Ankeda	NCT03169335	equivalence	RR=90%CI (0.75, 1.33)	NSCLC	QL1101	bevacizumab	269	266	ORR (18w)
NMPA	Airuituo	NCT05169801	equivalence	RR=90%CI (0.75, 1.33)	NSCLC	BP102	bevacizumab	262	255	ORR (18w)
NMPA	Beianting	NCT03196986	equivalence	RR=90%CI (0.75, 1.33)	NSCLC	MIL60	bevacizumab	257	260	ORR (12w)
NMPA	Pubeixi	NCT03329911	equivalence	RR=90%CI (0.75, 1.33)	NSCLC	BAT1706	bevacizumab	325	326	ORR (18w)
NMPA	Puxinting	NCT05427305	equivalence	RR=90%CI (0.75, 1.33)	NSCLC	TAB 008	bevacizumab	277	272	ORR (18w)

Rituximab biosimilars										
FDA/EMA/PMDA	Ruxience/Rituximab biosimilar	NCT02213263	equivalence	RD=95%CI (-16%, 16%)	FL	PF-05280587	rituximab	196	198	ORR (27w)
FDA	Truxima	NCT02260804	equivalence	RD=90%CI (-17%, 17%)	FL	CT-P10	rituximab	130	128	ORR (7m)
FDA/EMA	Riabni	NCT02747043	noninferiority	RD=90%CI (-15%, 35.5%)	FL	ABP 798	rituximab	128	128	ORR (28w)
EMA	Truxima	NCT02162771	noninferiority	one-sided 97.5% CI lay on the positive side of the –7% margin	FL	CT-P10	rituximab	70	70	ORR (24w)
PMDA	Rituximab biosimilar	NCT01419665	equivalence	RD=95%CI (-12%, 12%)	FL	GP2013	rituximab	314	315	ORR (21w)
NMPA	Hanlikang	NCT02787239; CTR20150583	equivalence	RD=95%CI (-12%, 12%)	DLBCL	HLX01	rituximab	201	206	ORR (18w)
NMPA	Dabohua	NCT02867566	equivalence	RD=95%CI (-12%, 12%)	DLBCL	IBI301	rituximab	209	210	ORR (18w)
Trastuzumab biosimilars										
FDA/EMA/PMDA	Herzuma/Rituximab biosimilar	NCT02162667	equivalence	RD=95%CI (-15%, 15%)	Early BC	CT-P6	trastuzumab	271	278	pCR (30w)
FDA/EMA	Ogivri	NCT02472964	equivalence	RD=95%CI (-15%, 15%)	mBC	MYL-14010	trastuzumab	250	250	ORR (24w)
FDA/EMA/PMDA	Kanjinti/Rituximab biosimilar	NCT01901146/CT 2012-004319-29	equivalence	RD=90%CI (-13%, 13%); RR=90%CI (0.759, 1.318)	Early BC	ABP 980	trastuzumab	364	361	pCR (7w)
FDA/EMA	Ontruzant	NCT02149524	equivalence	RD=95%CI(-13%, 13%); RR=95%CI (0.785, 1.546)	Early BC	SB3	trastuzumab	437	438	pCR (24w)
FDA/EMA/PMDA	Trazimera/Rituximab biosimilar	NCT01989676	equivalence	RR=95%CI (0.80, 1.25)	mBC	PF-05280014	trastuzumab	352	355	ORR (25w)
EMA/NMPA	Hanquyou	NCT03084237; EudraCT 2016-000206-10; CTR20160526	equivalence	RD=95%CI (-13.5%, 13.5%)	mBC	HLX02	trastuzumab	324	325	ORR (24w)

Abbreviations: NA, not available; ORR, objective response rate; pCR, pathologic complete response; PFS, progression-free survival; NSCLC, non-small cell lung cancer; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; Early BC, early breast cancer; mBC, metastatic breast cancer; FDA, US Food and Drug Administration; EMA, European Medicines Agency; PMDA, Japanese Pharmaceuticals and Medical Devices Agency; NMPA, National Medical Products Administration. RR, risk ratio; RD, risk difference; w, week; m, month.

eTable 11. Subgroup analysis of cancer biosimilars compared with reference drugs derived from randomized clinical trials.

Variables	Number of studies	Model	Heterogeneity	Outcomes	*P* value[a]
			I^2(%)	RR (95% CI)	
Bevacizumab versus bevacizumab biosimilar					
Stage of NSCLC					
IIIb /IV stage	4	Random	0	0.97 (0.93, 1.01)	0.0969
Others	12	Random	0	0.99 (0.95, 1.04)	
Country of the sponsor					
China	7	Random	0	0.98 (0.92, 1.04)	0.165
The United States	3	Random	0	0.96 (0.87, 1.07)	
European Union	3	Random	0	0.91 (0.83, 0.99)	
Others	3	Random	0	1.06 (0.95, 1.18)	
Number of included patients					
n⩽500	2	Random	0	0.98 (0.83,1.16)	0.953
n>500	14	Random	0	0.97 (0.93,1.01)	
Rituximab versus rituximab biosimilar					
Cancer type					
Follicular Lymphoma	7	Random	0	1.02 (0.98, 1.06)	0.762
Chronic Lymphocytic Leukemia	1	Random	NA	0.99 (0.81, 1.22)	
Diffuse large B cell lymphoma	3	Random	91	1.07 (0.93, 1.24)	
Indolent NHL	1	Random	NA	1.03 (0.93, 1.24)	
Country of the sponsor					
China	2	Random	52	0.99 (0.93, 1.04)	0.345
The United States	2	Random	0	1.09 (0.99, 1.19)	
European Union	3	Random	0	1.00 (0.95, 1.05)	
Others	5	Random	0	1.02 (0.96,1.08)	
Number of included patients					
n⩽300	7	Random	0	1.04 (0.98, 1.09)	0.137
n>300	5	Random	4	0.99 (0.96, 1.02)	
Trastuzumab versus trastuzumab biosimilar					
Cancer stage					
Early BC	5	Random	68	1.07 (0.91, 1.24)	0.522
mBC	5	Random	0	1.01 (0.95, 1.07)	
Country of the sponsor					
China	1	Random	NA	1.04 (0.96, 1.10)	0.0213
The United States	2	Random	0	1.22 (1.06, 1.41)	
European Union	2	Random	66	1.07 (0.91, 1.27)	
Others	4	Random	19	0.98 (0.90,1.06)	
Number of included patients					
n⩽600	5	Random	45	1.02 (0.94, 1.10)	0.440
n>600	5	Random	45	1.09 (0.92, 1.29)	

[a]*P* value indicates a comparison between different subgroups. RR, response rate; CI, confidence interval. FL, follicular lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; Indolent NHL, indolent non-Hodgkin lymphomas; Early BC, early breast cancer; mBC, metastatic breast cancer; NSCLC, non-small cell lung cancer; NA, not available.

eTable 12. Pooled analysis of efficacy (secondary end points), safety, and immunogenicity of cancer biosimilars derived from randomized clinical trials.

