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Neoadjuvant Inetetamab Plus Pyrotinib Phase II Trial for HER2-Positive Breast Cancer

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Title Page

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Abstract

This prospective multicenter single-arm phase II trial enrolled treatment-naive patients with stage II-III HER2-positive breast cancer to receive six cycles of neoadjuvant chemotherapy combined with the HER2-directed macromolecular agent Inetetamab and the tyrosine kinase inhibitor Pyrotinib. Between November 27, 2021, and December 18, 2025, 140 patients were enrolled, of whom 117 were evaluable for efficacy. The total pathologic complete response (tpCR; ypT0/is ypN0) rate was 61.5% (72/117; 95% CI, 52.6-70.5). The tpCR rate was significantly higher in hormone receptor (HR)-negative versus HR-positive tumors (76.2% vs 44.4%; odds ratio 0.25; 95% CI, 0.11-0.55; P<0.001). The most common adverse events were anemia (89.2%), diarrhea (82.4%), and hypokalemia (47.3%), with grade ≥3 events including anemia, diarrhea, and leukopenia; no treatment-related deaths occurred. Neoadjuvant Inetetamab plus Pyrotinib with chemotherapy demonstrated clinically meaningful antitumor activity and a manageable safety profile in this population, supporting further randomized trials.

Introduction

Breast cancer is the most common malignancy in women worldwide and a leading cause of cancer death, driven by its heterogeneity and metastatic potential[1]. Approximately 15%-20% of cases are HER2 positive and associated with aggressive disease and poor prognosis[2, 3]. The NCCN guidelines recommend taxane-platinum chemotherapy plus dual HER2 blockade (trastuzumab and pertuzumab) as the preferred neoadjuvant therapy[4]. However, 22% – 25% of patients develop primary or acquired resistance to standard anti-HER2 therapy, underscoring the need for novel strategies that more comprehensively inhibit HER2 signaling[5-7].

The combination of TKIs with monoclonal antibodies represents an encouraging strategy to enhance antitumor efficacy. In the NeoALTTO and CHER-LOB trials, trastuzumab plus the TKI lapatinib significantly improved tpCR rates and long-term survival versus antibody monotherapy[8, 9]. Pyrotinib, an oral irreversible pan-HER TKI targeting HER1, HER2, and HER4[10] , has further advanced the dual-blockade approach. In the PHILA study, the PyHT regimen (Pyrotinib, trastuzumab, and docetaxel) reduced the risk of disease progression or death by 59% versus standard therapy[11]. The phase II PHEDRA trial further confirmed the efficacy and tolerability of four-cycle neoadjuvant PyHT in early-stage and locally advanced HER2-positive breast cancer[12].

Inetetamab is an anti-HER2 monoclonal antibody with Fc modifications at positions 359 and 361, which enhance ADCC while retaining trastuzumab Fab[13]. In the phase III HOPES trial, Inetetamab with or followed by vinorelbine improved median PFS (39.1 vs. 14.0 weeks) and ORR (46.7% vs. 18.45%) versus vinorelbine alone in HER2-positive metastatic

breast cancer[14]. In subgroup analyses, when used as first-line therapy for advanced disease, Inetetamab was associated with a superior median PFS compared with trastuzumab in the H0648g trial (11.1 vs. 7.4 months)[15]. In the neoadjuvant setting, tpCR rate of 56.5% was reported for the combination of Inetetamab and pertuzumab[16].

The clinical benefits of combining monoclonal antibodies with small-molecule TKIs are increasingly recognized. However, evidence on the efficacy of modified monoclonal antibodies plus TKIs in the neoadjuvant setting remains limited. To address this limitation, a prospective, single-arm, multicenter phase II study was initiated. The study evaluated the efficacy and safety of neoadjuvant Inetetamab combined with Pyrotinib and chemotherapy in HER2-positive breast cancer patients with high tumor burden.

Results

Baseline characteristics

Between November 27, 2021, and December 18, 2025, 140 eligible patients were enrolled. All patients received at least one treatment cycle. Of these, 3 patients discontinued after the first cycle, 14 elected to proceed directly to surgery before completing neoadjuvant therapy, and 6 withdrew due to adverse events and received alternative regimens. Thus, 117 patients completed all six neoadjuvant cycles and were evaluable for the primary endpoint after surgery. Among them, 6 discontinued further participation after primary endpoint data collection (Figure 1).

In the enrolled population (Table 1), the median age was 52 years (range, 25-71). Premenopausal and postmenopausal status were noted in 63 (45.0%) and 77 (55.0%) patients, respectively. Clinically suspected or biopsy-confirmed axillary lymph node

metastasis was present in 90% of patients; matted axillary or abnormal supraclavicular lymph nodes were observed in over half (52.9%). Most patients had clinical stage III disease, with stage IIIA accounting for nearly half (40.7%). Pre-neoadjuvant immunohistochemistry showed strong HER2 positivity (IHC 3+) in 119 patients (85.0%). HR-positive and HR-negative disease were comparably distributed (48.6% vs. 51.4%). High Ki-67 expression (⩾30%) was observed in 107 patients (76.4%), and histologic grade III tumors in 53 patients (37.9%). No statistically significant differences in baseline characteristics were observed between the total enrolled population and the withdrawal group, excluding bias due to withdrawal. Detailed baseline characteristics are summarized in Supplementary Table 1.

Efficacy

Among the 117 evaluable patients with high tumor burden, tpCR was achieved in 72 (61.5%; 95% CI, 52.6-70.5), and bpCR in 78 (66.7%; 95% CI, 57.7-74.6) (Supplementary Figure 1). In subgroup analyses (Figure 2), higher tpCR and bpCR rates were observed in HR-negative than in HR-positive patients (tpCR: 76.2% vs 44.4%; bpCR: 79.4% vs 51.9%). Most patients with drug-resistant disease (MP grades 1-3) were HR-positive (Supplementary Figure 2). For the primary endpoint, a higher tpCR rate was seen in tumors with strong (+++) membranous staining than in those with HER2 (++) amplification (67.0% vs 29.4%). In subgroup analysis, a higher tpCR rate was observed among patients with high Ki67 expression (⩾30%) compared with those with low expression (<30%), suggesting a cytotoxic effect of the chemotherapy agents on highly proliferative tumors, potentially through mitotic interference. In univariate logistic regression analysis, HR status ($p < 0.001$) and HER2 status ($p = 0.006$) were significantly associated with tpCR; no

significant associations were found for other clinical factors. Multivariate analysis confirmed HR status ($p = 0.003$) and HER2 status ($p = 0.036$) as independent predictors of treatment response (Table 2).

