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2 **This supplement contains the following items:**

3 1. Original protocol (Page 2 – 44), final protocol (Page 45 –89),
4 amendment list (Page 90– 94).

5 2. Original statistical analysis plan (Page 95–106), final statistical
6 analysis plan (Page 107 – 118), amendment list (Page 119– 120).

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9

10 **A multicenter, phase III randomized study**
11 **of metronomic capecitabine maintenance**
12 **after standard treatment in patients with**
13 **operable triple–negative breast cancer**

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21
22 Principle Investigators

23 Zhong Yu YUAN, M.D. and Xi WANG, M.D.

24 Sun Yat–sen University Cancer Center

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92 **1. SYNOPSIS OF THE STUDY**

93 **1.1 Objectives**

94 This study is designed to compare the efficacy (disease-free
95 survival, DFS) and safety of metronomic capecitabine maintenance
96 for one year with observation after standard local and systemic
97 treatment in patients with operable triple negative breast cancer
98 (TNBC).

99

100 **1.2 Study Design**

101 This study is to be a multi-center, phase III, randomized controlled
102 trial. The study will include the following two treatment arms: 684
103 subjects will be randomized in a 1:1 fashion (342 in each arm) to
104 receive either metronomic capecitabine maintenance (experimental
105 arm) or observation (control arm) until objective disease recurrence,
106 protocol violation, intolerable toxicity, death, or withdrawal of
107 consent. Subjects will be stratified by lymph node status (positive or
108 negative). Subjects discontinuing from the active treatment phase
109 will enter the follow-up phase during which survival information will
110 be collected.

111

112 **1.3 Main Inclusion/ Exclusion Criteria**

113 **Main Inclusion Criteria:**

- 114 1) Female, aged ≥ 18 years old and ≤ 75 years.
- 115 2) Histologically confirmed invasive ductal carcinoma, no
116 specific type (NOS).
- 117 3) Pathologic stage $T_{1c-3}N_{0-2}M_0$.
- 118 4) estrogen receptor (ER)–/progesterone receptor
119 (PR)–negative and human epidermal growth factor receptor 2
120 (HER2) negative (ER– and PR–negative is defined by lower
121 than 1% immunohistochemistry staining; HER2–negative is
122 defined by IHC score 0,1 or 2 with HER2–fluorescence in situ
123 hybridization negative).
- 124 5) Have completed adequate surgery, neo–/adjuvant
125 chemotherapy and radiation therapy (if indicated).
- 126 6) Available results for contralateral mammography, chest X–ray,
127 abdominal ultrasonography, ^{99m}Tc –bone scanning (required
128 for patients with stage II b–IIIa disease) within 3 months
129 before randomization.
- 130 7) Adequate organ function including bone marrow, renal
131 function, hepatic function, et al.
- 132 8) Compliance with the study protocol.
- 133 9) Have provided written and signed informed consent.

134 **Main Exclusion Criteria:**

- 135 1) Patients with T4, including inflammatory carcinomas.
- 136 2) Patients with N3.
- 137 3) Previously diagnosed with other malignancies (not including
138 cured cervical carcinoma *in situ*, cutaneous squamous cell
139 carcinoma, and cutaneous basal cell carcinoma).
- 140 4) History of invasive breast cancer.
- 141 5) Patients who are receiving or will receive other biological
142 agents or immunotherapy.
- 143 6) Severe dysfunction of the heart, lung, liver, or kidney.
- 144 7) Patients with malabsorption syndrome diseases impairing GI
145 function, resection of stomach or small intestine, or who are
146 unable to swallow capecitabine tablets.
- 147 8) Patients who are pregnant or who are unwilling to use
148 contraception during the study period.
- 149 9) Known intolerance to capecitabine or allergy to its excipients.

150

151 **1.4 Investigational Drug and Administration**

152 Capecitabine group (experimental arm): Capecitabine will be
153 administered at a dose of 650 mg/m² orally twice daily (ie, total
154 daily dose = 1300 mg/m²) continuous for one year, starting within 2

155 weeks of randomization.

156

157 **1.5 Study Endpoints**

158 The primary efficacy parameter, DFS, will be analyzed in the full
159 analysis set (FAS) population.

160 The secondary efficacy parameters, including overall survival (OS),
161 disease-free survival (DDFS), and locoregional recurrence-free
162 survival (LRFS), will be analyzed in the FAS populations.

163 Safety and tolerability will be assessed using reporting of adverse
164 events (AEs), graded according to NCI-CTC (version 4.0).

165

166 **2. BACKGROUND**

167 Breast cancer comprises a group of diseases that show genetic
168 heterogeneity and biological diversity [1, 2], which could be
169 classified into five subtypes distinguished by their gene expression
170 profiles [3, 4], including luminal A, luminal B, HER2+, normal breast,
171 and basal-like [5]. The genotype of breast cancer is established
172 using complicated gene analysis, which unsuitable for formalin-
173 fixed specimens. Immunohistochemistry-based classification
174 (using ER, PR, HER2, and KI-67) is more widely used in clinical
175 practice [6-8], revealing a group of breast cancers characterized by

176 negative expression of ER, PR, and HER2, termed as
177 “triple–negative” breast cancer (TNBC) [9]. Basal–like breast
178 cancer and TNBC are differently defined, and might overlap with
179 each other. The majority of basal–like breast cancers are
180 triple–negative. Therefore, TNBC is used as an alternative
181 histopathological definition of basal–like breast cancer in clinical
182 practice, as well as in the inclusion criteria of most clinical trials.

183 TNBC comprises approximately 15%–25% of breast cancer in
184 women [10–14], and is considered an independent
185 clinicopathological subtype, with special clinical, pathological, and
186 molecular genetic characteristics. In terms of clinical characteristics,
187 TNBC is more common among young patients, with a high risk of
188 early (within 2 years after surgery) recurrence, distant metastasis,
189 and death [15–19]. TNBC has a shorter median survival after first
190 recurrence than other types of breast cancer, with most deaths
191 occurring within the first 5 years [10]. Visceral metastasis
192 (especially in the lung and brain) is more frequent than bone
193 metastasis, which might be one of the major contributors to the
194 poor prognosis of TNBC. Pathologically, TNBC is associated with
195 the presence of high histological grade, invasive ductal carcinoma,
196 a high proliferation index, and high expression of p53 and EGFR

197 [20-24]. Molecularly, gene expression profiles of TNBC have
198 revealed its high molecular homology [1, 4, 9].

199 For hormone receptor positive breast cancer, anti-estrogen
200 therapies have significantly reduced recurrence and death [25]. For
201 HER2+ breast cancers, anti-HER2 therapies (e.g., trastuzumab)
202 have also significantly reduced recurrence [26]. Currently, there are
203 few targeted therapies for TNBC, and chemotherapy is the only
204 effective strategy to reduce recurrence, which is another reason for
205 the poor prognosis of TNBC. Endocrine therapy for HR+ breast
206 cancer and anti-HER2 therapy for HER2+ breast cancer are all
207 long-term maintenance therapies after standard treatment [27].
208 Therefore, we propose that a long-term effective maintenance
209 treatment might significantly improve the outcome in patients with
210 early TNBC.

211 Most TNBC is more chemosensitive than HR+ breast cancer.
212 Traditional regimens tend to achieve a better response in patients
213 with TNBC; however, the duration of the response usually does not
214 last long. TNBC is still characterized with dismal DFS, PFS, and OS
215 [14, 28, 29]. Therefore, the aggressive biological behavior and the
216 lack of effective risk-reducing treatment have both contributed to
217 the poor prognosis of TNBC.

218 Metronomic chemotherapy is a relatively novel regimen using
219 continuous and low-dose chemotherapeutic agents with short or no
220 intervals. Browder and Klement, et al. reported the anti-tumor
221 activity of metronomic chemotherapy for the first time. The novel
222 pattern of dosage has a different mechanism compared with
223 conventional dosage regimens by exerting anti-angiogenesis
224 effects [30, 31]. In addition, metronomic chemotherapy also
225 produces antitumor effects by upregulating anti-tumor immune
226 response in the host [32]. Metronomic chemotherapy had achieved
227 good efficacy with low toxicity in advanced breast cancer [33–36].
228 Considering that angiogenesis and immune surveillance escape
229 are major mechanisms of tumor metastasis, metronomic
230 chemotherapy might be a potential therapeutic option for operable
231 TNBC with high risk of distant metastasis.