Outcome and cancer subgroup	RCTs, No.	Sample size, No.		Test of heterogeneity		Results of meta-analysis, effect estimates (95% CI)	*P* value[a]
		Biosimilar	Reference	I^2, %	*P* value		
Bevacizumab biosimilar vs. Bevacizumab							
Secondary efficacy endpoints							
OS (HR)	11	3044	3011	21	0.25	1.02 (0.94, 1.11)	0.51
PFS (HR)	10	3239	3239	10	0.35	1.03 (0.97, 1.10)	0.30
Safety outcome							
SAE	16	4692	4567	0	0.99	1.04 (0.97, 1.11)	0.24
Grade≥3 AEs	14	4071	3958	0	0.84	0.98 (0.95, 1.00)	0.08
Death	15	4457	4345	0	1.00	1.04 (0.97, 1.12)	0.25
Neutropenia (Grade≥3 AEs)	11	3504	3491	17	0.28	0.97 (0.84, 1.12	0.66
Thrombocytopenia (Grade≥3 AEs)	10	3125	3107	0	0.93	1.09 (0.86, 1.37)	0.48
Immunogenicity outcome							
ADA	13	3946	2884	0	0.63	1.04 (0.88, 1.25)	0.63
Nab	5	1591	1532	0	0.82	0.78 (0.45, 1.34)	0.36
Rituximab biosimilar vs. Rituximab							
Secondary efficacy endpoints							
OS (HR)	1	311	315	NA	NA	0.77 (0.45, 1.33)	0.34
PFS (HR)	3	646	649	42	0.18	1.16 (0.87, 1.54)	0.33
Safety outcome							
SAE	9	1541	1549	0	0.89	1.11 (0.98, 1.27)	0.11
Grade≥3 AEs	5	870	878	0	0.82	1.02 (0.96, 1.08)	0.61
Death	8	1471	1479	0	0.92	0.88 (0.64, 1.21)	0.45
Neutropenia (Grade≥3 AEs)	9	1260	1261	0	0.97	1.07 (0.88, 1.30)	0.48
Thrombocytopenia (Grade≥3 AEs)	3	485	486	47	0.15	2.20 (0.48, 10.11)	0.31
Immunogenicity outcome							
ADA	5	996	1005	0	0.58	1.06 (0.77, 1.46)	0.72
Nab	1	157	158	NA	NA	4.71 (0.21, 105.24)	0.33
Trastuzumab biosimilar vs. Trastuzumab							
Secondary efficacy endpoints							
OS (HR)	3	926	930	4	0.35	0.84 (0.65, 1.07)	0.15
PFS (HR)	3	926	930	0	0.64	0.89 (0.76, 1.04)	0.15
Safety outcome							
SAE	6	1789	1792	54	0.05	0.94 (0.73, 1.21)	0.63
Grade≥3 AEs	5	1562	1570	0	0.64	0.99 (0.94, 1.05)	0.84
Death	6	1729	1729	25	0.24	0.79 (0.54, 1.16)	0.23
Neutropenia (Grade≥3 AEs)	6	1789	1792	0	0.89	0.96 (0.74, 1.23)	0.74
Thrombocytopenia (Grade≥3 AEs)	3	1039	1043	0	0.84	1.95 (0.34, 11.20)	0.46
Immunogenicity outcome							
ADA	5	1626	1625	0	0.77	1.12 (0.58, 2.14)	0.74
Nab	2	439	435	0	0.80	0.82 (0.25, 2.66)	0.74

[a]*P* value indicates a comparison between different subgroups.

Abbreviations: NA, not available; ORR, objective response rate; PFS, progression-free survival; HR, hazard ratio; OS, overall survival; SAE, serious adverse event; ADA, anti-drug antibody; Nab, neutralizing antibody; CI, confidence interval.

eTable 13. Pooled analysis of efficacy, safety, and immunogenicity of cancer biosimilars derived from cohort studies.

Outcome and cancer subgroup	cohort studies, No.	Sample size, No.		Test of heterogeneity		Results of meta-analysis, effect estimates (95% CI)	*P* value[a]
		Biosimilar	Reference	I^2, %	*P* value		
Bevacizumab biosimilar vs. Bevacizumab							
Efficacy endpoints							
ORR	1	551	395	NA	NA	0.93 (0.77, 1.14)	0.50
Safety outcome							
Grade⩾3 AEs	1	551	395	NA	NA	1.14 (0.88, 1.45)	0.34
Neutropenia (Grade⩾3 AEs)	1	551	395	NA	NA	1.14 (0.80, 1.64)	0.47
Thrombocytopenia (Grade⩾3 AEs)	1	551	395	NA	NA	1.58 (0.55, 4.50)	0.39
Rituximab biosimilar vs. Rituximab							
Efficacy endpoints							
ORR	3	179	179	0	0.25	1.00 (0.92, 1.01)	0.88
Safety outcome							
Grade⩾3 AEs	2	87	119	0	0.66	0.78 (0.51, 1.18)	0.23
Neutropenia (Grade⩾3 AEs)	2	87	119	0	0.98	0.90 (0.49, 1.64)	0.75
Death	2	164	161	0	0.98	1.32 (0.43, 4.07)	0.63
Trastuzumab biosimilar vs. Trastuzumab							
Efficacy endpoints							
ORR	3	229	409	0	0.72	1.00 (0.87, 1.16)	0.96
pCR	5	294	298	0	0.91	1.04 [0.93; 1.17]	0.50
Safety outcome							
Grade⩾3 AEs	3	141	285	41	0.19	1.02 (0.81, 1.30)	0.86
Neutropenia (Grade⩾3 AEs)	1	65	40	NA	NA	1.86 (0.08, 44.67)	0.70
Thrombocytopenia (Grade⩾3 AEs)	1	65	40	NA	NA	1.53 (0.31, 7.56)	0.60

[a]*P* value indicates a comparison between different subgroups.

Abbreviations: NA, not available; ORR, objective response rate; pCR, pathologic complete response; PFS, progression-free survival; OS, overall survival; OS, overall survival; SAE, serious adverse event; CI, confidence interval.

eTable 14. The weighted mean price of rituximab, bevacizumab, trastuzumab, and their biosimilars (per unit) between 2015 and 2022.

	Bevacizumab（$/mg）			Rituximab（$/mg）			Trastuzumab（$/mg）		
Year	Biosimilar	Reference	B/R[a] (%)	Biosimilar	Reference	B/R[a] (%)	Biosimilar	Reference	B/R[a] (%)
2022	1.63	2.21	74	1.55	2.23	69	1.66	1.85	90
2021	1.67	2.23	75	1.59	2.35	68	1.68	1.86	90
2020	1.76	2.25	78	1.84	2.36	78	1.69	1.87	90
2019	1.79	3.03	59	2.37	2.47	96	NA	2.59	NA
2018	NA	3.09	NA	NA	3.40	NA	NA	2.64	NA
2017	NA	5.61	NA	NA	4.65	NA	NA	4.39	NA
2016	NA	8.64	NA	NA	5.93	NA	NA	8.42	NA
2015	NA	8.66	NA	NA	6.12	NA	NA	8.22	NA

Abbreviations: B, biosimilar; R, reference; [a]B/R is defined as the price ratio of the biosimilar to the reference drug; NA, not available.

eTable 15. Trends in the uptake rate of rituximab, bevacizumab, and trastuzumab biosimilars vs reference drugs after market entry as of December 2022

