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Interaction between hormone receptor status and the route of administration of dual HER2 blockade in HER2-positive breast cancer: a real-world exploratory study

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Research Article

Keywords: HER2-positive breast cancer, Neoadjuvant therapy, Pathological complete response, Hormone receptor status, Subcutaneous trastuzumab, Real-world study

Posted Date: November 11th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11499148/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose To compare pathological complete response (pCR) rates between all-intravenous (IV) dual HER2 blockade and a mixed regimen of subcutaneous (SC) trastuzumab plus IV pertuzumab in HER2-positive breast cancer, and to explore the interaction between route of administration and hormone receptor (HR) status.

Methods This single-center retrospective study stratified patients treated between January 2019 and December 2024 by route of administration. The primary endpoint was pCR (ypT0/is ypN0). The HR status × route interaction was assessed with an interaction term and the likelihood ratio test; sensitivity analyses used a clinical-stage proxy and a stricter HR-positivity threshold.

Results Of 562 eligible patients, 332 were analyzed. The overall pCR rate was 55.4% (184/332): 58.5% (110/188) with all-IV versus 51.4% (74/144) with SC + IV (P = 0.237). HR-negative status (adjusted OR = 2.13, 95% CI 1.34–3.38, P = 0.001) and high Ki67 expression (adjusted OR = 2.06, 95% CI 1.09–3.89, P = 0.025) predicted pCR independently, whereas route of administration did not (OR = 0.78, P = 0.284). In HR+/HER2 + patients, pCR was 52.0% (53/102) with all-IV versus 40.0% (32/80) with SC + IV; in HR−/HER2 + patients, 65.5% (55/84) versus 66.1% (39/59). The adjusted interaction OR was 0.57 (95% CI 0.22–1.46; P = 0.240); sensitivity analyses were non-significant.

Conclusion HR-negative status and high Ki67 independently predicted pCR. No significant interaction was found between HR status and route of administration, and the two regimens did not differ significantly overall; the difference favoring all-IV in HR+/HER2 + patients (Δ = 12.0%) is exploratory and requires prospective verification.

Introduction

HER2-positive breast cancer accounts for 15%–20% of all breast cancers and, without targeted therapy, is characterized by aggressive biology and poor prognosis [1, 2]. Trastuzumab substantially improved the long-term outcomes of this subtype [2], and the subsequent development of anti-HER2 agents—most notably the dual-blockade combination of trastuzumab and pertuzumab—transformed the neoadjuvant treatment landscape [3–5]; in pivotal trials, pCR rates of 16.8%–66.2% have been reported across treatment arms, depending on the regimen and the definition of pCR. Dual HER2 blockade has also been evaluated in randomized phase III adjuvant trials [6, 7]. Because pCR is closely associated with improved event-free survival [8, 9], it has been widely adopted as the primary endpoint of neoadjuvant trials.

International guidelines recommend dual-blockade regimens containing trastuzumab and pertuzumab as neoadjuvant therapy for HER2-positive breast cancer [10]. Conventional intravenous (IV) dual blockade requires separate infusions and is time-consuming. In October 2022, the subcutaneous (SC) formulation of trastuzumab (Herceptin® SC, fixed dose 600 mg) was approved in China and included in the National Reimbursement Drug List (NRDL) in March 2023. Because no standalone SC pertuzumab is available in China and the fixed-dose SC combination (Phesgo) has not become widely accessible, a

mixed regimen emerged spontaneously in practice: SC trastuzumab plus IV pertuzumab. This approach shortens trastuzumab administration time and reduces the burden of venipuncture while retaining routinely available IV pertuzumab; however, no head-to-head evidence compares it with all-IV dual blockade, leaving a clear evidence gap.

Because real-world data from Chinese populations are of particular value for understanding differences in treatment patterns and outcomes [11, 12], we conducted this single-center real-world study to compare pCR outcomes between all-IV dual blockade and SC trastuzumab plus IV pertuzumab, to identify independent predictors of pCR, and to explore a possible interaction between HR status and the route of administration. Given the retrospective design, all subgroup and interaction analyses were interpreted as exploratory (hypothesis-generating) findings.

Materials and methods

Study design and patients

This was a single-center retrospective study. Patients with HER2-positive breast cancer who received neoadjuvant therapy at our center between January 2019 and December 2024 were reviewed. Of 562 eligible patients, 332 with complete pathological assessment and a clearly documented route of administration of the targeted therapy were included (Fig. 1). The 230 excluded patients did not differ significantly from included patients in baseline characteristics (all $P > 0.40$).

Inclusion and exclusion criteria

Inclusion criteria: (1) histologically confirmed HER2-positive breast cancer (IHC 3 + or FISH+); (2) neoadjuvant chemotherapy combined with dual HER2 blockade; (3) completion of neoadjuvant therapy followed by surgical resection; (4) available postoperative pathological assessment; and (5) a clearly documented route of administration. Exclusion criteria: previous breast cancer, concomitant other malignancies, incomplete neoadjuvant treatment, missing pathological data, or an unclear route of administration.

Treatment regimens

In the dual-IV group, trastuzumab was given intravenously (loading dose 8 mg/kg, then 6 mg/kg maintenance, weight-based) with IV pertuzumab. In the SC + IV group, trastuzumab was given subcutaneously at a fixed 600 mg dose with IV pertuzumab. Both groups received neoadjuvant chemotherapy with dual HER2 blockade (TCbHP or other anthracycline/taxane-based regimens combined with dual blockade, i.e., THP or AC-TPH).

Efficacy assessment

The primary endpoint was pCR, defined as ypT0/is ypN0 in the surgical specimen (no residual invasive carcinoma in the breast or axillary lymph nodes; residual ductal carcinoma in situ allowed). Isolated tumor cells were recorded as ypN0(i+) and counted as node-negative (ypN0).

Statistical analysis

Categorical variables were compared using the χ^2 or Fisher's exact test and continuous variables using the independent-samples t test or the Mann–Whitney U test. Multivariable logistic regression was used to identify independent predictors of pCR, with results reported as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Missing data were handled by available-case analysis without imputation: percentages were calculated using the number of available cases for each variable as the denominator, and the multivariable models included only patients with complete covariates.

