Trastuzumab Plus Endocrine Therapy or Chemotherapy as First-line Treatment for Patients with Hormone Receptor–Positive and HER2-Positive Metastatic Breast Cancer (SYSUCC-002)

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ABSTRACT

Purpose: There is no research evidence demonstrate which is the better partner strategy, endocrine therapy or chemotherapy, to combine with anti-HER2 therapy as the first-line management of hormone receptor (HR)-positive (HR^+) and HER2-positive ($HER2^+$) metastatic breast cancer (MBC). We wished to ascertain if trastuzumab plus endocrine therapy is noninferior to trastuzumab plus chemotherapy.

Patients and Methods: We conducted an open-label, noninferiority, phase III, randomized, controlled trial (NCT01950182) at nine hospitals in China. Participants, stratified by previous adjuvant endocrine therapy and disease status (recurrent disease vs. *de novo* metastasis), were assigned randomly (1:1) to receive trastuzumab plus endocrine therapy (per investigator's choice of oestrogen-receptor modulators or aromatase inhibitor, with/without concurrent ovarian suppression) or chemotherapy (per investigator's choice of taxanes, capecitabine, or vinorelbine). The primary endpoint was progression-free survival (PFS) with a noninferiority upper margin of 1.35 for the HR. The intention-to-treat population was used in primary and safety analyses.

Results: A total of 392 patients were enrolled and assigned randomly to receive trastuzumab plus endocrine therapy (ET group, $n = 196$) or trastuzumab plus chemotherapy (CT group, $n = 196$). After a median follow-up of 30.2 months [interquartile range (IQR) 15.0–44.7], the median PFS was 19.2 months [95% confidence interval (CI), 16.7–21.7)] in the ET group and 14.8 months (12.8–16.8) in the CT group (hazard ratio, 0.88; 95% CI, 0.71–1.09; $P_{\text{noninferiority}} < 0.0001$). A significantly higher prevalence of toxicity was observed in the CT group compared with the ET group.

Conclusions: Trastuzumab plus endocrine therapy was noninferior to trastuzumab plus chemotherapy in patients with HR^+HER2^+ MBC.

Introduction

Hormone receptor-positive (HR^+) and HER2-positive ($HER2^+$) account for approximately 10% of all metastatic breast cancer (MBC; refs. 1, 2). Anti-HER2 therapy combined with chemotherapy as first-line treatment has shown survival benefit in patients with $HER2^+$ MBC (3). Usually, patients with HR^+HER2^+ MBC undergo anti-HER2 therapy plus chemotherapy (4).

However, endocrine-based therapy rather than chemotherapy is preferred as the priority recommendation in HR^+HER2^- MBC because it is effective and associated with less toxicity (5). In many parts of the world, anti-HER2 therapy with trastuzumab and pertuzumab plus chemotherapy is the gold standard first-line treatment based on CLEOPATRA which showed the longest overall survival (OS) and the OS benefit was seen in HR^+ patients too (6–9). However, CLEOPATRA did not allow use of endocrine therapy before

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Prior presentation: The initial results of this study were presented at the American Society of Clinical Oncology 2021 Annual Meeting; June 7, 2021; Chicago, IL.

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Clin Cancer Res 2022;28:637–45

doi: 10.1158/1078-0432.CCR-21-3435

Translational Relevance

Hormone receptor (HR)-positive (HR^+) and HER2-positive ($HER2^+$) account for approximately 10% of all metastatic breast cancer (MBC). Over the years, there are no evidence that showed which first-line regimens were preferred, either anti-HER2 therapy plus endocrine therapy or chemotherapy for HR^+HER2^+ MBC. This is the first randomized, phase III study to compare, in a head-to-head manner, the efficacy and safety of trastuzumab combined with endocrine therapy or with chemotherapy as first-line treatment for HR^+HER2^+ MBC. The final analysis showed that trastuzumab plus endocrine therapy was noninferior to trastuzumab plus chemotherapy in patients with HR^+HER2^+ MBC. HER2-targeted therapy combined with endocrine therapy could be an alternative to standard HER2-targeted therapy combined with chemotherapy— the priority principle of endocrine therapy is also applicable to patients with HR^+HER2^+ MBC.

progression for those with HR coexpression. This design flaw left many to question whether outcomes for HR^+ would differ if had endocrine therapy been allowed before the first progression or had endocrine therapy replaced the chemotherapy in the first line. Moreover, "economic toxicity" should also be taken into consideration, including the very expensive mAb of pertuzumab that is too huge a burden to bear for most patients (10, 11).

Anti-HER2 therapy plus endocrine therapy has also shown promising outcomes and relatively good tolerability in several studies of HR^+HER2^+ MBC (12–16). Avoiding chemotherapy may be appropriate in some HR^+HER2^+ MBC. Nevertheless, robust clinical evidence to demonstrate the superiority of anti-HER2 therapy plus chemotherapy to anti-HER2 therapy plus endocrine therapy is lacking due to an absence of direct head-to-head comparisons of these two treatment modalities. Whether anti-HER2 therapy plus endocrine therapy can be the optimal frontline option in HR^+HER2^+ MBC is largely unexplored. The clinical trial described here, SYSUCC-002, was designed to compare the efficacy and safety of trastuzumab combined with endocrine therapy or chemotherapy as first-line treatment for patients with HR^+HER2^+ MBC.

