Supplementary Online Content

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

eMethods. Search Strategy for the Systematic Review and Meta-Analysis

Our search strategy aimed to capture studies that undertook a comparative efficacy analysis of cancer biosimilars for one of three reference cancer biologics: bevacizumab, trastuzumab, and tituximab. The search was conducted in April 2021 and limited to English-language randomized clinical trials and observational studies. The search was conducted in Embase, Pubmed/Medline, and Clinicaltrials.gov.

Search terms for this study were designed to optimize both the search's sensitivity and precision to identify as many relevant publications as possible. These terms were designed to account for the variability in the types of language used in publications while yielding as many relevant results as possible. A common search term was used in Embase and Pubmed/Medline, while a different, simplified search term was used in Clinicaltrials.gov.

Search Term Used for Embase and Pubmed/Medline

The search term used in Embase and Pubmed/Medline was designed to ensure both a sensitive and precise search for this study, maximizing the number of relevant results. First, the search term was designed to ensure that drugs in the studies shared a common indication for various types of cancer, so the following terms were added:

("cancer" OR "oncology")

The next element of the search term was designed to ensure that studies found included biosimilars and their reference products. Thus, the following string was added:

“biosimilar” AND ("reference" OR "originator" OR "brand name" OR "brand-name")

We then added terms to ensure studies found by the search were comparative analyses of biosimilars and their reference products. Hence, we added the following:

("compared" OR "comparison" OR "compare" OR "contrast" OR "versus" OR "equivalence" OR "switching" OR "equivalent" OR "equivalence" OR "bioequivalence" OR "comparing")

Lastly, we wanted to ensure that all studies found analyzed one of the three specified biologics (Rituximab, Trastuzumab, and Bevacizumab) and a relevant biosimilar. Hence, we added the following terms to limit results to these drugs:

(((“Rituxan” OR “Rituximab”) OR (“Riabni” OR “Ruxience” OR “Truxima” OR “rituximab-arrx” OR “rituximab-pvvr” OR “rituximab-abbs”)) OR ((“Herceptin” OR “trastuzumab”) OR (“Herzuma” OR “trastuzumab-pkrb” OR “Kanjinti” OR “trastuzumab-anns” OR “Ogivri” OR “trastuzumab-dkst” OR “Ontruzant” OR “trastuzumab-dttb” OR “Trazimera” OR “trastuzumab-qyyp”)) OR ((“Avastin” OR “bevacizumab”) OR (“Mvasi” or “bevacizumab-awwb” OR “Zirabev” OR “bevacizumab-bvzr”)))

We joined each of these smaller terms with the AND operator to create the main search term:

("cancer" OR "oncology") AND "biosimilar" AND ("reference" OR "originator" OR "brand name" OR "brand-name") AND ("compared" OR "comparison" OR "compare" OR "contrast" OR "versus" OR "equivalence" OR "switching" OR "equivalent" OR "equivalence" OR "bioequivalence" OR "comparing") AND ((("Rituxan" OR "Rituximab") OR ("Riabni" OR "Ruxience" OR "Truxima" OR "rituximab-arrx" OR "rituximab-pvvr" OR "rituximab-abbs")) OR (("Herceptin" OR "trastuzumab") OR ("Herzuma" OR "trastuzumab-pkrb" OR "Kanjinti" OR "trastuzumab-anns" OR "Ogivri" OR "trastuzumab-dkst" OR "Ontruzant" OR "trastuzumab-dttb" OR "Trazimera" OR "trastuzumab-qyyp")) OR (("Avastin" OR "bevacizumab") OR ("Mvasi" or "bevacizumab-awwb" OR "Zirabev" OR "bevacizumab-bvzr")))

We ran this search in Pubmed/Medline and Embase, limiting results to randomized clinical trials and observational studies. This search yielded the studies, which were then screened and later used in this analysis.

Search Term Used for Clinicaltrials.gov

The search term used in Clinicaltrials.gov was a simplified version of the search term used in Pubmed/Medline and Embase in order to better fit the search function provided on that website. The goal of the search term was once again to ensure an optimally sensitive and precise search with as many relevant results as possible.