Time frames of market entry	Date of market entry	Biosimilar, mg	Reference, mg	Overall[a], mg	B/O[b] (%)
Bevacizumab biosimilar vs. Bevacizumab					
M_{1-3}	2019_{Q4}	7186	493757	500943	1
M_{4-6}	2020_{Q1}	36002	384235	420237	9
M_{7-9}	2020_{Q2}	226007	472741	698748	32
M_{10-12}	2020_{Q3}	377474	502235	879709	43
M_{13-15}	2020_{Q4}	485623	409156	894779	54
M_{16-18}	2021_{Q1}	837009	450771	1287780	65
M_{19-21}	2021_{Q2}	940418	383222	1323640	71
M_{22-24}	2021_{Q3}	1181508	394229	1575737	75
M_{25-27}	2021_{Q4}	1153490	351618	1505108	77
M_{28-30}	2022_{Q1}	1185853	294534	1480387	80
M_{31-33}	2022_{Q2}	1376403	269110	1645513	84
M_{34-36}	2022_{Q3}	1575914	308869	1884783	84
M_{37-39}	2022_{Q4}	1279435	233691	1513126	85
Rituximab biosimilar vs. Rituximab					
M_{1-3}	2019_{Q2}	717	385942	386659	0
M_{4-6}	2019_{Q3}	15498	373160	388658	4
M_{7-9}	2019_{Q4}	23788	303334	327122	7
M_{10-12}	2020_{Q1}	43346	202112	245458	18
M_{13-15}	2020_{Q2}	100002	276208	376210	27
M_{16-18}	2020_{Q3}	158286	229785	388071	41
M_{19-21}	2020_{Q4}	176735	164032	340767	52
M_{22-24}	2021_{Q1}	266696	230927	497623	54
M_{25-27}	2021_{Q2}	320382	205045	525427	61
M_{28-30}	2021_{Q3}	410411	243848	654259	63
M_{31-33}	2021_{Q4}	394913	188240	583153	68
M_{34-36}	2022_{Q1}	383601	180160	563761	68
M_{37-39}	2022_{Q2}	434918	155895	590813	74
M_{40-42}	2022_{Q3}	504666	157110	661776	76
M_{43-45}	2022_{Q4}	410409	121447	531856	77
Trastuzumab biosimilar vs. Trastuzumab					
M_{1-3}	2020_{Q3}	935	200390	201325	0
M_{4-6}	2020_{Q4}	18379	197674	216053	9
M_{7-9}	2021_{Q1}	83070	254566	337636	25
M_{10-12}	2021_{Q2}	120180	263731	383911	31

$M_{13\text{-}15}$	2021_{Q3}	176843	256501	433344	41
$M_{16\text{-}18}$	2021_{Q4}	196913	248212	445125	44
$M_{19\text{-}21}$	2022_{Q1}	215587	226398	441985	49
$M_{22\text{-}24}$	2022_{Q2}	248326	224295	472621	53
$M_{25\text{-}27}$	2022_{Q3}	303579	220637	524216	58
$M_{28\text{-}30}$	2022_{Q4}	279375	202689	482064	58

M_n, Month from launch; Q, Quarter; B, biosimilar; O, [a]overall, overall is defined as the sum of sales volume of biosimilars and reference drugs quarterly; [b]B/O is defined as the ratio of sales volume of biosimilars to overall quarterly.

eTable 16. Uptake rates of cancer biosimilars vs reference drugs in the first year, second year, and latest time on the market

Biosimilars	First year after launching	Second year after launching	Latest year (2022)
Bevacizumab	26%	68%	83%
Rituximab	6%	44%	74%
Trastuzumab	20%	47%	54%

The annual uptake rate for biosimilars is calculated by dividing the one-year sales of biosimilars by the one-year sales of their reference drugs.

eTable 17. Reimbursable cancer indications for the biosimilars and reference drugs of bevacizumab, rituximab, and trastuzumab in the National Reimbursement Drug List in China (As of July 1, 2023).

Originator	Reimbursable indications
Bevacizumab	1. Metastatic colorectal cancer 2. Advanced, metastatic, or recurrent non-small non-squamous cell lung cancer 3. Recurrent Glioblastoma 4. Hepatocellular carcinoma 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Cervical cancer
Rituximab	1. Non-Hodgkin' s lymphoma 2. Chronic lymphocytic leukemia
Trastuzumab	1. HER2-overexpressing metastatic breast cancer (MBC); 2. HER2-overexpressing early breast cancer (Adjuvant and neoadjuvant therapy, paid for no more than 12 months)[a]; 3. HER2-overexpressing metastatic gastric cancer[b].

[a]HER2-overexpressing early breast cancer indication is included in NRDL, but only paid for no more than 12 months;
[b]Trastuzumab is approved for HER2-overexpressing metastatic gastric or gastroesophageal junction enocarcinoma, but reimbursement only paid for HER2-overexpressing metastatic gastric cancer.

eTable 18. Comparison the approved indications of cancer biosimilars vs reference drugs by the NMPA, FDA, EMA, and PMDA (As of July 2023).

Number	NMPA	FDA	EMA	PMDA
Bevacizumab and Bevacizumab biosimilars				
Reference drug	**Avastin** **(Roche)** 1. Metastatic colorectal cancer 2. Advanced, metastatic, or recurrent non-small non-squamous cell lung cancer 3. Recurrent Glioblastoma 4. Hepatocellular carcinoma (HCC) 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Cervical cancer	**Avastin** **(Roche)** 1. Metastatic colorectal cancer 2. Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer 3. Recurrent glioblastoma 4. Hepatocellular carcinoma (HCC) 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Persistent, recurrent, or metastatic cervical cancer 7. Metastatic renal cell carcinoma	**Avastin** **(Roche)** 1. Metastatic carcinoma of the colon or rectum 2. Unresectable advanced, metastatic or recurrent nono-squamous non-small cell lung cancer 3. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 4. Persistent, recurrent, or metastatic carcinoma of the cervix 5. Advanced and/or metastatic renal cell cancer 6. Metastatic breast cancer	**Avastin** **(Roche)** 1. Unresectable advanced or recurrent colorectal cancer 2. Unresectable advanced or recurrent non-small cell lung cancer 3. Malignant Glioblastoma 4. Unresectable hepatocellular carcinoma (HCC) 5. Ovarian cancer 6. Advanced or recurrent cervical cancer 7. Inoperable or recurrent breast cancer
1	**Hanbeitai** **(Henlius)** **[HLX04]** 1. Metastatic colorectal cancer 2. Advanced, metastatic, or recurrent non-small non-squamous cell lung cancer 3. Recurrent Glioblastoma 4. Hepatocellular carcinoma 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Cervical cancer	**Zirabev** **(Pfizer)** **[PF-06439535]** 1. Metastatic colorectal cancer 2. Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer 3. Recurrent glioblastoma 4. Hepatocellular carcinoma (HCC) 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Persistent, recurrent, or metastatic cervical cancer 7. Metastatic renal cell carcinoma	**Zirabev** **(Pfizer)** **[PF-06439535]** 1. Metastatic carcinoma of the colon or rectum 2. Unresectable advanced, metastatic or recurrent nono-squamous non-small cell lung cancer 3. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 4. Persistent, recurrent, or metastatic carcinoma of the cervix 5. Advanced and/or metastatic renal cell cancer 6. Metastatic breast cancer	**Bevacizumab biosimilar** **(Pfizer)** **[PF-06439535]** 1. Unresectable advanced or recurrent colorectal cancer 2. Unresectable advanced or recurrent non-small cell lung cancer 3. Malignant Glioblastoma 4. Unresectable hepatocellular carcinoma (HCC) 5. Ovarian cancer 6. Advanced or recurrent cervical cancer 7. Inoperable or recurrent breast cancer
2	**Puxinting** **(TOT Biopharm)** **[TAB 008]** 1. Metastatic colorectal cancer 2. Advanced, metastatic, or recurrent non-small	**Alymsys** **(Amneal)** **[MB02]** 1. Metastatic colorectal cancer 2. Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer	**Alymsys** **(Mabxience)** **[MB02]** 1. Metastatic carcinoma of the colon or rectum 2. Unresectable advanced, metastatic or recurrent nono-squamous non-small cell lung cancer	**Bevacizumab biosimilar** **(Amgen/Daiichi-Sankyo)** **[ABP215]** 1. Unresectable advanced or recurrent colorectal cancer 2. Unresectable advanced or recurrent non-small cell lung cancer

