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Adjuvant Capecitabine With Docetaxel and Cyclophosphamide Plus Epirubicin for Triple-Negative Breast Cancer (CBCSG010): An Open-Label, Randomized, Multicenter, Phase III Trial

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abstract

PURPOSE Standard adjuvant chemotherapy for triple-negative breast cancer (TNBC) includes a taxane and an anthracycline. Concomitant capecitabine may be beneficial, but robust data to support this are lacking. The efficacy and safety of the addition of capecitabine into the TNBC adjuvant treatment regimen was evaluated.

PATIENTS AND METHODS This randomized, open-label, phase III trial was conducted in China. Eligible female patients with early TNBC after definitive surgery were randomly assigned (1:1) to either capecitabine (3 cycles of capecitabine and docetaxel followed by 3 cycles of capecitabine, epirubicin, and cyclophosphamide) or control treatment (3 cycles of docetaxel followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide). Randomization was centralized without stratification. The primary end point was disease-free survival (DFS).

RESULTS Between June 2012 and December 2013, 636 patients with TNBC were screened, and 585 were randomly assigned to treatment (control, 288; capecitabine, 297). Median follow-up was 67 months. The 5-year DFS rate was higher for capecitabine than for control treatment (86.3% *v* 80.4%; hazard ratio, 0.66; 95% CI, 0.44 to 0.99; $P = .044$). Five-year overall survival rates were numerically higher but not significantly improved (capecitabine, 93.3%; control, 90.7%). Overall, 39.1% of patients had capecitabine dose reductions, and 8.4% reported grade ≥ 3 hand-foot syndrome. The most common grade ≥ 3 hematologic toxicities were neutropenia (capecitabine, 136 [45.8%]; control, 118 [41.0%]) and febrile neutropenia (capecitabine, 50 [16.8%]; control, 46 [16.0%]). Safety data were similar to the known capecitabine safety profile and generally comparable between arms.

CONCLUSION Capecitabine when added to 3 cycles of docetaxel followed by 3 cycles of a 3-drug anthracycline combination containing capecitabine instead of fluorouracil significantly improved DFS in TNBC without new safety concerns.

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Triple-negative breast cancer (TNBC) is pathologically defined as an estrogen receptor (ER)–negative, progesterone receptor (PR)–negative, and human epidermal growth factor receptor 2 (HER2)–negative disease.[1] It accounts for 12%-17% of all breast cancers[1] and is characterized by higher relapse rates and shorter overall survival (OS).[2] An understanding of the mechanisms that drive resistance and identification of biomarkers to guide treatment decisions may help to improve survival.[3] To date, anthracycline- and taxane-based therapy remains the sole proven adjuvant systemic approach for prevention of recurrence and survival improvement.[4]

Capecitabine, an oral prodrug of fluorouracil, is metabolized in the liver and malignant tumors and ultimately converted to cytotoxic fluorouracil by thymidine phosphorylase (TP), which is highly expressed in

CONTEXT

Key Objective

Limited evidence exists for the efficacy and safety of adjuvant capecitabine in combination with standard chemotherapy for patients with triple-negative breast cancer (TNBC).

Knowledge Generated

The 5-year disease-free survival rate was significantly improved by adding capecitabine. Safety data were in line with the known capecitabine safety profile.

Relevance

Capecitabine concomitantly used with docetaxel and epirubicin is an alternative adjuvant regimen for TNBC.

breast tumors.[5] In xenograft models, administration of docetaxel, paclitaxel, or cyclophosphamide boosted TP expression in tumor tissue, which suggests possible synergy with capecitabine.

The CREATE-X trial demonstrated improved survival with the addition of capecitabine adjuvant therapy in HER2-negative patients with residual invasive disease after standard neoadjuvant chemotherapy, particularly in the TNBC subpopulation.[6] Current guidelines suggest that capecitabine should be considered for adjuvant treatment after standard neoadjuvant treatment with taxane- and anthracycline-based chemotherapy.[7] Clinical studies that have evaluated capecitabine without preoperative therapy are inconclusive. Randomized studies have evaluated capecitabine as adjuvant treatment in breast cancer overall[8-11] and in elderly patients with breast cancer.[12,13] However, none of these trials were focused solely on patients with TNBC. GEICAM 2003-11, which evaluated sequential monotherapy of capecitabine in TNBC, showed that capecitabine did not significantly increase disease-free survival (DFS) in the overall TNBC population after standard adjuvant chemotherapy.[14]

Evidence for the efficacy and safety of adjuvant capecitabine concomitant use with standard chemotherapy for TNBC is limited; this is a key unmet need for clinicians when determining optimal therapeutic strategies for their patients. We report the results from the Chinese Breast Cancer Study Group 010 (CBCSG010) trial, which was designed to investigate the efficacy and safety of adjuvant capecitabine in combination with docetaxel and cyclophosphamide plus epirubicin for patients with early TNBC.

PATIENTS AND METHODS

Study Design and Patients

This prospective, open-label, multicenter, randomized, phase III clinical trial was conducted at 35 medical institutions in China within the CBCSG (Appendix Table A1, online only). The study protocol is available in the Data Supplement (online only).