232 Capecitabine is an effective agent with good tolerability and is
233 convenient for breast cancer [37–41], which makes it an optimal
234 choice for long-term metronomic use. The most common adverse
235 events of capecitabine include hand-foot syndrome (HFS),
236 diarrhea, and stomatitis, which are non-life threatening and can be
237 managed using education without impairing efficacy [40]. Two recent
238 phase III trials (FinXX and USO), which enrolled all subtypes of

239 breast cancer, have shown by subgroup analysis that the addition
240 of capecitabine to standard treatment significantly reduced the risk
241 of relapse for TNBC, especially the risk of distant metastases.

242 In summary, high rate of distant metastases and lack of effective
243 treatment are the major reasons for the poor prognosis of TNBC.
244 As a novel model of treatment, metronomic chemotherapy might be
245 effective for TNBC by targeting angiogenesis and immune escape.
246 The good efficacy and tolerability of capecitabine make it an
247 optimal drug for metronomic chemotherapy. Clinical studies have
248 also demonstrated a reduced risk of relapse in patients with TNBC
249 receiving capecitabine in addition to standard treatment. This study
250 aims to evaluate the efficacy and safety of capecitabine
251 metronomic chemotherapy after standard treatment in patients with
252 early TNBC.

253

254 **3. OBJECTIVES**

255 **3.1 Primary Endpoint**

256 To compare the DFS in patients who are randomized at enrollment
257 to treatment with metronomic capecitabine maintenance
258 (experimental arm) with in observation arm (control arm).

259 DFS is defined as time from randomization to the first of any of

260 the following events:

- 261 1) Relapse of invasive breast cancer in the ipsilateral chest wall
262 and regional lymph nodes
- 263 2) Distant metastases (histologically confirmed or clinically
264 diagnosed)
- 265 3) Breast cancer related, non–breast cancer related or unknown
266 deaths
- 267 4) Contralateral invasive breast cancer.

268

269 **3.2 Secondary Endpoints**

270 To compare the overall survival (OS), distant disease–free survival
271 (DDFS), locoregional recurrence–free survival (LRFS) and safety
272 between the experimental arm and observation arm. In addition,
273 exploratory analysis will include biomarkers that predict the efficacy
274 and toxicity of capecitabine.

275 OS is defined as time from randomization to death caused by any
276 reason.

277 DDFS is defined as time from randomization to the first
278 occurrence of any of the following events: Distant metastases,
279 death caused by any reason, and contralateral invasive breast
280 cancer (NEJM 2005; 353:2747).

281 LRFS is defined as time from randomization to locoregional
282 invasive recurrence or death.

283 Safety: The frequency and severity degree of AEs were judged
284 based on NCI CTC V4.0.

285

286 **4. STUDY DESIGN**

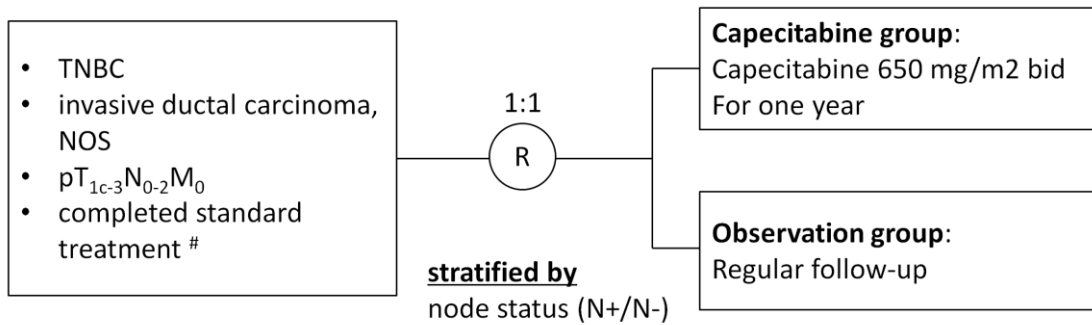
287 **4.1 Summary of Design**

288 This is a multi-center, phase III, randomized controlled study of
289 metronomic capecitabine maintenance versus observation.

290 Approximately 684 subjects with TNBC will be randomized in a
291 1:1 fashion (342 in each arm) to receive treatment with either:
292 Metronomic capecitabine maintenance (experimental arm); or
293 observation (control arm) until objective disease recurrence,
294 protocol violation, intolerable toxicity, death, or withdrawal of
295 consent. Subjects will be stratified by lymph node status (positive or
296 negative).

297 Subjects will participate in the study within 4 weeks after
298 completion of standard curative treatment including surgery,
299 neo-/adjuvant chemotherapy and radiotherapy. Patients in the two
300 arms will be follow-up every 3 months using physical, laboratory,
301 and radiological examinations according to the study protocol. This

302 study will be completed in approximately 72 months including 48
 303 months for accrual and approximately 36 months of follow-up
 304 survival for the last subject enrolled. An overview of the study
 305 design is depicted below:



standard treatment including surgery, (neo)adjuvant chemotherapy and radiation therapy (if indicated)

306
307

308 **Recommended chemotherapy regimens:** According to the
 309 NCCN guidelines version 2010, recommended chemotherapy
 310 regimens and dosage are listed in Table 1. Dosages adjustment
 311 according to a patient's toleration will be allowed with no more than
 312 25% reduction of standard dose. A minimum of four cycles of
 313 neo-/adjuvant chemotherapy should be delivered. For
 314 node-positive patients, chemotherapy regimens containing
 315 anthracyclines and taxanes are recommended.

316 Recommended indications for post-operative radiotherapy
 317 include: Involvement of \geq four axillary nodes, primary tumor \geq 5 cm
 318 in size, post breast conserving surgery, positive surgical margins,

319 involvement of internal mammary nodes (in selected cases), and
 320 involvement of 1–3 axillary nodes (in selected cases).

321 **Table 1** Recommended chemotherapy regimen and dosage

Regimens(drugs)		Dose(mg/m ²)
CMF	cyclophosphamide/methotrexate/fluorouracil	500/ 40/ 600
AC	doxorubicin/cyclophosphamide	60/ 600
EC	epirubicin/cyclophosphamide	75–90/ 600
FAC	5–fluorouracil/doxorubicin/cyclophosphamide	500/ 50/ 500
FEC	5–fluorouracil/epirubicin/cyclophosphamide	500/ 75–90/ 500
TAC	docetaxel/doxorubicin/cyclophosphamide	75/ 50/ 500
TEC	docetaxel/epirubicin/cyclophosphamide	75/ 75/ 500
AC–P	doxorubicin/cyclophosphamide→paclitaxel weekly or every 3–weeks	60/ 600→80 (qw), 175 (q3w)
EC–P	epirubicin/cyclophosphamide→paclitaxel weekly or every 3–weeks	90/ 600→80 (qw), 175 (q3w)
AC–wP	doxorubicin/cyclophosphamide→paclitaxel (Dose–dense)	60/ 600→175 (q2w)
FEC–T	5–fluorouracil/epirubicin/cyclophosphamide→docetaxel, every 3 weeks	500/ 75–90/ 500→75
TC	docetaxel/cyclophosphamide	75/ 600

322

323 4.2 Randomization

324 On verification of the inclusion and exclusion criteria, eligible
 325 patients will be randomized using the method of stratified permuted
 326 blocks to receive metronomic capecitabine maintenance or
 327 observation in a 1:1 ratio. Patients will be stratified according to
 328 lymph node status (negative vs. positive). A computerized number
 329 generator in the SAS software (version 8.01) generate a
 330 randomization table, the results of which were placed in
 331 sequentially numbered opaque envelopes and remained concealed

332 until after enrollment.

333 Central randomization will be performed. When a suitable patient
334 is to be enrolled into the study, the Investigator site will contact
335 principal investigator (PI) site, and will be informed over the
336 telephone at the time of individual patient enrollment what the
337 treatment allocation is, and to which treatment arm the patient has
338 been randomized. This is a multicenter study to be conducted at
339 approximately 15 study sites.

340

341 **4.3 Capecitabine Administration**

342 **4.3.1 Initiating Dose**

343 The approved dose of capecitabine was 1250 mg/m² bid, days
344 1–14 every 21 days. However, the dose of capecitabine for
345 metronomic chemotherapy is uncertain, particularly in the adjuvant
346 setting. Several studies suggested that capecitabine at 650 mg/m²
347 bid, continuously for one year in metastatic breast cancer had lower
348 toxicity and was well tolerated [42–44]. The initiate dose of
349 capecitabine was 650 mg/m² bid, continuously for one year.