Number	NMPA	FDA	EMA	PMDA
	non-squamous cell lung cancer 3. Recurrent Glioblastoma 4. Hepatocellular carcinoma 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Cervical cancer	3. Recurrent glioblastoma 4. Hepatocellular carcinoma (HCC) 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Persistent, recurrent, or metastatic cervical cancer 7. Metastatic renal cell carcinoma	3. Epithelial ovarian, fallopian tube, or primary peritoneal cancer. 4. Persistent, recurrent, or metastatic carcinoma of the cervix 5. Advanced and/or metastatic renal cell cancer 6. Metastatic breast cancer	3. Malignant Glioblastoma 4. Unresectable hepatocellular carcinoma (HCC) 5. Ovarian cancer 6. Advanced or recurrent cervical cancer 7. Inoperable or recurrent breast cancer
3	**Beianting (Betta/ Mabwork) [MIL60]** 1. Metastatic colorectal cancer 2. Advanced, metastatic, or recurrent non-small non-squamous cell lung cancer 3. Recurrent Glioblastoma 4. Hepatocellular carcinoma 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Cervical cancer	**Vegzelma (Celltrion) [CT-P16]** 1. Metastatic colorectal cancer 2. Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer 3. Recurrent glioblastoma 4. Hepatocellular carcinoma (HCC) 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Persistent, recurrent, or metastatic cervical cancer 7. Metastatic renal cell carcinoma	**Vegzelma (Celltrion) [CT-P16]** 1. Metastatic carcinoma of the colon or rectum 2. Unresectable advanced, metastatic or recurrent nono-squamous non-small cell lung cancer 3. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 4. Persistent, recurrent, or metastatic carcinoma of the cervix 5. Advanced and/or metastatic renal cell cancer 6. Metastatic breast cancer	**Bevacizumab biosimilar (Nipponkayaku/ Celltrion) [CT-P16]** 1. Unresectable advanced or recurrent colorectal cancer 2. Unresectable advanced or recurrent non-small cell lung cancer 3. Malignant Glioblastoma 4. Unresectable hepatocellular carcinoma (HCC) 5. Ovarian cancer 6. Advanced or recurrent cervical cancer 7. Inoperable or recurrent breast cancer
4	**Pubeixi (Bio-Thera) [BAT1706]** 1. Metastatic colorectal cancer 2. Advanced, metastatic, or recurrent non-small non-squamous cell lung cancer 3. Recurrent Glioblastoma 4. Hepatocellular carcinoma 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Cervical cancer	**Mvasi (Amgen) [ABP215]** 1. Metastatic colorectal cancer 2. Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer 3. Recurrent glioblastoma 4. Hepatocellular carcinoma (HCC) 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Persistent, recurrent, or metastatic cervical cancer 7. Metastatic renal cell carcinoma	**Mvasi (Amgen) [ABP215]** 1. Metastatic carcinoma of the colon or rectum 2. Unresectable advanced, metastatic or recurrent nono-squamous non-small cell lung cancer 3. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 4. Persistent, recurrent, or metastatic carcinoma of the cervix 5. Advanced and/or metastatic renal cell cancer 6. Metastatic breast cancer	**Bevacizumab biosimilar (Nichiiko) [MB02]** 1. Unresectable advanced or recurrent colorectal cancer 2. Unresectable advanced or recurrent non-small cell lung cancer 3. Malignant Glioblastoma 4. Unresectable hepatocellular carcinoma (HCC) 5. Ovarian cancer 6. Advanced or recurrent cervical cancer 7. Inoperable or recurrent breast cancer

Number	NMPA	FDA	EMA	PMDA
5	**Airuituo** **(Hengrui)** **[BP102]** 1. Metastatic colorectal cancer 2. Advanced, metastatic, or recurrent non-small non-squamous cell lung cancer 3. Recurrent Glioblastoma 4. Hepatocellular carcinoma 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Cervical cancer		**Abevmy** **(Mylan)** **[MYL-1402O]** 1. Metastatic carcinoma of the colon or rectum 2. Unresectable advanced, metastatic or recurrent nono-squamous non-small cell lung cancer 3. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 4. Persistent, recurrent, or metastatic carcinoma of the cervix 5. Advanced and/or metastatic renal cell cancer 6. Metastatic breast cancer	
6	**Boyounuo** **(Luye)** **[LY01008]** 1. Metastatic colorectal cancer 2. Advanced, metastatic, or recurrent non-small non-squamous cell lung cancer 3. Recurrent Glioblastoma 4. Hepatocellular carcinoma 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Cervical cancer		**Aybintio** **(Samsung)** **[SB8]** 1. Metastatic carcinoma of the colon or rectum 2. Unresectable advanced, metastatic or recurrent nono-squamous non-small cell lung cancer 3. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 4. Persistent, recurrent, or metastatic carcinoma of the cervix 5. Advanced and/or metastatic renal cell cancer 6. Metastatic breast cancer	

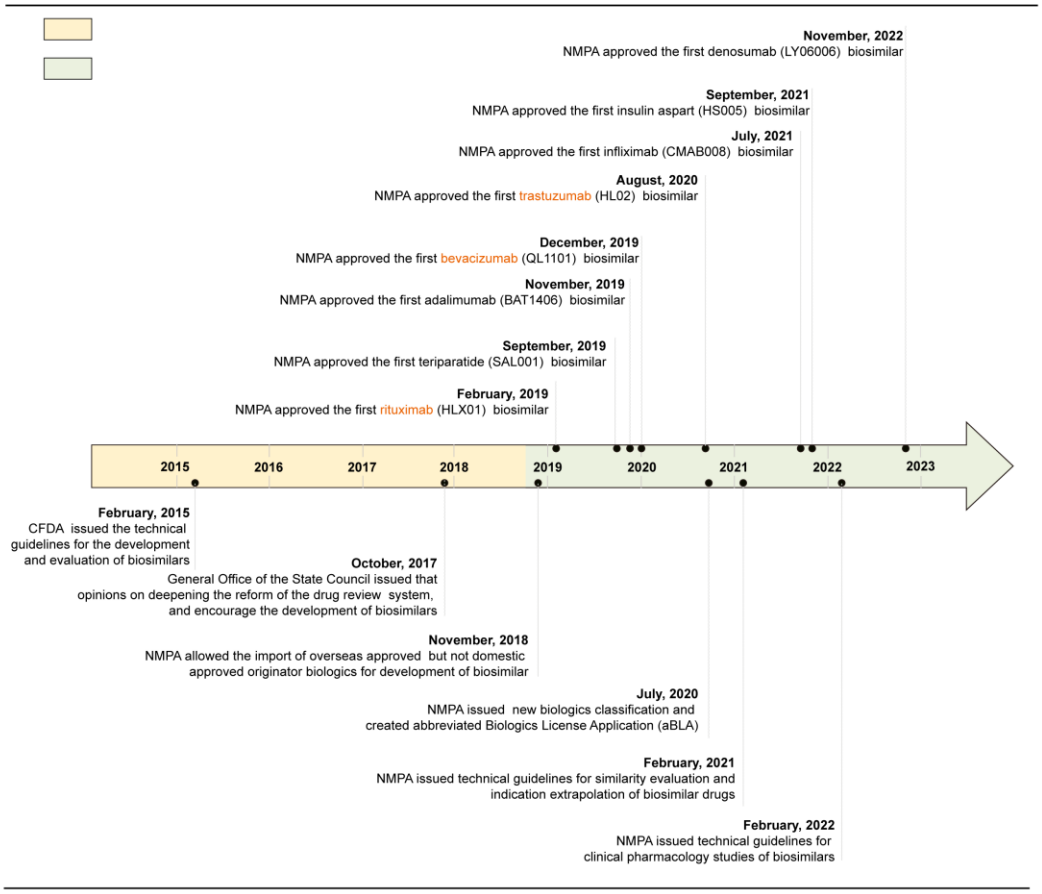
Number	NMPA	FDA	EMA	PMDA
7	**Dayoutong (Innovent）[IBI305]** 1. Metastatic colorectal cancer 2. Advanced, metastatic, or recurrent non-small non-squamous cell lung cancer 3. Recurrent Glioblastoma 4. Hepatocellular carcinoma 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Cervical cancer		**WITHDRAWAL** **Equidacent (Centus) [FKB-238]** 1. Metastatic carcinoma of the colon or rectum 2. Unresectable advanced, metastatic or recurrent no-squamous non-small cell lung cancer 3. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 4. Persistent, recurrent, or metastatic carcinoma of the cervix 5. Advanced and/or metastatic renal cell cancer 6. Metastatic breast cancer	
8	**Ankeda (Qilu) [QL1101]** 1. Metastatic colorectal cancer 2. Advanced, metastatic, or recurrent non-small non-squamous cell lung cancer 3. Recurrent Glioblastoma 4. Hepatocellular carcinoma 5. Epithelial ovarian, fallopian tube, or primary peritoneal cancer 6. Cervical cancer			
Rituximab versus rituximab biosimilar				