Patients and Methods

Ethical approval of the study protocol

This clinical trial was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the ethics committee of Sun Yat-sen University Cancer Center (SYSUCC) in Guangzhou, China, together with the ethics committees of each participating institution. All patients provided written informed consent.

Study design and participants

This multicenter, open-label, noninferiority, phase III, randomized, controlled trial was carried out in nine hospitals in China (Supplement appendix). We aimed to compare the efficacy and safety of trastuzumab combined with endocrine therapy or with chemotherapy as first-line treatment for HR^+HER2^+ MBC.

Eligible female patients were aged ≥18 years old with locally histology-confirmed MBC that was deemed estrogen receptor (ER)-positive (ER^+) and/or progesterone receptor (PR)-positive (PR^+; ≥10% positive cells by IHC staining) and $HER2^+$ (IHC staining = 3+, or FISH-positive/chromogenic *in situ* hybridization–positive) at each site (17, 18).

The full inclusion and exclusion criteria are listed in the Supplement appendix. The main inclusion criteria were women with: (i) One or more measurable lesions, and/or nonmeasurable disease (RECIST v1.1); (ii) Eastern Cooperative Oncology Group status of 0 to 1; (iii) adequate function of the bone marrow, liver, and kidneys; (iv) life expectancy ≥12 weeks; (v) adequate cardiac reserve with ≥45% of left ventricular ejection fraction according to echocardiography. Previous adjuvant therapy with trastuzumab was allowed for study inclusion. However, disease-free interval (DFI; defined as the time from the diagnosis of the primary breast cancer to the first recurrence in patients who received (neo)adjuvant therapy had to be >12 months (19). The main exclusion criteria were women who (i) were pregnant or breast-feeding; (ii) showed evidence of active acute infection or chronic infection; (iii) received systemic therapy previously for metastatic disease.

Randomization and masking

Eligible patients were assigned randomly (1:1) to two groups with a block size of six (known only to the statistician). One group received trastuzumab plus endocrine therapy (ET). The other group was administered trastuzumab plus chemotherapy (CT). Participants were stratified by previous adjuvant endocrine therapy (aromatase inhibitors vs. estrogen receptor modulators (ERM)] and disease status (recurrent disease vs. *de novo* metastasis). Assignment was done by a computer-generated random number code at the Clinical Trials Centre of SYSUCC. Details of the random allocations were contained in sequentially numbered, opaque, sealed envelopes prepared by a statistician (Y. Guo), who was involved in statistical analyses/interpretation and review of toxicity data. The procedures of randomization and allocation concealment were done according to practical guidance (20). Patients and clinicians were unmasked to treatment assignments. After written informed consent had been obtained from eligible patients, the investigator (Y.-Y. Z) opened the envelopes sequentially and allocated patients to the corresponding interventions.

Procedures

Trastuzumab was given to the CT group and ET group. Trastuzumab was administered on day 1 of study treatment as an initial loading dose of 8 mg/kg bodyweight. Subsequent dosing and scheduling of trastuzumab was 6 mg/kg every 3 weeks. Endocrine therapy or chemotherapy were given simultaneously with trastuzumab, and were prescribed according to guidelines set by the National Comprehensive Cancer Network (21).

For chemotherapy, taxanes are recommended for patients with *de novo* metastatic breast cancer or taxane-sensitive recurrent disease [defined as the interval between the last day of taxane administration in the (neo)adjuvant setting and the day of first recurrence must be ≥6 months; ref. 19]. Capecitabine or vinorelbine could be chosen as first-line chemotherapy for patients with recurrent disease (22, 23). Details were described in the protocol (Supplement appendix). For endocrine therapy, aromatase inhibitors (anastrozole, letrozole, exemestane) or ERMs (tamoxifen or toremifene) are recommended for *de novo* MBC; drugs of different mechanisms (ERMs, steroidal/nonsteroidal aromatase inhibitors) are recommended for recurrent disease with previous endocrine therapy in the (neo)adjuvant setting. For premenopausal patients, ovarian suppression is recommended with the endocrine therapy described above. Ovarian function suppression can be achieved by castration (surgical or drug); the main drugs used for chemical castration are growth hormone-releasing hormone

analogues such as goserelin or leuprorelin. Details of treatment procedures were described in the protocol (Supplement appendix).

The response to treatment was evaluated after every 3 cycles starting from the first cycle of treatment. The evaluation was based on the RECIST v1.1. This was done until there was radiographically confirmed disease progression, initiation of new anticancer therapy, or the participant discontinued the study (e.g., request to withdraw from the study, loss to follow-up, death). Adverse events (AE) during treatment were graded according to the Common Toxicity Criteria for Adverse Events v4.0 set by the U.S. NCI.