Eligibility criteria included females age 18-70 years with newly diagnosed, unilateral invasive breast cancer after primary surgery with clear margin; histologically confirmed triple-negative status defined as ER and/or PR $< 10\%$ by local immunohistochemical (IHC) analysis at each participating institution and HER2 IHC0-1+ or IHC2+ with negative (no amplification) in situ hybridization, no evidence of metastasis (M0), regional node-positive disease (at least N1mic), or node-negative disease with primary tumor diameter ≥ 10 mm; Eastern Cooperative Oncology Group performance score 0 or 1; an interval of > 7 and < 30 days between surgery and random assignment; normal renal, cardiac, and hepatic function; and normal blood counts. Key exclusion criteria included presence of distant metastases, tumor stage $>$ T4a, clinically significant cardiac disease, previous neoadjuvant chemotherapy, presence of peripheral neuropathy of any grade, child-bearing potential and not using contraception, current pregnancy or lactation, other invasive malignant diseases within the past 5 years (except excised basal cell skin carcinoma and cervical carcinoma in situ), any other physical or psychological condition that affected the patient's health or conduct of the study, participation in another clinical trial, and known hypersensitivity to study treatment agents.

The study protocol was approved by independent ethics committees at each participating center, and the study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

Random Assignment and Masking

Eligible patients were randomly assigned (1:1) to receive either a capecitabine-containing chemotherapy (capecitabine group) or a control regimen. Randomization was done through an interactive web response system with no stratification factors. Patients and investigators were aware of the treatment group assignment.

Procedures

The capecitabine group received capecitabine plus docetaxel (XT: capecitabine 1,000 mg/m^2 twice daily by

mouth, days 1-14; docetaxel 75 mg/m^2 as a 1-hour intravenous infusion on day 1 of every 3-week cycle) for 3 cycles, followed by capecitabine, epirubicin, and cyclophosphamide (XEC: capecitabine 1,000 mg/m^2 twice daily, days 1-14; epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m^2 on day 1; every 3-week cycle) for 3 cycles. The control group received docetaxel followed by fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2 (T-FEC), all administered on day 1 of every 3-week cycle for 3 cycles. Patients received locoregional radiotherapy according to each institution's practice after completion of chemotherapy.

Standard prophylactic oral corticosteroids and histamine antagonists were given before docetaxel to prevent hypersensitivity reactions. Granulocyte colony-stimulating factor was allowed for symptomatic neutropenia but not prophylactically in the first cycle. Febrile neutropenia was managed according to institutional treatment guidelines in China. A dose reduction gradient was used in the event of grade 2-4 toxicity for docetaxel and epirubicin as follows: grade 2 event, treatment was held for up to 7 days and then resumed at the same dose once resolved to grade ≤ 1; grade ≥ 3 event, treatment was held and if toxic effects resolved to grade < 2 within 7 days, treatment was dose reduced (first appearance, 80% of the dose; second appearance, 60% of the starting dose). Up to 2 dose reductions were allowed, and treatment was permanently discontinued if toxic effects did not resolve to grade < 2 within 7 days of holding treatment. The dose reduction gradient for capecitabine was 1,000, 900, 825, 750, and 675 mg/m^2. For grade ≥ 3 events, capecitabine was interrupted and resumed at a lower dose after the toxic effect was resolved to grade < 2. Only the agent associated with an adverse event, as judged by the investigator, was dose reduced. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Staging examinations (breast ultrasound, mammogram, chest computed tomography [CT] scan, and abdominal ultrasound) were mandatory at screening; laboratory tests (CBC and serum chemistry) were performed within the 3 days before the start of every chemotherapy cycle. All events that occurred during study treatment or within 28 days of the last dose of chemotherapy were recorded. Follow-up of study patients was scheduled every 3 months