350 Body surface area is calculated from height and body weight.
351 Given that the height and weight of Chinese woman are 150–180
352 cm and 40–80 kg, respectively, their body surface area lie between

353 1.30 m² and 2.0 m². Combining the availability of capecitabine in
354 China with the convenience of patients, the daily actual dose will be
355 decided upon by using the **Table 2**.

356 **Table 2 The daily dose of capecitabine**

357

Body surface area (m ²)	Total Daily Dose (mg)	Morning dose (mg)	Evening dose (mg)
1.30–1.32	1690–1716	1000	500
1.33–1.71	1729–2223	1000	1000
1.72–2.0	2236–2600	1500	1000

358

359 **4.3.2 Dose Adjustment**

360 The most common AEs of capecitabine is HFS, and grading of HFS
361 is listed in **Table 3**. Studies suggested that almost all AEs could
362 improve after dose modification [45]. Dose adjustment of
363 capecitabine in patients who experience HFS is listed in **Table 4**.
364 Note, because of lower dose in patients with body surface areas
365 1.3–1.32 m², only one dose reduction of capecitabine is allowed,
366 from 1500 mg to 1000mg (morning 500mg, evening 500mg). In
367 addition, once a dose has been reduced for a subject, all
368 subsequent doses should be administered at that dose, unless
369 further dose reduction is required. Dose reescalation is not
370 permitted. If dosage delay occurs because of AEs, whether to
371 continue treatment should be determined by the investigator by

372 balancing the benefit and risk on an individual basis. Regardless of
 373 the cause of the delay, patients who discontinue dosage for more
 374 than 4 weeks should terminate treatment and withdraw from the
 375 trial.

376 **Table 3 Grading of HFS Caused by Capecitabine**

Grade	Manifestation
1	Numbness, tingling sensation, erythema of hands and/or feet that cause painless swelling or discomfort without affecting daily activities
2	Painful erythema or swelling of hands and/or feet that affect daily activities
3	Wet desquamation, ulceration, blistering, severe pain of hands and/or feet, and/or unable to work or perform daily activities

377
 378
 379

Table 4 Dose Adjustment of Capecitabine

Grade	Dose modification of capecitabine
1	Dose modifications are not recommended
2	<ul style="list-style-type: none"> –First appearance: Interrupt therapy until resolved to grade 0 or 1 and maintain the dose level for the next treatment at 100% –Second appearance: Interrupt therapy until resolved to grade 0 or 1 and maintain the dose level for the next treatment at 75% –Third appearance: Interrupt therapy until resolved to grade 0 or 1 and maintain the dose level for the next treatment at 50% –Fourth appearance: Discontinue therapy permanently
3	<ul style="list-style-type: none"> –First appearance: Interrupt therapy until resolved to grade 0 or 1 and begin the next cycle at 75% of the starting dose –Second appearance: Interrupt therapy until resolved to grade 0 or 1 and begin the next cycle at 50% of the starting dose –Third appearance: Discontinue therapy permanently
4	First appearance: Discontinue therapy permanently, or if the physician

	deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0 or 1 and begin the next cycle at 50% of the starting dose
--	--

380

381 **4.3.3 Concomitant and Prophylactic Medication**

382 In addition to HFS, the other common toxicities of capecitabine are
383 diarrhea and stomatitis. Symptom-relieving treatment can be given
384 by investigators according to clinical need and should be recorded.
385 Dose adjustment is not required for patients with mild to moderate
386 hepatic impairment. Currently there are no data on the
387 pharmacokinetics of capecitabine in patients with renal dysfunction
388 (as evaluated by serum creatinine levels).

389 Mild myelosuppression related to capecitabine and the
390 predominance of its active metabolic enzymes inside tumor cells
391 mean that, hematologic toxicities of grade ≤ 2 can be managed
392 according to clinical routine without discontinuation of capecitabine.
393 For patients experiencing hematologic toxicities of grade ≥ 3 ,
394 capecitabine should be interrupted until resolved to grade 0.
395 Treatment should be terminated if dosage interruption occurs for
396 more than 4 weeks. Treatment should be terminated if patients
397 experience two episodes of grade ≥ 3 hematological toxicities
398 consecutively, with any episode resulting in drug discontinuation for
399 more than 2 weeks. Patient should be followed-up after termination

400 of therapy and toxicities and prognosis should be recorded.

401

402 **5. SELECTION OF SUBJECTS**

403 **5.1 Enrollment**

404 All patients meeting the inclusion criteria must be provided with
405 detailed information about this study and written informed consent
406 for participation must be obtained. The patients will then be
407 randomly assigned into the observation arm or capecitabine arm
408 using a random number table, and the assignment will be recorded
409 on the case report form (CRF) by investigators. Analysis will be
410 stratified by lymph node status (N0 or N+).

411

412 **5.2 Inclusion Criteria**

413 Patients must fulfill **ALL** of the following criteria to be eligible for
414 study
415 enrollment and randomization.

- 416 1) Female, aged ≥ 18 years old and ≤ 75 years old.
- 417 2) Histologically confirmed invasive ductal carcinoma, no
418 specific type (NOS).
- 419 3) Pathologic stage $T_{1c-3}N_{0-2}M_0$.
- 420 4) ER-, PR-, and HER2-negative (ER- and PR-negative is

421 defined by lower than 1% immunohistochemistry (IHC)
422 staining; HER2 negative is define by an IHC score of 0, 1 or 2,
423 with HER2–fluorescence *in situ* hybridization negative).

424 5) Have completed adequate surgery, neo-/adjuvant
425 chemotherapy and radiation therapy (if indicated).

426 6) Available results of contralateral mammography, chest X–ray,
427 abdominal ultrasonography, and ^{99m}Tc–bone scanning within 3
428 months before randomization.

429 7) Adequate organ function:

430 a) Bone marrow: ANC $\geq 1.5 \times 10^9/L$; platelet count \geq
431 $100 \times 10^9/L$; hemoglobin ≥ 10 g/dL

432 b) Renal function: Serum creatinine $\leq 1.5 \times ULN$ by local
433 laboratory

434 c) Hepatic function: Total bilirubin $\leq 1.5 \times ULN$; AST \leq
435 $1.5 \times ULN$, ALT $\leq 1.5 \times ULN$

436 8) Compliance with study protocol.

437 9) Providing written and signed informed consent.

438

439 **5.3 Exclusion Criteria**

440 Patients meeting **ANY** of the following criteria are not eligible for
441 study enrollment and randomization.

- 442 1) Patients with T4, including inflammatory carcinomas.
- 443 2) Patients with N3.
- 444 3) Previously diagnosed other malignancies (not including cured
445 cervical carcinoma in situ, cutaneous squamous cell
446 carcinoma, and cutaneous basal cell carcinoma).
- 447 4) History of invasive breast cancer.
- 448 5) Patients who are receiving or will receive other biological
449 agents or immunotherapy.
- 450 6) Severe dysfunction of the heart, lung, liver, or kidney.
- 451 7) Patients with malabsorption syndrome diseases impairing GI
452 function, resection of stomach or small intestine, or unable to
453 swallow capecitabine tablets.
- 454 8) Patient who are pregnant or who are unwilling to use
455 contraception during the study period.
- 456 9) Known intolerance to capecitabine or allergy to its excipients.

457

458 **5.4 Discontinuation Criteria**

- 459 1) Recurrence of breast cancer.
- 460 2) Development for serious advent event develops.
- 461 3) Patients desire to withdraw from the study.
- 462 4) Patients are unable to receive treatment or follow-up

463 according to the study protocol.

464 5) Patients receive other anti-tumor treatment or other treatment
465 that might affect the study results without the consent of the
466 investigators.

467 6) Dosage discontinuation for more than 28 days.

468

469 **6. STUDY PROTOCOL**

470 **6.1 Study Drug:**

471 Capecitabine (Xeloda[®], Roche, Basel, Switzerland), 500mg per
472 tablet. The treatment schedule is described in section 4.3.

473

474 **6.2 Assessment and Follow-up**

475 The schedule of assessment during treatment and follow-up
476 are showed in Appendix 1.

477

478 **6.2.1 Baseline Assessment**

479 Baseline assessment should complete within 1 week before
480 enrollment).

481 ✓ Screening form. Patients who meet all inclusion criteria and
482 do not meet any exclusion criteria are eligible for this study.
483 Investigators must complete a screening form at baseline.