Participants continued to receive trastuzumab plus endocrine therapy or chemotherapy until disease progression, symptomatic deterioration, unacceptable toxicity, withdrawal of consent, or death. Patients in the CT group who did not have progressive disease could receive capecitabine or vinorelbine (orally) combined with trastuzumab as maintenance treatment according to the choice of the physician. Switch to the other group before first progression was not permitted to avoid confounding treatment effects, and the switch was allowed after first progression.

Outcomes

The primary endpoint was progression-free survival (PFS), which was defined as the time from random assignment to the first date of confirmed progression, or death due to any cause, whichever occurred first. The secondary endpoints were the objective response rate [ORR; defined as the proportion of participants who achieved confirmed complete remission (CR) or a partial response (PR)], OS (defined as the time from the date of randomization until the date of death, censored at the last known date alive), and the safety profile of the two treatment groups (prevalence and severity of AEs in each group).

Statistical analyses

The primary hypothesis of the study was that the median PFS with trastuzumab plus endocrine therapy was noninferior to that of trastuzumab plus chemotherapy. Tripathy and colleagues estimated the median PFS of trastuzumab plus chemotherapy (control group) in patients with HR^+HER2^+ MBC to be 9.5 months (24). We anticipated the median PFS in patients receiving trastuzumab plus endocrine therapy (test group) reached 7.0 months, it could be considered noninferior than the control group. A median PFS of 7.0 months was deemed acceptable considering the potential clinical benefits of ET, referring to the results of well-known trials (15, 16). The noninferiority margin of 1.35 for the hazard ratio (estimated median PFS of 9.5 months for the CT group vs. 7.0 months for the ET group) was determined according to medical judgment of a clinically appropriate and acceptable margin referring to similar trial (25). The use of an upper margin of 1.35 for the hazard ratio and a one-sided significance level of 0.025 ensured a power of 80% to show the noninferiority of ET compared with CT. Accordingly, after accounting for an annual dropout rate of 7%, enrolment of ≥392 patients (196 in each group) was set for our clinical trial. A superiority test would be conducted if the noninferiority hypothesis was proven, and the upper margin for the hazard ratio was set as 1.0.

Cumulative survival probabilities were estimated using the Kaplan–Meier method and compared using the log-rank test stratified by the randomization strata. Hazard ratio with 95% confidence intervals (CI) were estimated using the stratified Cox proportional hazards model with randomization stratification factors. The assumption of proportional hazards was checked based on Schoenfeld residual test. Prespecified exploratory subgroup analyses were conducted according to prognostic factors: age, receptor status, visceral involvement, previous adjuvant endocrine therapy, metastasis number, and DFI. The consistency of the treatment effect was measured for each prespecified subgroup and evaluated using an unadjusted Cox proportional hazard model. Treatment effects were evaluated among subgroups by adding interaction terms to Cox proportional hazards models. The ORR was assessed by the χ^2 test. The prevalence of acute toxicity was compared using two-sample tests of proportion. Efficacy and safety analyses were evaluated on an intent-to-treat (ITT) population, which included all randomly assigned patients who received protocol-defined treatment. No statistical method was used to deal with missing data. All other statistical tests were two-sided, and $P < 0.05$ was considered significant. Analyses were based on data received up to December 29, 2020. Analyses were done using SAS v9.4 (SAS Institute) and R v3.4.1 (R Center for Statistical Computing).

Data sharing statement

Considering patients' privacy and related regulations in China, we chose not to make the database public to everyone. If a researcher wants to use our raw data for scientific research purposes, he or she could apply for use with our corresponding author and database administrator.

Results

Demographics

Between September 16, 2013 and December 28, 2019, 392 patients were enrolled across nine sites and assigned randomly to receive CT ($n = 196$) or ET ($n = 196$) as first-line therapy for HR^+HER2^+ MBC. Twenty patients were identified as ineligible after enrolment or did not receive any study treatment (**Fig. 1**). The demographic characteristics of patients in the two groups at baseline are shown in **Table 1**. Of these 392 eligible patients, 317 (80.9%) had ER^+PR^+ breast cancer. A total of 233 patients (59.4%) had visceral involvement. We found that 284 of all eligible patients had recurrent disease, and 148 (52.1%) had recurrent disease within 24 months since the diagnosis of primary breast cancer. Of those 284 patients, 166 (58.5%) received aromatase inhibitors and 118 (41.5%) received ERMs as adjuvant endocrine therapy; 268 (94.3%) underwent (neo)adjuvant chemotherapy. There were 348 (88.8%) patients received breast cancer therapies after first-line treatment of the study, the proportions of patients who received various drugs was balanced in the two study groups (**Table 2**).