Number	NMPA	FDA	EMA	PMDA
reference drug	**MabThera** **(Roche)** 1. Non-Hodgkin' s lymphoma (NHL) 2. Chronic lymphocytic leukemia (CLL)	**Rituxan** **(Roche)** 1. Non-Hodgkin' s lymphoma (NHL) 2. Chronic lymphocytic leukemia (CLL) 3. Pediatric mature B-cell NHL, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL)	**MabThera** **(Roche)** 1. Non-Hodgkin's lymphoma (NHL) 2. Chronic lymphocytic leukaemia (CLL) 3. Pediatric advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL)	**Rituxan** **(Zenyaku)** 1. Non-Hodgkin's lymphoma (NHL) 2. Chronic lymphocytic leukaemia (CLL) 3. B-cell lymphoproliferative disease under immunosuppressive conditions
1	**Dabohua** **(Innovent)** **[IBI301]** 1. Non-Hodgkin' s lymphoma (NHL) 2.Chronic lymphocytic leukemia (CLL)	**Riabni** **(Amgen)** **[ABP 798]** 1. Non-Hodgkin' s lymphoma (NHL) 2. Chronic lymphocytic leukemia (CLL) 3. Pediatric mature B-cell NHL, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL)	**Rixathon** **(Sandoz)** **[GP2013]** 1. Non-Hodgkin's lymphoma (NHL) 2. Chronic lymphocytic leukaemia (CLL) 3. Pediatric advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL)	**Rituximab biosimilar-1** **(Sandoz/Kyowa)** **[GP13-301]** 1. Non-Hodgkin's lymphoma (NHL) 2.Chronic lymphocytic leukaemia (CLL) 3. B-cell lymphoproliferative disease under immunosuppressive conditions
2	**Hanlikang** **(Henlius)** **[HLX01]** 1. Non-Hodgkin' s lymphoma (NHL) 2. Chronic lymphocytic leukemia (CLL)	**Ruxience** **(Pfizer)** **[PF-05280586]** 1. Non-Hodgkin' s lymphoma (NHL) 2. Chronic lymphocytic leukemia (CLL) 3. Pediatric mature B-cell NHL, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL)	**Ruxience** **(Pfizer)** **[PF-05280586]** 1. Non-Hodgkin's lymphoma (NHL) 2. Chronic lymphocytic leukaemia (CLL) 3. Pediatric advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL)	**Rituximab biosimilar-2** **(Pfizer)** **[PF-05280586]** 1. Non-Hodgkin's lymphoma (NHL) 2.Chronic lymphocytic leukaemia (CLL) 3. B-cell lymphoproliferative disease under immunosuppressive conditions
3		**Truxima** **(Celltrion)** **[CT-P10]** 1. Non-Hodgkin' s lymphoma (NHL) 2. Chronic lymphocytic leukemia (CLL) 3. Pediatric mature B-cell NHL, diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL)	**Truxima** **(Celltrion)** **[CT-P10]** 1. Non-Hodgkin's lymphoma (NHL) 2. Chronic lymphocytic leukaemia (CLL) 3. Pediatric advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL)	

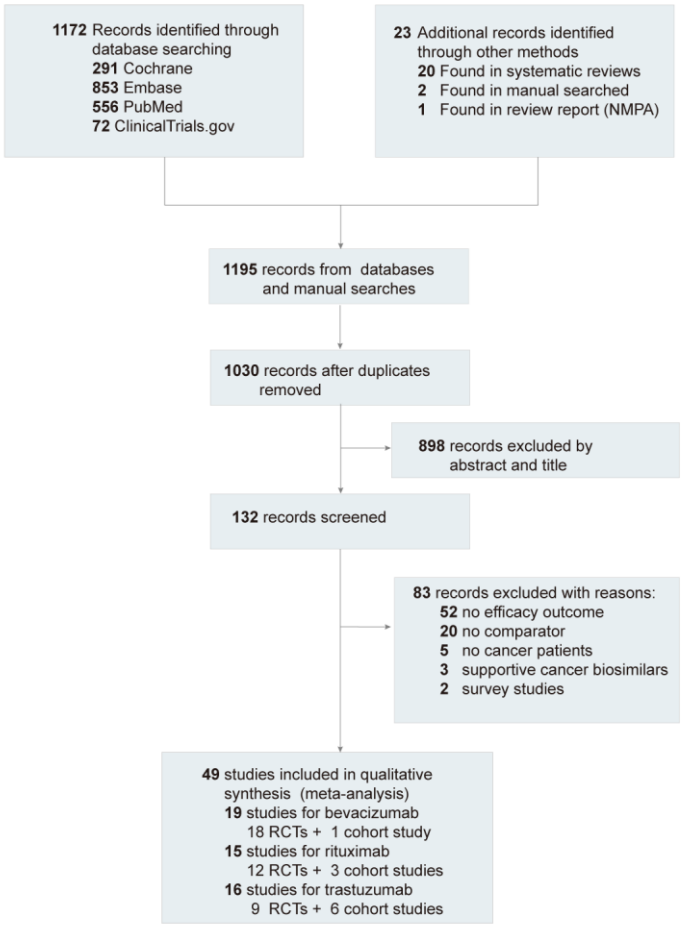
Number	NMPA	FDA	EMA	PMDA
Trastuzumab versus trastuzumab biosimilar				
Reference drug	**Herceptin** **(Roche)** 1.HER2-overexpressing metastatic breast cancer (MBC) 2.HER2-overexpressing early breast cancer (EBC) 3.HER2-overexpressing metastatic gastric or gastroesophageal junction enocarcinoma	**Herceptin** **(Roche)** 1.HER2-overexpressing metastatic breast cancer (MBC) 2.Adjuvant therapy of HER2-overexpressin breast cancer 3.HER2-overexpressing metastatic gastric or gastroesophageal junction enocarcinoma	**Herceptin** **(Roche)** 1. HER2-positive metastatic breast cancer (MBC) 2.HER2-positive early breast cancer (EBC) 3.HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction	**Herceptin** **(Chugai)** 1. HER2-positive breast cancer 2. HER2-positive unresectable advanced or recurrences of gastric cancer 3. HER2-positive unresectable advanced recurrent salivary gland cancer 4. HER2-positive unresectable advanced and recurred colorectal cancer
1	**Hanquyou** **(Henlius)** **[HLX02]** 1. HER2-overexpressing metastatic breast cancer (MBC) 2. HER2-overexpressing early breast cancer (EBC) 3. HER2-overexpressing metastatic gastric or gastroesophageal junction enocarcinoma	**Kanjinti** **(Amgen)** **[ABP 980]** 1. HER2-overexpressing metastatic breast cancer (MBC) 2. Adjuvant therapy of HER2-overexpressin breast cancer 3. HER2-overexpressing metastatic gastric or gastroesophageal junction enocarcinoma	**Kanjinti** **(Amgen)** **[ABP 980]** 1. HER2-positive metastatic breast cancer (MBC) 2. HER2-positive early breast cancer (EBC) 3.HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction	**Trastuzumab biosimilar-2** **(Daiichi-Sankyo/AMGEN)** **[ABP 980]** 1. HER2-positive breast cancer 2. HER2-positive unresectable advanced or recurrences of gastric cancer 3. HER2-positive unresectable advanced recurrent salivary gland cancer 4. HER2-positive unresectable advanced and recurred colorectal cancer
2		**Trazimera** **(Pfizer)** **[PF-05280014]** 1. HER2-overexpressing metastatic breast cancer (MBC) 2. Adjuvant therapy of HER2-overexpressin breast cancer 3. HER2-overexpressing metastatic gastric or gastroesophageal junction enocarcinoma	**Trazimera** **(Pfizer)** **[PF-05280014]** 1. HER2-positive metastatic breast cancer (MBC) 2. HER2-positive early breast cancer (EBC) 3. HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction	**Trastuzumab biosimilar-3** **(Pfizer)** **[PF-05280014]** 1. HER2-positive breast cancer 2. HER2-positive unresectable advanced or recurrences of gastric cancer 3. HER2-positive unresectable advanced recurrent salivary gland cancer 4. HER2-positive unresectable advanced and recurred colorectal cancer