- 484 ✓ Medical history and clinical examination. Medical history,
485 including risk factors for cardiac disease and their medical
486 history of nervous system diseases must be collected before
487 enrollment.
- 488 ✓ Complete blood count, hepatic function (including AST, ALT,
489 T-Bil, D-Bil, TP, and ALB), renal function (including BUN
490 and Cr), serum electrolytes (including K⁺ and Ca²⁺), serum
491 LDH, AKP, and blood glucose.
- 492 ✓ Electrocardiogram and echocardiogram;
- 493 ✓ Serum CEA and CA153;
- 494 ✓ Imaging studies including chest X-ray, and abdominal
495 ultrasonography. A bone ECT scan is recommended for
496 patients with disease of stage ≥ IIb, unexplained bone pain,
497 or elevated serum ALP
- 498 ✓ 10 mL of peripheral blood will be collected for biomarker
499 analysis.

500

501 **6.2.2 Assessment during Treatment (repeated every 3 months)**

502 Assessment during Treatment are to repeat every 3 monthsS.

- 503 ✓ Physical examination and vital signs;
- 504 ✓ Complete blood count, hepatic function, and renal function;

- 505 ✓ Serum CEA and CA153;
- 506 ✓ Electrocardiogram;
- 507 ✓ Abdominal ultrasonography.

508

509 **6.2.3 Assessment during Follow-up**

510 Several randomized studies have shown that regular examination
511 comprising bone scans, liver US, chest X-rays, and blood tests
512 could not improve the survival and quality of life (QoL) of patients,
513 compared with routine physical examination [46, 47]. Therefore,
514 every 3 months during follow-up, physical examination and
515 mammography are required for asymptomatic patients in both arms.
516 However, this is the minimum requirement specified by the protocol,
517 and investigators are allowed to perform additional evaluations
518 according to the individual situation of the patients.

519

520 **6.2.4 Follow-up**

521 Follow-up of patients in both arms will be initiated after
522 randomization and will be repeated every 3 months (\pm 28 days)
523 during the first 2 years after randomization. Patients in the
524 capecitabine arm are allowed to take medicine at home but must
525 return to the study site every 3 months (\pm 28 days) for follow-up.

526 Follow-up will be repeated every 6 months (\pm 28 days) during the
527 3rd to 5th year after randomization, and then annually thereafter.

528 Diagnosis of relapse will be established on clinical manifestation,
529 radiological findings, and/or histological evidence. If the diagnosis
530 of relapse is based on clinical symptoms without laboratory or
531 radiological evidence, other supporting evidence should be
532 collected as much as possible. After a diagnosis of recurrence is
533 established, the sites and date of relapse should be recorded.

534 Diagnosis of relapse could also be established if the treatment
535 strategy is altered based on the hypothesis of relapse, even without
536 adequate evidence.

537 Chest wall relapse: Defined as soft tissue recurrence in the area
538 comprising the sternum as the middle line, the clavicle as the upper
539 margin, the rib as the lower margin, and the posterior axillary line as
540 lateral margin.

541 Regional relapse: Defined as relapse in the area of the
542 supraclavicular fossa, subclavicular area, ipsilateral internal
543 mammary area, and/or ipsilateral axillary lymph nodes. Tissue
544 biopsy should be performed whenever possible.

545 Distant metastases: Cutaneous or subcutaneous metastasis
546 should be supported by histological or cytological evidence. Bone

547 metastasis should be supported by imaging studies (e.g., X-ray or
548 MR). Metastasis in the lung, liver, or brain should be supported by
549 CT or MRI.

550

551 **7. SAFETY ASSESSMENT**

552 **7.1 Adverse Events**

553 **7.1.1 Definition of Adverse Events**

554 An AE is defined as any untoward medical occurrence during the
555 period from randomization to the 28th day after the last dose or to
556 the most recent follow-up, regardless of causal attribution with the
557 study drug. An AE can be any of the following: A symptom, a sign,
558 abnormal examination results, or a disease, which may occur at
559 any time since the initiation of treatment.

560 An AE should be accurately recorded during the study, including
561 its time, severity, duration, management, and prognosis.

562

563 **7.1.2 Severity of Adverse Events**

564 Severity of AEs is graded according to NCI CTCAE 4.0 (Appendix
565 2). Grades of AEs that are not listed in Appendix 2 are as follows:

- 566 ● Mild: An effect on the daily function of subjects.
- 567 ● Moderate: A mild effect on the daily function of subjects.

568 ● Severe: A significant effect on the daily function of subjects.

569

570 **7.1.3 Association between AEs and Study Treatment**

571 The relationship between AEs and the study drug should be
572 assessed by investigators according to the following criteria:

573 Definitely related: An AE that follows a reasonable temporal
574 sequence from administration of the study intervention, follows a
575 known or expected response pattern to the suspected intervention,
576 and is confirmed by improvement on stopping and reappearance of
577 the event on repeated exposure

578 Probably related: An AE that follows a reasonable temporal
579 sequence from administration of the study intervention, follows a
580 known or expected response pattern to the suspected intervention,
581 but that could readily have been produced by the patient's clinical
582 conditions or other treatments.

583 Probably unrelated: An AE that does not follow a reasonable
584 temporal sequence from administration of the study intervention,
585 does not follow a known or expected response pattern to the
586 suspected intervention, and could readily have been produced by
587 the patient's clinical conditions or other treatments.

588 Unrelated: An AE that does not follow a reasonable temporal

589 sequence from administration of the study intervention, but follows
590 a known or expected response pattern to other treatments, and
591 could readily have been produced by the patient's clinical
592 conditions or other treatments. The AE can be relieved by
593 improvement of the clinical conditions or stopping other treatments,
594 and reappears after repeating other treatments.

595 Unable to determine: An AE that does not follow a reasonable
596 temporal sequence from administration of the study intervention,
597 but follows a known or expected response pattern to the study
598 intervention, and could readily have been produced by other
599 treatments.

600

601 **7.2 Serious Adverse Events (SAEs)**

602 **7.2.1 Definition of SAEs**

- 603 ● Results in death.
- 604 ● Is life-threatening.
- 605 ● Requires or prolongs hospitalization.
- 606 ● Causes persistent or significant disability or incapacity.
- 607 ● Results in congenital anomalies or birth defects.

608

609 **7.2.2 SAE Reporting**

610 Any SAEs occurring during the study or follow-up should be
611 reported to the PI and ethics committee by telephone within 24
612 hours regardless of their causal relationship with the study drug.
613 The PI is responsible of reporting SAEs to the State Food and Drug
614 Administration (SFDA) (also to the drug manufacturer within 24
615 hours if the SAE is considered to be related to the study drug).

616

617 **8. STATISTICS**

618 Additional details of the analysis will be provided in the statistical
619 analysis plan.

620 **8.1 Statistical Methods**

621 The primary endpoint is DFS, defined as time from randomization
622 to the first of breast cancer recurrence or death from any reason.

623 The secondary endpoints include OS, DDFS, LRFS, and safety.

624 Efficacy analyses will be based on the FAS population, defined
625 as all randomized patients excluding those who withdraw informed
626 consent before protocol treatment, or who had no follow-up data
627 after randomization. Safety analyses will be based on the safety
628 analyses set (SAS) population, defined as all randomized patients
629 who initiated the protocol treatment and who undergo safety
630 assessment.

631 For the efficacy analysis, PFS, OS, DDFS, and LRFS will be
632 analyzed using the Kaplan–Meier method and will be compared
633 using the log–rank test. The hazard ratio and corresponding 95%
634 confidence interval will be calculated using stratified Cox
635 proportional hazard regression.

636 AEs and SAEs will be summarized by arm. The incidence of
637 grade 3 HFS will be compared between the two arms using Fisher’s
638 exact test.

639 For continuous variables, the distribution, mean, median,
640 standard deviation, and interquartile rang (IQR) will be calculated
641 and compared using a *t*–test or non–parametric test. For
642 categorical variables, the number and percentage will be presented
643 in contingency table data and compared using the chi–squared test
644 or Fisher's exact test.

645 All statistical tests are two–sided with a *P* value of < 0.05 being
646 considered statistically significant.

647

648 **8.2 Sample Size**

649 The assumptions for sample size calculations are as follows:
650 5–year DFS is 68% in the control arm [10, 13, 28], and 80% in the
651 experimental arm. The estimated periods of enrollment and

652 follow-up will be 48 and 36 months, respectively. The design is
653 based on a 2-sided log-rank test with $\alpha = 0.05$, power = 90%,
654 and an interim analysis when the last one patient has completed 12
655 months of follow-up. The dropout rate is assumed to be 20%.
656 Approximately 684 patients (342 patients in each arm) will be
657 enrolled.

