



# Anti-HER2 antibody prolongs overall survival disproportionately more than progression-free survival in HER2-Positive metastatic breast cancer patients



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## ABSTRACT

**Background:** This meta-analysis aimed to test the hypothesis that the HER2-positive metastatic breast cancer (mBC) patients treated with anti-HER2 antibodies in trial intervention arms have a greater prolongation of overall survival (OS) than of progression-free survival (PFS) and this extra-prolongation of median survival time in OS relates specifically to the anti-HER2 antibody.

**Methods:** The NCBI/Pubmed and Cochrane databases were searched systematically for HER2-positive or mBC trials published in English during January 1999–November 2017. Treatment arms with shorter PFS were considered as the “control” arm, whereas those with longer PFS as the “test” arm. The between-treatment drug differences were grouped into nine categories. Groups with or without anti-HER2 antibodies were pooled respectively for comparisons. The interrelationships between PFS and OS hazard ratios (HRs) and median survival time differences were investigated by conducting fixed-effects and mixed-effects linear meta-regression analyses.

**Results:** Twenty-eight trials (10,928 patients) from 438 articles were collected, and four with missing data were excluded in meta-regression analysis. Overall median PFS (HR = 0.73, 95% CI: 0.68–0.78) and median OS (HR = 0.82, 95% CI: 0.77–0.87) weakly favored the longer PFS arm with a weak correlation between the PFS and OS HRs. However, the between-treatment drug difference was anti-HER2 antibody, the absolute increment in median OS time was double that of median PFS time ( $p < 0.001$ ) and linearly correlated, which was not found with any non-anti-HER2 antibody drug differences.

**Conclusions:** Anti-HER2 antibody in patients with HER2-positive mBC prolonged OS more than PFS and mandates further investigation.

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## 1. Introduction

Several reviews and meta-analyses of anticancer therapies for mBC have found improved progression-free survival (PFS) hazard ratio (HR) to be only moderately associated with improved OS HR [1–3]. The surrogacy of PFS HR for OS HR improvement depends on

the tumor type, survival post-progression, and crossover design [4]. Nevertheless, several investigators have tried to delineate the relationship between PFS and OS in mBC; closer correlations have been reported with percentage increases in median PFS [1], PFS in later-line disease ( $\geq 2$  lines) [5], and in trials of targeted therapies [2]. However, the correlation between PFS and OS benefit in mBC subtype analyses remain equivocal.

For human epidermal growth factor receptor 2 (HER2) positive mBC patients, Michiels et al. [6] reported a modest correlation of PFS and OS when patients received anti-HER2 targeted agents. U.S. Food and Drug Administration approved trastuzumab for HER2

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positive mBC patients in 1998 for its improvement in OS [7–9]. Trastuzumab linked covalently to emtansine (T-DM1) delivers this cytotoxic drug to kill HER2-positive cancer cells more effectively than trastuzumab alone [10]. Pertuzumab is a monoclonal antibody that prevents HER2 dimerization [11]. T-DM1 and pertuzumab further prolonged OS of patients with HER2-positive mBC [5,9]. HER2 tyrosine kinase inhibitors (TKIs) such as lapatinib [12,13] and neratinib [14,15] broadened the treatment options for HER2-positive mBC; however, neither TKI demonstrated a clear OS benefit in clinical trials [16]. A drug mechanism-based investigation is mandatory to explore the relationship between PFS and OS in HER2-positive mBC patients.

It is noted that when trials incorporated trastuzumab or pertuzumab into intervention arms [17–23], the absolute increment in median OS always exceeded that of median PFS. This phenomenon is analogous to the findings observed in contemporary immune checkpoint inhibitor studies that immunotherapy provides durable long-term OS benefit more than PFS benefit [24]. Trastuzumab is known to exert its anti-tumor function via antibody-dependent cellular toxicity (ADCC) [24]. These immune-modulation similarities between trastuzumab and immune checkpoint inhibitor raised the possibility that adding an anti-HER2 antibody improves OS more than PFS in HER2-positive mBC. Hence, we aimed to test the hypothesis that the HER2-positive metastatic breast cancer (mBC) patients treated with anti-HER2 antibodies in trial intervention arms have a greater prolongation of OS than of PFS — that is, we aimed to investigate whether a differential benefit in OS versus PFS is antibody-specific, or merely coincidental.

## 2. Material and methods

### 2.1. Systematic review

Authors I.C.C and Y.S.L searched the NCBI/PubMed, Cochrane databases, and international conference abstracts for relevant articles published between January 1999 and November 2017, using the terms “HER2 positive breast cancer,” “metastatic breast cancer,” and “clinical trials.” The inclusion criteria were: (1) Phase II or III randomized controlled trial of treatment for HER2-positive mBC; (2) Interventional drug trial; (3) OS and PFS data reported; (4) English language article. Phase I studies, case reports, and studies not reporting OS data, in adjuvant/neoadjuvant settings, or with non-randomized designs were excluded (Fig. 1). The Cochrane toolkit was used to assess potential biases of the selected trials in terms of randomization, participant, and personnel blinding to allocation and outcome assessment, incomplete outcome data, and selective reporting [25]. I.C.C and Y.S.L discussed and resolved discrepant assessments.

### 2.2. Data extraction

I.C.C. and Y.S.L independently extracted relevant information from included studies as metadata, using a standardized measurement tool with fields including author, publication year, journal, patient numbers treated, median follow-up duration, treatment regimens, patient characteristics (age, estrogen receptor positivity, prior anti-HER2 treatment, and treatment crossover), hazard ratios (HRs) with 95% confidence intervals (CIs) of PFS and OS, and absolute median PFS and median OS.

To investigate the interdependence of median PFS and OS, included study treatment arms were further grouped into those with longer PFS (test) and shorter PFS (control), based on median PFS in their final analyses, and the same grouping was applied to the comparison of median OS. This stratification was done to unify improvements of median PFS across studies and facilitate

comparison of its interrelationship with median OS.