A total of 124 patients were included in the radiologic evaluation set. Based on preoperative imaging, complete response was achieved in 11 patients (8.9%) and partial response in 98 patients (79.0%), yielding an ORR of 87.9% (109/124; 95% CI, 82.1-93.7) and DCR of 100% (Figure 3). An increase in ORR was observed with treatment progression: 61.9% after 2 cycles, 73.9% after 4 cycles, and 87.9% after 6 cycles (Supplementary Figure 3). In over half of the patients (58.3%), response was first achieved by cycle 2. These findings suggest a rapid onset of antitumor activity with this regimen.

In subgroup analyses of time to maximal tumor reduction (TTMTR), no substantial difference was observed between HR-positive and HR-negative groups; in both subgroups, more than half of the patients achieved early maximal tumor reduction during the initial phase of neoadjuvant therapy (Supplementary Figure 4). In the HER2 subgroup, TTMTR within the first 2 cycles was observed predominantly in patients with strong HER2-positive expression (IHC 3+), suggesting that the efficacy of anti-HER2 therapy in this regimen is correlated with HER2 expression level. In the Ki-67 subgroup, TTMTR within the first 2 cycles was achieved in most patients with high Ki-67 expression ($\geqslant$30%); in contrast, more than one-third of patients with low Ki-67 expression (<30%) achieved maximal tumor reduction only during the last 2 cycles, indicating that these patients may require completion of all six cycles.

With a median follow-up of 27.7 months (range, 7.0-52.2 months), survival data remained immature; therefore, exploratory time-to-event outcomes were not formally analyzed, and

only descriptive follow-up data are presented. Among the 117 patients included in the efficacy analysis, four were lost to follow-up. During follow-up, six patients developed distant metastases, including brain metastases in three patients (EFS: 5.3, 15.4, and 19.6 months), lung metastasis in one patient (EFS: 24.4 months), multiple bone metastases in one patient (EFS: 24.6 months), and multiorgan metastases involving the liver, lungs, and brain in one patient (EFS: 25.9 months). One additional patient developed contralateral breast cancer at an EFS time of 25.3 months.

Safety

Adverse events were assessed and graded according to NCI-CTCAE v5.0 criteria. Treatment-related adverse events were generally manageable. The most frequent events were anemia (89.2%), diarrhea (82.4%), and hypokalemia (47.4%), mostly grade 1-2. Grade 3-4 events were less common, including anemia (16.1%), diarrhea (13.1%), and leukopenia (8.8%) (Table 3). During neoadjuvant therapy, gastrointestinal events (e.g., diarrhea, nausea) were most frequently observed during cycle 1 (75.9%), whereas hematologic toxicities were observed throughout the entire treatment course; a trend toward increased new-onset incidence was observed with cumulative cycles and drug exposure (Supplementary Figure 5). Pyrotinib dose reduction combined with antidiarrheal treatment (smectite or loperamide) was required in 28 patients (20.4%), and symptoms were effectively mitigated. Neoadjuvant therapy was discontinued in six patients (4.4%) due to intolerance to diarrhea. As of manuscript submission, no treatment-related deaths were reported. Overall, the safety profile of neoPICD was broadly consistent with that reported in representative HER2-positive neoadjuvant trials, and no unexpected safety signals were observed.

Discussion

In patients with HER2-positive advanced breast cancer, a novel neoadjuvant regimen combining inetetamab and pyrotinib was evaluated. Favorable efficacy and manageable toxicity were observed. The tpCR rate was 61.5%, and the ORR was 87.9%.

Current guidelines recommend chemotherapy plus trastuzumab and pertuzumab as the standard neoadjuvant regimen for HER2-positive breast cancer[17]. The tpCR rates range from 45% to 70%, depending on chemotherapy backbone and number of cycles. In this trial, the same chemotherapy backbone was used to assess the combination of a monoclonal antibody and a small-molecule TKI. In the KRISTINE trial, the tpCR rate in the antibody-containing arm was slightly lower than that in the present study (55.7% vs. 61.5%)[18]. Subgroup analyses by clinical stage also suggested superiority of our regimen (stage II-IIIA: 43.0% vs. 63.7%; stage IIIB-IIIC: 51.4% vs. 53.8%). In TRYPHAENA, only 42% of patients had stage III disease, and the tpCR rate was 63.6% (versus 65.8% stage III in our study)[19]. Data from the Chinese HELEN-006 trial further indicated that, after accounting for ethnic differences, our regimen achieved higher tpCR rates and favorable subgroup outcomes by tumor stage and nodal status[20].

Six cycles of chemotherapy combined with a monoclonal antibody and a small-molecule TKI yielded a tpCR rate of 61.5% in HER2-positive breast cancer. Numerically, this rate surpassed both monoclonal antibody-alone regimens and regimens combining trastuzumab with a TKI on the same chemotherapy backbone. Published trials with TCb chemotherapy reported tpCR rates of 50%-55% in the neoadjuvant setting[5,21], notably lower than our primary endpoint. This difference may be attributable to enhanced ADCC of inetetamab, which could synergize with TKIs. However, the NeoATP and ECPy-THPy regimens

yielded slightly higher tpCR rates (73.6% and 68.6%, respectively)[22], possibly due to shorter neoadjuvant durations or smaller baseline tumor burdens in those populations.