To evaluate the interaction between HR status and the route of administration, an HR status × route interaction term was introduced and models with and without the interaction term were compared using the likelihood ratio test; the interaction model was adjusted for Ki67 expression and age, and sensitivity analyses used a clinical-stage proxy variable and a stricter definition of HR positivity (estrogen receptor [ER] or progesterone receptor [PR] ≥ 2%). Simple effects within subgroups were estimated within the same adjusted model framework and were not independent unadjusted 2×2 tests. The interaction between HR status and Ki67 expression (> 20% vs ≤ 20%) was assessed in the same framework, adjusted for the route of administration and age, with a sensitivity analysis using the stricter HR-positivity definition.

Post hoc sensitivity power estimations were performed for the subgroup comparisons: taking the observed 12.0% pCR difference in the HR+/HER2 + subgroup as the target effect size, power was approximately 36.0% for that comparison, 25.3% for the overall comparison, and 5.1% for the HR− subgroup. Because the interaction and subgroup analyses were post hoc and exploratory, no adjustment for multiple comparisons was applied; subgroup P values are descriptive only, and interaction was assessed solely by the likelihood ratio test of the interaction term.

The analysis dataset and code versions were locked in advance, and all statistics presented in the figures and tables were generated directly by the analysis code without manual modification. Analyses were performed using SPSS 26.0 and R 4.3.1; two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 332 patients were included (dual-IV, n = 188; SC + IV, n = 144). The two groups were well balanced in age, body weight, HR status, Ki67 expression, comorbidities, and menopausal status (all $P > 0.05$). Because some patients had been diagnosed and partially evaluated at other hospitals before referral, the corresponding pathological and clinical data could not be completely retrieved, and the

number of available cases differed across variables: HR status, 325 (7 missing); Ki67 expression, 324 (8 missing); body weight and menopausal status, 257 each (75 missing each). All patients received dual HER2 blockade combined with chemotherapy: 81.0% (269/332) received TCbHP and 19.0% (63/332) other regimens combined with targeted therapy (THP or AC-TPH). Remaining baseline characteristics are summarized in Table 1.

Table 1
Baseline characteristics of the two treatment groups (n = 332).

Characteristic	Dual-IV group (n = 188)	SC + IV group (n = 144)	P value
Age, mean ± SD (years)	51.2 ± 10.5	51.5 ± 9.7	0.819
Body weight, mean ± SD (kg)	62.8 ± 9.4	64.6 ± 10.4	0.168
HR-positive, n (%)	102 (54.8%)	80 (57.6%)	0.708
Ki67 > 20%, n (%)	158 (85.4%)	116 (83.5%)	0.744
Postmenopausal, n (%)	97 (55.7%)	41 (49.4%)	0.412
Comorbidity present, n (%)	49 (26.1%)	33 (22.9%)	0.596
Chemotherapy regimen: TCbHP, n (%)	146 (77.7%)	123 (85.4%)	0.100

Note: Continuous variables are expressed as mean ± SD and categorical variables as n (%); P values were derived from independent-samples t tests and χ^2 tests, respectively. HR, hormone receptor; TCbHP, docetaxel + carboplatin + trastuzumab + pertuzumab. Percentages for categorical variables were calculated using the number of available cases for each variable as the denominator: age, 332; body weight, 257; HR status, 325; Ki67, 324; menopausal status, 257; comorbidities, 332; chemotherapy regimen, 332; missing values were not imputed.

Overall efficacy

The overall pCR rate was 55.4% (184/332): 58.5% (110/188) in the dual-IV group and 51.4% (74/144) in the SC + IV group (Δ = 7.1%; χ^2 test with Yates' correction, P = 0.237; Fisher's exact test, P = 0.221). The difference was not statistically significant.

Univariable analysis

Results of the univariable analyses are shown in Table 2. Among the 325 patients with known HR status, the pCR rate was significantly higher in HR-negative than in HR-positive patients (65.7% vs 46.7%, χ^2 P < 0.001); it was also higher in patients with Ki67 > 20% (n = 324; 58.0% vs 38.0%, P = 0.014). Route of administration (P = 0.237), age (P = 0.920), menopausal status (P = 0.197), comorbidities (P = 0.128), and chemotherapy regimen (P = 0.907) were not statistically significant.

When HR status and Ki67 expression were combined, pCR rates showed a clear gradient across the four subgroups: 67.2% (86/128) in HR-negative/Ki67 > 20%, 53.3% (8/15) in HR-negative/Ki67 ≤ 20%, 50.0%

(73/146) in HR-positive/Ki67 > 20%, and 31.4% (11/35) in HR-positive/Ki67 ≤ 20% (Fig. 2).

Table 2
Univariable analysis of predictors of pCR.

Variable	Category	pCR, n/N (%)	P value	n
HR status	HR-negative	94/143 (65.7%)	< 0.001	325
	HR-positive	85/182 (46.7%)		
Ki67	> 20%	159/274 (58.0%)	0.014	324
	≤ 20%	19/50 (38.0%)		
Treatment regimen	Dual-IV	110/188 (58.5%)	0.237	332
	SC + IV	74/144 (51.4%)		
Age	> 55 years	68/121 (56.2%)	0.920	332
	≤ 55 years	116/211 (55.0%)		
Comorbidity	Present	39/82 (47.6%)	0.128	332
	Absent	145/250 (58.0%)		
Menopausal status	Postmenopausal	84/138 (60.9%)	0.197	257
	Premenopausal	62/119 (52.1%)		
Chemotherapy regimen	TCbHP	150/269 (55.8%)	0.907	332
	HP + other chemotherapy	34/63 (54.0%)		

Note: Percentages for each variable were calculated using the number of available cases as the denominator; missing values were not imputed: HR status unknown in 7 patients (n = 325), Ki67 missing in 8 patients (n = 324), menopausal status missing in 75 patients (n = 257). P values were derived from χ^2 tests with Yates' correction. All percentages were calculated directly from the counts. pCR, pathological complete response.

Multivariable logistic regression analysis

Results are presented in Table 3 and Fig. 3 (complete-case analysis set, n = 324). HR-negative status (adjusted OR = 2.13, 95% CI 1.34–3.38, P = 0.001) and high Ki67 expression (adjusted OR = 2.06, 95% CI 1.09–3.89, P = 0.025) were independent predictors of pCR, whereas the main effect of the route of administration was not statistically significant (adjusted OR = 0.78, 95% CI 0.50–1.23, P = 0.284). Stratified and interaction analyses were conducted within the adjusted covariate framework; interaction was assessed solely by the likelihood ratio test of the interaction term, and stratified subgroup P values were not used for inference.