Moreover, we categorized drug differences between treatment arms in HER2-positive mBC clinical trials into nine groups: (1) Anti-HER2 antibody: added trastuzumab, pertuzumab, or T-DM1 versus no intervention used to control treatment; (2) Anti-HER2 antibody versus physician's choice therapy; (3) Anti-HER2 antibody versus anti-HER2 TKI: added anti-HER2 antibody versus anti-HER2 TKI (lapatinib, neratinib, or afatinib) to control treatment; (4) Anti-HER2 TKI: added anti-HER2 TKIs versus no intervention used to control treatment; (5) Added anti-HER2 TKI A plus chemotherapy versus anti-HER2 TKI B to control treatment; (6) Chemotherapy A versus chemotherapy B (7) Anti-angiogenesis: added anti-angiogenic drug (e.g., bevacizumab); versus nothing to control treatment; (8) Other targeted therapy: added another targeted therapy (e.g., everolimus) versus no intervention used to control treatment; and (9) Added concurrent versus sequential anti-HER2 antibody to control treatment. To investigate the role of anti-HER2 antibodies and their contribution to the increased median OS, we pooled between-treatment drug difference groups into two main categories: anti-HER2 antibody (Groups 1–3) versus non-anti-HER2 antibody (Groups 4–9).

### 2.3. Meta-analysis and meta-regression analysis

We used the R statistical software, Version 3.5.1, to perform meta-analyses and meta-regression analyses of (1) the natural logarithm of the hazard ratio,  $\log(\text{HR})$ , and (2) the median survival time differences for PFS and OS respectively. Two-sided  $p$ -value  $\leq 0.05$  was considered statistically significant unless specified otherwise. The Mantel-Haenszel method was used to calculate the weighted average of individual-trial  $\log(\text{HR})$ 's and median survival time differences for PFS and OS as the fixed-effects estimates of pooled  $\log(\text{HR})$  and pooled median survival difference. Since it was difficult to obtain the 95% confidence interval (CI) for the median survival difference from each trial, we used the weight of  $\log(\text{HR})$  (i.e., the inverse of the variance of  $\log(\text{HR})$ ) from each trial instead in our meta-analyses and meta-regression analyses of the median PFS and OS differences for consistency.

Heterogeneity among the included trials were assessed using the Chi-square  $Q$  test ( $p < 0.15$ ) and the  $I^2$  statistic ( $>50\%$ ) [26,27]. If substantial heterogeneity existed, the fixed-effects linear meta-regression used for modeling the mean values of  $\log(\text{HR})$  and median survival time difference for PFS and OS respectively were fitted to the meta-data by the weighted least squares method to identify the relevant covariates which affected the outcomes and accounted for the observed heterogeneity. The mixed-effects linear meta-regression analyses of  $\log(\text{HR})$  and median survival time difference for PFS and OS respectively were performed with the added random-effects to account for the unknown sources of residual heterogeneity. The  $\log(\text{HR})$  and median survival time difference for PFS were included as covariates into our meta-regression analyses of  $\log(\text{HR})$  and median survival time difference for OS to explore their effects on OS.

The model-fitting techniques for (1) variable selection, (2) goodness-of-fit (GOF) assessment, and (3) regression diagnostics were used in our meta-regression analysis. Specifically, the step-wise variable selection procedure (with the iterations between the forward and backward steps) were applied to obtain the final multiple linear meta-regression model of  $\log(\text{HR})$  and median survival time difference for PFS and OS respectively. As listed in Table 1, all relevant covariates according to our knowledge and some of their interaction terms were included in the variable list for selection. The significance levels for entry (SLE) and stay (SLS) were set to 0.15. With the aid of substantive knowledge, the best final multiple linear meta-regression model was identified manually by

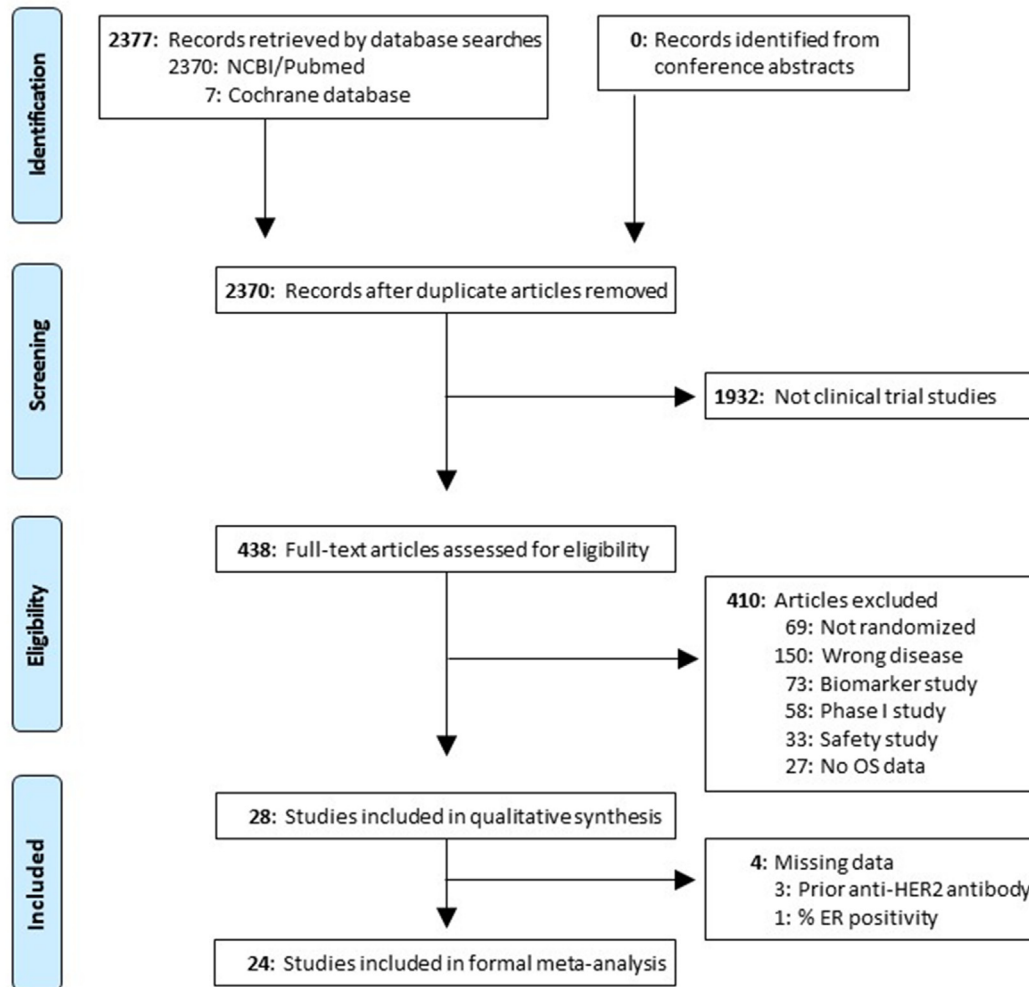


Fig. 1. The PRISMA study selection flowchart. OS: overall survival; ER: estrogen receptor.

dropping the covariates with  $p$  value  $> 0.05$  one at a time until all meta-regression coefficients were significantly different from 0. Next, we computed Pearson's correlation coefficients of the observed and predicted  $\log(\text{HR})$  or median survival difference to obtain the coefficients of determination,  $R^2$ , for assessing the GOF of the fitted multiple linear meta-regression models. And, the statistical tools of regression diagnostics for the examination of publication bias, residual analysis, detection of influential studies, and check of multicollinearity were applied to discover any model or data problems. Finally, conditional effect plots were created by plotting the predicted values of the continuous response variables stratified by a chosen categorical covariates of interest, given the mean values of the other covariates in the fitted linear meta-regression models, for visualizing the estimated adjusted effects of the interested covariates [28].