The most common adverse events were anemia and diarrhea, mostly grade 1-2. Diarrhea (82.4%) was managed with smectite (3 g tid) or loperamide (4 mg tid). Severe cases received pyrotinib dose reduction (to 320 or 240 mg) plus intensified loperamide (2 mg) and electrolyte replacement. The overall diarrhea incidence was lower than in PHEDRA (100%), Panphila (94.6%), and HELEN-006 (93.8%)[12,20,21]. The anemia rate (88.9%) was comparable to Panphila (94.6%) and HELEN-006 (89.6%)[20,21]. Grade 3-4 diarrhea (13.1%) was lower than in PLEHERM (18.9%), PICTURE (24%), Panphila (43.2%), and PHEDRA (44.4%)[12,20,23,24]. These findings underscore the importance of optimized dosing and proactive supportive care to reduce severe gastrointestinal toxicity, improve adherence, and prevent early discontinuation. Hypokalemia was also notable, presumably related to diarrhea. Serum potassium should be closely monitored, and patient education on severe hypokalemia is recommended, as this may be overlooked. Grade 3-4 leukopenia and neutropenia occurred in only 8.8% and 1.5% of patients, respectively, likely due to routine prophylactic G-CSF. No cardiac events of any grade were reported, suggesting this regimen may be safer for patients with cardiac comorbidities.

HER2 expression intensity was significantly associated with efficacy. In our study, the tpCR rate was 67.0% (67/100) in HER2 IHC 3+ patients and 29.4% (5/17) in IHC 2+/FISH+ patients. Similar trends were observed in Panphila (60.7% vs. 30.8%) and NeoPaTHer (37.0% vs. 15.0%)[20,25]. These findings align with a large cohort study (n=7,390) showing higher tpCR rates in IHC 3+ versus IHC 2+/FISH+ tumors (57% vs. 22%, $p<0.001$)[26]. The dual regimen appeared to preferentially increase tpCR in HER2 3+ disease.

HR status was also an independent predictor of tpCR, consistent with prior studies[5,22]; HR-negative patients had higher tpCR rates. Collectively, these data support that HR-negative and HER2-overexpressing tumors are more sensitive to dual HER2 blockade.

The mechanistic basis of neoadjuvant pyrotinib plus monoclonal antibody was further explored. Two major challenges are predicting response to anti-HER2 antibodies and selecting optimal candidates for pyrotinib. Imaging mass cytometry was applied to tumor samples from a subset of patients to analyze spatial expression of over 40 functional proteins at single-cell resolution[27]. Sensitive tumors were enriched in IDOhiHLA-DRhi epithelial cells interacting with Ki67+ T cells and CD163-M1 macrophages, indicating a highly immunogenic microenvironment. Conversely, fibroblast-driven immune barriers were associated with resistance, which appeared to be overcome by pyrotinib combination. This spatial proteomic analysis provides a framework for developing biomarker panels incorporating tissue spatial features, cellular neighborhood scores, and functional phenotype co-expression.

Several limitations should be acknowledged. First, this phase II trial included 140 patients; a prospective multicenter randomized phase III trial is warranted. Second, short follow-up precluded mature survival data, limiting confirmation of tpCR translation into DFS/OS benefit. Third, the population was exclusively Asian, providing evidence only for this ethnic group. Fourth, cross-trial comparisons are limited by differences in baseline characteristics, evaluation schedules, and historical contexts; conclusions from such comparisons are exploratory and should not be interpreted as confirmatory.

In summary, this trial evaluated a macromolecular monoclonal antibody plus a small-molecule TKI in the neoadjuvant setting for HER2-positive breast cancer. Six cycles of

chemotherapy with inetetamab and pyrotinib achieved a tpCR rate of 61.5% with manageable toxicity. These findings support further evaluation in randomized phase III trials to confirm clinical benefit.

Methods

Study design and participants

This prospective, multicenter, single-arm, phase II clinical trial was conducted in accordance with the Declaration of Helsinki and in compliance with good clinical practice. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (approval number: KY-2021-113) and by the relevant ethics committees of the participating centers. All participants provided written informed consent before enrollment. The trial was registered at ClinicalTrials.gov (NCT06234137; registered 23 January 2024) and the Chinese Clinical Trial Registry (ChiCTR2200066066; registered 23 November 2022).

Between November 2021 and December 2025, a total of 140 female patients were enrolled across seven participating centers in China. Eligible patients were aged ≥18 years and had treatment-naïve, histologically confirmed HER2-positive breast cancer with clinical stage II or higher, defined according to the 8th edition of the *American Joint Committee on Cancer (AJCC)* staging system. HER2 positivity was established by immunohistochemistry (IHC) 3+, or IHC 2+ with HER2 gene amplification confirmed by fluorescence in situ hybridization (FISH). Other inclusion criteria were: an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1; baseline left ventricular ejection fraction (LVEF) of ≥50%; adequate hepatic and coagulation function; bone

marrow reserves; and with no history of severe endocrine disorders or major organ diseases. Patients were excluded if they had metastatic breast cancer; a prior history of anticancer therapy or radiation for any malignancy (except for basal cell carcinoma, cutaneous squamous cell carcinoma, or adequately treated in situ carcinoma); prior systemic therapy related to breast cancer treatment or prevention; severe hypersensitivity to study drugs; active infections; or any other medical condition considered unsuitable by the investigators.

Procedures and treatment

Patients received six cycles of neoadjuvant therapy (21-day cycles) with Inetetamab (loading dose 8 mg/kg, then 6 mg/kg maintenance), Pyrotinib (400 mg/d, titrated from 320 mg/d as tolerated), docetaxel (75 mg/m^2 on day 1), and carboplatin (AUC 6 on day 1). Dose modifications were allowed for toxicity. Definitive surgery (breast-conserving or total mastectomy) was performed 2-4 weeks after the last neoadjuvant dose. Postoperatively, patients continued the same doses of Inetetamab and Pyrotinib as adjuvant therapy to complete a total targeted treatment duration of 1 year.