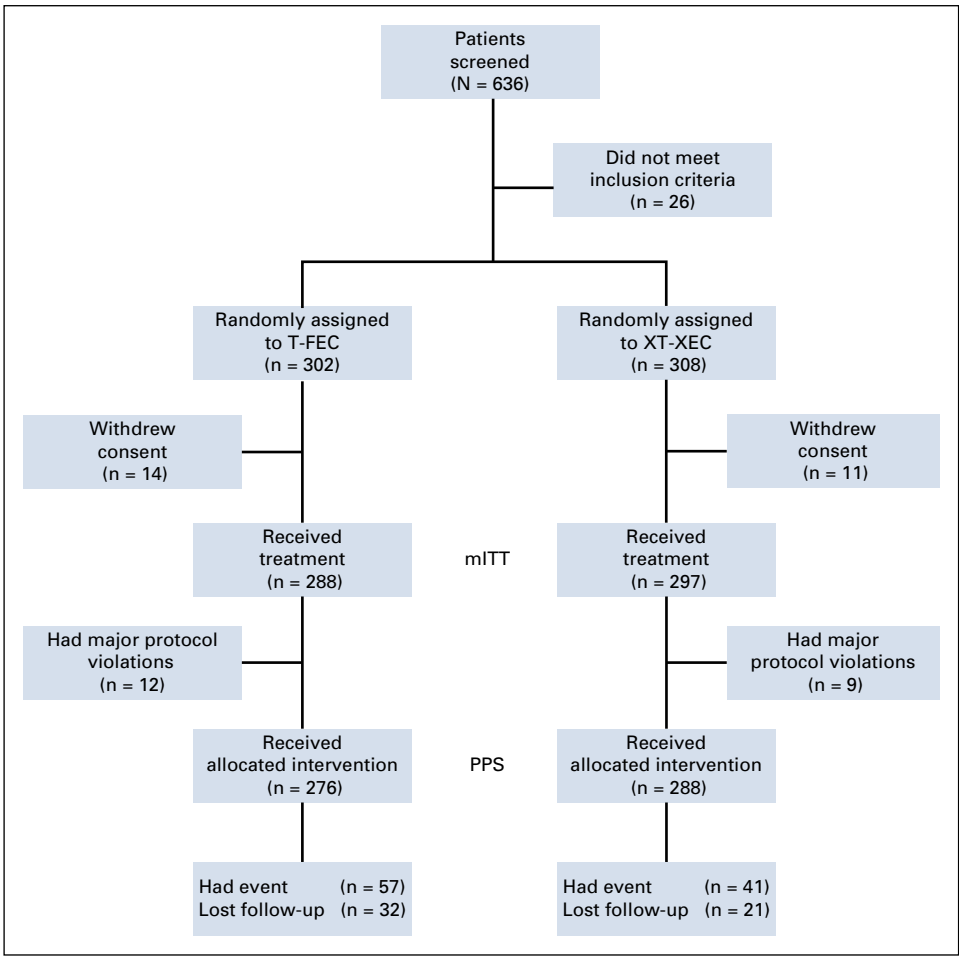

FIG 1. CONSORT diagram of patient disposition. mITT, modified intention to treat; PPS, per-protocol set; T-FEC, 3 cycles of docetaxel followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide; XT-XEC, 3 cycles of capecitabine plus docetaxel followed by 3 cycles of capecitabine, epirubicin, and cyclophosphamide.

TABLE 1. Baseline Patient Demographics and Clinical Characteristics (mITT population)

Characteristic	T-FEC, No. (%)	XT-XEC, No. (%)
No. of patients	288	297
Mean age, (SD)	48.3 ± 8.7	49.1 ± 10.4
Mean body surface area, m^2 (SD)	1.6 ± 0.1	1.6 ± 0.1
Menstruation		
Premenopausal	166 (59.3)	154 (53.3)
Postmenopausal	114 (40.7)	135 (46.7)
Family history	75 (26.0)	79 (26.6)
Operation type		
Breast conserving	59 (20.6)	74 (24.9)
Mastectomy	228 (79.4)	223 (75.1)
Sentinel lymph node biopsy	75 (26.1)	75 (25.3)
Axillary dissection	212 (73.9)	222 (74.7)
Nodal status		
N0	185 (64.9)	196 (66.9)
N1	68 (23.9)	71 (24.2)
N2	20 (7.0)	12 (4.1)
N3	12 (4.2)	14 (4.8)
T stage		
T1a,b	12 (4.8)	10 (3.9)
T1c	104 (41.9)	109 (42.7)
T2	120 (48.4)	132 (51.8)
T3	12 (4.8)	4 (1.6)
Histology		
Invasive ductal carcinoma	255 (89.2)	265 (89.5)
Invasive lobular carcinoma	2 (0.7)	4 (1.4)
Other	29 (10.1)	27 (9.1)
Grade		
1	10 (4.0)	6 (2.5)
2	116 (46.6)	100 (40.8)
3	123 (49.4)	139 (56.7)
ER and/or PR 1%-9%	5 (1.7)	5 (1.7)
ER and PR < 1%	283 (98.3)	292 (98.3)
Ki-67 < 30% positive	53 (19.5)	53 (18.9)
Ki-67 ≥ 30% positive	219 (80.5)	227 (81.1)
Lymphovascular invasion positive	40 (14.1)	29 (9.8)
Mean time from surgery to chemotherapy, days (SD)	17.2 ± 7.9	18.0 ± 9.1

Abbreviations: ER, estrogen receptor; Ki-67, protein encoded by the *MKI67* gene; mITT, modified intention to treat; PR, progesterone receptor; SD, standard deviation; T-FEC, 3 cycles of docetaxel followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide; XT-XEC, 3 cycles of capecitabine plus docetaxel followed by 3 cycles of capecitabine, epirubicin, and cyclophosphamide.

after chemotherapy for a minimum of 5 years after random assignment, including physical examination with breast and abdominal ultrasound every 3 months, and mammogram and chest CT yearly. Patients without any component of the specific time-to-end point events were censored at their last follow-up.

Outcomes

The primary end point was DFS, defined as the time from random assignment to the first occurrence of any event (both in situ and invasive), including local relapse, distant metastasis, contralateral breast cancer, second primary cancer, or death as a result of any cause. Secondary end

points included recurrence-free survival (RFS; time from random assignment to date of diagnosis of invasive breast cancer recurrence or death), distant DFS (DDFS; time from random assignment to date of diagnosis of distant recurrence or death), OS (time from random assignment to death as a result of any cause), and safety. Quality of life was measured by Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) scale scores at baseline and after every cycle. Events were reviewed by an independent data monitoring committee (IDMC) every 6 months. Exploratory subgroup analyses were performed to investigate the association between baseline characteristics and treatment efficacy.

Statistical Analysis

With an estimated recruitment period of 2 years, we expected that the 5-year DFS rate would rise from 73% to 83% (hazard ratio [HR], 0.59) after a median follow-up of 5 years. Accordingly, 116 events were needed for a 2-sided type I error rate of 5% and a power of 80% to detect a significant difference between the 2 treatment groups. Assuming 10% loss to follow-up, 600 randomly assigned patients were required. The modified intention-to-treat (mITT) population included randomly assigned patients who received at least 1 dose of any study treatment. The per-protocol set (PPS) population included patients who received allocated interventions without major protocol violations. Survival data were assessed using the Kaplan-Meier method and compared using log-rank tests. HRs and corresponding 95% CIs were estimated using the Cox proportional hazards regression model. Subgroups were analyzed according to menstrual status, nodal status, T stage, TNM, tumor grading, and protein encoded by the *MKI67* gene. Because of a lower overall event rate than expected after all patients had been followed for at least 5 years, at the recommendation of the IDMC, the CBCSG010 steering committee agreed to analyze and report the final results with 98 events at the cutoff date of March 20, 2019.