### 3. Results

#### 3.1. Systematic literature review

Fig. 1 shows the study selection flowchart. A total of 2377 publications were identified by the search strategy, but 7 studies were duplicated and 1932 non-clinical trial studies were excluded. We assessed the 438 full-text articles for eligibility. Finally, 28

randomized controlled trials (10,928 patients) were thoroughly reviewed and 24 were included in the meta-regression analysis, excluding 4 due to missing data. In the selected 24 randomized controlled trials, only 4 were non-superiority trials.

The pooled groups of drug differences between longer PFS and shorter PFS arms included seven anti-HER2 antibody studies [17–23,29,30] and 22 non-anti-HER2 antibody studies [12,16,31–52] (LACOG 0801,<sup>31</sup> which had three treatment arms, was analyzed as two separate studies) (Table 1). Twenty-one studies (79%) were phase III, and the enrollment timeframe of all studies included were from 1995 to 2013. Prior exposure to trastuzumab ranged from 0% to 100%, median age from 43 to 60 years, and 38%–100% of patients were estrogen receptor positive. At first glance, when drug difference between experimental and control treatment arms are anti-HER2 antibodies (Fig. 2(A)), median OS is always longer in the experimental arm than that in the control arm. However, when drug difference between treatments is non-anti-HER2 antibodies (Fig. 2(B)), median OS is not always longer in the experimental arms. Therefore, we further examined the relationship between median PFS and median OS in the meta-analysis.

#### 3.2. Meta-analysis of PFS and OS HR differences

Fig. 3 summarizes the results of random-effects meta-analysis of

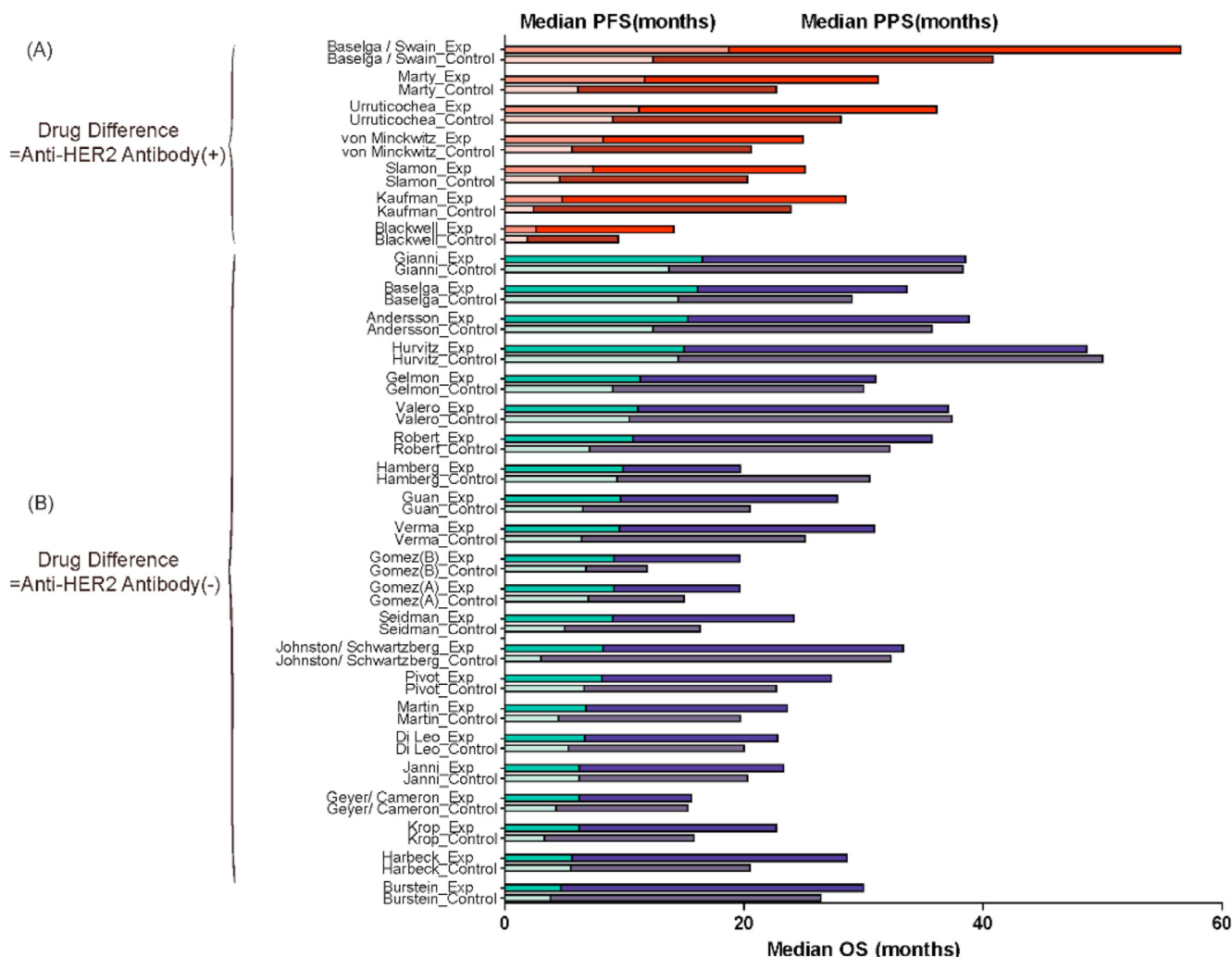
**Table 1**  
Characteristics of the collected 28 randomized clinical trials categorized into nine drug difference groups.