Assessments

Clinical evaluations (physical examination, hematology and biochemistry, vital signs, ECG, ECOG PS) were conducted at baseline and before each cycle. Tumor response was assessed by clinical breast examination and imaging (ultrasound/MRI) every two cycles (42 ± 7 days), using the same imaging modality consistently for each patient. Safety was monitored at each visit and within 30 days after the last dose. Post-treatment follow-up (hematologic and imaging) was performed every 3 months to evaluate long-term safety and disease status.

Endpoints

The primary endpoint of this study was the tpCR rate, defined as the absence of invasive

carcinoma in both breast tissue and regional lymph nodes (ypT0/is, ypN0) according to the criteria of the 8th edition of the *AJCC* staging system. Pathological response was evaluated by local histopathological examination of resected surgical specimens following completion of neoadjuvant therapy[28]. The secondary endpoints included the ORR, time to response (TTR) and safety. Exploratory time-to-event outcomes included event-free survival (EFS), disease-free survival (DFS), distant disease-free survival (DDFS), central nervous system disease-free survival (CNS-DFS), and overall survival (OS), which will be analyzed after longer follow-up. Adverse events (AEs) were graded according to the *National Cancer Institute Common Terminology Criteria for Adverse Events* (NCI-CTCAE), version 5.0.

Statistical analysis

The study used a Simon two-stage optimal design to evaluate the primary endpoint (tpCR rate). Assuming a null hypothesis response rate (P_0) of 45% and an alternative hypothesis rate (P_1) of 60%, with a one-sided $\alpha = 0.05$ and 90% power, 40 patients were enrolled in the first stage. The study would terminate early if fewer than 19 tpCRs were observed. If criteria were met, enrollment continued to a total of 116 evaluable patients. The regimen was considered effective if > 60 tpCRs were achieved overall. The design parameters were generated using PASS 2021 (NCSS, Kaysville, UT).

Efficacy analyses were based on the efficacy analysis set, which based on patients who completed all six cycles of treatment and had postoperative pathology. Efficacy was assessed based on postoperative histopathological evaluation of resected specimens, and patients without evaluable pathology were conservatively classified as non-tpCR. The radiological response analysis set was based on patients who underwent ultrasound

imaging for lesion assessment during treatment. The safety analysis set was based on patients who received at least one cycle of treatment. The tpCR rate and its 95% confidence interval (CI), together with breast pathological complete response (bpCR), ORR, and disease control rate (DCR) were estimated using the Clopper-Pearson exact method. Differences in tpCR rates between subgroups with different clinicopathological characteristics and baseline differences among patients who withdrew from the study were assessed using chi-square or Fisher's exact tests. Univariable and multivariable logistic regression models were used to explore factors associated with tpCR, with odds ratios (ORs) and 95% CIs reported. Continuous variables were summarized as means (± standard deviations [SD]) or medians (range), and categorical variables as frequencies and percentages. All statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY).

Full prespecified statistical analysis plan, including interim analysis rules, endpoint definitions, multiplicity adjustment, and sensitivity analyses, is provided in Supplementary Appendix.

Data availability

The study protocol is available in this article. De-identified patient data are available upon reasonable request. Requests should be submitted via email to the corresponding author. No time limit is imposed on data access after publication.

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Author contributions

Wang O designed the study, Jiang C, Xia E, Dai J, Yao S, Ru J, Dai X, Wang Y, Guo G, Zheng S, Liu H, Li Q, Huang D, Chen Y, Lin K, Ye Z, Zheng Y, Dong S, Jiang P, Zhang W, Hu H, Yang C, Wang W, Wu W, Wu W, Li X, Liu Y, Zheng M and Ma Z collected clinical data, XY, WX and LC performed statistical analysis, XY and LC drafted the manuscript. All authors approved the final manuscript.

Competing interests

No potential conflicts of interest were reported.

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Figure Legends

Figure 1. CONSORT diagram of patient disposition, treatment allocation, and analysis sets. The efficacy analysis set included patients who completed six cycles of neoadjuvant therapy and underwent surgery with available tpCR data. The radiological response analysis set comprised patients with at least one evaluable post-baseline imaging assessment and was used for ORR and DCR analyses. The longitudinal imaging subset, derived from patients with complete evaluable imaging at cycles 2, 4, and 6, was used for TTR, TRR, and TTMR analyses. The safety analysis set included all patients who received at least one cycle of treatment and had post-baseline safety data.

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Table1 Baseline characteristics of enrolled patients.

Characteristics	All(*n*=140)
Median age at diagnosis(range)	52 (25-71)
< 50 years, *n(%)*	57 (40.7)
≥50 years, *n(%)*	83 (59.3)
Menopausal status, *n(%)*	
Premenopausal	63 (45.0)
Postmenopausal	77 (55.0)
Clinical T stage, *n(%)*	
T1	7 (5.0)
T2	80 (57.1)
T3	47 (33.6)
T4	6 (4.3)
Clinical N stage, *n(%)*	
N0	14 (10.0)
N1	52 (37.1)
N2	52 (37.1)
N3	22 (15.7)
TNM stage, *n(%)*	
IIa	8 (5.7)
IIb	45 (32.1)
IIIa	57 (40.7)
IIIb	7 (5.0)
IIIc	23 (16.4)
HER2 status, *n(%)*	
IHC++(FISH positive)	21 (15.0)
IHC+++	119 (85.0)
HR status, *n(%)*	
ER and/or PR positive	68 (48.6)
ER and PR negative	72 (51.4)

Ki-67 status, *n(%)*		
＜30%	33	(23.6)
≥30%	107	(76.4)
Histological grade, *n(%)*		
II	76	(54.3)
III	53	(37.9)
Unknown	11	(7.9)

Abbreviations: IHC, immunohistochemistry; ER, estrogen receptor; PR, progesterone receptor; FISH, fluorescence in situ hybridization

Table2 Univariate and multivariate analyses of clinical characteristics associated with total pathological complete response (tpCR)