Efficacy

With a median follow-up of 30.2 (interquartile range, 15.0–44.7) months for the ITT population, the median PFS was 19.2 (95% CI, 16.7–21.7) months in the ET group and 14.8 (12.8–16.8) months in the CT group (**Fig. 2**). The corresponding hazard ratio was 0.88 (95% CI, 0.71–1.09), and the upper margin of the 95% CI was less than the predefined noninferiority margin of 1.35 (Cox proportional hazards model, $P_{\text{noninferiority}} < 0.0001$), whereas the prespecified test for superiority at an upper margin of the hazard ratio of 1.0 was not significant (Cox proportional hazards model; $P = 0.248$). The median OS (in months) was 33.9 (95% CI, 28.8−39.0) in the ET group and 32.5 (26.0−39.0) in the CT group (hazard ratio, 0.82; 95% CI, 0.65−1.04; $P_{\text{superiority}} = 0.094$; **Fig. 2**).

In the ITT population, 13 (6.6%) in the CT group versus 5 (2.6%) in the ET group had CR ($P = 0.054$). A total of 71 (36.2%) in the CT group and 68 (34.7%) in the ET group achieved a partial response (PR). In the CT group, stable disease (SD) was observed in 95 (48.5%) patients,

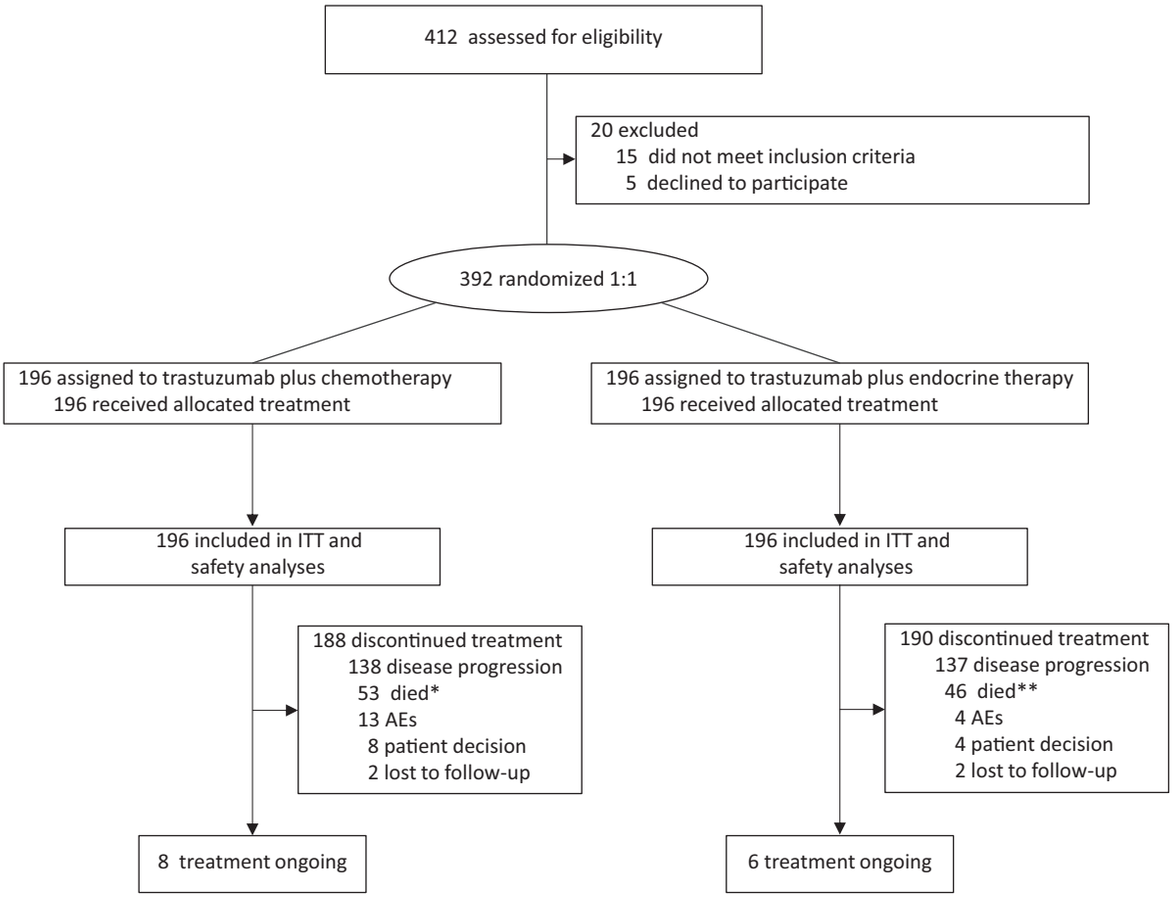

Figure 1.
Trial profile. *, In total 53 patients died, of which 26 patients died with disease progression and 27 patients died without disease progression. **, In total 46 patients died, of which 3 patients died with disease progression and 43 patients died without disease progression.

whereas SD duration <6 months was found in 11 (5.6%) patients. In the ET group, 102 (52.0%) had SD, and 8 (4.1%) of them had SD duration <6 months. There was no significant difference in the ORR between the CT group and ET group (42.9% in the CT group vs. 37.2% in the ET group; $P = 0.257$).