First author	Name	Control vs test regimens (N)	Median age (years)	ER positive	Prior anti-HER2
<b>1. Anti-HER2 antibody</b>					
Slamon [17] <sup>a</sup>	NA	Control: chemotherapy (234) Test: chemotherapy/trastuzumab (235)	NA NA	NA NA	NA NA
Marty [20]	M77001 <sup>b</sup>	Control: docetaxel (94) Test: docetaxel/trastuzumab (94)	55.0 53.0	56% 41%	NA NA
Kaufman [21]	TAnDEM	Control: anastrozole (104) Test: anastrozole/trastuzumab (103)	54.0 56.0	100% 100%	NA NA
von Minckwitz [19,29]	GBG26/BIG03-05	Control: capecitabine (78) Test: capecitabine/trastuzumab (78)	59.0 52.5	62% 56%	100% 96%
Blackwell [22]	EGF104900	Control: lapatinib (148) Test: lapatinib/trastuzumab (148)	51.0 52.0	49% 49%	NA NA
Baselga [18]/ Swain [30]	CLEOPATRA	Control: placebo/trastuzumab/docetaxel (402) Test: pertuzumab/trastuzumab/docetaxel (406)	54.0 54.0	49% 47%	10% 12%
Urruticochea [23]	Pherexa	Control: capecitabine/trastuzumab (224) Test: capecitabine/trastuzumab/pertuzumab (228)	55.0 54.0	55% 55%	100% 100%
<b>2. Anti-HER2 antibody versus physician's choice therapy</b>					
Krop [5,42]	Th3resa	Control: lapatinib or trastuzumab/chemotherapy (198) Test: trastuzumab-emtansine (404)	54.0 53.0	52% 51%	100% 100%
<b>3. Anti-HER2 antibody versus anti-HER2 tyrosine kinase inhibitor</b>					
Verma [32]	EMILIA	Control: lapatinib/capecitabine (496) Test: trastuzumab-emtansine (495)	53.0 53.0	53% 57%	100% 100%
Pivot [40]	EGF111438	Control: capecitabine/lapatinib (271) Test: capecitabine/trastuzumab (269)	53.0 56.0	49% 45%	62% 60%
Gelmon [12]	MA.31	Control: taxane/lapatinib (326) Test: taxane/trastuzumab (326)	55.4 54.4	65% 64%	18% 18%
Harbeck [41]	LUX-Breast1	Control: vinorelbine/afatinib (339) Test: vinorelbine/trastuzumab (169)	51.8 53.1	48% 48%	100% 100%
<b>4. Anti-HER2 Tyrosine kinase inhibitor</b>					
Geyer [33]	NA	Control: capecitabine (201) Test: capecitabine/lapatinib (198)	51.0 54.0	46% 48%	98% 99%
Cameron [34]	EGF30001	Control: paclitaxel/placebo (288) Test: paclitaxel/lapatinib (291)	52.4 51.3	50% 44%	0% 0%
Johnston [36]/ Schwartzberg [37]	NA	Control: letrozole/placebo (109) Test: letrozole/lapatinib (111)	59.0 60.0	96% 91%	0% 0%
Guan [38] <sup>a</sup>	NA	Control: paclitaxel/placebo (222) Test: paclitaxel/lapatinib (222)	50.5 50.0	51% 50%	NA NA
Burstein [39]	CALGB 40302	Control: fulvestrant/placebo (145) Test: fulvestrant/lapatinib (146)	55.0 55.0	97% 99%	3% 2%
<b>5. Anti-HER2 tyrosine kinase inhibitor A plus chemotherapy versus anti-HER2 tyrosine kinase inhibitor B</b>					
Martin [16]	NA <sup>b</sup>	Control: neratinib (116) Test: lapatinib/capecitabine (117)	52.0 56.0	44% 40%	99% 100%
<b>6. Chemotherapy A versus chemotherapy B</b>					
Robert [43] <sup>a</sup>	NA	Control: paclitaxel/trastuzumab (98) Test: carboplatin/paclitaxel/trastuzumab (98)	55.0 56.0	52% 64%	NA NA
Seidman [44]	CALGB 9840	Control: three-weekly paclitaxel/trastuzumab (123) Test: weekly paclitaxel/trastuzumab (168)	NA NA	56% 56%	0% 0%
Andersson [45]	HERNATA	Control: docetaxel/trastuzumab (143) Test: vinorelbine/trastuzumab (141)	56.0 57.0	53% 60%	1% 0%
Valero [46] <sup>a</sup>	BCIRG007	Control: carboplatin/docetaxel/trastuzumab (132) Test: docetaxel/trastuzumab (131)	51.0 52.0	63% 73%	NA NA
Baselga [47]	NA	Control: paclitaxel/liposomal doxorubicin/trastuzumab (182) Test: paclitaxel/trastuzumab (181)	53.0 52.0	45% 41%	2% 1%
Janni [48,49]	VITAL <sup>b</sup>	Control: lapatinib/capecitabine (37) Test: lapatinib/vinorelbine (75)	58.0 57.0	51% 49%	100% 100%
Goméz [31]	LACOG 0801-A <sup>b</sup>	Control: lapatinib/vinorelbine (45) Test: lapatinib/capecitabine (51)	55.0 52.0	38% 45%	47% 49%
	LACOG 0801-B <sup>b</sup>	Control: lapatinib/gemcitabine (46) Test: lapatinib/capecitabine (51)	43.0 52.0	45% 45%	52% 49%
<b>7. Other targeted agents</b>					
Hurvitz [50]	BOLERO-1	Control: placebo/trastuzumab/paclitaxel (239) Test: everolimus/trastuzumab/paclitaxel (480)	52.0 54.0	57% 57%	11% 11%
<b>8. Anti-angiogenesis agent</b>					
Gianni [51]	AVEREL	Control: placebo/paclitaxel/carboplatin/trastuzumab (216) Test: bevacizumab/paclitaxel/carboplatin/trastuzumab (208)	53.0 55.0	53% 51%	12% 13%
<b>9. Concurrent versus sequential anti-HER2 antibody</b>					
Hamberg [52]	HERTAX <sup>b</sup>	Control: concurrent docetaxel/trastuzumab (53) Test: Sequential docetaxel/trastuzumab (46)	50.0 54.0	49% 52%	NA NA

ER: Estrogen receptor; NA: Not available.

<sup>a</sup> They were excluded from the final meta-regression analysis due to missing data.