Characteristic	Univariate logistic analysis			Multivariate logistic analysis		
	β	p	OR(95%CI)	β	p	OR(95%CI)
Age						
< 50 years			1.00 (Reference)			
⩾50 years	0.318	0.407	1.38(0.65-2.92)			
Menopausal status						
Premenopausal			1.00 (Reference)			
Postmenopausal	0.14	0.708	1.15 (0.55-2.39)			
cT						
1-2			1.00 (Reference)			
3-4	-0.288	0.456	0.75 (0.35-1.60)			
cN						
0			1.00 (Reference)			
1	-0.23	0.765	0.79 (0.18-3.61)			
2	-0.25	0.744	0.78 (0.17-3.51)			
3	-0.24	0.778	0.79 (0.15-4.21)			
cTNM						

Ⅱ			1.00 (Reference)			
Ⅲ	-0.56	0.177	0.57 (0.25-1.29)			
HR status						
Negative			1.00 (Reference)			1.00 (Reference)
Positive	-1.39	**＜0.001**	0.25 (0.11-0.55)	-1.21	**0.003**	0.30 (0.13-0.67)
HER2 status						
++(FISH positive)			1.00 (Reference)			1.00 (Reference)
+++	1.58	**0.006**	4.87 (1.58-14.99)	1.26	**0.036**	3.51 (1.09-11.35)
Ki-67						
< 30%			1.00 (Reference)			
⩾30%	0.63	0.153	1.87 (0.79-4.42)			
Histology						
Unknown			1.00 (Reference)			
2	0.24	0.745	1.28(0.29-5.54)			
3	0.95	0.226	2.58 (0.56-12.02)			

Abbreviations: OR, Odds Ratio; CI, Confidence Interval

Table3 Treatment-related adverse events during neoadjuvant therapy

	All Patients(*n*=137)	
	Grade 1-2	**Grade 3-4**
Anemia	100 (73.1%)	22 (16.1%)
Diarrhea	95 (69.3%)	18 (13.1%)
Hypokalemia	57 (41.6%)	8 (5.8%)
ALT/AST increased	56 (40.9%)	6 (4.4%)
SCr increased	52 (38.0%)	1 (0.7%)
Leukopenia	38 (27.7%)	12 (8.8%)
Platelet decreased	39 (28.5%)	3 (2.2%)

Hypoalbuminemia	40 (29.2%)	0
Loss of appetite	33 (24.1%)	0
Nausea	28 (20.4%)	0
Vomiting	27 (19.7%)	0
Hyponatremia	23 (16.8%)	0
ALP increased	21 (15.3%)	0
Asthenia	20 (14.6%)	0
Neutropenia	12 (8.8%)	2 (1.5%)
Rash	9 (6.6%)	0
Hypocalcemia	6 (4.4%)	0
Mouth ulcers	4 (2.9%)	0
Chest tightness	4 (2.9%)	0
Pulmonary infection	2 (1.5%)	0

Supplementary table

Table1 Baseline characteristics of enrolled patients.

Characteristics	Enrolled *(n=140)*	Collected *(n=117)*	Excluded *(n=23)*	p value
Median age at diagnosis(range)	52 (25-71)	52 (25-71)	54 (33-71)	
＜50 years, *n(%)*	57 (40.7)	49 (41.9)	8 (34.8)	0.526
⩾50 years, *n(%)*	83 (59.3)	68 (58.1)	15 (65.2)	
Menopausal status, *n(%)*				
Premenopausal	63 (45.0)	54 (46.2)	9 (39.1)	0.536
Postmenopausal	77 (55.0)	63 (53.8)	14 (60.9)	
Clinical T stage, *n(%)*				
T1	7 (5.0)	5 (4.3)	2 (8.7)	
T2	80 (57.1)	65 (55.6)	15 (65.2)	0.445
T3	47 (33.6)	41 (35.0)	6 (26.1)	
T4	6 (4.3)	6 (5.1)	0 (0)	
Clinical N stage, *n(%)*				
N0	14 (10.0)	9 (7.7)	5 (21.7)	
N1	52 (37.1)	44 (37.6)	8 (34.8)	0.248
N2	52 (37.1)	46 (39.3)	6 (26.1)	
N3	22 (15.7)	18 (15.4)	4 (17.4)	
TNM stage, *n(%)*				
IIa	8 (5.7)	5 (4.3)	3 (13.0)	
IIb	45 (32.1)	36 (30.8)	9 (39.1)	
IIIa	57 (40.7)	50 (42.7)	7 (30.4)	0.219
IIIb	7 (5.0)	7 (6.0)	0 (0)	
IIIc	23 (16.4)	19 (16.2)	4 (17.4)	
HER2 status, *n(%)*				
IHC++(FISH positive)	21 (15.0)	17 (14.5)	4 (17.4)	0.975
IHC+++	119 (85.0)	100 (85.5)	19 (82.6)	
HR status, *n(%)*				
ER and/or PR positive	68 (48.6)	54 (46.2)	14 (60.9)	0.197
ER and PR negative	72 (51.4)	63 (53.8)	9 (39.1)	
Ki-67 status, *n(%)*				
＜30%	33 (23.6)	28 (23.9)	5 (21.7)	0.821
⩾30%	107 (76.4)	89 (76.1)	18 (78.3)	
Histological grade, *n(%)*				
II	76 (54.3)	66 (56.4)	10 (43.5)	
III	53 (37.9)	43 (36.8)	10 (43.5)	0.435
Unknown	11 (7.9)	8 (6.8)	3 (13.0)	

Abbreviations: IHC, immunohistochemistry; ER, estrogen receptor; PR, progesterone receptor; FISH, fluorescence in situ hybridization