Table 3
Multivariable logistic regression analysis of pCR (main model, n = 324).

Variable	Category	Adjusted OR	95% CI	P value
HR status	HR-negative vs HR-positive	2.13	1.34–3.38	0.001
Ki67 expression	> 20% vs ≤ 20%	2.06	1.09–3.89	0.025
Treatment regimen	SC + IV vs dual-IV	0.78	0.50–1.23	0.284
Age	> 55 vs ≤ 55 years	0.88	0.55–1.41	0.590

Note: OR, odds ratio; CI, confidence interval. The model included HR status, Ki67 expression, treatment regimen, and age (> 55 years). Because HR status was missing in 7 patients and Ki67 in 8 patients, the complete-case analysis set comprised n = 324.

Interaction between HR status and the route of administration

The interaction between HR status and the route of administration did not reach statistical significance. In the multivariable model adjusted for Ki67 expression and age (n = 324), the HR status × route interaction term had an OR of 0.57 (95% CI 0.22–1.46; likelihood ratio test $\chi^2 = 1.38$, df = 1, P = 0.240); the unadjusted model yielded an OR of 0.60 (95% CI 0.24–1.50, P = 0.274). Using “node-positive disease or largest tumor diameter > 50 mm” as a clinical-stage proxy variable (n = 309), the interaction OR was 0.44 (95% CI 0.16–1.17, $\chi^2 = 2.77$, P = 0.096); repeating the analysis with a stricter HR-positivity definition (ER or PR ≥ 2%) yielded interaction P values of 0.160–0.383. Thus the interaction effect was not statistically significant under any covariate-adjustment strategy or HR threshold. Adjusted simple effects within subgroups are provided for descriptive reference only: HR+/HER2+, OR = 0.64 (95% CI 0.35–1.18, P = 0.157); HR−/HER2+, OR = 1.14 (95% CI 0.55–2.35, P = 0.723). The corresponding observed pCR rates are shown in Fig. 4: 52.0% (53/102) with all-IV dual blockade versus 40.0% (32/80) with the mixed regimen in HR+/HER2 + patients, and 65.5% (55/84) versus 66.1% (39/59) in HR−/HER2 + patients. Both the simple effects and the unadjusted 2×2 stratified results are descriptive; interaction was assessed solely by the likelihood ratio test of the interaction term.

Interaction between HR status and Ki67 expression

The interaction between HR status and Ki67 expression did not reach statistical significance. In the model adjusted for the route of administration and age (n = 324), the HR status × Ki67 interaction term had an OR of 1.29 (95% CI 0.34–4.94; likelihood ratio test $\chi^2 = 0.14$, df = 1, P = 0.711); the unadjusted model yielded an OR of 1.22 (95% CI 0.32–4.62, P = 0.772). Repeating the analysis with a stricter HR-positivity definition (ER or PR ≥ 2%) yielded interaction P values of 0.845–0.947. Adjusted simple effects within subgroups are provided for descriptive reference only: in HR+/HER2 + tumors, high Ki67 expression was associated with a higher pCR rate (OR = 2.37, 95% CI 1.07–5.26, P = 0.034), whereas the

corresponding association in HR−/HER2 + tumors was not statistically significant (OR = 1.74, 95% CI 0.58–5.21, P = 0.322). The observed pCR rates across the four subgroups are shown in Fig. 2.

Discussion

In this single-center real-world study of 332 patients receiving neoadjuvant dual HER2 blockade for HER2-positive breast cancer, the overall pCR rate was 55.4%. HR-negative status (P = 0.001) and high Ki67 expression (P = 0.025) were independent predictors of pCR, whereas the main effect of the route of administration was not statistically significant. No statistically significant interaction between HR status and the route of administration was demonstrated (P = 0.240), and the 12.0% numerical pCR difference in the HR+/HER2 + subgroup is an exploratory finding requiring prospective verification.

Overall pCR rate: context and interpretation

The overall pCR rate was 55.4%. NeoSphere reported pCR (ypT0/is) rates of 16.8%–45.8% across four treatment arms [4], TRYPHAENA 57.3%–66.2% across its three arms, including 66.2% in the carboplatin-containing arm [5], and TRAIN-2 68% (140/206) with the anthracycline-free TCbHP regimen (ypT0/is, ypN0) [13]. Our relatively high rate is plausibly explained by the fact that 81.0% (269/332) of patients received TCbHP, a regimen with high pCR rates in HER2-positive disease [13], and by reimbursement through the NRDL since March 2023, which reduced treatment interruptions caused by financial barriers. Compared with TRAIN-2, however, our cohort shows a real-world implementation gap, reflecting heterogeneity in dose intensity and adherence outside trials. Overall, our results are comparable to those of previous trials of carboplatin-containing dual-blockade neoadjuvant therapy.

HR status: a core predictor of pCR

HR-negative status was the strongest independent predictor of pCR (adjusted OR = 2.13, 95% CI 1.34–3.38, P = 0.001), with a 19-percentage-point difference in pCR rates (65.7% vs 46.7%, P < 0.001). HR-positive (luminal B/HER2+) tumors harbor dual oncogenic drivers—the HER2 pathway and ER signaling—so that even when HER2 signaling is suppressed, ER-mediated transcription can sustain cell survival. Preclinical work shows that ER activation upregulates PI3K/Akt signaling downstream of HER2, partially bypassing HER2 blockade [14]. In contrast, the proliferative drive of HR−/HER2+ (HER2-enriched) tumors depends almost entirely on the HER2 amplicon, rendering them highly sensitive to dual blockade. This is consistent with NeoALTTO (pCR in the dual-blockade arm: 61.3% in HR-negative vs 41.6% in HR-positive tumors) [15] and with a pooled analysis of 12 neoadjuvant trials [8].

HR+/HER2 + disease is molecularly heterogeneous. Transcriptome-based subtyping shows that approximately 30% of HR+/HER2 + tumors are of the HER2-enriched (HER2-E) PAM50 subtype, characterized by highly activated ERBB2 signaling and relatively suppressed ER signaling, and are relatively sensitive to anti-HER2 therapy; the remaining ~ 70% display a luminal phenotype dominated by ER signaling and respond poorly to chemotherapy plus anti-HER2 therapy [16]. This is consistent with the lower pCR rate we observed in HR-positive patients (46.7%) and indicates that HR+/HER2 + disease is

not homogeneous but contains an internal response gradient determined by the balance between ER and HER2 signaling. In a meta-analysis of 16 neoadjuvant studies, the HER2-E subtype was associated with higher pCR rates (OR = 3.50, P < 0.001) in both HR-positive (OR = 3.61) and HR-negative (OR = 2.28) tumors, and HR-negative status was itself an independent predictor (OR = 2.41, P < 0.001) [17]. HR status and intrinsic subtype are therefore highly correlated but not interchangeable, and together they may characterize the driver-dependency landscape of the tumor.