658

659 **9. ETHICS**

660 **9.1 Informed Consent**

661 Before enrollment, study physicians are responsible for a complete
662 and comprehensive presentation to patients of the study purpose,
663 the properties of the drug, its possible side effects and potential
664 risks. Patients should be informed of their rights, the risk, and the
665 benefit. It should be emphasized that they can withdraw from the
666 trial at any stage without affecting their subsequent treatment.
667 Subjects should be promptly informed of any updates of the study,
668 and a renewed informed consent to continue in the study should be
669 obtained. Patients should sign the informed consent in duplicate
670 with their name and date. One copy is given to the patient and the
671 other is kept in the study archives.

672

673 **9.2 Ethic Policies and Regulations**

674 The investigator will ensure that this study is conducted in full
675 conformance with the principles of the “Declaration of Helsinki” as
676 well as “Guideline for Good Clinical Practice (GCP)” and relevant
677 laws and regulations of the SFDA, whichever affords the greater
678 protection to the individual.

679 The study will be initiated only after the protocol is approved by
680 the ethics committee of the Sun Yat–sen University Cancer Center.
681 Any changes to the protocol during the study should be reported to
682 the ethics committee and filed.

683

684 **9.3 Protocol Modifications**

685 All protocol modifications must be submitted to the Independent
686 Ethics Committee (IEC). Approval must be awaited before any
687 changes can be implemented, except for changes necessary to
688 eliminate an immediate hazard to the trial patients, or when the
689 change involve only logistical or administrative aspects of the trial.

690

691 **10. QUALITY ASSURANCE**

692 To ensure accordance with study protocols, physicians are asked to
693 strictly follow the requirements of GCP throughout the trial, to

694 achieve standard procedures, accurate data, and reliable
695 conclusions. Specific requirements are as follows:

696 ✓ Obtain informed consent that is signed by each subject or
697 their agents.

698 ✓ Complete the case report form (CRF) as required.

699 ✓ Follow-up on schedule.

700 ✓ Keep complete records of laboratory examinations, clinical
701 records, and the original medical documents of the subjects.

702

703 **11. DATA PROCESSING AND STORAGE**

704 **11.1 Case Report Form (CRF)**

705 The CRF will be completed by investigators in a timely manner to
706 ensure the accuracy and timeliness of the content. Generally, the
707 CRF should not be altered. If there are any errors to be corrected,
708 the original record should be crossed out with a horizontal line, and
709 the modified text should be signed and dated. The completed CRFs
710 are reviewed by the quality control officer for data input. No further
711 modification of CRFs is allowed once the database is locked.

712 **11.2 Database Establishment**

713 Statisticians will have questions in the CRFs checked with
714 investigators, who should reply and return the CRFs promptly.

715 Statisticians should establish the database in a timely manner, and
716 the data will be locked by investigators, statisticians, and research
717 assistants after the database has been reviewed. To ensure data
718 security, a non-permitted person cannot modify the data, and the
719 data must be backed up.

720 **11.3 Data Storage**

721 Investigators should keep the data intact. According to the principle
722 of GCP in China, research data should be stored for at least five
723 years.

724

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886

887 **13. APPENDIX 1**

888

889

890

Schedule of the Study

	Baseline (Within 7 days before enrollment)	Treatment	End of treatment	Follow-up (d)	
Informed consent	√				
Screening form	√				
Blood samples	√	√	√	as clinically indicated	
Medical records and examinations					
Observation items	Medical history(a)	√			
	Physical examination	√	√	√	
	Vital signs	√	√	√	
	ECOG score	√	√	√	
	Complete blood count	√	√	√	as clinically indicated
	Blood chemistry test(b)	√	√	√	as clinically indicated
	Coagulation function (4 items)	√	√	√	as clinically indicated
	CEA/CA153	√	√	√	as clinically indicated
	Electrocardiogram	√	√	√	as clinically indicated
	Echocardiogram	√		√	as clinically indicated
	Imaging examination(c)	√		√	as clinically indicated
	Adverse events		√	√	√
	Concomitant medication		√	√	√
Assessment of recurrence and metastasis		√	√	√	

891

892 **NOTES:**

893 a) Medical history: Risk factors of heart disease and history of nervous system

894 disease should be recorded;

- 895 b) Blood chemistry tests: Hepatic function (AST, ALT, T-Bil, D-Bil, TP, and
896 ALB), renal function (BUN and Cr), serum electrolytes (K⁺ and Ca²⁺),
897 serum LDH and AKP, and serum glucose.
- 898 c) Imaging examination: Including chest X-ray and abdominal ultrasonography.
899 Bone ECT scan is recommended for patients with disease of stage ≥ IIB,
900 unexplained bone pain, or elevated serum ALP; Mammography is repeated
901 annually;
- 902 d) Follow-up is repeated every 3 months (± 28 days) during the first 2 years
903 after randomization, every 6 months (± 28 days) during the 3rd to 5th year
904 after randomization, and then annually thereafter.
- 905
- 906

907 **APPENDIX 2 Common Terminology Criteria for Adverse**
908 **Events v4.0**

909 ✓ The CTCAE v4.0 manual can be found at the following URL:

910 <http://ctep.cancer.gov/forms/CTCAEv4.pdf>.

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**A multicenter, phase III randomized study
of metronomic capecitabine maintenance
after standard treatment in patients with
operable triple–negative breast cancer**

(Protocol code: SYSUCC–EBC–CHEMO–001)

(Coding description: Sun Yat–sen University Cancer Center–Early
Breast Cancer–Chemotherapy–001)

Version: 3.0

Principle Investigators

Zhong Yu YUAN, M.D. and Xi WANG, M.D.

Sun Yat–sen University Cancer Center

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992 **1. SYNOPSIS OF THE STUDY**

993 **1.1 Objectives**

994 This study is designed to compare the efficacy (disease-free
995 survival, DFS) and safety of metronomic capecitabine maintenance
996 for one year with observation after standard local and systemic
997 treatment in patients with operable triple negative breast cancer
998 (TNBC).

999

1000 **1.2 Study design**

1001 This study is to be a multi-center, phase III, randomized controlled
1002 trial. The study will include the following two treatment arms: 424
1003 subjects will be randomized in a 1:1 fashion (212 in each arm) to
1004 receive treatment with either: Metronomic capecitabine
1005 maintenance (experimental arm); or observation (control arm) until
1006 objective disease recurrence, protocol violation, intolerable toxicity,
1007 death, or withdrawal of consent. Subjects will be stratified by lymph
1008 node status (positive or negative). Subjects discontinuing from the
1009 active treatment phase will enter the follow-up phase during which
1010 survival information will be collected.

1011

1012 **1.3 Main Inclusion/Exclusion Criteria**

1013 Main Inclusion Criteria:

- 1014 1) Female, aged ≥ 18 years old and ≤ 70 years.
- 1015 2) Histologically confirmed invasive ductal carcinoma, no
1016 specific type (NOS).
- 1017 3) Stage Ib–IIIc disease (N3 disease with involvement of the
1018 supraclavicular or internal mammary lymph nodes will be
1019 excluded).
- 1020 4) estrogen receptor (ER)–/progesterone receptor
1021 (PR)–negative and human epidermal growth factor receptor 2
1022 (HER2) negative (ER– and PR–negative is defined by lower
1023 than 1% immunohistochemistry staining; HER2–negative is
1024 defined by IHC score 0,1 or 2 with HER2–fluorescence in situ
1025 hybridization negative).
- 1026 5) Have completed adequate surgery, neo-/adjuvant
1027 chemotherapy and radiation therapy (if indicated).
- 1028 6) Available results for contralateral mammography, chest X–ray,
1029 abdominal ultrasonography, ^{99m}Tc –bone scanning (required
1030 for patients with stage Ib–IIIc disease) within 3 months before
1031 randomization.
- 1032 7) Adequate organ function including bone marrow, renal
1033 function, hepatic function.

1034 8) Compliance with the study protocol.

1035 9) Have provided written and signed informed consent.

1036 Main Exclusion Criteria:

1037 1) Inflammatory or bilateral breast cancer.

1038 2) Previously diagnosed with other malignancies (not including
1039 cured cervical carcinoma *in situ*, cutaneous squamous cell
1040 carcinoma, and cutaneous basal cell carcinoma).