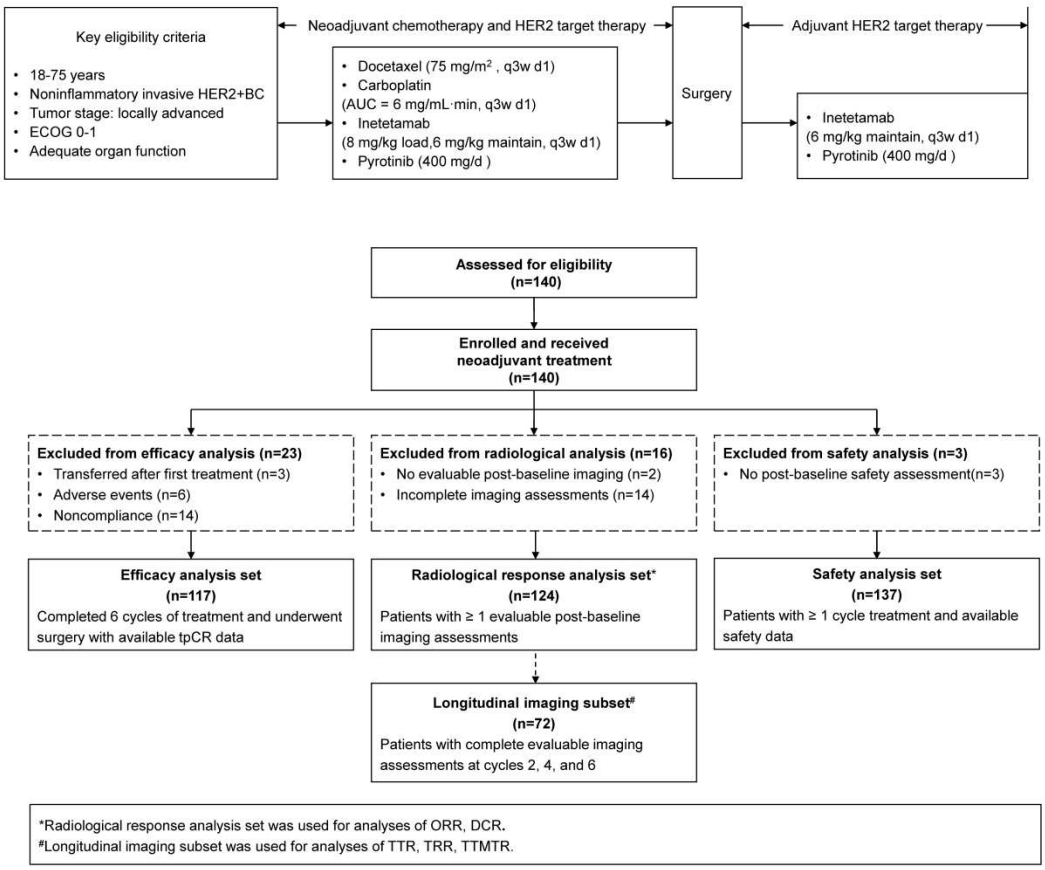


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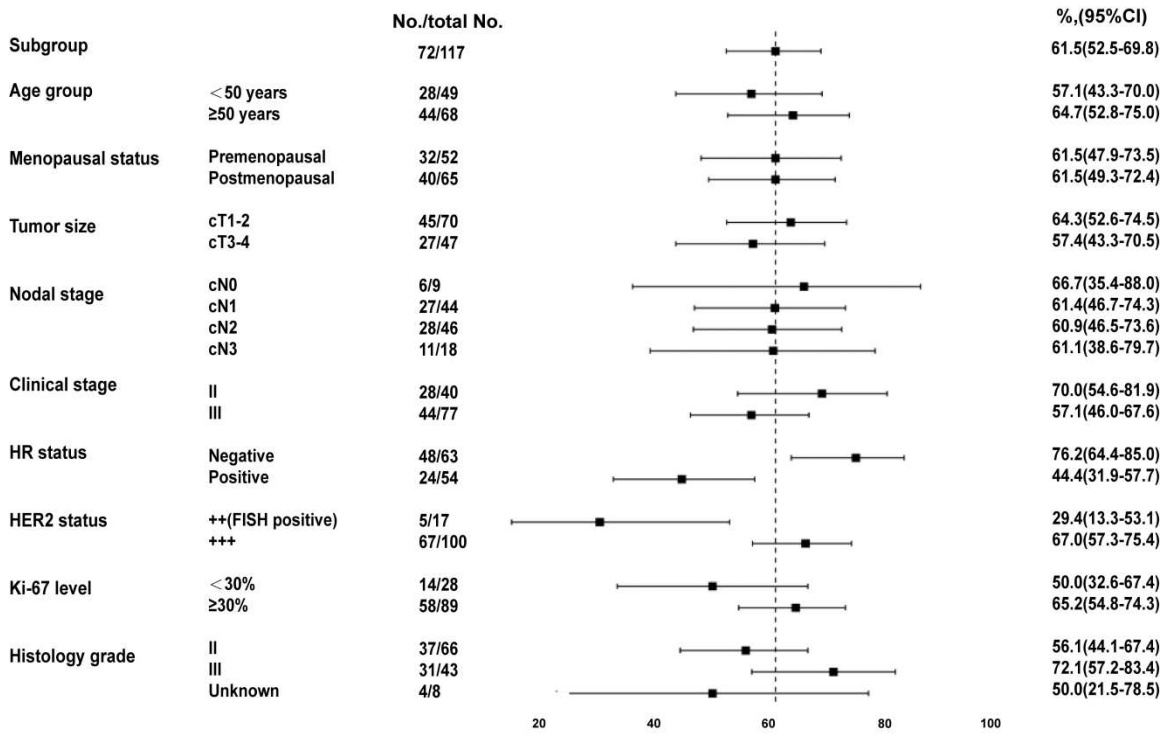