All P values were 2-sided; $P \leq .05$ was considered significant. All statistical procedures were carried out using SAS 9.1.3 software (SAS Institute, Cary, NC).

RESULTS

Patients

Between June 4, 2012, and December 27, 2013, 636 patients with TNBC were screened at 35 centers in China; 26 patients did not meet the inclusion criteria. Of the 610 randomly assigned patients, 25 withdrew consent before starting treatment. The mITT population comprised 585 patients (control, 288; capecitabine, 297). Among them, 21 patients (control, 12; capecitabine, 9) had major protocol violations. The PPS population comprised 564 patients (control, 276; capecitabine, 288; Fig 1). Fifty-three patients were lost to follow-up. Baseline characteristics were relatively well balanced (Table 1). Most patients were premenopausal (56%) and underwent a mastectomy (77%) and axillary dissection (74%). Node-positive disease was reported in 34% of patients; 47% had T1 disease, and approximately half had grade 3 disease. The median time from surgery to chemotherapy was 17.5 days.

Efficacy Outcomes

At the analysis cutoff date (March 20, 2019), median follow-up was 67 months (interquartile range, 61-71 months). A total of 98 events (contralateral breast, second primary, distant or local relapse, and death) had occurred (control, 57 [19.8%]; capecitabine, 41 [13.8%]; Table 2). The 5-year DFS rates (primary end point) were 86.3% and 80.4% in the capecitabine and control groups, respectively (HR, 0.66; 95% CI, 0.44 to 0.99; $P = .044$ in favor of capecitabine). For secondary end points, treatment with capecitabine was associated with improvement in 5-year RFS (89.5%) compared with control (83.1%; HR, 0.59; 95% CI, 0.38 to 0.93; $P = .02$) and in 5-year DDFS (89.8% *v* 84.2%; HR, 0.63; 95% CI, 0.39 to 1.0; $P = .048$). There was no significant difference in OS between the 2 groups (93.3% *v* 90.7%; HR, 0.67; 95% CI, 0.37 to 1.22; $P = .19$). Figure 2 shows the Kaplan-Meier estimates for 5-year DFS, RFS, DDS, and OS. Appendix Figure A1 (online only) shows the Kaplan-Meier estimates for 5-year DFS in

TABLE 2. Number of Events (mITT population)

Event	T-FEC (n = 288)	XT-XEC (n = 297)
Any event (%)	57 (19.8)	41 (13.8)
Second primary	4	5
Contralateral breast	5	6
Local recurrence	18	7
Ipsilateral breast/chest	13	5
Regional lymph nodes	8	3
Distant recurrence	37	29
Liver	3	7
Lung	17	14
Bone	6	7
Other	27	14
Death[a] (%)	26 (9.0)	19 (6.4)

NOTE. First disease-free survival event and cumulative deaths are listed. More than 1 event could occur in a patient.

Abbreviations: mITT, modified intention to treat; T-FEC, 3 cycles of docetaxel followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide; XT-XEC, 3 cycles of capecitabine plus docetaxel followed by 3 cycles of capecitabine, epirubicin, and cyclophosphamide.

[a]Two deaths in the T-FEC group and one in the XT-XEC occurred without any disease-free survival event.