<sup>b</sup> Phase II studies, all the others were Phase III.



**Fig. 2.** Swimmer plot for median PFS and median OS. PFS: progression-free survival, PPS: post-progression survival, OS: overall survival. Light-colored bars = median progression-free survival, deep-colored bars = median post-progression survival.

median survival differences in PFS and OS. Median PFS and OS of each study are listed according to the longer PFS (test) and shorter PFS (control) arms. The HR for PFS from all studies was 0.73 (95% CI 0.68, 0.78), which favored the arms with longer PFS (test). The HR of OS also favored study arms with longer PFS (HR = 0.82, 95% CI 0.77, 0.87).

Added Anti-HER2 Antibody Independently Predicted PFS but not OS in Conventional Meta-analysis.

The conventional multivariate meta-analysis of factors predicting HRs for PFS and OS included estrogen receptor positivity, prior anti-HER2 antibody treatment, and drug difference groups (anti-HER2 antibody, chemotherapy A versus B, anti-HER2 TKI, anti-HER2 antibody versus anti-HER2 TKI, anti-angiogenesis, other targeted therapy, and anti-HER2 antibody versus physician's choice therapy). The meta-regression model excluded four studies with missing data: one did not report the estrogen receptor positivity rate, and three did not report rates of prior anti-HER2 antibody treatment.

Table 2(A) summarizes the results of our mixed-effects linear meta-regression analyses of log(HR) for PFS and OS respectively. After adjusting for the effects of other covariates, the mean value of log(HR) for PFS was 0.45 less in studies with the drug difference of anti-HER2 antibody vs. physician's chosen therapy (HR = 0.64,

$p < 0.001$ , 95% C.I.: 0.50, 0.80) and 0.157 less in studies with only the drug difference of anti-HER2 antibody (HR = 0.86,  $p = 0.003$ , 95% C.I.: 0.77, 0.95). Furthermore, after adjusting for the effects of other covariates, the mean value of log(HR) for OS would be 0.358 more in studies with the drug difference of other targeted agents (HR = 1.43,  $p = 0.005$ , 95% C.I.: 1.12, 1.84), 0.758 more in studies with drug difference of concurrent vs. sequential anti-HER2 antibody (HR = 2.14,  $p = 0.003$ , 95% C.I.: 1.28, 3.55), and 0.172 more in studies where the median trial participant age was >54.74 years (HR = 1.19,  $p = 0.025$ , 95% C.I.: 1.02, 1.38). We included the interaction term, "drug difference of anti-HER2 antibody  $\times$  log(HR) of PFS," as a covariate in the mixed-effects linear meta-regression analysis of HR for OS, but it did not reach statistical significance in the final mixed-effects linear meta-regression model.

Absolute Improvement in Median OS Exceeded that of PFS when an Anti-HER2 Antibody included the Drug Difference.

When the between-treatment drug difference was an anti-HER2 antibody, the increase in median OS was consistently prolonged compared with median PFS (Fig. 4). The OS difference between treatment arms (blue bars) was consistently longer than the PFS difference between treatment arms (yellow bars). There was no consistent relationship when the drug difference was not an anti-HER2 antibody (Supplemental Figure 1).

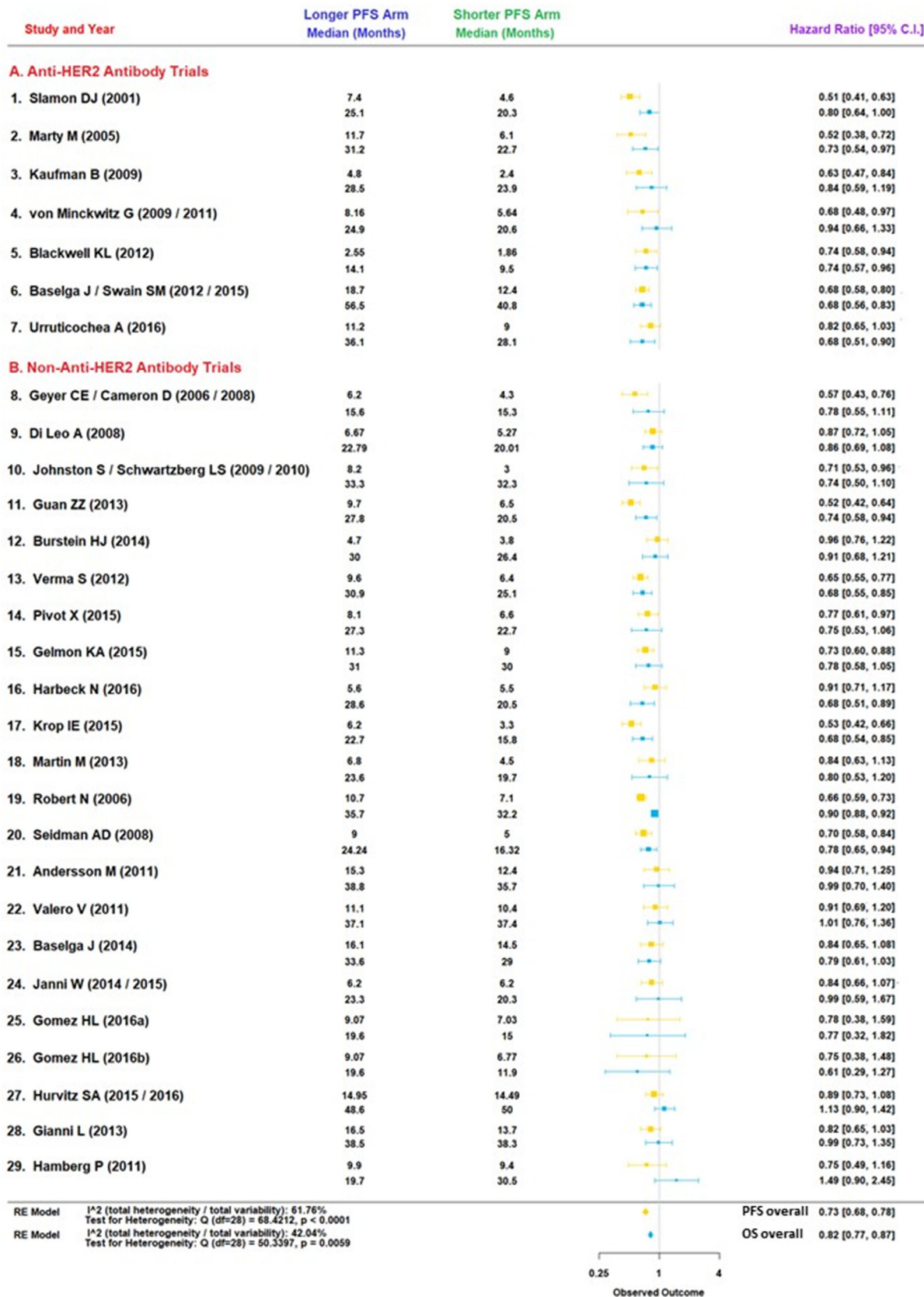


Fig. 3. Random-effects meta-analysis of hazard ratios for trials with/without anti-HER2 antibodies. Points/bars correspond to hazard ratios (95% C.I.) for median differences: Yellow = progression-free survival; Blue = overall survival.