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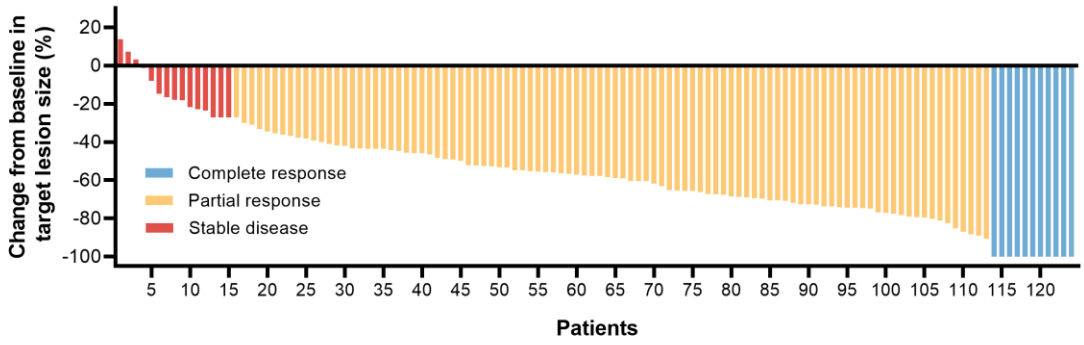


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Supplementary figure

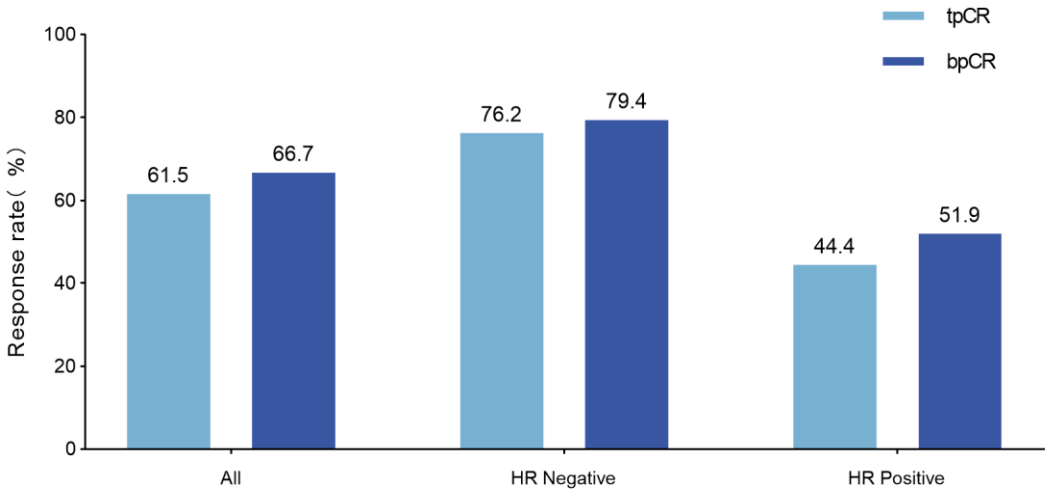


Figure S1

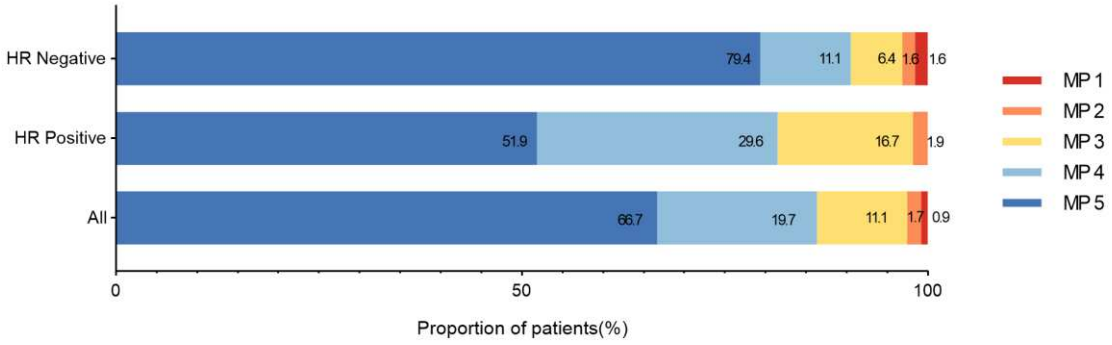
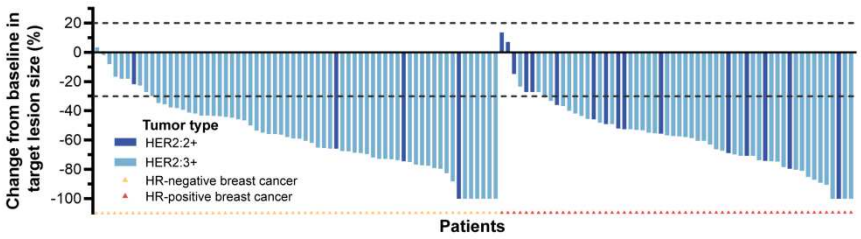


Figure S2



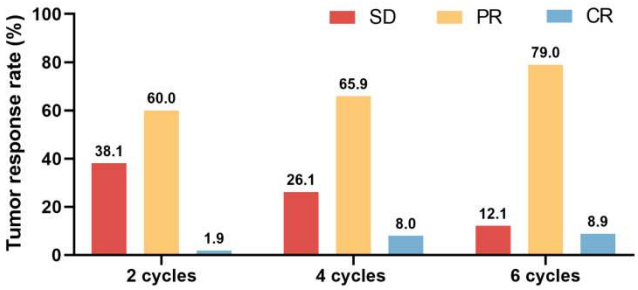
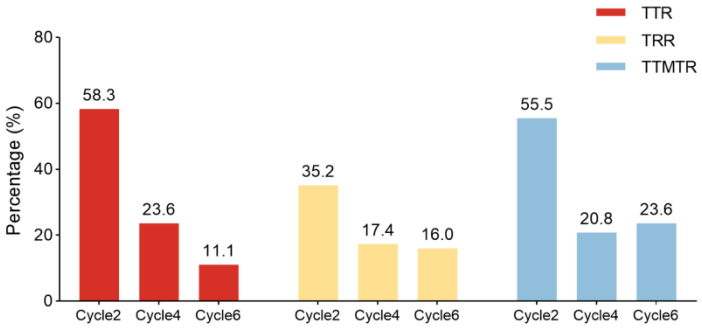