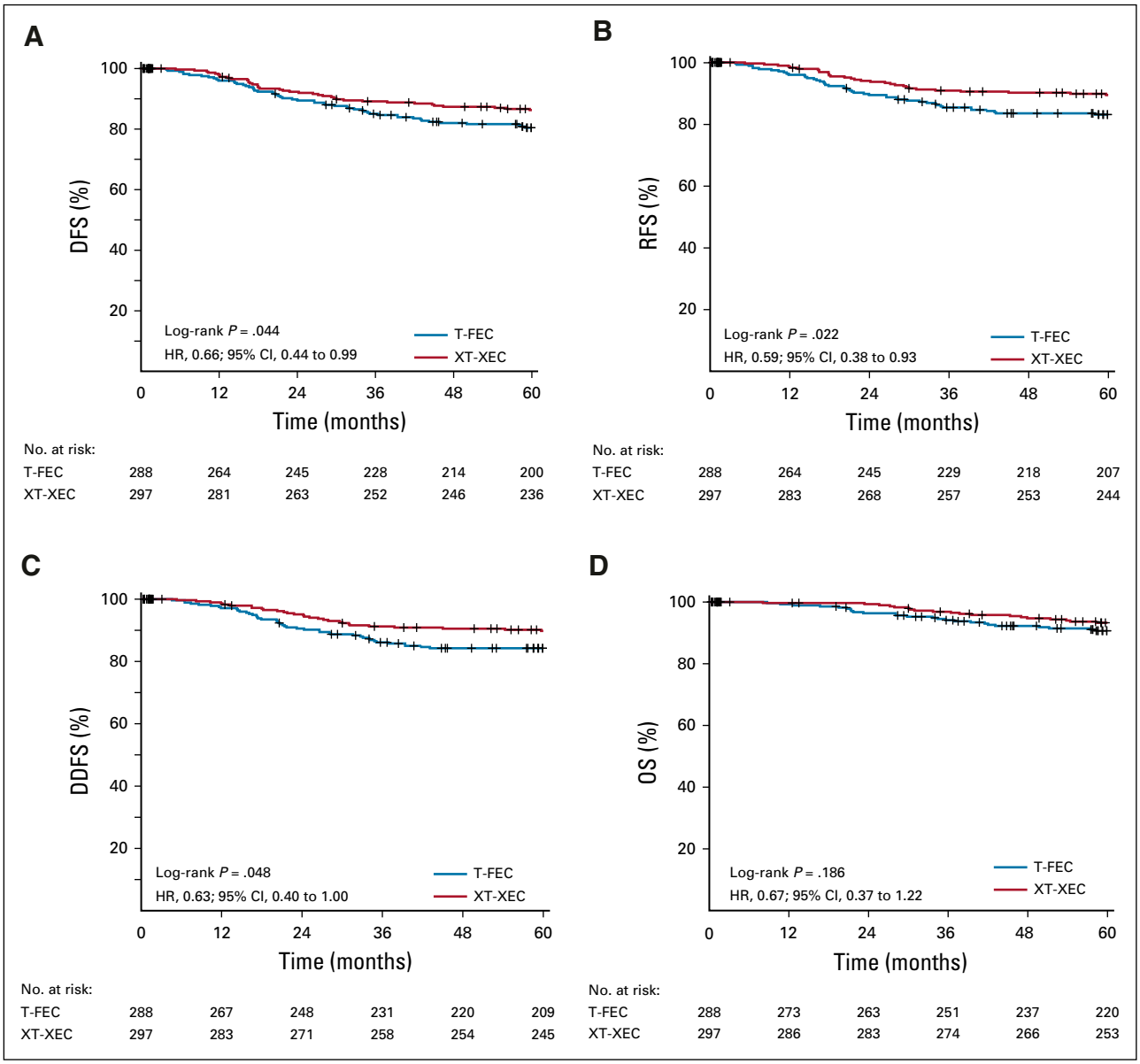

FIG 2. Kaplan-Meier estimates of 5-year survival (modified intention-to-treat population; n = 585). (A) Disease-free survival (DFS), (B) recurrence-free survival (RFS), (C) distant DFS (DDFS), and (D) overall survival (OS). HR, hazard ratio; T-FEC, 3 cycles of docetaxel followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide; XT-XEC, 3 cycles of capecitabine plus docetaxel followed by 3 cycles of capecitabine, epirubicin, and cyclophosphamide.

the PPS population. Capecitabine benefits for DFS were consistent across patient subgroups (Fig 3); treatment effect interactions were not significant for any of the subgroups considered.

Safety Outcomes

The safety profiles of the 2 regimens are listed in Table 3. There were no notable differences in the incidence of alopecia, nausea and vomiting, peripheral neuropathy, or fatigue between the 2 groups. The most common grade ≥ 3 hematologic toxicities were neutropenia (capecitabine, 136 [45.8%]; control, 118 [41.0%]) and febrile neutropenia (capecitabine, 50 [16.8%]; control, 46 [16.0%]). Patients who received capecitabine had a higher incidence (52.5%) of hand-foot syndrome (HFS), of which 8.4% was grade ≥ 3. More patients treated with capecitabine had grade ≥ 3 stomatitis (5.1% *v* 1.0% [control]). No patients died during chemotherapy.

Dose reductions of docetaxel and/or epirubicin were needed for 19 and 20 patients in the capecitabine and control groups, respectively. Overall, 113 patients (39.1%) had capecitabine dose reductions (cycle 1, 22.5%; cycle 2, 24.7%; cycle 3, 27.3%; cycle 4, 28.8%; cycle 5, 31.5%; cycle 6, 33.3%). Seven patients required a capecitabine