Notably, the effect sizes of HR-negative status and high Ki67 expression in our model were similar (adjusted ORs 2.13 and 2.06) and pointed in the same direction. A real-world cohort of 353 Chinese patients similarly found ER status, PR status, HER2 expression intensity, and Ki67 to be independent predictors of pCR (nomogram AUC 0.73), with the highest pCR rate in ER − PR−HER2 + patients (131/208) and the lowest in ER + PR+HER2 + patients (19/73) [12]—consistent with our finding of a higher pCR rate in HR−/HER2+ (65.5%) than in HR+/HER2 + patients (46.7%). These findings, echoing previous Chinese and international cohorts, indicate that HR status maintains stable discriminative performance as a stratification marker of neoadjuvant response in a Chinese real-world population.

Ki67: an independent proliferation-related predictor

High Ki67 expression (> 20%) was associated with a significantly higher pCR rate (58.0% vs 38.0%, P = 0.014; adjusted OR = 2.06, 95% CI 1.09–3.89, P = 0.025). Highly proliferative tumors depend more heavily on active DNA replication and are therefore more susceptible to taxanes and platinum agents that disrupt mitotic spindle assembly. The value of proliferative activity as a predictor of pCR has been confirmed in multiple studies [18], and analysis of the GeparSixto trial showed that immune-related markers, including tumor-infiltrating lymphocytes, predict neoadjuvant response in HER2-positive patients [19].

The predictive value of Ki67 in HER2-positive breast cancer remains controversial, mainly because of interobserver variability and the lack of a uniformly accepted cutoff; reported thresholds vary widely (14%–40%) [20, 21]. In a real-world study of 353 HER2-positive patients, a 30% cutoff was significantly associated with pCR (P = 0.010) and remained an independent predictor in multivariable analysis [12]; in a bi-centric cohort of 244 patients, however, Ki67 categorized as ≤ 15%, 15%–35%, or > 35% was not associated with pCR (P = 0.25), and only HER2 IHC 3+ (63.2% vs 45%, P = 0.031) and HR status (74.4% vs 53.1%, P = 0.001) were predictive [22]. Ki67 performance therefore depends markedly on threshold and population. The 20% cutoff used here balances clinical operability and captured a significant signal, but requires prospective validation.

HR negativity and high Ki67 partially overlap in HER2-positive disease, but their independent contributions in the multivariable model indicate distinct biological information: HR status reflects pathway redundancy and endocrine survival signaling, whereas Ki67 reflects proliferation rate and chemotherapy sensitivity. Both provide additive, actionable information for predicting pCR. Consistent with this interpretation, no statistically significant HR status × Ki67 interaction was observed (P = 0.711);

the association between high Ki67 expression and pCR was numerically stronger in HR+/HER2 + tumors (adjusted OR = 2.37, P = 0.034) than in HR−/HER2 + tumors (OR = 1.74, P = 0.322).

Route of administration and HR status: a numerical difference rather than a statistical interaction

The mixed regimen of SC trastuzumab plus IV pertuzumab is now widely used in China, but real-world head-to-head evidence against all-IV dual blockade is lacking; to our knowledge this is the first real-world comparison. FeDeriCa (n = 500) established the non-inferiority of the fixed-dose SC combination Phesgo versus all-IV dual blockade (pCR 59.7% vs 59.5%) [23], and the Chinese FDChina study (n = 200) showed comparable total pCR rates (55.6% vs 56.4%) [24]; our results apply only to the mixed regimen and cannot be extrapolated to Phesgo or other fully SC dual-blockade formulations. The single-arm MetaPHER study in metastatic breast cancer confirmed only acceptable safety without a comparator [25]. Because most patients prefer SC administration [26, 27] and SC may save administration time and costs [28], regimen choice should not rest solely on pCR differences.

In the HR+/HER2 + subgroup, the pCR rate with the mixed regimen was 12.0 percentage points lower than with all-IV dual blockade (40.0% vs 52.0%), whereas in the HR−/HER2 + subgroup the rates were almost identical (66.1% vs 65.5%, Δ = 0.6%). However, the adjusted interaction analysis did not confirm a statistically significant HR status × route interaction: the interaction term OR was 0.57 (95% CI 0.22–1.46, P = 0.240), the unadjusted model gave P = 0.274, and across sensitivity analyses the interaction P values ranged from 0.096 to 0.383. The 12.0% difference in HR+/HER2 + patients is therefore an exploratory numerical difference that cannot yet be attributed to effect modification by HR status and requires verification in larger or prospective studies.

Because no significant interaction was demonstrated, the following pharmacokinetic explanation is an exploratory, post hoc hypothesis and remains to be verified. Population pharmacokinetic analyses indicate that exposure to the fixed-dose SC formulation is influenced by covariates such as lean body weight and Asian region, although these were not considered clinically relevant in that study [29]; their impact under the Chinese body-weight distribution remains to be verified directly. We hypothesize that Chinese patients generally weigh less than Western populations (baseline weight here 62.8–64.6 kg), that the fixed 600 mg SC dose produces exposure varying with body weight differently from weight-based IV dosing, and that in HR−/HER2 + tumors the intrinsically high sensitivity to dual blockade makes small exposure differences unlikely to affect efficacy, whereas HR+/HER2 + tumors, which are also driven by endocrine signaling, have lower baseline sensitivity and may be more sensitive to subtle exposure differences. Serum concentrations were not measured, so this remains a conjecture.

Beyond pharmacokinetics, bidirectional ER–HER2 crosstalk provides mechanistic support: ER can activate shared growth factor kinase cascades (including AKT and ERK1/2 MAPK), whereas HER2 signaling can enhance ER transcriptional activity [30, 31]. When HER2 inhibition is incomplete, residual crosstalk can sustain proliferation. This hypothesis could be tested prospectively by stratifying patients by HR status with pre-specified measurement of trastuzumab trough concentrations.