The search term first was designed to ensure studies focused on one of the three cancer biologic medications. Hence, the string began:

(*Rituximab* OR *Trastuzumab* OR *Bevacizumab***)**

Next, the string was appended with additional terms to ensure that the search would yield studies that undertook comparative efficacy analyses of biosimilars for the three relevant biologics. As a result, the following substring was appended to the main search term:

Biosimilar AND ("compared" OR "comparison" OR "compare" OR "contrast" OR "versus" OR "equivalence" OR "switching" OR "equivalent" OR "equivalence" OR "bioequivalence" OR "comparing")

The two smaller strings were then joined by an AND operator to create the final string:

(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")

The final string was entered into the Advanced Search feature provided in Clinicaltrials.gov. The additional parameter of "Recruitment: Completed" was selected in order to ensure studies had finished recruiting patients and could at least report intermediate results.

eTable 1. Oncology Biosimilar Efficacy Trials

First Author	Year	Design & Blinding	Cancer & Stage	Exposure	Reference	Total Study Patients	Age, median (range or IQR) or mean (SD)	Gender	ECOG perf. status
Kaplanov et al.	2014	open-label RCT	Follicular lymphoma	BCD-020	rituximab	92	Median, Range: 57.5 (50 - 65)		0-2: 100%
Filon et al.	2015	double-blind RCT	Advanced nonsquamous non-small cell lung cancer (NSCLC)	BCD-021	bevacizumab	138	Mean, SD: 58.23 (8.61)	F: 36.6% M: 63.4%	0-2: 100%
Stebbing et al.	2017	double-blind RCT	Early HER2-positive breast cancer	CT-P6	trastuzumab	549	Median, Range: 53 (24–78)	F: 100%	0: 88% 1: 12%
Jurczak et al.	2017	double-blind RCT	Advanced follicular lymphoma	GP2013	rituximab	629	Mean, SD: 56.9 (11.79)	F: 58% M: 42%	0: 57% 1: 40% 2: 2% Missing: 1%
Apsangikar et al.	2017	open-label RCT	Metastatic colorectal cancer (mCRC)	BevaciRel	bevacizumab	119	Mean, SD: 48.1 (11.94)	F: 34.45% M: 65.55%	0: 28.57% 1: 63.03% 2: 8.40%
Rugo et al.	2017	double-blind RCT	Metastatic HER2-positive breast cancer	MYL-1401O	trastuzumab	500	Median, Range: 55.0 (26-79)	F: 100%	0: 51.4% 1: 46.6% 2: 2.0%

First Author	Year	Design & Blinding	Cancer & Stage	Exposure	Reference	Total Study Patients	Age, median (range or IQR) or mean (SD)	Gender	ECOG perf. status
Kim et al.	2017	double-blind RCT	Advanced follicular lymphoma	CT-P10	rituximab	140	Median, Range: 57.5 (26 - 85)	M: 45% F: 55%	
von Minckwitz et al.	2018	double-blind RCT	early HER2-positive breast cancer	ABP 980	trastuzumab	725	Median, Range: 53 (46–60)	F: 100%	0: 82% 1: 18%
Pivot et al.	2018	double-blind RCT	Early HER2-positive breast cancer	SB3	trastuzumab	875	Median, Range: 51 (24-65)	F: 100%	0: 83.8% 1: 16.2%
Advani et al.	2018	open-label RCT	Metastatic colorectal cancer (mCRC)	Hetero-Bevacizumab	bevacizumab	111	Median: 48* *Range unavaliable	F: 38.89% M: 61.11%	
Lammers et al.	2018	double-blind RCT	Eearly HER2-positive breast cancer	PF-05280014	trastuzumab	226	Mean, SD: 52.6 (12.3)	F: 100%	
Ogura et al.	2018	double-blind RCT	Early follicular lymphoma	CT-P10	rituximab	258	Mean, SD: 57.7 (12.7)	M: 51% F: 49%	0: 84% 1: 16%
Romera et al.	2018	open-label RCT	Metastatic colorectal cancer (mCRC)	BEVZ92	bevacizumab	142	Median, Range: 56.3 (29-83)	M:57% F:43%	0: 10% 1:83% 2:7%