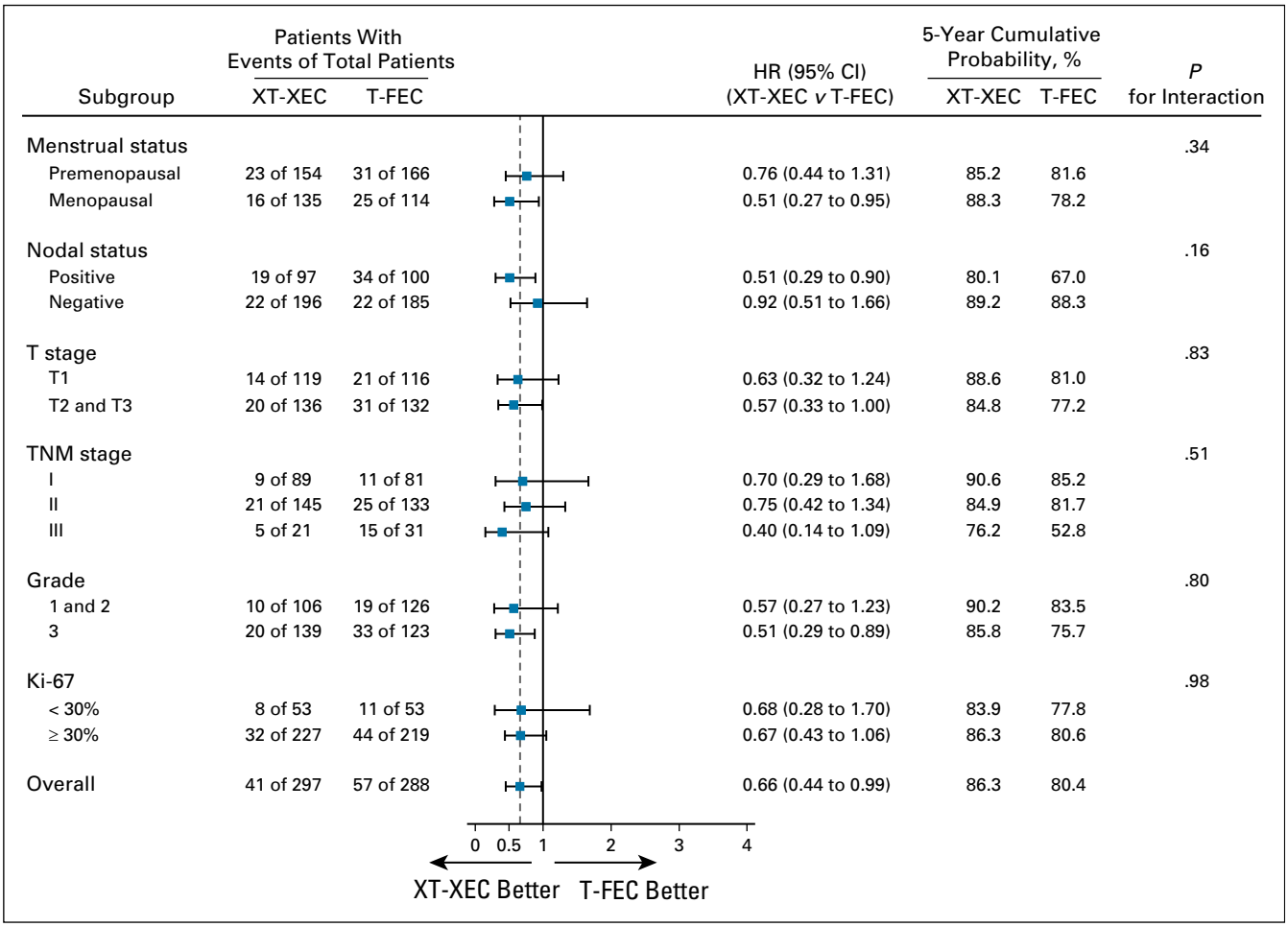

FIG 3. Results of exploratory subgroup analyses for disease-free survival. A forest plot shows the hazard ratios (HRs) and 95% CIs (horizontal lines) according to menstrual status, tumor size, nodal status, grade, and protein encoded by the *MKI67* gene (Ki-67) status. Data are from the log-rank test. Data are presented as number of patients with events of total number of patients. T-FEC, 3 cycles of docetaxel followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide; XT-XEC, 3 cycles of capecitabine plus docetaxel followed by 3 cycles of capecitabine, epirubicin, and cyclophosphamide.

dose reduction to ≤ 750 mg/m^2, and all others had a dose reduction to 900 mg/m^2 or 825 mg/m^2. A similar proportion of patients completed all 6 planned chemotherapy cycles (capecitabine, 252 [84.9%] of 297; control, 248 [86.1%] of 288). In the capecitabine group, the noncompletion rate was 9.4% (28 of 297) during XT and 14.5% (43 of 297) during XEC. In the control group, the noncompletion rate was 8.3% (24 of 288) during docetaxel and 12.5% (36 of 288) during FEC. No differences in quality of life by FACT-B were found between the 2 groups.

DISCUSSION

To our knowledge, the CBCSG010 study is the first randomized controlled trial to investigate the efficacy and safety of capecitabine in combination with taxane and anthracycline as adjuvant treatment specifically for patients with TNBC. Importantly, CBCSG010 met its primary end point. Capecitabine added to standard adjuvant chemotherapy regimen significantly improved the 5-year DFS, RFS, and DDFS rates and was well-tolerated.

Adjuvant taxane- and anthracycline-based chemotherapy is the standard of care after TNBC resection. The ECOG 1199[15] and SWOG S0221[16] studies reported that doxorubicin plus cyclophosphamide followed by paclitaxel yielded substantial benefits in patients with TNBC. EBCTCG analysis confirmed a moderate reduction in 10-year risk of recurrence and death with an increase in the dose intensity and density of adjuvant chemotherapy, especially for TNBC.[17] The IBCSG 22-00 study indicated that low-dose oral cyclophosphamide and methotrexate maintenance for 1 year reduced the risk of a DFS event, especially for node-positive TNBC.[18]

A meta-analysis (8 studies, 9,302 patients) showed that capecitabine plus standard chemotherapy significantly improved DFS in TNBC (HR, 0.72).[19] While the exact mechanism remains unclear, daily dosing of capecitabine may

TABLE 3. Summary of Adverse Events (mITT population)