Study limitations

This study has several limitations. First, it was a single-center retrospective study without randomized allocation; despite baseline balance, selection bias from unmeasured confounders cannot be excluded and generalizability is limited. Second, the interaction and subgroup analyses were post hoc and exploratory, without adjustment for multiple comparisons, so type I error inflation is possible. The post hoc sensitivity power estimation indicated that even if a between-group pCR difference of 12.0% truly existed, the current sample size would be unlikely to detect it reliably; therefore a real subgroup difference or interaction cannot be completely excluded. This estimate is a post hoc sensitivity calculation, not a pre-specified sample size calculation. Third, pCR was the sole surrogate efficacy endpoint; long-term outcomes such as event-free survival and overall survival were not collected, and between-group pCR differences do not necessarily translate into survival benefit. Fourth, SC + IV here denotes the mixed regimen of SC trastuzumab plus IV pertuzumab, not the globally approved fully SC fixed-dose combination Phesgo, so our results cannot be extrapolated to Phesgo or other fully SC formulations. Fifth, serum trastuzumab concentrations were not measured, so the exposure hypothesis could not be verified directly.

Future directions

Future research should: run a prospective HR-stratified randomized trial in HR+/HER2 + patients comparing SC trastuzumab plus IV pertuzumab with all-IV dual blockade, using the 12.0% pCR difference as the target effect size (> 300 patients per group at 80% power), which would provide the most reliable test of the hypothesis; measure trastuzumab trough concentrations prospectively in SC and IV cohorts, correlated with HR status and pCR; directly compare Phesgo with the mixed regimen; explore adaptive approaches based on interim magnetic resonance imaging response after 2–3 cycles together with immune-combination strategies, since immune checkpoint inhibition has not yet demonstrated a clear benefit in HER2-positive breast cancer [32–34]; validate the findings across multiple centers; and build a composite nomogram integrating HR status and Ki67 into a validated pCR prediction model.

Conclusion

In this real-world cohort of 332 patients receiving neoadjuvant dual HER2 blockade for HER2-positive breast cancer, the overall pCR rate was 55.4%, confirming the effectiveness of TCbHP-based dual-blockade neoadjuvant therapy in a Chinese real-world population. HR-negative status and high Ki67 expression were independent predictors of pCR. The mixed regimen and all-IV dual blockade showed comparable efficacy, and no statistically significant interaction between the route of administration and HR status was identified: a 12.0% numerical pCR difference was observed in the HR+/HER2 + subgroup, whereas the two regimens performed similarly in the HR−/HER2 + subgroup (Δ = 0.6%). This numerical difference is exploratory and requires prospective verification. The sample size is insufficient to demonstrate equivalence between the regimens and only indicates that no statistically significant difference was observed; a real pCR difference of approximately 12% in the HR+/HER2 + subgroup

cannot be completely excluded. Current guideline recommendations therefore need not be changed, and regimen choice should consider patient preference, convenience of administration, drug availability, and cost. This is the first real-world head-to-head comparison of the mixed regimen with all-IV dual blockade in a Chinese population, filling an evidence gap not addressed by existing trials.

Abbreviations

Abbreviation	Full term
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor (estrogen receptor and/or progesterone receptor)
ER	Estrogen receptor
PR	Progesterone receptor
pCR	Pathological complete response
SC	Subcutaneous (injection)
IV	Intravenous (injection)
OR	Odds ratio
CI	Confidence interval
IHC	Immunohistochemistry
FISH	Fluorescence in situ hybridization
TCbHP	Docetaxel + carboplatin + trastuzumab + pertuzumab
MRI	Magnetic resonance imaging

Declarations

Funding This research was funded by the Science & Technology Development Fund of Tianjin Education Commission for Higher Education (No. 2024KJ028).

Competing interests The authors have no competing interests to declare.

Ethics approval and consent to participate This study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (approval No. EK20250140) and performed in accordance with the Declaration of Helsinki. Because of the retrospective design, informed consent was waived; the study was not prospectively registered.

Consent for publication Not applicable.

Data availability The original patient-level data are not publicly available due to patient privacy; the cleaned dataset and analysis code are available from the corresponding author upon reasonable request

and with ethics committee approval.

Author contributions Conceptualization: Shu Wang; Methodology: Shu Wang; Software: Lei Ren; Formal analysis: Cong Su; Investigation: Lidan Wang; Data curation: Lidan Wang; Writing – original draft: Shu Wang; Visualization: Lei Ren; Supervision: Jian Yin; Project administration: Jian Yin.

Use of AI and AI-assisted technologies The authors used DeepSeek solely for language editing. The authors reviewed and edited the content and take full responsibility for the content of the publication.

Acknowledgements The authors thank the clinical staff of the Department of Breast Reconstruction for data collation and clinical support for this retrospective real-world study.

References

1. Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019;321:288–300. https://doi.org/10.1001/jama.2018.19323.
2. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365:1273–83. https://doi.org/10.1056/NEJMoa0910383.
3. Jackisch C, Cortazar P, Geyer CE Jr, et al. Risk-based decision-making in the treatment of HER2-positive early breast cancer: recommendations based on the current state of knowledge. Cancer Treat Rev. 2021;99:102229. https://doi.org/10.1016/j.ctrv.2021.102229.
4. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17:791–800. https://doi.org/10.1016/S1470-2045(16)00163-7.
5. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol. 2013;24:2278–84. https://doi.org/10.1093/annonc/mdt182.
6. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med. 2017;377:122–31. https://doi.org/10.1056/NEJMoa1703643.
7. de Azambuja E, Piccart-Gebhart M, Fielding S, et al. Final analysis of the ALTTO trial: adjuvant trastuzumab in sequence or in combination with lapatinib in patients with HER2-positive early breast cancer [BIG 2–06/NCCTG N063D (Alliance)]. ESMO Open. 2024;9:103938. https://doi.org/10.1016/j.esmoop.2024.103938.
8. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384:164–72. https://doi.org/10.1016/S0140-6736(13)62422-8.