First Author	Year	Design & Blinding	Cancer & Stage	Exposure	Reference	Total Study Patients	Age, median (range or IQR) or mean (SD)	Gender	ECOG perf. status
Toogeh et al.	2018	double-blind RCT	Chronic lymphocytic leukemia (CLL)	Zytux	rituximab	70	Mean, SD: 57.94 (8.44)	M: 80% F:20%	
Pegram et al.	2019	double-blind RCT	Metastatic HER2-positive breast cancer	PF-05280014	trastuzumab	707	Median, Range: 54.0 (19-85)	F: 100%	0: 53.7% 1: 41.9% 2: 4.4%
Thatcher et al.	2019	double-blind RCT	Advanced nonsquamous non-small cell lung cancer (NSCLC)	ABP 215	bevacizumab	642	Mean, SD: 61.6 (8.98)	M: 59.8% F: 40.2%	0: 38.7% 1: 61.3%
Reinmuth et al.	2019	double-blind RCT	Advanced nonsquamous non-small cell lung cancer (NSCLC)	PF-06439535	bevacizumab	719	Median, Range: 62.0 (25-87)	M: 66.2% F: 33.8%	0: 29.3% 1:70.4 %
Candelaria et al.	2019	double-blind RCT	Diffuse large B-cell lymphoma (DLBCL)	RTXM83	rituximab	272	Median, IQR: 51 (40.0,58.0)	F: 43% M: 57%	0: 62% 1: 38% Missing: <1%
Viswabandya et al.	2019	double-blind RCT	Diffuse large B-cell lymphoma (DLBCL)	DRL-rituximab	rituximab	151	Mean, SD: 47.2 (11.75)	F: 35.5% M: 64.5%	
Poddunaya et al.	2019	open-label RCT	Follicular lymphoma	BCD-020	rituximab	174	Median, IQR: 58.0 (49,64)*	F: 52.8% M: 47.2%	0: 23.6%, 1: 66.3%, 2: 7.9%, 3: 2.2%

First Author	Year	Design & Blinding	Cancer & Stage	Exposure	Reference	Total Study Patients	Age, median (range or IQR) or mean (SD)	Gender	ECOG perf. status
Reck et al.	2019	double-blind RCT	Advanced nonsquamous non-small cell lung cancer (NSCLC)	SB8	bevacizumab	763			
Yang et al.	2019	double-blind RCT	Advanced nonsquamous non-small cell lung cancer (NSCLC)	IBI305	bevacizumab	450	Mean, SD: 57.4 (8.98)	M: 63.3% F: 36.7%	0: 24.9% 1: 75.1%
Sharman et al.	2020	double-blind RCT	Follicular lymphoma	PF-05280586	rituximab	394	Mean, SD: 58.7 (12.1)	F: 56.1% M: 43.9%	0: 87.2% 1: 12.8%
Rezvani et al.	2020	double-blind RCT	Metastatic colorectal cancer (mCRC)	BE1040V	bevacizumab	126	Mean, SD: 56.26 (11.94)	F: 62.20% M: 37.80%	0 or 1: 100%
Shi et al.	2020	double-blind RCT	Diffuse large B-cell lymphoma (DLBCL)	HLX01	rituximab	402	Median, IQR: 54 (46, 61)	F: 40.7% M: 59.3%	0: 37.7% 1: 47.2% 2: 15.1%
Niederwieser et al.	2020	double-blind RCT	Follicular lymphoma	ABP 798	rituximab	256	Median: 58.5 (24-84)	F: 50.8% M: 49.2%	0: 84.8% 1: 15.2%
Hii et al.	2020	double-blind RCT	Early HER2-positive breast cancer	HD201	trastuzumab	502			

First Author	Year	Design & Blinding	Cancer & Stage	Exposure	Reference	Total Study Patients	Age, median (range or IQR) or mean (SD)	Gender	ECOG perf. status
Alexeev et al.	2020	double-blind RCT	Metastatic HER2-positive breast cancer	BCD-022	trastuzumab	225	Mean, SD: 50.63 (10.415)	F: 100%	0-2: 100%
Millan et al.	2020	double-blind RCT	Advanced nonsquamous non-small cell lung cancer (NSCLC)	MB02	bevacizumab	627	Median, Range: 61.0 (55.0 - 67.0)	M:61.1% F: 38.9%	
Qin et al.	2021	double-blind RCT	Metastatic colorectal cancer (mCRC)	HLX04	bevacizumab	677			0: 32.5% ; 1: 67.5%
Xu et al.	2021	double-blind RCT	Metastatic HER2-positive breast cancer	HLX02	trastuzumab	649	Median, Range: 54 (30 - 80). Mean, SD: 53.6 (9.7)	F: 100%	0: 42.6% 1: 57.4%