	All Grades, No. (%)		Grade 3 or 4, No. (%)	
Event	**T-FEC (n = 288)**	**XT-XEC (n = 297)**	**T-FEC (n = 288)**	**XT-XEC (n = 297)**
All	282 (97.9)	289 (97.3)	238 (82.6)	241 (81.1)
Alopecia	253 (87.9)	254 (85.5)	205 (71.2)	206 (69.4)
Neutropenia	222 (77.1)	224 (75.4)	118 (41.0)	136 (45.8)
Febrile neutropenia	46 (16.0)	50 (16.8)	46 (16.0)	50 (16.8)
Thrombocytopenia	38 (13.2)	36 (12.1)	5 (1.7)	11 (3.7)
Increased ALT and/or AST	72 (25.0)	81 (27.3)	10 (3.5)	4 (1.4)
Stomatitis	113 (39.2)	110 (37.0)	3 (1.0)	15 (5.1)
Nausea	251 (87.2)	235 (79.1)	4 (1.4)	5 (1.7)
Vomiting	198 (68.8)	184 (62.0)	14 (4.9)	9 (3.0)
Diarrhea	52 (18.1)	46 (15.5)	3 (1.0)	3 (1.0)
Constipation	102 (35.4)	105 (35.4)	2 (0.7)	2 (0.7)
Peripheral neuropathy	106 (36.8)	121 (40.7)	1 (0.4)	1 (0.3)
Fatigue	227 (78.8)	237 (79.8)	2 (0.7)	5 (1.7)
Pain	122 (42.4)	112 (37.7)	3 (1.0)	9 (3.0)
Myalgia	134 (46.5)	130 (43.8)	5 (1.7)	5 (1.7)
Rash	40 (13.9)	49 (16.5)	4 (1.4)	1 (0.3)
Hand-foot syndrome	95 (33.0)	156 (52.5)	0 (0)	25 (8.4)

NOTE. Adverse events of all grades that occurred in ≥ 10% of patients are listed. Grade 3 or 4 adverse events are listed that occurred in ≥ 1% of patients.

Abbreviations: mITT, modified intention to treat; T-FEC, 3 cycles of docetaxel followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide; XT-XEC, 3 cycles of capecitabine plus docetaxel followed by 3 cycles of capecitabine, epirubicin, and cyclophosphamide.

intensify the chemotherapy regimen and increase cytotoxic exposure of tumor cells; alternatively, tumors with defective DNA repair mechanisms (frequent in TNBC) may be particularly sensitive to capecitabine (DNA synthesis inhibitor).[20] However, in the GeparQuattro and NSABP B40 trials, the addition of capecitabine to neoadjuvant therapy did not improve the rates of pathologic complete response.[21,22]

Several randomized clinical trials have evaluated capecitabine as adjuvant treatment of early breast cancer. While these studies varied in patient population, capecitabine administration, and number of treatment cycles,[6,8,11-14] several suggested a possible efficacy benefit with capecitabine. Subgroup analysis in patients with TNBC (USON 01062) demonstrated that 4 cycles of capecitabine (concomitantly with docetaxel) suggest benefit in OS from the addition of capecitabine.[9] Exploratory analysis in the FinXX trial showed that 6 cycles of additional capecitabine were associated with longer RFS.[22] CREATE-X reported that 8 cycles of adjuvant capecitabine monotherapy prolonged DFS and OS (HER2-negative residual invasive disease after standard neoadjuvant therapy), particularly in patients with TNBC.[6] In the CIBOMA/GEICAM 2003-11 study, 8 cycles of capecitabine after standard adjuvant chemotherapy did not improve DFS; however, patients with a nonbasal-like phenotype showed DFS improvement with capecitabine.[14]

Clinical data that directly evaluate capecitabine concomitantly used with taxane and anthracycline as adjuvant treatment specifically for TNBC are lacking; our study showed that the 5-year DFS rate was significantly higher for capecitabine than control treatment (86.3% *v* 80.4%). Treatment effect interactions were not significant for any of the subgroups considered, but the benefit of capecitabine in patients with high-risk disease was notable; for example, in node-positive disease, the HR was 0.51 (95% CI, 0.29 to 0.90; Fig 3). The 5-year DFS rate for T-FEC was higher than expected, which might be due to the current study including a substantial number of patients with lower-risk disease (47% T1 and 65% N0), and outcomes for the control arm align with previously reported control data,[10,23,24] which confirm the reliability and add to the credibility of our findings.

We selected our treatment regimen for optimal capecitabine treatment benefit without undue increase in toxicity. Although FEC followed by docetaxel is a standard adjuvant regimen,[24] the increased incidence of febrile neutropenia reported with higher doses of docetaxel has hindered its application.[25] Furthermore, time to progression is similar between 75 mg/m^2 and 100 mg/m^2 docetaxel in advanced breast cancer.[26] Hence, we set our starting dose at 75 mg/m^2 for both docetaxel and epirubicin in the control arm, and

it might be an alternative/noninferior strategy to initiating chemotherapy with docetaxel.[27]

A previous study that investigated capecitabine (1,250 mg/m^2 twice daily plus docetaxel) in advanced disease reported that 80% of patients required dose reductions, with capecitabine commonly reduced to 950 mg/m^2.[28] In consideration of the better tolerance of capecitabine in East Asian populations,[29] the starting dose of capecitabine in our trial was 1,000 mg/m^2. However, capecitabine dose reduction rates increased through the 6 treatment cycles (22.4% [cycle 1] to 33.3% [cycle 6]); overall, 39.1% patients had a dose reduction, although the majority required reduction to 900 or 825 mg/m^2. Approximately one half of patients (52.53%) who received capecitabine reported HFS of any grade; 8.42% had grade ≥ 3 HFS. The capecitabine regimen in the FinXX study was associated with a higher incidence of HFS (80% all grades, 11% grade ≥ 3),[8] while in monotherapy trials, rates were 73.4% (CREATE-X)[6] and 70.2% (CIBOMA/GEICAM 2003-11).[14] In our study, 85% of patients completed all 6 cycles of chemotherapy, in line with completion rates reported for the CIBOMA/GEICAM 2003-11 study (85.2%; median dose intensity, 86.3%)[14] and the capecitabine group in the FinXX study (76%).[8] More grade ≥ 3 stomatitis events were observed with capecitabine compared with control (5.1% *v* 1.0%), while grade ≥ 3 neutropenia and febrile neutropenia were similar between groups. No other substantial differences between the 2 arms or new safety concerns were reported.