A prespecified exploratory subgroup analysis was carried out (**Fig. 3**). There was a significant interaction effect between DFI and the treatment modality (ET vs. CT) upon PFS ($P = 0.016$). For patients with DFI ≤24 months, the hazard ratio for the risk of disease progression or death was 1.39 (95% CI, 0.97–1.98; $P = 0.073$). For patients with a DFI >24 months, the hazard ratio for the risk of disease progression or death was 0.77 (95% CI, 0.53–1.10; $P = 0.147$). No other significant interactions were found between the treatment groups and other subgroups.

Safety

Overall, 357 (91.1%) patients (165 in the ET group and 192 in the CT group) experienced ≥1 AE during the trial (**Table 3**). Treatment-related death was not observed in either group. Most AEs in the ET group were grade 1 to 2. The most common AEs were joint pain (16.8%), muscle pain (16.3%), and fatigue (15.8%). The most frequently reported AEs in the CT group were alopecia (63.8%), leucopenia (50.0%), and nausea (47.5%). Patients in the ET group had a significantly lower prevalence of AEs of grade 3 to 4 compared with those in the CT group [6 (3.1%) vs. 100 (51.0%); $P < 0.01$].

Discussion

To our knowledge, the SYSUCC-002 trial is the first randomized, phase III study to compare, in a head–to–head manner, the efficacy and safety of trastuzumab combined with endocrine therapy or with chemotherapy as first-line treatment for HR^+HER2^+ MBC. The results of this study showed that the efficacy of trastuzumab plus endocrine therapy was not inferior to that of trastuzumab plus chemotherapy. Notably, a significant interaction effect between the DFI and the treatment arms for PFS was found. Besides, trastuzumab plus endocrine therapy displayed a better safety profile, especially for grade 3 to 4 treatment-related hematologic and gastrointestinal toxicities.

The median PFS in the trastuzumab plus docetaxel arm of the CLEOPATRA trial was 12.4 months for $HER2^+$ MBC, which enrolled about half patients with HR- (6). As this study included all $HER2^+$ HR^+ patients, PFS of CT group (14.8 months) was assumed to be longer than that control group in the CLEOPATRA trial. Meanwhile, for the well-known trials evaluating endocrine therapy and HER2 targeted therapy [TAnDEM (15), EGF30008 (16), and PERTAIN (13)], the PFS results

Table 1. Patient characteristics at baseline.

Variable	ET group ($n = 196$)	CT group ($n = 196$)
Age, years		
≤40	31 (15.8%)	42 (21.4%)
>40	165 (84.2%)	154 (78.6%)
Median, IQR	50 (45–57)	49 (42–55)
Premenopausal	61 (31.1%)	59 (30.1%)
Receptor status		
ER^+ and PR^+	157 (80.1%)	157 (80.1%)
ER^+ or PR^+	39 (19.9%)	39 (19.9%)
Visceral involvement[a]	114 (58.2%)	119 (60.7%)
Number of metastases		
≥2	56 (28.6%)	57 (29.1%)
<2	140 (71.4%)	139 (70.9%)
DFI[b]		
≤24 months	64 (32.7%)	78 (39.8%)
>24 months	78 (39.8%)	64 (32.7%)
Previous adjuvant endocrine therapy		
Aromatase inhibitors	83 (42.3%)	83 (42.3%)
ERMs	59 (30.1%)	59 (30.1%)
Previous (neo)adjuvant chemotherapy		
Anthracyclines and taxanes	105 (53.6%)	113 (57.7%)
Taxanes	13 (6.6%)	10 (5.1%)
Anthracyclines	13 (6.6%)	12 (6.1%)
Other	2 (1.0%)	0
Previous anti-HER2 therapy	41 (20.9%)	48 (24.5%)
De novo metastases	54 (27.6%)	54 (27.6%)

Note: Data are the number (%), unless stated otherwise. Owing to rounding up, some percentages may not add up to 100%. Data for DFI and previous endocrine therapy were available only for patients who were diagnosed initially with early breast cancer and then experienced relapse of disease; percentages are calculated based on available data.

Abbreviation: IQR, interquartile range.

[a]Visceral involvement was defined as lung, liver, brain, pleural, and peritoneal involvement.

[b]DFI was defined as the time from the diagnosis of the primary breast cancer to the first recurrence in patients who received (neo)adjuvant therapy.

Table 2. Breast cancer treatments received by patients who discontinued study treatment.