eTable 2. Quality Assessment Criteria and Risk of Bias Assessment

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
Kaplanov et al.	2014	?	-	-	-	-	+	+	high
Filon et al.	2015	?	?	?	?	+	+	+	unclear
Stebbing et al.	2017	+	+	+	+	+	+	+	low
Jurczak et al.	2017	+	+	+	+	+	+	+	low
Apsangikar et al.	2017	?	-	-	-	?	+	+	high
Rugo et al.	2017	+	+	+	+	+	+	+	low
Kim et al.	2017	?	+	+	+	+	+	+	low
von Minckwitz et al.	2018	+	+	+	+	+	+	+	low
Pivot et al.	2018	+	+	+	?	+	+	+	low
Pegram et al.	2018	+	+	+	+	+	+	+	low
Advani et al.	2018	+	?	-	+	-	+	+	unclear
Lammers et al.	2018	+	?	+	+	+	+	+	low
Ogura et al.	2018	+	+	+	+	+	+	+	low
Romera et al.	2018	+	-	-	?	+	+	+	unclear
Toogeh et al.	2018	+	+	+	+	+	+	+	low
Thatcher et al.	2019	+	+	?	+	+	+	+	low
Reinmuth et al.	2019	+	+	+	-	+	+	+	low
Candelaria et al.	2019	+	+	+	-	+	+	+	low
Viswabandya et al.	2019	+	?	+	?	+	+	+	low
Poddunaya et al.	2019	?	?	-	-	+	+	+	unclear
Reck et al.	2019	?	+	+	+	-	+	+	unclear
Yang et al.	2019	+	+	+	+	+	+	+	low

Sharman et al.	**2020**	+	?	+	?	+	+	+	**low**
Rezvani et al.	**2020**	+	+	+	+	+	+	+	**low**
Shi et al.	**2020**	?	?	+	?	+	+	+	**unclear**
Niederwieser et al.	**2020**	+	+	+	+	?	+	+	**low**
Hii et al.	**2020**	?	?	+	?	-	+	+	**unclear**
Alexeev et al.	**2020**	?	?	+	+	+	+	+	**low**
Millan et al.	**2020**	?	?	+	?	-	+	+	**unclear**
Qin et al.	**2021**	+	+	+	+	+	+	+	**low**
Xu et al.	**2021**	+	+	+	+	+	+	+	**low**