1041 3) History of invasive breast cancer.

1042 4) Patients who are receiving or will receive other biological
1043 agents or immunotherapy.

1044 5) Severe dysfunction of the heart, lung, liver, or kidney.

1045 6) Patients with malabsorption syndrome diseases impairing GI
1046 function, resection of stomach or small intestine, or who are
1047 unable to swallow capecitabine tablets.

1048 7) Patients who are pregnant or who are unwilling to use
1049 contraception during the study period.

1050 8) Known intolerance to capecitabine or allergy to its excipients.

1051

1052 **1.4 Investigational Drug and Administration**

1053 Capecitabine group (experimental arm): Capecitabine will be
1054 administered at a dose of 650 mg/m² orally twice daily (total daily

1055 dose = 1300 mg/m²) continuously for one year, starting within 2
1056 weeks from randomization.

1057

1058 **1.5 Study Endpoints**

1059 The primary efficacy parameter, DFS, will be analyzed in the full
1060 analysis set (FAS) population.

1061 The secondary efficacy parameters, including overall survival (OS),
1062 disease-free survival (DDFS), and locoregional recurrence-free
1063 survival (LRFS), will be analyzed in FAS population.

1064 Safety and tolerability will be assessed using reporting of adverse
1065 events (AEs), graded according to NCI-CTC (version 4.0).

1066

1067 **2. BACKGROUND**

1068 Breast cancer comprises a group of diseases that show genetic
1069 heterogeneity and biological diversity [1, 2], which could be
1070 classified into five subtypes distinguished by their gene expression
1071 profiles [3, 4], including luminal A, luminal B, HER2+, normal breast,
1072 and basal-like [5]. The genotype of breast cancer is established
1073 using complicated gene analysis, which unsuitable for formalin-
1074 fixed specimens. Immunohistochemistry-based classification
1075 (using ER, PR, HER2, and KI-67) is more widely used in clinical

1076 practice [6–8], revealing a group of breast cancers characterized by
1077 negative expression of ER, PR, and HER2, termed as
1078 “triple–negative” breast cancer (TNBC) [9]. Basal–like breast
1079 cancer and TNBC are differently defined, and might overlap with
1080 each other. The majority of basal–like breast cancers are
1081 triple–negative. Therefore, TNBC is used as an alternative
1082 histopathological definition of basal–like breast cancer in clinical
1083 practice, as well as in the inclusion criteria of most clinical trials.

1084 TNBC comprises approximately 15%–25% of breast cancer in
1085 women [10–14], and is considered an independent
1086 clinicopathological subtype, with special clinical, pathological, and
1087 molecular genetic characteristics. In terms of clinical characteristics,
1088 TNBC is more common among young patients, with a high risk of
1089 early (within 2 years after surgery) recurrence, distant metastasis,
1090 and death [15–19]. TNBC has a shorter median survival after first
1091 recurrence than other types of breast cancer, with most deaths
1092 occurring within the first 5 years [10]. Visceral metastasis
1093 (especially in the lung and brain) is more frequent than bone
1094 metastasis, which might be one of the major contributors to the
1095 poor prognosis of TNBC. Pathologically, TNBC is associated with
1096 the presence of high histological grade, invasive ductal carcinoma,

1097 a high proliferation index, and high expression of p53 and EGFR
1098 [20-24]. Molecularly, gene expression profiles of TNBC have
1099 revealed its high molecular homology [1, 4, 9].

1100 For hormone receptor positive breast cancer, anti-estrogen
1101 therapies have significantly reduced recurrence and death [25]. For
1102 HER2+ breast cancers, anti-HER2 therapies (e.g., trastuzumab)
1103 have also significantly reduced recurrence [26]. Currently, there are
1104 few targeted therapies for TNBC, and chemotherapy is the only
1105 effective strategy to reduce recurrence, which is another reason for
1106 the poor prognosis of TNBC. Endocrine therapy for HR+ breast
1107 cancer and anti-HER2 therapy for HER2+ breast cancer are all
1108 long-term maintenance therapies after standard treatment [27].
1109 Therefore, we propose that a long-term effective maintenance
1110 treatment might significantly improve the outcome in patients with
1111 early TNBC.

1112 Most TNBC is more chemosensitive than HR+ breast cancer.
1113 Traditional regimens tend to achieve a better response in patients
1114 with TNBC; however, the duration of the response usually does not
1115 last long. TNBC is still characterized with dismal DFS, PFS, and OS
1116 [14, 28, 29]. Therefore, the aggressive biological behavior and the
1117 lack of effective risk-reducing treatment have both contributed to

1118 the poor prognosis of TNBC.

1119 Metronomic chemotherapy is a relatively novel regimen using
1120 continuous and low-dose chemotherapeutic agents with short or no
1121 intervals. Browder and Klement, et al. reported the anti-tumor
1122 activity of metronomic chemotherapy for the first time. The novel
1123 pattern of dosage has a different mechanism compared with
1124 conventional dosage regimens by exerting anti-angiogenesis
1125 effects [30, 31]. In addition, metronomic chemotherapy also
1126 produces antitumor effects by upregulating anti-tumor immune
1127 response in the host [32]. Metronomic chemotherapy had achieved
1128 good efficacy with low toxicity in advanced breast cancer [33–36].
1129 Considering that angiogenesis and immune surveillance escape
1130 are major mechanisms of tumor metastasis, metronomic
1131 chemotherapy might be a potential therapeutic option for operable
1132 TNBC with high risk of distant metastasis.

1133 Capecitabine is an effective agent with good tolerability and is
1134 convenient for breast cancer [37–41], which makes it an optimal
1135 choice for long-term metronomic use. The most common adverse
1136 events of capecitabine include hand-foot syndrome (HFS),
1137 diarrhea, and stomatitis, which are non-life threatening and can be
1138 managed using education without impairing efficacy [40]. Two recent

1139 phase III trials (FinXX and USO), which enrolled all subtypes of
1140 breast cancer, have shown by subgroup analysis that the addition
1141 of capecitabine to standard treatment significantly reduced the risk
1142 of relapse for TNBC, especially the risk of distant metastases.

1143 In summary, high rate of distant metastases and lack of effective
1144 treatment are the major reasons for the poor prognosis of TNBC.
1145 As a novel model of treatment, metronomic chemotherapy might be
1146 effective for TNBC by targeting angiogenesis and immune escape.
1147 The good efficacy and tolerability of capecitabine make it an
1148 optimal drug for metronomic chemotherapy. Clinical studies have
1149 also demonstrated a reduced risk of relapse in patients with TNBC
1150 receiving capecitabine in addition to standard treatment. This study
1151 aims to evaluate the efficacy and safety of capecitabine
1152 metronomic chemotherapy after standard treatment in patients with
1153 early TNBC.

1154

1155 **3. OBJECTIVES**

1156 **3.1 Primary Endpoint**

1157 To compare the DFS in patients who are randomized at enrollment
1158 to treatment with metronomic capecitabine maintenance
1159 (experimental arm) with in observation arm (control arm).

1160 DFS is defined as time from randomization to the first of any of
1161 the following events:

1162 5) Relapse of invasive breast cancer in the ipsilateral chest wall
1163 and regional lymph nodes

1164 6) Distant metastases (histologically confirmed or clinically
1165 diagnosed)

1166 7) Breast cancer related, non–breast cancer related or unknown
1167 deaths

1168 8) Contralateral invasive breast cancer

1169

1170 **3.2 Secondary Endpoints**

1171 To compare the overall survival (OS), distant disease–free survival
1172 (DDFS), locoregional recurrence–free survival (LRFS) and safety
1173 between the experimental arm and observation arm. In addition,
1174 exploratory analysis will include biomarkers that predict the efficacy
1175 and toxicity of capecitabine.

1176 OS is defined as time from randomization to death caused by any
1177 reason.

1178 DDFS is defined as time from randomization to the first
1179 occurrence of any of the following events: Distant metastases,
1180 death caused by any reason, and contralateral invasive breast

1181 cancer (NEJM 2005; 353:2747).