Figure S3



TTR: Time to response; TRR: Tumor reduction rate; TTMTR: Time to maximal tumor reduction

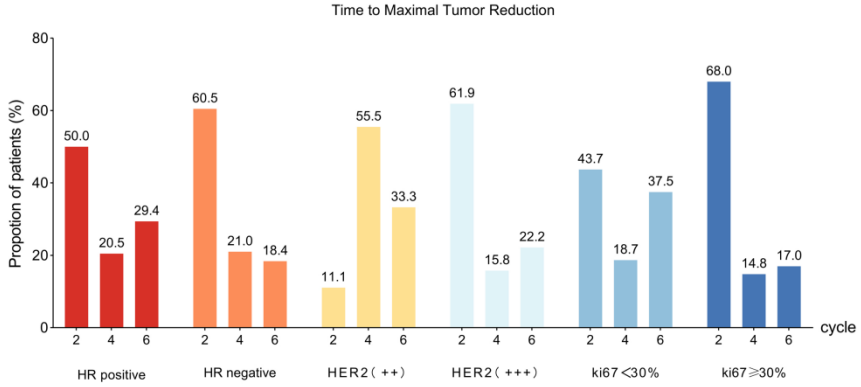


Figure S4

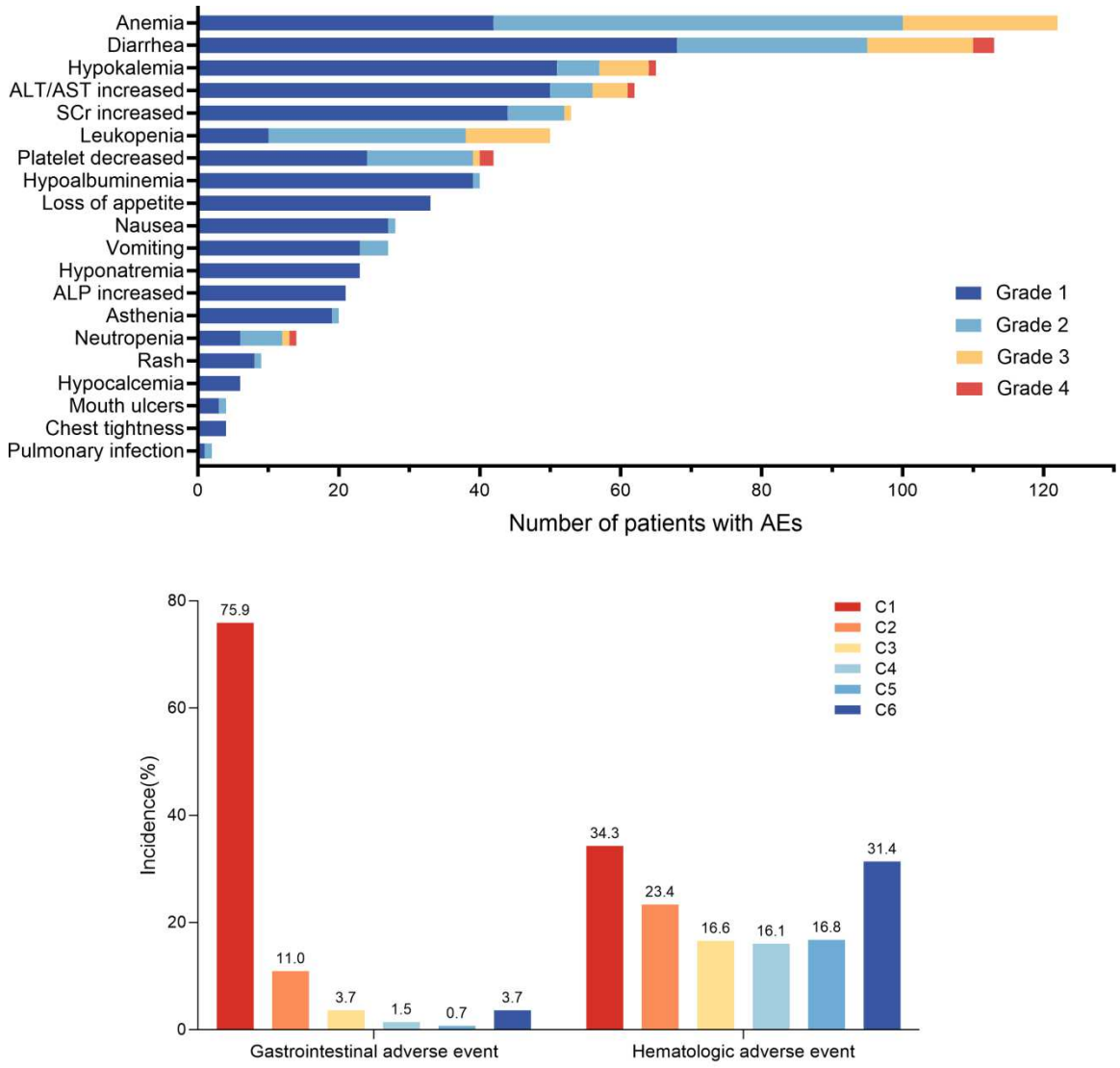

Anemia
Diarrhea
Hypokalemia
ALT/AST increased
SCr increased
Leukopenia
Platelet decreased
Hypoalbuminemia
Loss of appetite
Nausea
Vomiting
Hyponatremia
ALP increased
Asthenia
Neutropenia
Rash
Hypocalcemia
Mouth ulcers
Chest tightness
Pulmonary infection
Grade 1
Grade 2
Grade 3
Grade 4
0
20
40
60
80
100
120
Number of patients with AEs
Incidence(%)
0
20
40
60
80
C1
C2
C3
C4
C5
C6
75.9
11.0
3.7
1.5
0.7
3.7
34.3
23.4
16.6
16.1
16.8
31.4
Gastrointestinal adverse event
Hematologic adverse event

Figure S5