9. Spring LM, Fell G, Arfe A, et al. Pathologic complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: a comprehensive meta-analysis. Clin Cancer Res. 2020;26:2838–48. https://doi.org/10.1158/1078-0432.CCR-19-3492.
10. National Comprehensive Cancer Network. (2026) NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 6.2026. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419. Accessed 6 October 2026.
11. Huang J, Chen L, Song L, et al. Real-world treatment patterns and outcomes among patients with HER2-positive unresectable or metastatic breast cancer in China. Front Oncol. 2025;15:1527990. https://doi.org/10.3389/fonc.2025.1527990.
12. Yang ZJ, Xin F, Chen ZJ, et al. Real-world data on neoadjuvant chemotherapy with dual-anti HER2 therapy in HER2 positive breast cancer. BMC Cancer. 2024;24:134. https://doi.org/10.1186/s12885-024-11871-0.
13. van Ramshorst MS, van der Voort A, van Werkhoven ED, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018;19:1630–40. https://doi.org/10.1016/S1470-2045(18)30570-9.
14. Schiff R, Massarweh SA, Shou J, et al. Advanced concepts in estrogen receptor biology and breast cancer endocrine resistance: implicated role of growth factor signaling and estrogen receptor coregulators. Cancer Chemother Pharmacol. 2005;56(Suppl 1):10–20. https://doi.org/10.1007/s00280-005-0108-2.
15. Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2012;379:633–40. https://doi.org/10.1016/S0140-6736(11)61847-3.
16. Liu C, Sun L, Niu N, et al. Molecular classification of hormone receptor-positive/HER2-positive breast cancer reveals potential neoadjuvant therapeutic strategies. Signal Transduct Target Ther. 2025;10:97. https://doi.org/10.1038/s41392-025-02181-3.
17. Schettini F, Pascual T, Conte B, et al. HER2-enriched subtype and pathological complete response in HER2-positive breast cancer: a systematic review and meta-analysis. Cancer Treat Rev. 2020;84:101965. https://doi.org/10.1016/j.ctrv.2020.101965.
18. Fasching PA, Heusinger K, Haeberle L, et al. Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer. 2011;11:486. https://doi.org/10.1186/1471-2407-11-486.
19. Denkert C, von Minckwitz G, Brase JC, et al. Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. J Clin Oncol. 2015;33:983–91. https://doi.org/10.1200/JCO.2014.58.1967.
20. Nielsen TO, Leung SCY, Rimm DL, et al. Assessment of Ki67 in breast cancer: updated recommendations from the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst.

2021;113:808–19. https://doi.org/10.1093/jnci/djaa201.

21. Petrelli F, Viale G, Cabiddu M, Barni S. Prognostic value of different cut-off levels of Ki-67 in breast cancer: a systematic review and meta-analysis of 64,196 patients. Breast Cancer Res Treat. 2015;153:477–91. https://doi.org/10.1007/s10549-015-3559-0.
22. Weydandt L, Agabejli S, Lia M, et al. The predictive role of Ki67 in pathological complete response (pCR) and invasive disease-free survival (IDFS) in HER2-positive breast cancer: a bi-centric retrospective cohort study of 244 cases. Arch Gynecol Obstet. 2026;313:189. https://doi.org/10.1007/s00404-026-08401-7.
23. Tan AR, Im SA, Mattar A, et al. Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection plus chemotherapy in HER2-positive early breast cancer (FeDeriCa): a randomised, open-label, multicentre, non-inferiority, phase 3 study. Lancet Oncol. 2021;22:85–97. https://doi.org/10.1016/S1470-2045(20)30536-2.
24. Huang T, Fan Z, Wang Y, et al. The fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in Chinese patients with HER2-positive early breast cancer: primary analysis of the phase III, randomized FDChina study. Int J Clin Oncol. 2026;31:1189–200. https://doi.org/10.1007/s10147-025-02935-7.
25. Kuemmel S, Tondini CA, Abraham J, et al. Subcutaneous trastuzumab with pertuzumab and docetaxel in HER2-positive metastatic breast cancer: final analysis of MetaPHER, a phase IIIb single-arm safety study. Breast Cancer Res Treat. 2021;187:467–76. https://doi.org/10.1007/s10549-021-06145-3.
26. O'Shaughnessy J, Sousa S, Cruz J, et al. Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PHranceSCa): a randomised, open-label phase II study. Eur J Cancer. 2021;152:223–32. https://doi.org/10.1016/j.ejca.2021.03.047.
27. Pivot X, Gligorov J, Müller V, et al. Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. Lancet Oncol. 2013;14:962–70. https://doi.org/10.1016/S1470-2045(13)70383-8.
28. Farolfi A, Silimbani P, Gallegati D, et al. Resource utilization and cost saving analysis of subcutaneous versus intravenous trastuzumab in early breast cancer patients. Oncotarget. 2017;8:81343–9. https://doi.org/10.18632/oncotarget.18527.
29. Wang B, Deng R, Hennig S, et al. Population pharmacokinetic and exploratory exposure-response analysis of the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer in the FeDeriCa study. Cancer Chemother Pharmacol. 2021;88:499–512. https://doi.org/10.1007/s00280-021-04296-0.
30. Shou J, Massarweh S, Osborne CK, et al. Mechanisms of tamoxifen resistance: increased estrogen receptor-HER2/neu cross-talk in ER/HER2-positive breast cancer. J Natl Cancer Inst. 2004;96:926–35. https://doi.org/10.1093/jnci/djh166.

31. Yan S, Ji J, Zhang Z, et al. Targeting the crosstalk between estrogen receptors and membrane growth factor receptors in breast cancer treatment: advances and opportunities. Biomed Pharmacother. 2024;175:116615. https://doi.org/10.1016/j.biopha.2024.116615.
32. Krasniqi E, Barchiesi G, Pizzuti L, et al. Immunotherapy in HER2-positive breast cancer: state of the art and future perspectives. J Hematol Oncol. 2019;12:111. https://doi.org/10.1186/s13045-019-0798-2.
33. Loi S, Giobbie-Hurder A, Gombos A, et al. Pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, HER2-positive breast cancer (PANACEA): a single-arm, multicentre, phase 1b-2 trial. Lancet Oncol. 2019;20:371–82. https://doi.org/10.1016/S1470-2045(18)30812-X.
34. Rinnerthaler G, Egle D, Bartsch R, et al. Neoadjuvant atezolizumab in combination with dual HER2 blockade plus epirubicin in women with early HER2-positive breast cancer: the randomized phase 2 ABCSG-52/ATHENE trial. Nat Cancer. 2025;6:41–50. https://doi.org/10.1038/s43018-024-00890-2.