1182 LRFS is defined as time from randomization to locoregional
1183 invasive recurrence or death.

1184 Safety: The frequency and severity degree of AEs were judged
1185 based on NCI CTC V4.0.

1186

1187 **4. STUDY DESIGN**

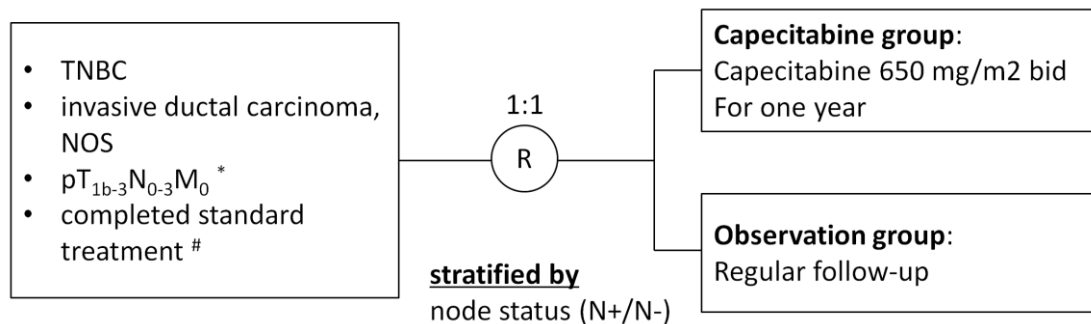
1188 **4.1 Summary of Design**

1189 This is a multi-center, phase III, randomized controlled study of
1190 metronomic capecitabine maintenance versus observation.

1191 Approximately 424 subjects with TNBC will be randomized in a
1192 1:1 fashion (212 in each arm) to receive treatment with either:
1193 Metronomic capecitabine maintenance (experimental arm); or
1194 observation (control arm) until objective disease recurrence,
1195 protocol violation, intolerable toxicity, death, or withdrawal of
1196 consent. Subjects will be stratified by lymph node status (positive or
1197 negative).

1198 Subjects will participate in the study within 4 weeks after
1199 completion of standard curative treatment including surgery,
1200 neo-/adjuvant chemotherapy and radiotherapy. Patients in the two
1201 arms will be followed-up every 3 months using physical, laboratory,

1202 and radiological examinations according to the study protocol. This
 1203 study will be completed in approximately 108 months including 72
 1204 months for accrual and approximately 36 months of follow-up
 1205 survival for the last subject enrolled. An overview of the study
 1206 design is depicted below:



*N3: Not including internal mammary or supraclavicular nodes involvement
 # standard treatment including surgery, (neo)adjuvant chemotherapy and radiation therapy (if indicated)

1207
 1208

1209 **Recommended chemotherapy regimens:** According to the
 1210 NCCN guidelines version 2010, recommended chemotherapy
 1211 regimens and dosages are listed in Table 1. Dosage adjustment
 1212 according to a patient's toleration will be allowed with no more than
 1213 25% reduction of the standard dose. A minimum of four cycles of
 1214 neo-/adjuvant chemotherapy should be delivered. For
 1215 node-positive patients, chemotherapy regimens containing
 1216 anthracyclines and taxanes are recommended.

1217 Recommended indications for post-operative radiotherapy

1218 include: Involvement of \geq four axillary nodes, primary tumor \geq 5 cm
 1219 in size, post breast conserving surgery, positive surgical margins,
 1220 involvement of internal mammary nodes (in selected cases), and
 1221 involvement of 1–3 axillary nodes (in selected cases).

1222 **Table 1** Recommended chemotherapy regimen and dosage

	Regimens(drugs)	Dose(mg/m ²)
CMF	cyclophosphamide/methotrexate/fluorouracil	500/ 40/ 600
AC	doxorubicin/cyclophosphamide	60/ 600
EC	epirubicin/cyclophosphamide	75–90/ 600
FAC	5–fluorouracil/doxorubicin/cyclophosphamide	500/ 50/ 500
FEC	5–fluorouracil/epirubicin/cyclophosphamide	500/ 75–90/ 500
TAC	docetaxel/doxorubicin/cyclophosphamide	75/ 50/ 500
TEC	docetaxel/epirubicin/cyclophosphamide	75/ 75/ 500
AC–P	doxorubicin/cyclophosphamide→weekly or every–3–week paclitaxel	60/ 600→80 (qw), 175 (q3w)
EC–P	epirubicin/cyclophosphamide→weekly or every–3–week paclitaxel	90/ 600→80 (qw), 175 (q3w)
AC–wP	doxorubicin/cyclophosphamide→paclitaxel (Dose–dense)	60/ 600→175 (q2w)
FEC–T	5–fluorouracil/epirubicin/cyclophosphamide→docetaxel, every 3 weeks	500/ 75–90/ 500→75
TC	docetaxel/cyclophosphamide	75/ 600

1223
 1224

1225 **4.2 Randomization**

1226 On verification of inclusion and exclusion criteria, eligible patients
 1227 will be randomized using the method of stratified permuted blocks
 1228 to receive metronomic capecitabine maintenance or observation in
 1229 a 1:1 ratio. Patients will be stratified according to lymph node status

1230 (negative vs. positive). A computerized number generator in the
1231 SAS Software (version 8.01) will generate a randomization table,
1232 the results of which were placed in sequentially numbered opaque
1233 envelopes and remained concealed until after enrollment.

1234 Central randomization will be performed. When a suitable patient
1235 is to be enrolled into the study, the Investigator site will contact
1236 principal investigator (PI) site, and will be informed over the
1237 telephone system at the time of individual patient enrollment what
1238 the treatment allocation is, and to which treatment arm the patient
1239 has been randomized. This is a multicenter study to be conducted
1240 at approximately 15 study sites.

1241

1242 **4.3 Capecitabine Administration**

1243 **4.3.1 Initiating Dose**

1244 The approved dose of capecitabine was 1250 mg/m² bid, days
1245 1–14 every 21 days. However, the dose of capecitabine for
1246 metronomic chemotherapy is uncertain, particularly in the adjuvant
1247 setting. Some small sample studies suggested that capecitabine at
1248 650 mg/m² bid, continuously for one year in metastatic breast
1249 cancer had lower toxicity and was well tolerated [42–44]. The
1250 initiate dose of capecitabine was 650 mg/m² bid, continuously for

1251 one year.

1252 Body surface area is calculated from height and body weight.
1253 Given that the height and weight of Chinese woman are 150–180
1254 cm and 40–80 kg, respectively, their body surface area lie between
1255 1.30 m² and 2.0 m². Combining the availability of capecitabine in
1256 China with the convenience of patients, the daily actual dose will be
1257 decided upon by using the **Table 2**.

1258 **Table 2 The daily dose of capecitabine**

Body surface area (m ²)	Total Daily Dose (mg)	Morning dose (mg)	Evening dose (mg)
1.30–1.32	1690–1716	1000	500
1.33–1.71	1729–2223	1000	1000
1.72–2.0	2236–2600	1500	1000

1259

1260 **4.3.2 Dose Adjustment**

1261 The most common AEs of capecitabine is HFS, and grading of HFS
1262 is listed in **Table 3**. Studies suggested that almost all AEs could
1263 improve after dose modification [45]. Dose adjustment of
1264 capecitabine in patients who experience HFS is listed in **Table 4**.
1265 Note, because of lower dose in patients with body surface areas
1266 1.3–1.32 m², only one dose reduction of capecitabine is allowed,
1267 from 1500 mg to 1000mg (morning 500mg, evening 500mg). In
1268 addition, once a dose has been reduced for a subject, all

1269 subsequent doses should be administered at that dose, unless
 1270 further dose reduction is required. Dose reescalation is not
 1271 permitted. If dosage delay occurs because of AEs, whether to
 1272 continue treatment should be determined by the investigator by
 1273 balancing the benefit and risk on an individual basis. Regardless of
 1274 the cause of the delay, patients who discontinue dosage for more
 1275 than 4 weeks should terminate treatment and withdraw from the
 1276 trial.