eFigure 1. Funnel Plot Analysis

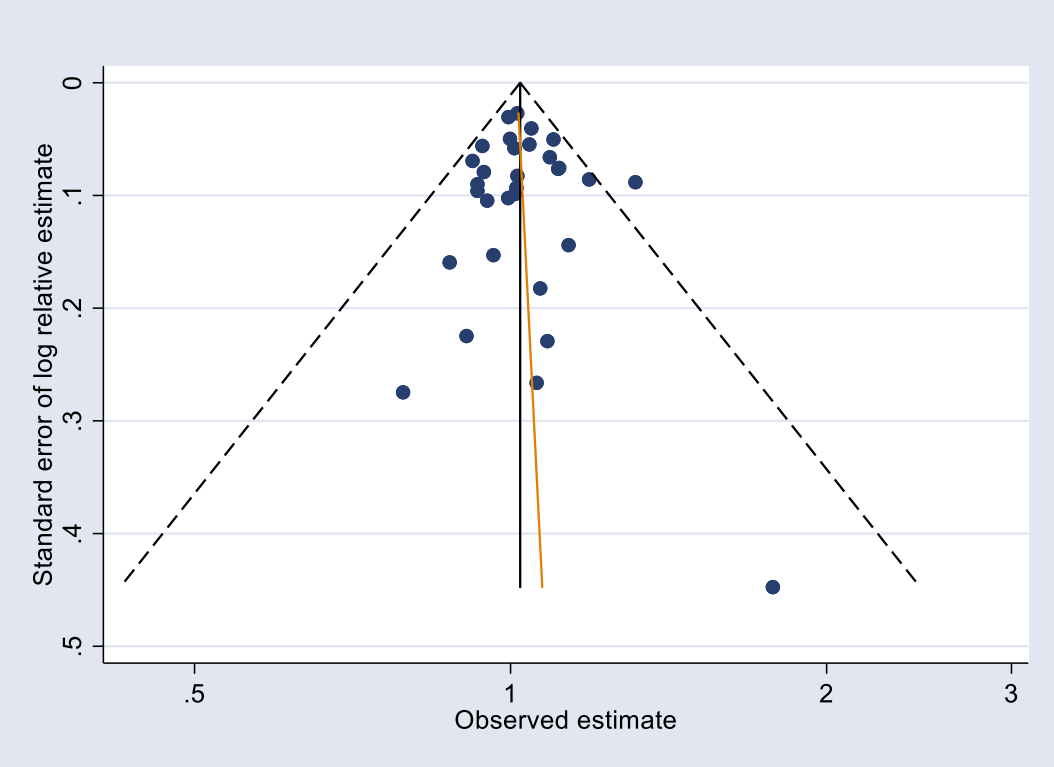


Figure Legend: Funnel plot showing symmetrical distribution of studies (full blue circles) indicating absence of publication bias. The full black line represents the expected pooled estimate, while the dashed lines represent upper and lower confidence intervals, respectively. The red line represents the observed pooled estimate across all the trials.

eTable 3. Begg's Test for Small-Study Effects

Rank correlation between standardized intervention effect and its standard error	
adj. Kendall's Score (P-Q)	5
Std. Dev. of Score	58.84
Number of Studies	31
Z (continuity corrected)	0.07
Pr > |z|(continuity corrected)	0.946

Interpretation: Begg and Mazumdar's test for rank correlation gave a p-value of 0.946, no suggesting evidence of publication bias.

eTable 4. Egger's Test for Small-Study Effects

Number of studies = 31				**Root MSE = 1.03**		
Std_Eff	**Coef.**	**Std. Err.**	**t**	**P>|t|**	**95% Conf. Interval**	
					Lower Bound	**Upper Bound**
slope	.014	.023	0.60	0.550	-.033	.061
bias	.123	.351	0.35	0.728	-.595	.842

Test of H0: no small-study effects P = 0.728

Interpretation: Egger's test for a regression intercept gave a p-value of 0.728, no suggesting evidence of publication bias.