Figures

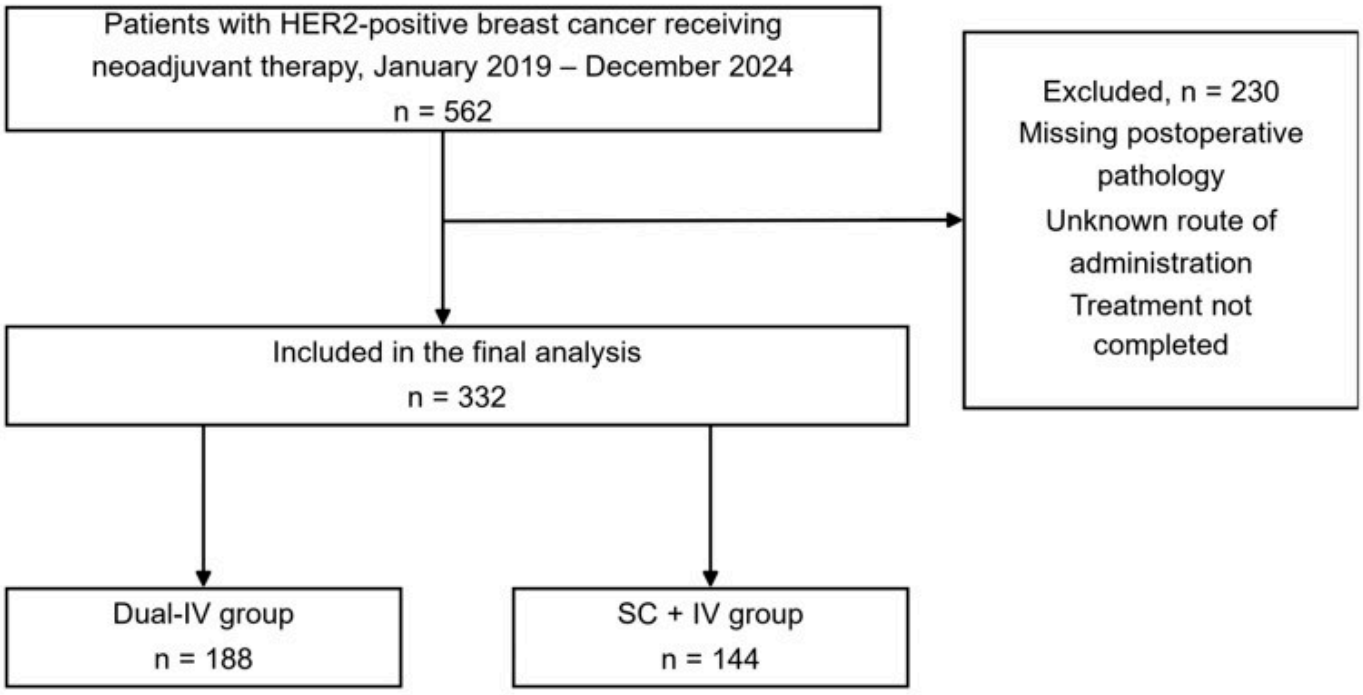


Figure 1

Patient enrollment flowchart.

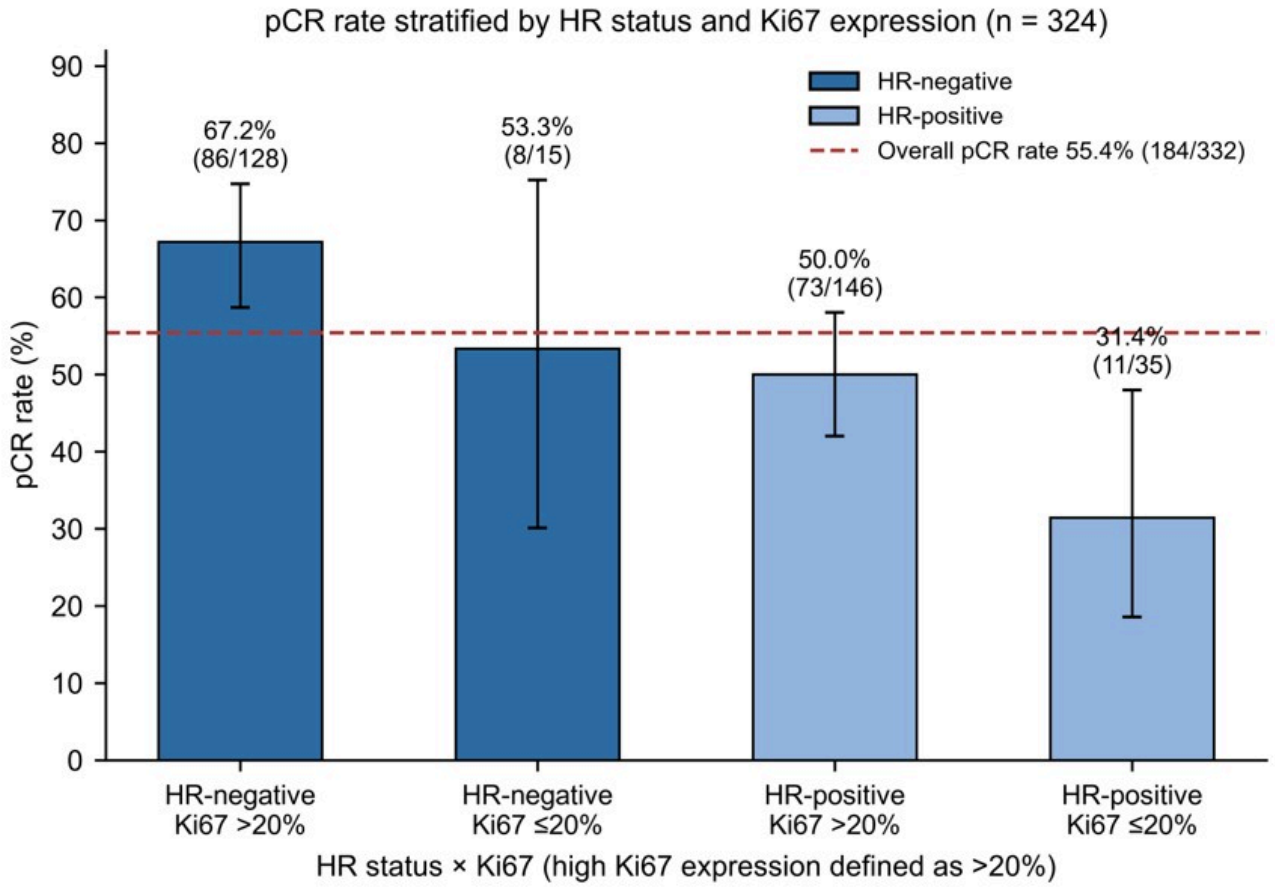


Figure 2

pCR rates stratified by HR status and Ki67 expression (error bars represent 95% confidence intervals).