**Table 2**  
Multiple linear meta-regression models for examining predictors of (A) log-hazard ratios for PFS and OS and (B) median survival time differences for PFS and OS respectively.<sup>a</sup>

Covariate	Regression coefficient estimate	Standard Error	z value	p value	Estimated hazard ratio (95% CI)
<b>A. log(Hazard ratio):</b>					
<b>1. PFS<sup>b</sup></b>					
Intercept	-0.184	0.038	-4.841	<.001	—
Drug difference: Anti-HER2 antibody vs. Physician's chosen therapy	-0.454	0.121	-3.767	<.001	0.64 (0.50, 0.80)
Drug difference: Anti-HER2 antibody	-0.157	0.052	-2.994	0.003	0.86 (0.77, 0.95)
<b>2. OS<sup>c</sup></b>					
Intercept	-0.360	0.048	-7.499	<.001	—
Drug difference: Other targeted agent	0.358	0.127	2.815	0.005	1.43 (1.12, 1.84)
Drug difference: Concurrent vs. Sequential anti-HER2 antibody	0.758	0.259	2.926	0.003	2.14 (1.28, 3.55)
Median trial participant age > 54.74 years	0.172	0.077	2.249	0.025	1.19 (1.02, 1.38)
Covariate	Regression coefficient estimate	Standard Error	z value	p value	(95% CI)
<b>B. Median survival time difference:</b>					
<b>1. PFS<sup>d</sup></b>					
Intercept	0.390	0.535	0.730	0.466	—
Median trial participant age >52.81 years	1.432	0.541	2.648	0.008	(0.37, 2.49)
Drug difference: Anti-HER2 antibody	1.129	0.566	1.994	0.046	(0.02, 2.24)
Prior anti-HER2 antibody use < 54.2%	1.149	0.494	2.324	0.020	(0.18, 2.12)
Drug difference: Other targeted agent	-2.511	1.232	-2.039	0.042	(-4.92, -0.10)
<b>2. OS<sup>e</sup></b>					
Intercept	-3.129	1.828	-1.712	0.103	—
Drug difference: Anti-HER2 antibody × Median PFS difference	2.007	0.396	5.073	<.0001	(1.18, 2.84)
Prior anti-HER2 antibody use	4.873	1.558	3.128	0.006	(1.61, 8.13)
Drug difference: Alternative chemotherapy × Median PFS difference	2.273	0.850	2.674	0.015	(0.49, 4.05)
Phase III trial	3.106	1.5714	1.977	0.063	(-0.18, 6.39)

<sup>a</sup> Multivariable meta-regression analysis of 24 randomized clinical trials was conducted using the `escal()` and `rma()` functions in the 'Metafor' package of the R 3.5.1 software (R Foundation for Statistical Computing, Vienna, Austria), with the stepwise variable selection procedure, to fit meta-regression models of the log(hazard ratio) and the median survival time differences respectively, where "log" was the natural logarithm.

<sup>b</sup> Test of residual heterogeneity,  $\chi^2$  statistic (df = 21) = 22.03,  $p = 0.398$ , so that the fixed-effects model was reported ( $R^2 = 0.34$ ).

<sup>c</sup> Test of residual heterogeneity,  $\chi^2$  statistic (df = 19) = 7.08,  $p = 0.994$ , so that the fixed-effects model was reported ( $R^2 = 0.80$ ).

<sup>d</sup> Test of residual heterogeneity,  $\chi^2$  statistic (df = 19) = 2197.35,  $p < 0.0001$ , so that the mixed-effects linear meta-regression model ( $\tau$  [2] estimator: Maximum likelihood, ML) was reported ( $R^2 = 0.46$ ).

<sup>e</sup> Test of residual heterogeneity,  $\chi^2$  [2] statistic (df = 19) = 5952.24,  $p < 0.0001$ , so that the mixed-effects linear meta-regression model ( $\tau$  [2] estimator: Maximum likelihood, ML) was reported ( $R^2 = 0.62$ ).

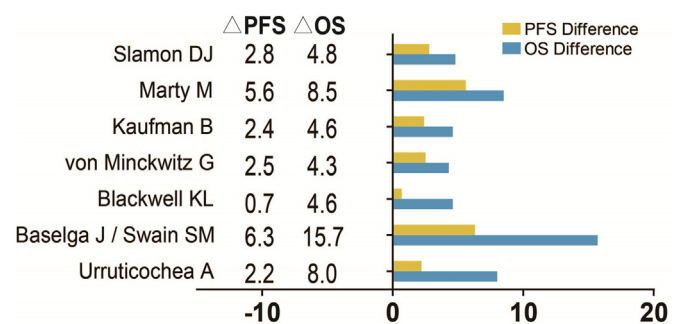
Table 2(B) summarizes the results of our mixed-effects linear meta-regression analyses for the median survival time differences in PFS and OS respectively. After adjusting for the effects of other covariates, the mean value of the median survival time difference in PFS (in months) was 1.432 months higher in studies with the median trial participant age > 52.81 years ( $p = 0.008$ , 95% C.I.: 0.37, 2.49), 1.129 months greater in studies with the drug difference of anti-HER2 antibody ( $p = 0.046$ , 95% C.I.: 0.02, 2.24), 1.149 months more in studies with a prior anti-HER2 antibody use < 54.2% ( $p = 0.020$ , 95% C.I.: 0.18, 2.12), but 2.51 months less in studies with the drug difference of other targeted agents ( $p = 0.042$ , 95% C.I.: -4.92, -0.10). Next, after adjusting for the effects of other covariates, the mean value of the median survival time difference in OS (in months) was (2.007 × median PFS difference in months) higher in studies with the drug difference of anti-HER2 antibody ( $p < 0.0001$ , 95% C.I.: 1.18, 2.84), 4.87 months more in studies with a prior anti-HER2 antibody use ( $p = 0.006$ , 95% C.I.: 1.61, 8.13), (2.273 × median PFS difference in months) more in studies with the drug difference of alternative chemotherapy ( $p = 0.015$ , 95% C.I.: 0.49, 4.05), and 3.11 months more in Phase III trials ( $p = 0.063$ , 95% C.I.: -0.18, 6.39), with borderline statistical significance.