Number	NMPA	FDA	EMA	PMDA
3		**Ontruzant** **(Samsung)** **[SB3]** 1. HER2-overexpressing metastatic breast cancer (MBC) 2. Adjuvant therapy of HER2-overexpressin breast cancer 3. HER2-overexpressing metastatic gastric or gastroesophageal junction enocarcinoma	**Ontruzant** **(Samsung)** **[SB3]** 1. HER2-positive metastatic breast cancer (MBC) 2. HER2-positive early breast cancer (EBC) 3. HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction	**Trastuzumab biosimilar-1** **(Celltrion)** **[CT-P6]** 1. HER2-positive breast cancer 2. HER2-positive unresectable advanced or recurrences of gastric cancer 3. HER2-positive unresectable advanced recurrent salivary gland cancer 4. HER2-positive unresectable advanced and recurred colorectal cancer
4		**Herzuma** **(Celltrion)** **[CT-P6]** 1. HER2-overexpressing metastatic breast cancer (MBC) 2. Adjuvant therapy of HER2-overexpressin breast cancer 3. HER2-overexpressing metastatic gastric or gastroesophageal junction enocarcinoma	**Herzuma** **(Celltrion)** **[CT-P6]** 1. HER2-positive metastatic breast cancer (MBC) 2. HER2-positive early breast cancer (EBC) 3. HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction	
5		**Ogivri** **(Viatris)** **[MYL-1401O]** 1. HER2-overexpressing metastatic breast cancer (MBC) 2. Adjuvant therapy of HER2-overexpressin breast cancer 3. HER2-overexpressing metastatic gastric or gastroesophageal junction enocarcinoma	**Ogivri** **(Viatris)** **[MYL-1401O]** 1. HER2-positive metastatic breast cancer (MBC) 2. HER2-positive early breast cancer (EBC) 3. HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction	
6			**Zercepac** **(Accord)** **[HLX02]** 1. HER2-positive metastatic breast cancer (MBC) 2. HER2-positive early breast cancer (EBC) 3. HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction	

Red font indicates that the four regulators (NMPA, FDA, EMA and PMDA) have approved the originator's indication, but the biosimilar has not yet been approved for that indication.
Abbreviations: FDA, US Food and Drug Administration; EMA, European Medicines Agency; PMDA, Japanese Pharmaceuticals and Medical Devices Agency; NMPA, National Medical Products Administration.

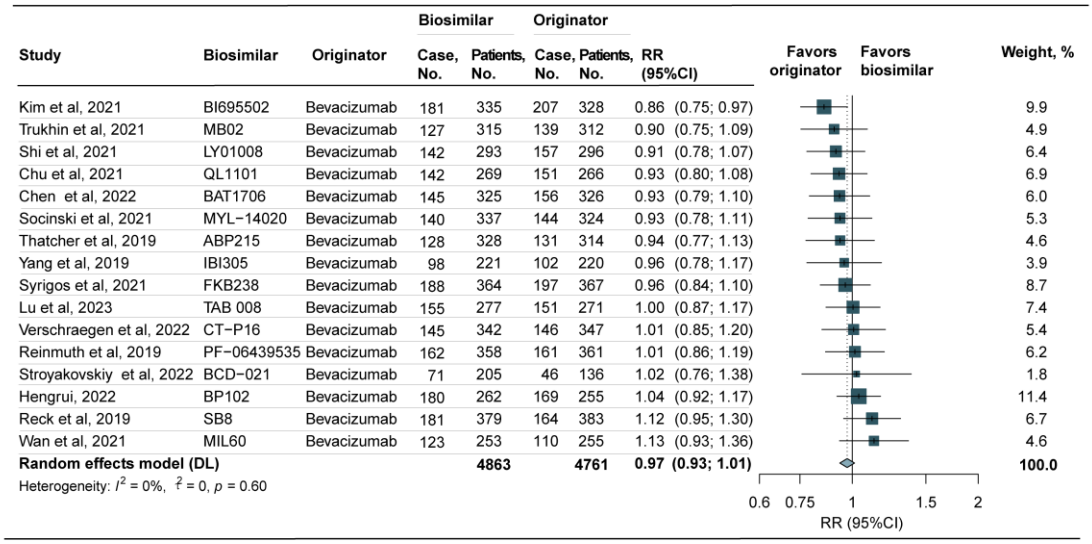


eFigure 1. The development history of biosimilars in China.
CFDA: China Food and Drug Administration. NMPA: National Medical Products Administration (Name changed to NMPA in September, 2018).