Treatment	ET group ($n = 196$)	CT group ($n = 196$)
Any treatment received after discontinuing study treatment	175 (89.3%)	173 (88.3%)
Anti-HER2 therapy	160 (81.6%)	165 (84.2%)
Lapatinib	121 (61.7%)	122 (62.2%)
Trastuzumab	117 (59.7%)	124 (63.3%)
Pyrotinib	35 (17.9%)	46 (23.5%)
Trastuzumab emtansine	26 (13.3%)	23 (11.7%)
Chemotherapy	151 (77.0%)	143 (73.0%)
Capecitabine	104 (53.1%)	99 (50.5%)
Vinorelbine	71 (36.2%)	86 (43.9%)
Taxanes	58 (29.6%)	60 (30.6%)
Gemcitabine	37 (18.9%)	35 (17.9%)
Carboplatin or Cisplatin	35 (17.9%)	26 (13.3%)
Cyclophosphamide	22 (11.2%)	14 (7.1%)
Etoposide	11 (5.6%)	10 (5.1%)
Endocrine therapy	101 (51.5%)	108 (55.1%)
Aromatase inhibitors	83 (42.3%)	87 (44.4%)
Fulvestrant	67 (34.2%)	71 (36.2%)
ERMs	13 (6.6%)	9 (4.6%)

vary widely (range from 4.8 to 15.8 months). It is puzzling that the PFS of TAnDEM (4.8 months) were quite worse than that of EGF30008 (8.2 months), given that the NCIC CTG MA.31 trial demonstrated that trastuzumab combined with taxane was associated with longer PFS compared with lapatinib combined with taxane (26). In fact, the control group of PERTAIN (15.8 months) also had higher PFS than the TAnDEM (4.8 months). The PFS of current study (19.2 months) is consistent with that of PERTAIN (15.8 months), considering that we adopted HR^+ as >10% which would contribute to a better efficacy of endocrine therapy. In addition, the quality of HER2 tests has improved and the experience of health care in managing trastuzumab therapy has increased. Meanwhile, racial differences can also affect treatment outcomes, all participants in this study were Chinese (27, 28), which may be different from European and American ethnic groups. It should be noted that comparisons between our study and earlier trials should be made with caution because of inherent differences, such as patient populations and treatments, between studies.

In general, MBC is incurable, and the goal of treatment is to optimize the quality and length of life. The optimal treatment modality for patients with HR^+HER2^+ MBC is not known. A combination of anti-HER2 therapy with chemotherapy, which is considered first-line treatment for $HER2^+$ MBC regardless of expression of hormonal receptors, has improved the OS of patients with $HER2^+$ MBC dramatically (7, 29). The intrinsic link between the HR and HER2 may contribute to resistance to endocrine therapy or anti-HER2 therapy in HR^+HER2^+ MBC, which could be solved by blocking ER and HER2 signaling pathways simultaneously (30–32). Several randomized studies have demonstrated quite good PFS and good toleration of treatment with anti-HER2 therapy plus endocrine therapy (12–14, 33).

We provided, for the first time, clinical evidence that anti-HER2 therapy plus endocrine therapy could be first-line treatment in patients with HR^+HER2^+ MBC. This chemotherapy-free strategy displayed similar efficacy to that of anti-HER2 therapy plus chemotherapy, and had better tolerability. Notably, exploratory analyses revealed that the noninferiority of ET versus CT in MBC was overall fining, but in those with a DFI < 24 months CT might offer a better trend towards DFI compared with ET. This might be clinically relevant in this subgroup, even with small numbers, to opt for CT over ET. The reason why patients with a DFI ≤24 months had a worse outcome with anti-HER2 therapy plus endocrine therapy might because they displayed endocrine resistance, including recurrence and/or metastases within 24 months from the beginning of endocrine therapy. Patients with early relapse (DFI ≤ 24 months) are probably not the best candidates for anti-HER2 therapy plus endocrine therapy, this observation of treatment heterogeneity requires further study.

Current study had several limitations. First, dual blockade of HER2 with trastuzumab and pertuzumab has been shown to further improve survival outcomes compared with that using single anti-HER2 therapy, and has been recommended as first-line anti-HER2 therapy (34). This trial was registered in 2013, which was before the era of pertuzumab treatment in mainland China. The conclusion from this trial is likely to be valid also in the dual anti-HER2 therapy era according to CLEOPATRA (6) and PERTAIN (13), which needs to be confirmed by prospective clinical trials. With the development of new drugs, it is inevitable that many new drugs with high efficacy will be included and treatment recommendations will be continuously updated, but the therapeutic concepts presented by these classical schemes still have important enlightening meanings (schemes go out of date but concepts