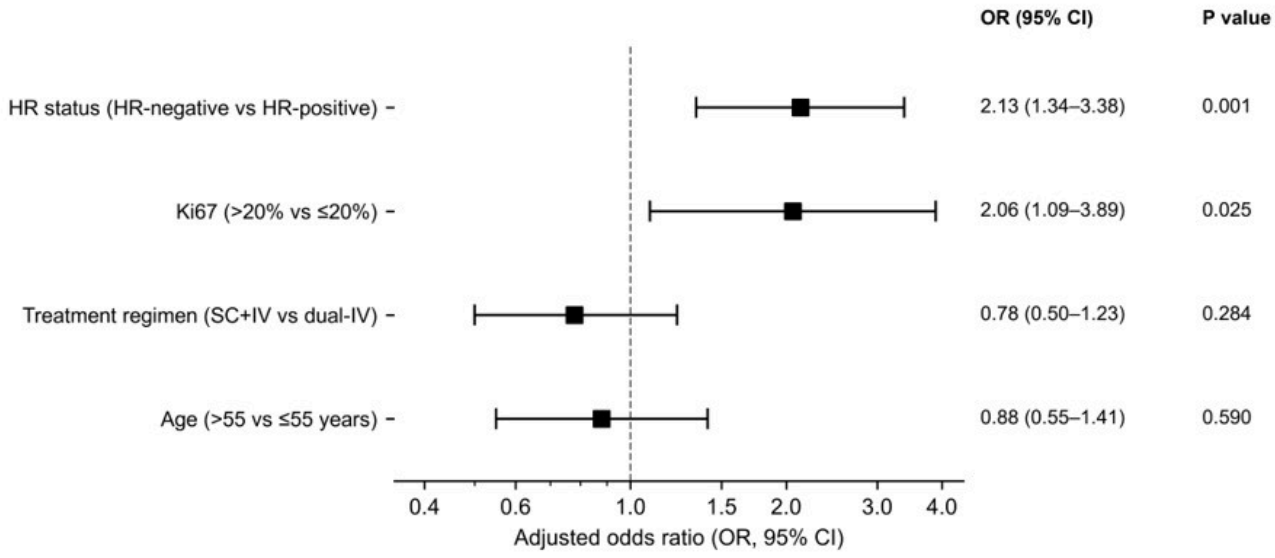


Figure 3

Forest plot of the multivariable logistic regression analysis of predictors of pCR (n = 324).

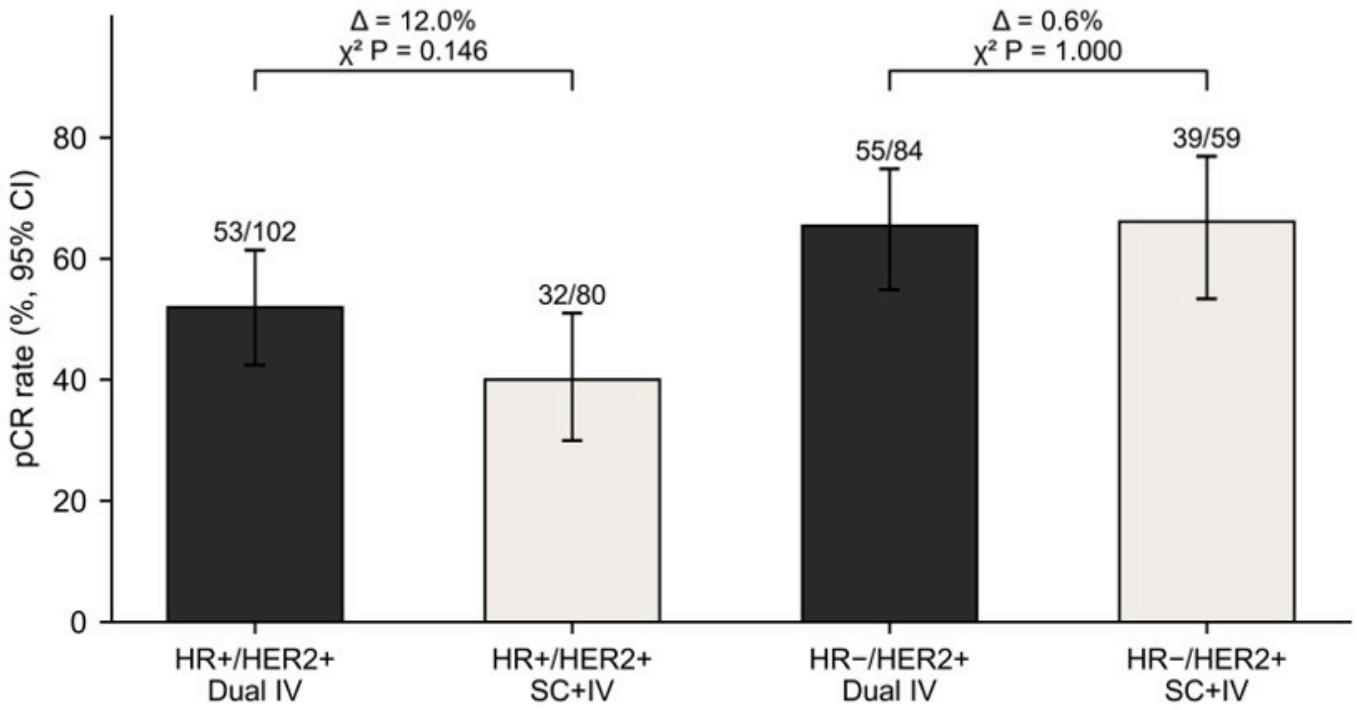


Figure 4

Subgroup pCR rates by HR status and route of administration (error bars represent 95% confidence intervals).

Note: Bar heights represent pCR rates, error bars represent 95% confidence intervals (Wilson method), and the numbers above the bars indicate the number of pCR events/the total number in each subgroup. The P values shown in the figure are unadjusted 2×2 χ² test results within subgroups; the interaction and simple-effect results of the adjusted model are reported in the main text.