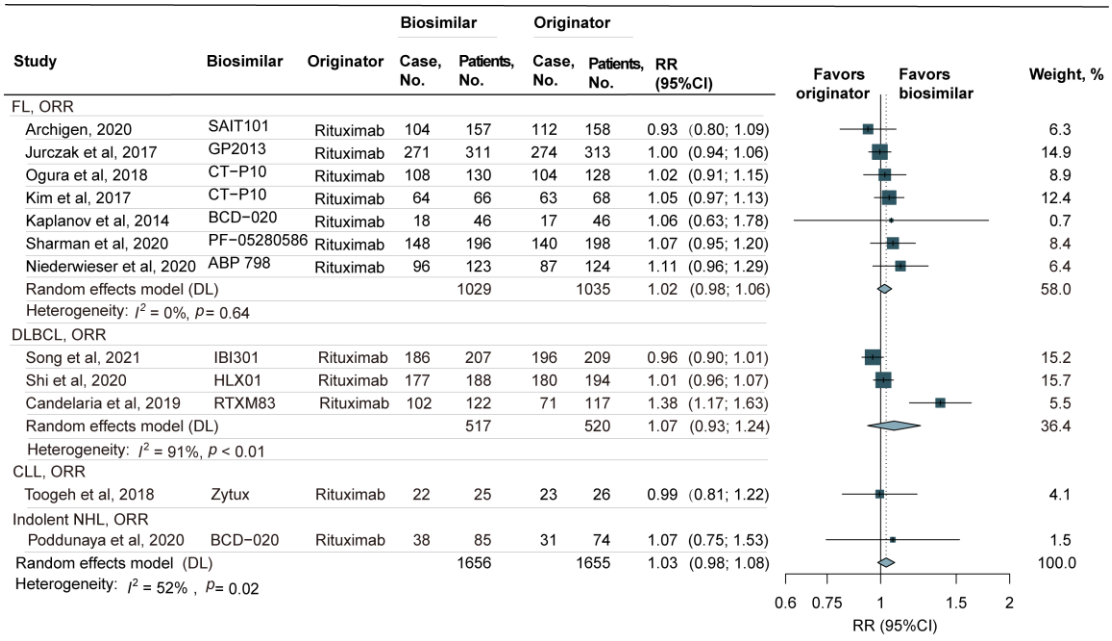
eFigure 2. Flowchart of included studies for the systematic review and meta-analysis.

Abbreviations: NMPA, National Medical Products Administration; RCT, randomized clinical trial.



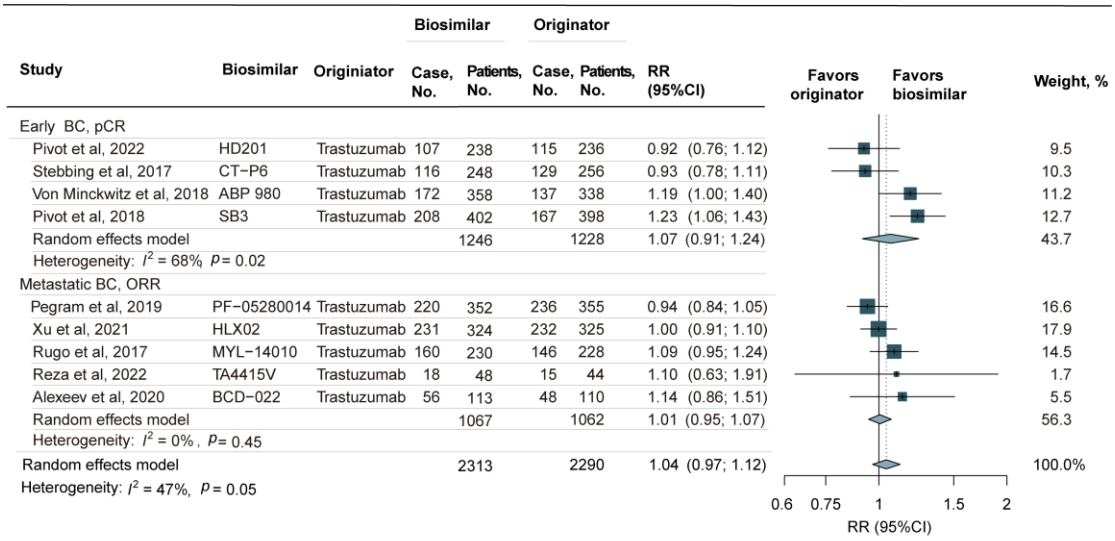
eFigure 3. Meta-analysis of the primary efficacy end points between bevacizumab biosimilars and the originator derived from RCTs.

Abbreviations: RR, risk ratio. DL, dersimonian and laird method. CI, confidence interval.



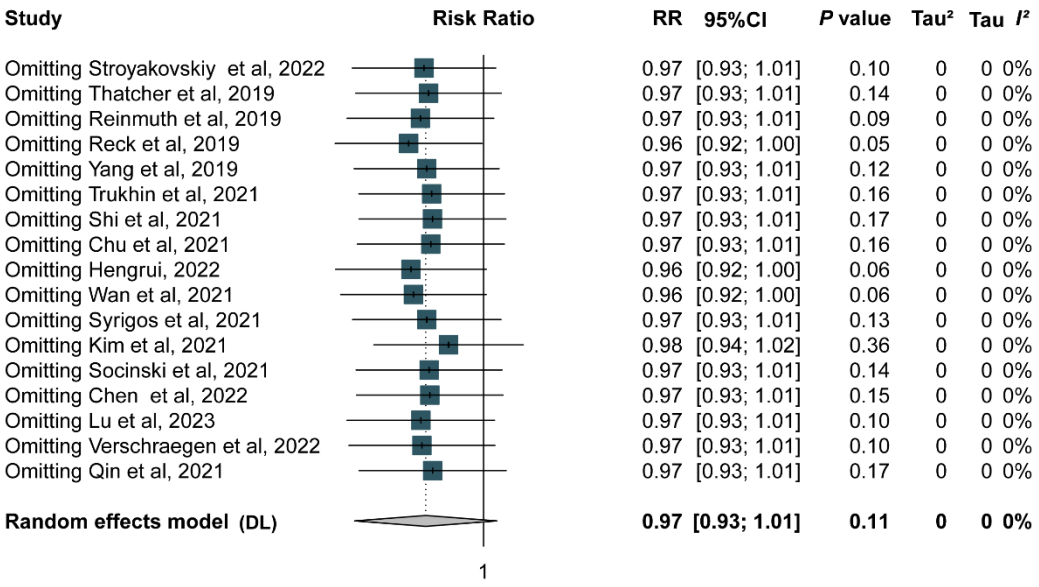
eFigure 4. Meta-analysis of the primary efficacy end points between rituximab biosimilars and the originator stratified by cancer type derived from RCTs.

Abbreviations: RR, risk ratio. DL, dersimonian and laird method. CI, confidence interval.



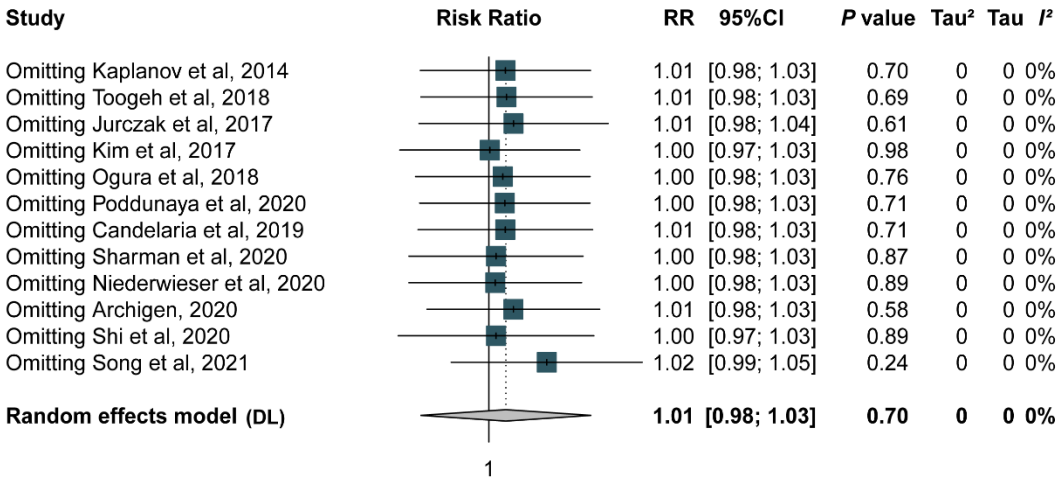
eFigure 5. Meta-analysis of the primary efficacy end points between trastuzumab biosimilars and the originator stratified by cancer type derived from RCTs.