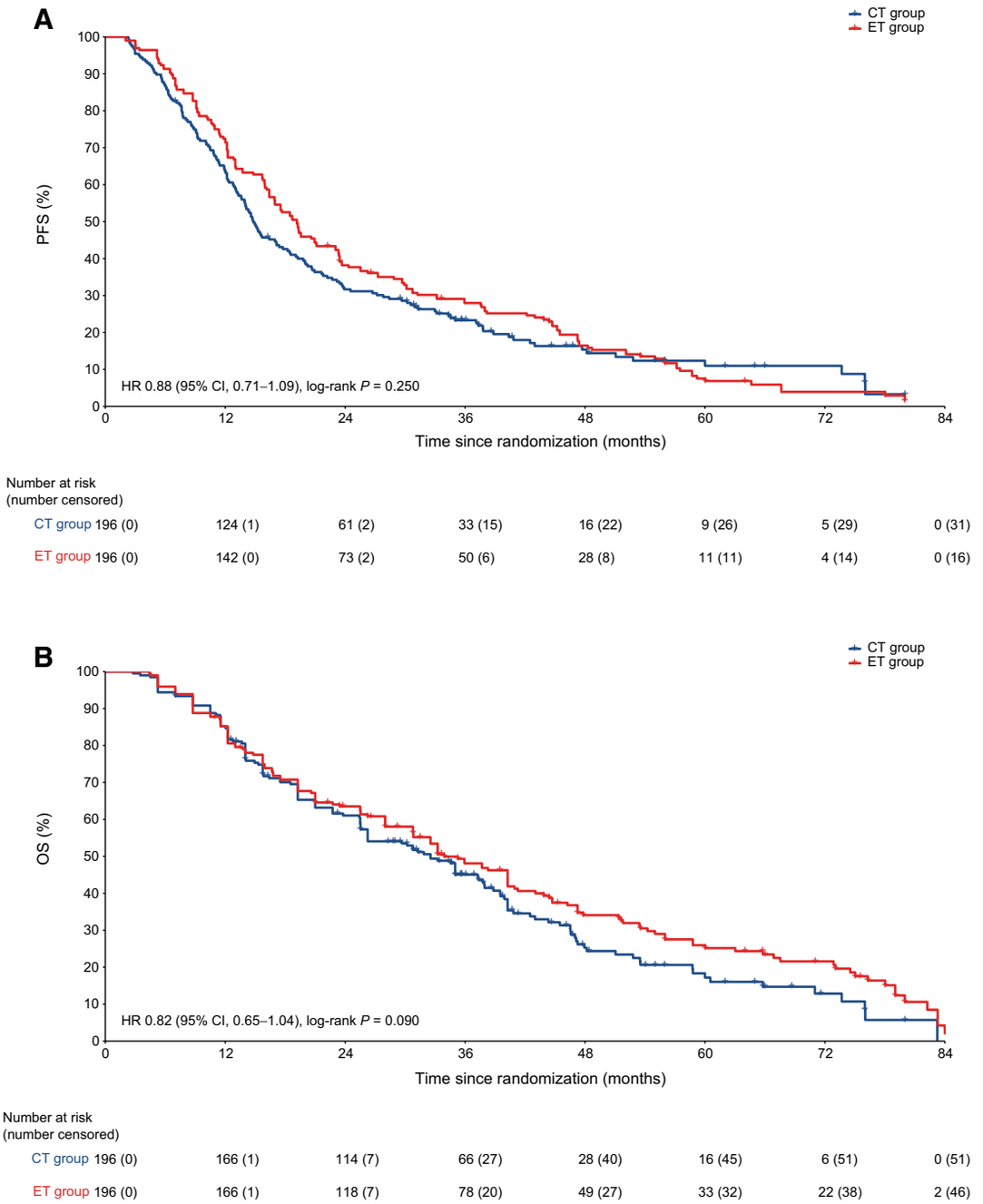

Figure 2.
PFS and OS. **A,** PFS; **B,** OS.

don't). When strictly considered in the context of the results from SYSUCC-002, ET + trastuzumab provides a lower toxicity option for first-line therapy in HR^+HER2^+ MBC that could be favored at least for patients who cannot afford pertuzumab, or in countries where pertuzumab has not been approved by regulatory authorities. Second, the design and approval of our study protocol was before the era of cyclin-dependent kinase (CDK) 4/6 inhibitors, so the latter were not administrated in the ET group. CDK4/6 inhibitors in combination with endocrine therapy have played a major part against ER^+ disease (35). A combination of CDK4/6 inhibitors, hormonal therapy, and anti-HER2 agents has demonstrated promising efficacy in several phase I/II trials (36, 37). Whether this novel combination is superior to chemotherapy plus anti-HER2 agents in first line treatment of patients with $HR^+/HER2^+$ MBC warrants investigation using randomized controlled trials. Third, although the chemotherapy regimens of this study were not uniform,