Our study has several limitations. First, the College of American Pathologists guidelines for hormone receptor positivity cutoff values were modified after our trial had been designed; thus, our study might have a different definition of TNBC. However, ER 1%-9% stained is considered equivocal, and low ER-positive and ER-negative patients have similar survival rates and may not benefit from endocrine therapy.[30] Only 10 patients in our study (5/group) had ER/PR 1%-9% disease. Second, FEC followed by docetaxel, with each given every 3 weeks, a preferred regimen when the trial was designed, is no longer a primary recommendation. Preferred regimens now include dose-dense sequential anthracycline and taxane therapy. The control regimen, every-3-week dosing, and lower doses of docetaxel and epirubicin used in this trial may have amplified the benefit from capecitabine. Third, because CBCSG010 was investigator initiated, central pathology readings to confirm triple-negative subtype or central assessment of recurrence or related adverse events could not be performed because of financial limitations. Finally, the current study was limited to Chinese patients, although the results of our trial are expected to be applicable to patients in Western countries with dose reductions as indicated.

In conclusion, the results of our study indicate that capecitabine concomitantly used with docetaxel and epirubicin (XT-XEC) is an alternative adjuvant regimen for TNBC, with clinically meaningful improvement in DFS and modest toxicity. These data support the subset analysis of the CREATE-X trial as well as the recent meta-analysis of capecitabine for early-stage TNBC.[31]

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Manuscript writing: All authors
Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Adjuvant Capecitabine With Docetaxel and Cyclophosphamide Plus Epirubicin for Triple-Negative Breast Cancer (CBCSG010): An Open-Label, Randomized, Multicenter, Phase III Trial

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APPENDIX

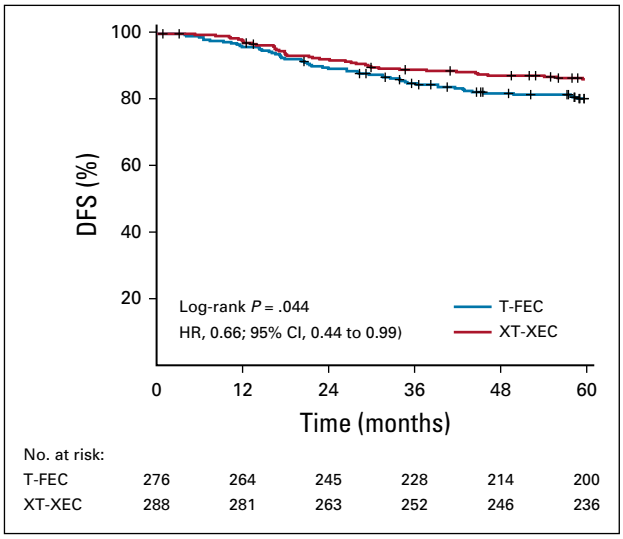

FIG A1. Kaplan-Meier estimates of 5-year disease-free survival (DFS) per-protocol set population (n = 564). HR, hazard ratio; T-FEC, 3 cycles of docetaxel followed by 3 cycles of fluorouracil, epirubicin, and cyclophosphamide; XT-XEC, 3 cycles of capecitabine plus docetaxel followed by 3 cycles of capecitabine, epirubicin, and cyclophosphamide.

TABLE A1. Recruitment by Institution

Institution	No. of Randomly Assigned Patients
Fudan University Shanghai Cancer Center	112
The Third Affiliated Hospital of Harbin Medical University	30
Jilin Cancer Hospital and Institute	34
Southwest Hospital	31
Gansu Cancer Hospital	31
The Fourth Clinical Medical College of Hebei Medical University	26
The First Affiliated Hospital, Zhejiang University	23
Changhai Hospital of Shanghai	22
Cancer Hospital of Shantou Medical College	20
The Third Affiliated Hospital of Nanchang University	14
The International Peace Maternity and Child Health Hospital of China Welfare Institute	20
Henan Cancer Hospital Affiliated to Zhengzhou University	20
The Second Affiliated Hospital of Medical College of Xi'An Jiaotong University	20
The First Affiliated Hospital of Chongqing Medical University	16
Shanxi Cancer Hospital	17
Eastern Hospital of Suzhou Municipal Hospital	16
Guangdong Provincial Hospital of Traditional Chinese Medicine	16
Beijing Friendship Hospital	8
Jiangsu Cancer Hospital	13
The First Hospital of Wenzhou Medical College	12
The First Hospital of Jilin University	13
The Second Affiliated Hospital of Soochow University	10
Tianjin Medical University Cancer Institute and Hospital	10
The General Hospital of the People's Liberation Army	7
Zhongshan Hospital Fudan University	7
Jiangsu Province Hospital	8
The Second Affiliated Hospital of Harbin Medical University	6
The First Hospital of China Medical University	5
The Second Affiliated Hospital of Zhongshan University	4
Xinjiang Cancer Hospital	3
Shanghai Sixth People's Hospital	2
Cancer Institute and Hospital Chinese Academy of Medical Sciences	3
Shanghai First Maternity and Infant Hospital Corporation	3
Shanghai General Hospital	2
Peking Union Medical College Hospital	1