### 3.3. Median OS difference correlated significantly with PFS when an Anti-HER2 antibody was the drug difference

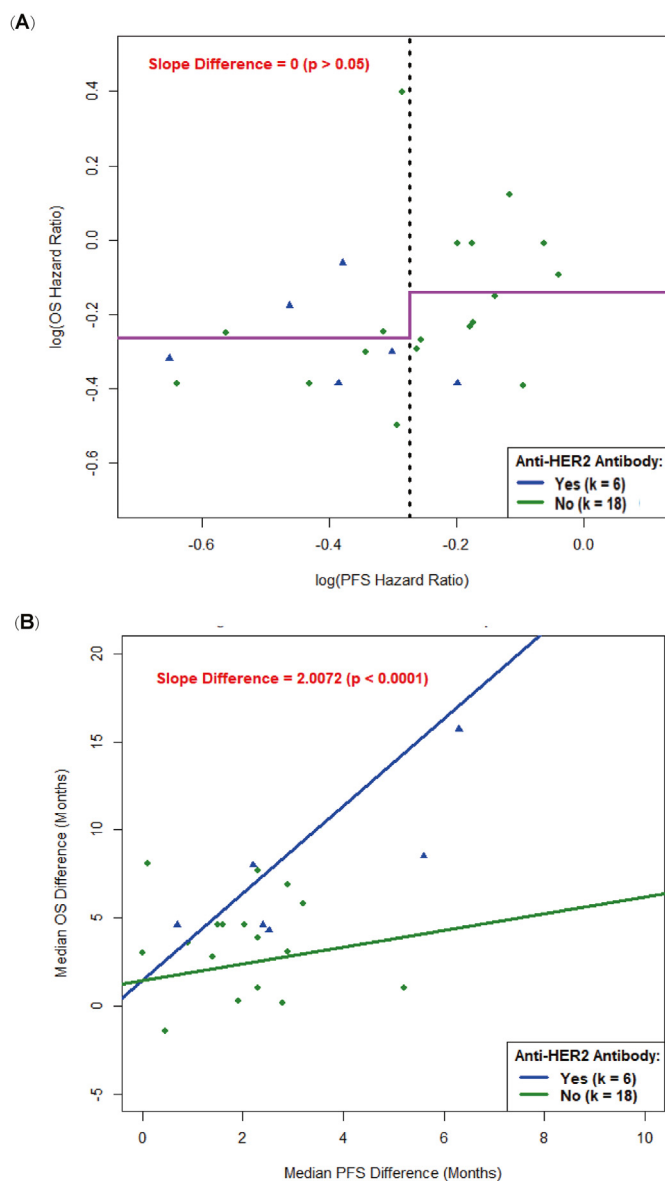
Based on the results of our fixed-effects linear meta-regression analyses, we repeated the PFS and OS HR meta-regression analysis by stratifying the drug difference into anti-HER2 antibody versus non-anti-HER2 antibody treatments. A conditional effect

plot shows the relationship between log PFS HR and log OS HR (Fig. 5(A)); the slopes for treatments differing in presence/absence of anti-HER2 antibody were the same (slope difference = 0). The mean value was used for all other variables in the final OS HR meta-regression model.

We tested the interrelationship between median PFS differences and drug difference variables in the final mixed-effects meta-regression model. After controlling for other variables, median OS difference increased linearly with median PFS difference in studies where anti-HER2 antibody became the difference between treatment arms (Fig. 5(B)), with a statistically significant positive correlation ( $p < 0.0001$ ), but this phenomenon was not apparent when the drug difference was not an anti-HER2 antibody.



**Fig. 4.** Differences between median PFS and median OS in the random-effect meta-analysis. PFS: progression-free survival; OS: overall survival. Median OS difference is longer than media PFS difference in trials differ in anti-HER2 antibodies.



**Fig. 5.** The conditional effect plots from the linear meta-regression analyses. PFS: progression-free survival; OS: overall survival. (A): The conditional effect plot of  $\log(\text{PFS Hazard Ratio})$  versus  $\log(\text{OS Hazard Ratio})$  stratified by “Drug difference: Anti-HER2 antibody” (Yes versus No), based on the fitted fixed-effects linear meta-regression model (see Table 2(A)-2) conditioning on the mean values of all covariates except for the stratified variable, “Drug difference: Anti-HER2 antibody.” We used the blue color to label the studies with “Drug difference: Anti-HER2 antibody” and the green color for the studies without “Drug difference: Anti-HER2 antibody” in the scatter plot. Yet, since the stratified covariate, “Drug difference: Anti-HER2 antibody,” did not stay in the fitted final fixed-effects linear meta-regression model (see Table 2(A)-2), the blue and green curves of the step functions for the studies with and without “Drug difference: Anti-HER2 antibody” inevitably overlapped in the conditional effect plot, and thus we used the purple color to draw the overlapped curves of the step functions for the studies with and without “Drug difference: Anti-HER2 antibody.” (B): The conditional effect plot of median PFS difference (months) versus median OS difference (months) stratified by “Drug difference: Anti-HER2 antibody” (Yes versus No), based on the fitted mixed-effects linear meta-regression model (see Table 2(B)-2) conditioning on the mean values of all covariates except for the stratified variable, “Drug difference: Anti-HER2 antibody.” We used the blue color to label the studies with “Drug difference: Anti-HER2 antibody” and the green color for the studies without “Drug difference: Anti-HER2 antibody” in the scatter plot. Since the stratified covariate, “Drug difference: Anti-HER2 antibody,” interacted with “Median PFS difference” (i.e., “Drug difference: Anti-HER2 antibody  $\times$  Median PFS difference,” regression coefficient estimate = 2.007,  $p < 0.0001$ , 95% CI: 1.18, 2.84) in the fitted final mixed-effects linear meta-regression model (see Table 2(B)-2), the blue and green curves of the straight lines for the

#### 4. Discussion

Our linear meta-regression analyses found that between-treatment difference of anti-HER2 antibody in randomized clinical trial participants with HER2-positive mBC consistently prolonged median OS more than median PFS; this phenomenon was not apparent in other treatment arms. These results suggest that prolonged PFS is a good predictor of OS where only HER2-positive mBC treatment regimens include an anti-HER2 antibody without any other kind of anticancer drugs. The prolongation of OS is disproportionately longer than that of the PFS when an anti-HER2 antibody involves the drug difference between treatment arms.