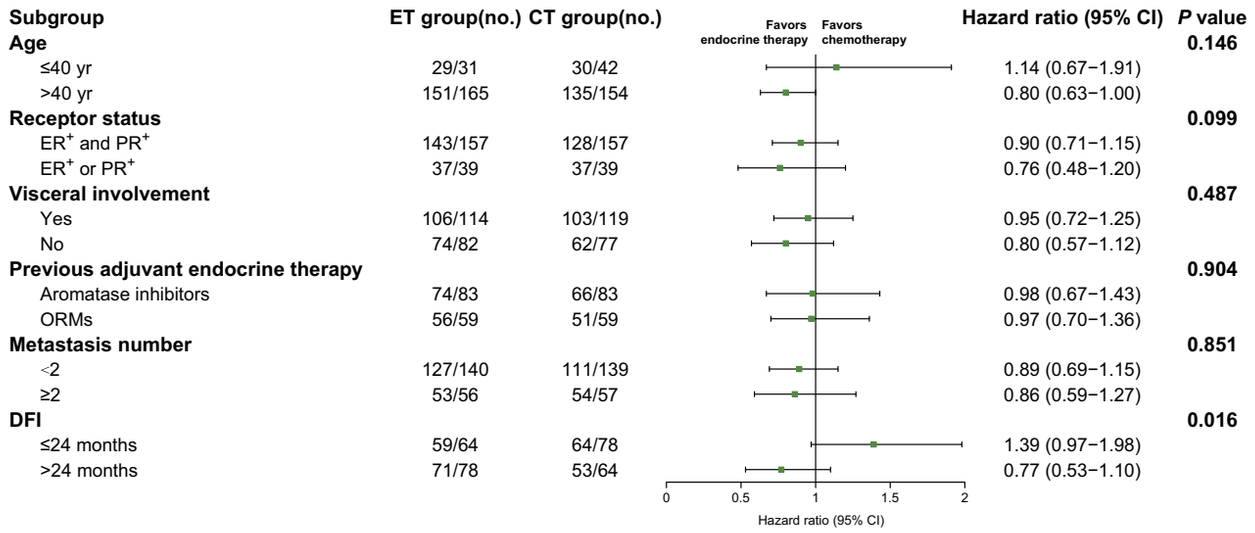

Figure 3.

Subgroup analyses of PFS. Exploratory subgroup analyses were conducted using the unadjusted Cox model to estimate hazard ratios with 95% CIs and to test for interactions among subgroups using two-sided *P* values.

Table 3. AEs for the safety population.

Event	ET group ($n = 196$)			CT group ($n = 196$)		
Grade	**1–2**	**3**	**4**	**1–2**	**3**	**4**
Leucopenia	12 (6.1%)	1 (0.5%)	0	57 (29.1%)	31 (15.8%)	10 (5.1%)
Anemia	15 (7.7%)	1 (0.5%)	0	33 (16.8%)	0	0
ALT/AST increase	22 (11.2%)	0	0	41 (20.9%)	0	0
Abdominal pain/diarrhea	20 (10.2%)	0	0	59 (30.1%)	5 (2.6%)	0
Stomatitis	5 (2.6%)	0	0	43 (21.9%)	0	0
Fatigue	31 (15.8%)	0	0	47 (24.0%)	0	0
Nausea	24 (12.2%)	0	0	88 (44.9%)	5 (2.6%)	0
Vomiting	12 (6.1%)	0	0	38 (19.4%)	7 (3.6%)	0
Anorexia	8 (4.1%)	0	0	46 (23.5%)	0	0
HFS	0	0	0	62 (31.6%)	31 (15.8%)	0
Paresthesia	0	0	0	68 (34.7%)	3 (1.5%)	0
Joint pain	33 (16.8%)	0	0	47 (24.0%)	0	0
Muscle pain	28 (14.3%)	4 (2.0%)	0	43 (21.9%)	4 (2.0%)	0
Headache	24 (12.2%)	0	0	55 (28.1%)	10 (5.1%)	0
Alopecia	8 (4.1%)	0	0	125 (63.8%)	0	0

Note: Data are the number (%). Grade 5 AEs did not occur during treatment.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HFS, hand–foot syndrome.

trastuzumab plus vinorelbine or capecitabine has been commonly accepted by various national guidelines as a treatment option and yielded similar efficacy (22, 23, 38, 39). In case of the similar efficacy of different chemotherapy regimens, our study was focused on the efficacy of chemotherapy versus endocrine therapy. Additionally, the HR and HER2 status were confirmed at each site which may have a practice changing potential.

Conclusions

This study suggests that anti-HER2 therapy plus endocrine therapy might be an efficacious, well tolerated, and more convenient alternative to anti-HER2 therapy plus chemotherapy as optimal first-line treatment for patients with HR^+HER2^+ MBC.

Authors' Disclosures

J.-J. Huang reports grants from Sci-Tech Project Foundation of Guangzhou City, Natural Science Foundation of Guangdong Province; and grants from cultivation foundation for the junior teachers in Sun Yat-sen University during the conduct of the study. No disclosures were reported by the other authors.

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Acknowledgments

We thank the patients who participated in this study and their families, as well as the nursing and research staff at the study centers. This study was supported by grants from the Sci-Tech Project Foundation of Guangzhou City (no. 202002020033), the Natural Science Foundation of Guangdong Province (no. 2019A151011781), and the cultivation foundation for the junior teachers in Sun Yat-sen University (no. 20ykpy164).

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Received September 23, 2021; revised October 29, 2021; accepted November 19, 2021; published first November 22, 2021.

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