eFigure 2. Funnel Plot by Disease-Measurement Subgroup

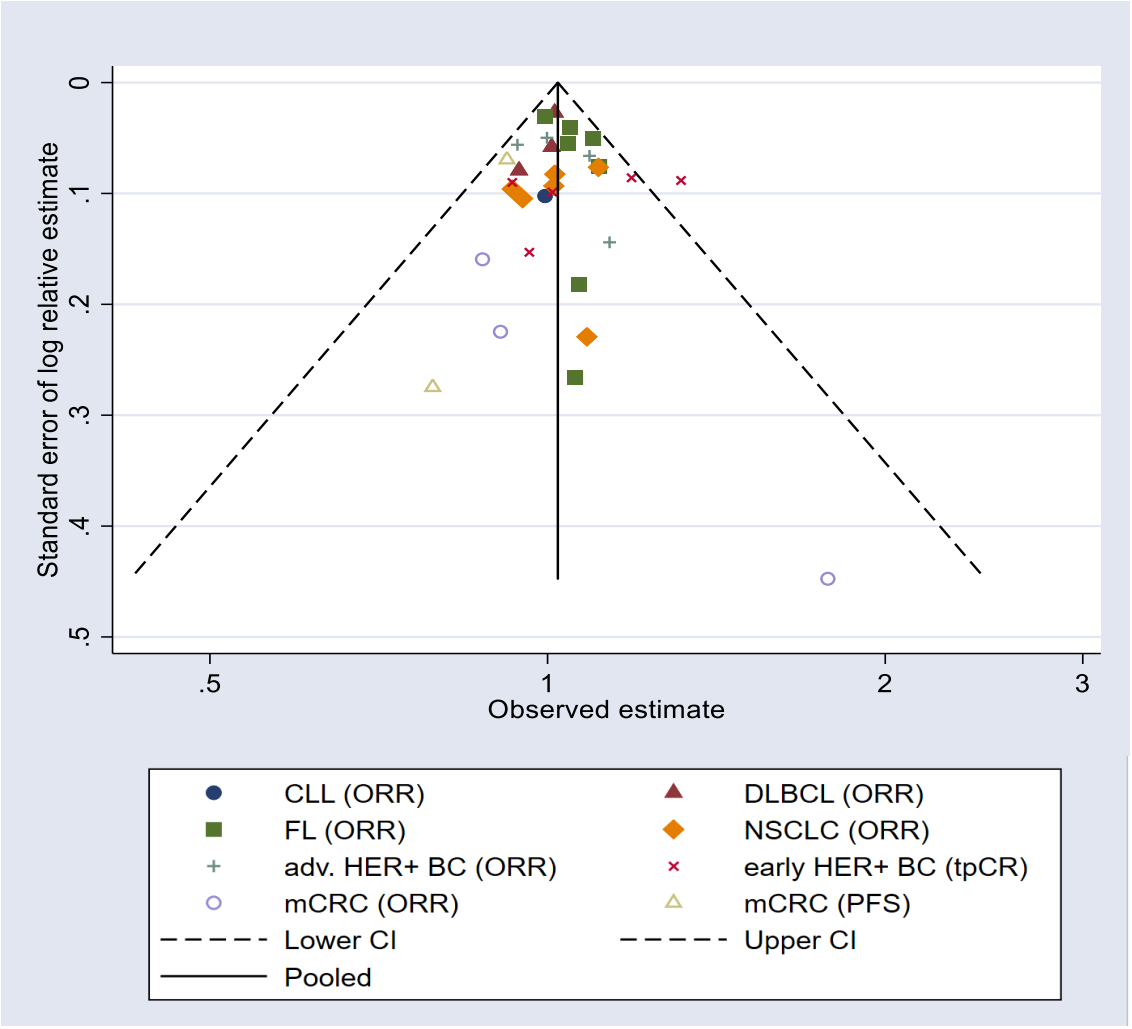
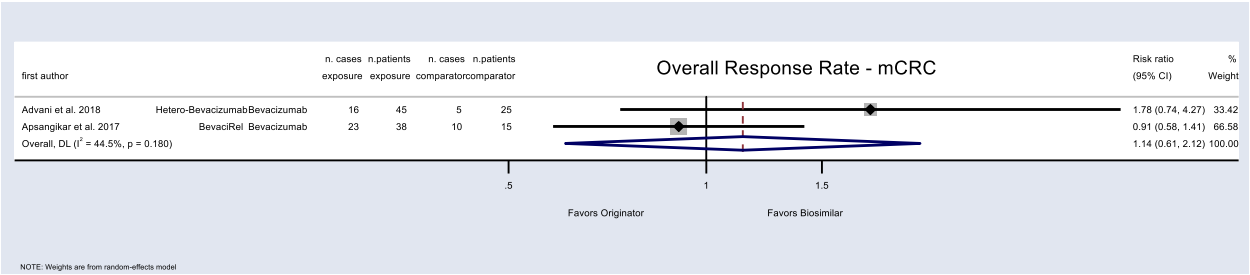
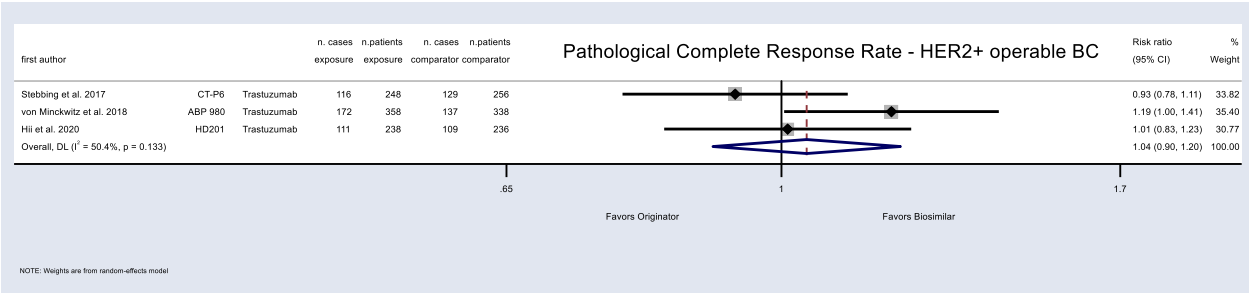


Figure Legend: Funnel plot showing symmetrical distribution of studies by cancer type and drug class. The full black line represents the expected pooled estimate, while the dashed lines represent upper and lower confidence intervals, respectively

eFigure 3. Sensitivity Analysis for ORR, mCRC Removing Romera et al.



eFigure 4. Sensitivity Analysis for pCR, ERBB2+ Early Breast Cancer Removing Pivot et al. and Lammers et al.



eFigure 5. Sensitivity Analysis for ORR, DLBCL Removing Viswabandya et al.