Abbreviations: RR, risk ratio. DL, dersimonian and laird method. CI, confidence interval.



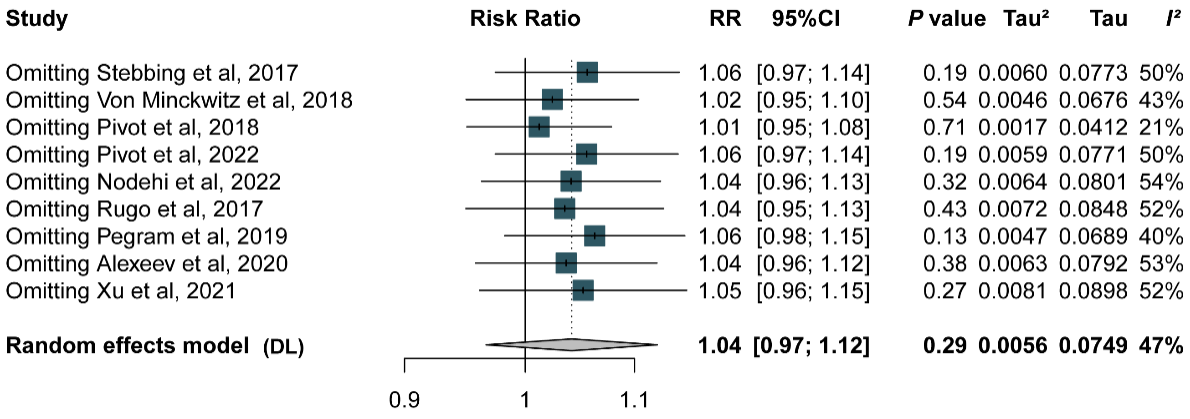
eFigure 6. Sensitivity analysis of primary efficacy end points for bevacizumab derived from RCTs.

Abbreviations: DL, dersimonian and laird method. CI, confidence interval.



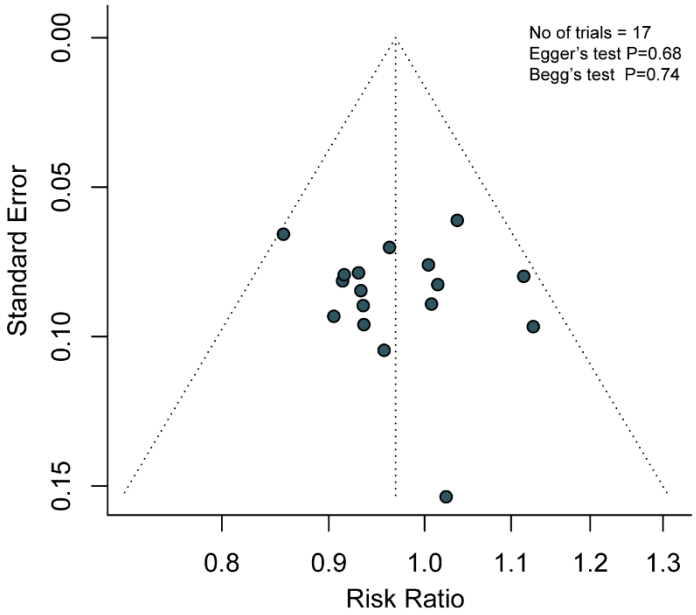
eFigure 7. Sensitivity analysis of primary efficacy end points for rituximab derived from RCTs.

Abbreviations: DL, dersimonian and laird method. CI, confidence interval.

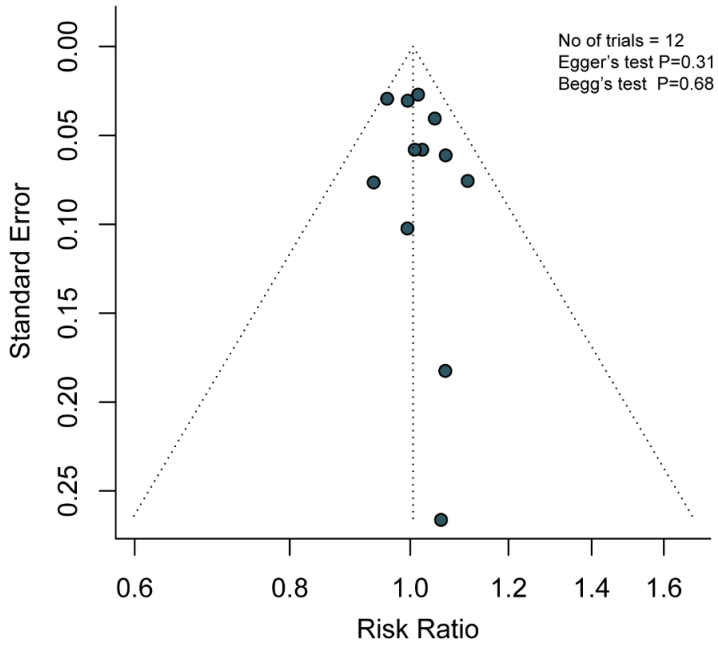


eFigure 8. Sensitivity analysis of primary efficacy end points for trastuzumab derived from RCTs.

Abbreviations: DL, dersimonian and laird method. CI, confidence interval.

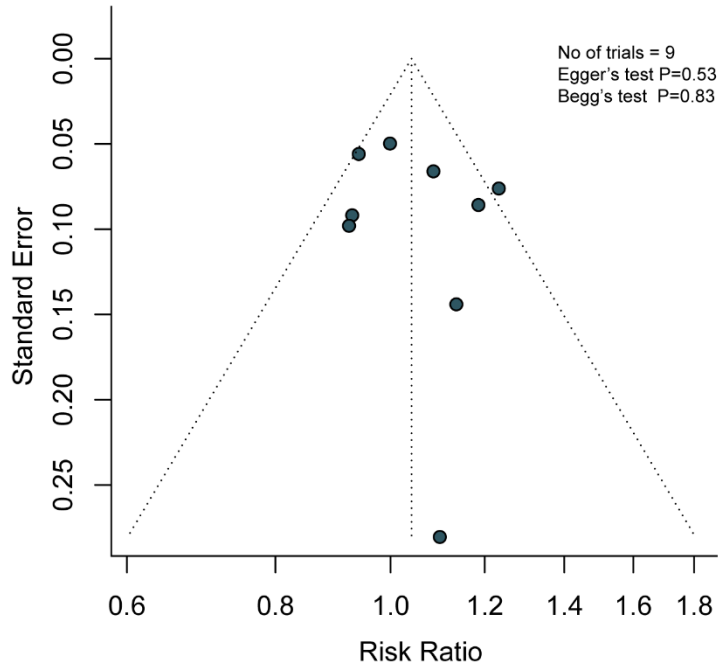


eFigure 9. Publication bias assessment of primary efficacy end points for bevacizumab derived from RCTs.
Abbreviations: RCTs: randomized controlled trials.



eFigure 10. Publication bias assessment of primary efficacy end points for rituximab derived from RCTs.

Abbreviations: RCTs: randomized controlled trials.



eFigure 11. Publication bias assessment of primary efficacy end points for trastuzumab derived from RCTs.

Abbreviations: RCTs: randomized controlled trials.

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eAppendix 3

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