Conventional HR analysis revealed that PFS HR improvement was only moderately associated with OS HR, consistent with other reports [3]; the remarkable absolute median OS improvement was associated with anti-HER2 antibodies but no other drug classes. Our findings are consistent with another recent meta-analysis, which supported surrogacy of disease-free survival for OS in HER2-positive early breast cancer treated with trastuzumab for at least 1 year [53]. Although that study did not analyze non-trastuzumab adjuvant regimens for HER2-positive early breast cancer, and results from adjuvant therapies should not be extrapolated, that finding provide a similar conclusion to this study, that use of anti-HER2 antibodies may conduce to surrogacy of PFS for OS.

Anti-HER2 antibodies and anti-HER2 TKIs both trigger blockades of downstream signaling pathways. Differentially prolonged absolute median OS compared with PFS, suggests that this difference probably reflects antibody-specific effects rather than attenuated HER2-related signaling. Specifically, only anti-HER2 antibodies mediate antibody-dependent cell-mediated cytotoxicity [25,54,55], antibody-dependent phagocytosis [56,57], and the interferon-gamma response [58] in HER2-positive mBC. These immune-related effects maybe conducive to durable and extended antitumor immunity, and thus account for the long-term OS benefit we observed. The durable OS prolongation seen with anti-HER2 antibody therapy is analogous to the 15–20% complete response rate of metastatic melanoma patients treated with immunotherapy [24,59]; the carry-over effect is similar in either case, even after discontinuing anti-HER2 antibody or immunotherapy.

Unique OS benefit associated with anti-HER2 antibody treatment supports the rationale for adding another anti-HER2 antibody if the first trial fails. In the GBG26 trial [19,29], retaining trastuzumab in the treatment for HER2-positive mBC beyond progression on trastuzumab was associated with longer PFS and post-progression survival. In the recent HER2CLIMB [61] study, when tucatinib is added to trastuzumab and capecitabine, the presence of trastuzumab in the treatment might contribute to the OS benefit. This OS benefit was not seen when anti-HER2 TKI, like lapatinib or neratinib, was added to capecitabine. Although anti-HER2 antibodies double the increment of median OS compared with median PFS, prior anti-HER2 exposure also contributes to prolonging median OS.

We observed no consistent interrelationship between increments of PFS or OS after including agents other than anti-HER2 antibody. In our meta-regression model for median OS difference, drug difference of chemotherapy A versus B reached statistical significance in the final model; however, the differences in median PFS and median OS were distributed randomly (Supplement

studies with and without “Drug difference: Anti-HER2 antibody” were notably separated by the difference of 2.007 in slope in the conditional effect plot, which revealed the magnified effect of “Drug difference: Anti-HER2 antibody” on OS. In other words, anti-HER2 antibody prolonged the OS disproportionately more than the PFS in the HER2-positive metastatic breast cancer patients.



Figure 1), suggesting that the significant difference observed for chemotherapy A versus B may have been coincidental.

Linear improvement of OS was double that of PFS when the between-treatment drug difference was anti-HER2 antibody, but not an anti-HER2 TKI, chemotherapy, or other targeted therapy, suggesting that anti-HER2 TKIs and anti-HER2 antibodies should not be considered equivalent. Indeed, PFS improvement from a non-anti-HER2 antibody would not reasonably be expected to predict the OS benefit in mBC [62–64]. Therefore, the expected OS benefit based on between-treatment drug differences should be considered when using effect size to estimate sample size in HER2-positive mBC trials.

This study has limitations. First, most included trials did not report post-progression treatment results, making it difficult to estimate the contribution of differing drug exposures to the differential median OS increment. If the subsequent lines of therapies were randomly chosen, the performance of PFS as a surrogate to OS would be worse [64]. Cross-over percentage was also not all reported, and this would have made the estimation of PFS to OS difficult. Secondly, T-DM1 was considered an anti-HER2 antibody; although T-DM1 retains most of the antitumor actions of trastuzumab [56], as an antibody-drug conjugate it can induce cancer cell apoptosis and mitotic catastrophe [65]. Thirdly, to explore how including another anti-HER2 antibody affected the interaction between absolute median PFS difference and median OS difference, we pooled between-group treatment differences with those with or without anti-HER2 antibodies. However, other groupings could be applied to analyze data from a different perspective. Our categorization precluded further dissection of the number or sequence of anti-HER2 antibodies that contributed to the median OS benefit. Fourth, the follow-up protocol in all the trials was not uniform and this would result in a lead time bias in PFS. We can not adjust our analysis to take the issue of different follow-up time periods [63]. Finally, we excluded four studies with missing data from the meta-regression analysis, including the pivotal trastuzumab study by Slamon et al. [17] (insufficient estrogen receptor positivity data); however, the median OS increment exceeded that of median PFS in that study. Adding an anti-HER2 antibody remained an independent factor for differential median OS increment even when our analysis included these four trials.

## 5. Conclusions

We corroborated the hypothesis that anti-HER2 antibodies are specifically associated with a consistent and linear increment of OS, which can be predicted from the PFS increment using a predefined statistical model. The mechanistic explanation remains unclear, warranting further investigation.

### Ethical approval and consent to participate

Not applicable

### Consent for publication

All authors approved the version submitted for publication.

### Availability of supporting data

Not applicable

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## Author contributions

I.C.C and Y.S.L had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. I.C.C and Y.S.L collected and assessed the raw data. F.C.H., I.C.C., and Y.S.L analyzed the data. I.C.C., F.C.H., C.H.L., S.M.H., D.Y.C., A.L.C, and Y.S.L drafted the manuscript. I.C.C. and Y.S.L finalized the manuscript and all authors approved the version submitted.

## Declaration of competing interest

Dr. Lu reports consultation and speaker fees from Novartis, Pfizer, Roche, Merck Sharp & Dohme, study grants from Novartis, Roche, and Merck Sharp & Dohme. Other authors have no related conflict of interest to disclose.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2021.07.006>.

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