1277 **Table 3 Grading of HFS Caused by Capecitabine**

Grade	Manifestation
1	Numbness, tingling sensation, erythema of hands and/or feet that cause painless swelling or discomfort without affecting daily activities
2	Painful erythema or swelling of hands and/or feet that affect daily activities
3	Wet desquamation, ulceration, blistering, severe pain of hands and/or feet, and/or unable to work or perform daily activities

1278

1279 **Table 4 Dose Adjustment of Capecitabine**

Grade	Dose modification of capecitabine
1	Dose modifications are not recommended
2	<ul style="list-style-type: none"> –First appearance: Interrupt therapy until resolved to grade 0 or 1 and maintain the dose level for the next treatment at 100% –Second appearance: Interrupt therapy until resolved to grade 0 or 1 and maintain the dose level for the next treatment at 75% –Third appearance: Interrupt therapy until resolved to grade 0 or 1 and maintain the dose level for the next treatment at 50% –Fourth appearance: Discontinue therapy permanently

3	<ul style="list-style-type: none"> –First appearance: Interrupt therapy until resolved to grade 0 or 1 and begin the next cycle at 75% of the starting dose –Second appearance: Interrupt therapy until resolved to grade 0 or 1 and begin the next cycle at 50% of the starting dose –Third appearance: Discontinue therapy permanently
4	<p>First appearance: Discontinue therapy permanently, or if the physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0 or 1 and begin the next cycle at 50% of the starting dose</p>

1280

1281 **4.3.3 Concomitant and Prophylactic Medication**

1282 In addition to HFS, the other common toxicities of capecitabine are
1283 diarrhea and stomatitis. Symptom-relieving treatment can be given
1284 by investigators according to clinical need and should be recorded.
1285 Dose adjustment is not required for patients with mild to moderate
1286 hepatic impairment. Currently there are no data on the
1287 pharmacokinetics of capecitabine in patients with renal dysfunction
1288 (as evaluated by serum creatinine levels).

1289 Mild myelosuppression related to capecitabine and the
1290 predominance of its active metabolic enzymes inside tumor cells
1291 mean that, hematologic toxicities of grade ≤ 2 can be managed
1292 according to clinical routine without discontinuation of capecitabine.
1293 For patients experiencing hematologic toxicities of grade ≥ 3 ,
1294 capecitabine should be interrupted until resolved to grade 0.
1295 Treatment should be terminated if dosage interruption occurs for

1296 more than 4 weeks. Treatment should be terminated if patients
1297 experience two episodes of grade ≥ 3 hematological toxicities
1298 consecutively, with any episode resulting in drug discontinuation for
1299 more than 2 weeks. Patient should be followed-up after termination
1300 of therapy and toxicities and prognosis should be recorded.

1301

1302 **5. SELECTION OF SUBJECTS**

1303 **5.1 Enrollment**

1304 All patients meeting the inclusion criteria must be provided with
1305 detailed information about this study and written informed consent
1306 for participation must be obtained. The patients will then be
1307 randomly assigned into the observation arm or capecitabine arm
1308 using a random number table, and the assignment will be recorded
1309 on the case report form (CRF) by investigators. Analysis will be
1310 stratified by lymph node status (N0 or N+).

1311

1312 **5.2 Inclusion Criteria**

1313 Patients must fulfill **ALL** of the following criteria to be eligible for
1314 study enrollment and randomization.

- 1315 1) Female, aged ≥ 18 years old and ≤ 70 years old.
- 1316 2) Histologically confirmed invasive ductal carcinoma, no specific

- 1317 type (NOS).
- 1318 3) Stage Ib–IIIc (N3 not including internal mammary or
1319 supraclavicular nodes involvement).
- 1320 4) ER–, PR–, and HER2–negative (ER– and PR–negative is
1321 defined by lower than 1% immunohistochemistry (IHC)
1322 staining; HER2 negative is define by an IHC score of 0,1 or 2
1323 with HER2–fluorescence *in situ* hybridization negative).
- 1324 5) Have completed adequate surgery, neo-/adjuvant
1325 chemotherapy and radiation therapy (if indicated).
- 1326 6) Available results of contralateral mammography, chest X–ray,
1327 abdominal ultrasonography, and ^{99m}Tc–bone scanning within 3
1328 months before randomization.
- 1329 7) Adequate organ function:
- 1330 d) Bone marrow: ANC $\geq 1.5 \times 10^9/L$; platelet count \geq
1331 $100 \times 10^9/L$; hemoglobin ≥ 10 g/dL
- 1332 e) Renal function: serum creatinine $\leq 1.5 \times ULN$ by local
1333 laboratory
- 1334 f) Hepatic function: total bilirubin $\leq 1.5 \times ULN$; AST \leq
1335 $1.5 \times ULN$, ALT $\leq 1.5 \times ULN$
- 1336 8) Compliance with study protocol.
- 1337 9) Providing written informed and signed consent.

1338

1339 **5.3 Exclusion Criteria**

1340 Patients meeting **ANY** of the following criteria are not eligible for
1341 study enrollment and randomization.

1342 1) Inflammatory or bilateral breast cancer.

1343 2) Other previously diagnosed other malignancies (not including
1344 cured cervical carcinoma *in situ*, cutaneous squamous cell
1345 carcinoma, and cutaneous basal cell carcinoma).

1346 3) History of invasive breast cancer.

1347 4) Patients who are receiving or will receive other biological
1348 agents or immunotherapy.

1349 5) Severe dysfunction of the heart, lung, liver, or kidney.

1350 6) Patients with malabsorption syndrome diseases impairing GI
1351 function, resection of stomach or small intestine, or unable to
1352 swallow capecitabine tablets.

1353 7) Patient who are pregnant or who are unwilling to use
1354 contraception during the study period.

1355 8) Known intolerance to capecitabine or allergy to its excipients.

1356

1357 **5.4 Discontinuation Criteria**

1358 1) Recurrence of breast cancer.

- 1359 2) Development of serious AEs.
- 1360 3) Patients desire to withdraw from the study.
- 1361 4) Patients are unable to receive treatment or follow-up
1362 according to the study protocol.
- 1363 5) Patients receive other anti-tumor treatment or other treatment
1364 that might affect the study results without the consent of the
1365 investigators.
- 1366 6) Dosage discontinuation for more than 28 days.

1367

1368 **6. STUDY PROTOCOL**

1369 **6.1 Study Drug:**

1370 Capecitabine (Xeloda[®], Roche, Basel, Switzerland), 500mg per
1371 tablet. The treatment schedule is described in section 4.3

1372

1373 **6.2 Assessment and Follow-up**

1374 The schedule of assessment during treatment and follow-up
1375 are shown in Appendix 1.

1376

1377 **6.2.1 Baseline Assessment**

1378 Baseline assessment should complete within 1 week before
1379 enrollment.

- 1380 ✓ Screening form. Patients who meet all inclusion criteria and
1381 do not meet any exclusion criteria are eligible for this study.
1382 Investigators must complete a screening form at baseline.
- 1383 ✓ Medical history and clinical examination. Medical history,
1384 including risk factors for cardiac disease and their medical
1385 history of nervous system diseases must be collected before
1386 enrollment.
- 1387 ✓ Complete blood count, hepatic function (including AST, ALT,
1388 T-Bil, D-Bil, TP, and ALB), renal function (including BUN
1389 and Cr), serum electrolytes (including K⁺ and Ca²⁺), serum
1390 LDH, AKP, and blood glucose.
- 1391 ✓ Electrocardiogram and echocardiogram;
- 1392 ✓ Serum CEA and CA153;
- 1393 ✓ Imaging studiesy including chest X-ray, and abdominal
1394 ultrasonography. A Bone ECT scan is recommended for
1395 patients with disease of stage ≥ IIB, unexplained bone pain,
1396 or elevated serum ALP
- 1397 ✓ 10 mL of peripheral blood was collected for biomarker
1398 analysis.

1399

1400 **6.2.2 Assessment during Treatment**

1401 Assessment during treatment are to repeat every 3 months.

1402 ✓ Physical examination and vital signs;

1403 ✓ Complete blood count, hepatic function, and renal function;

1404 ✓ Serum CEA and CA153;

1405 ✓ Electrocardiogram;

1406 ✓ Abdominal ultrasonography.

1407

1408 **6.2.3 Assessment during Follow-up**

1409 Several randomized studies have shown that regular examination
1410 comprising bone scans, liver US, chest X-rays, and blood tests
1411 could not improve the survival and quality of life (QoL) of patients,
1412 compared with routine physical examination [46, 47]. Therefore,
1413 every 3 months during follow-up, physical examination and
1414 mammography are required for asymptomatic patients in both arms.
1415 However, this is the minimum requirement specified by the protocol,
1416 and investigators are allowed to perform additional evaluations
1417 according to the individual situation of the patients.

1418

1419 **6.2.4 Follow-up**

1420 Follow-up of patients in both arms will be initiated after
1421 randomization and will be repeated every 3 months (\pm 28 days)

1422 during the first 2 years after randomization. Patients in the
1423 capecitabine arm are allowed to take medicine at home but must
1424 return to the study site every 3 months (\pm 28 days) for follow-up.
1425 Follow-up will be repeated every 6 months (\pm 28 days) during the
1426 3rd to 5th year after randomization, and then annually thereafter.

1427 Diagnosis of relapse will be established on clinical manifestation,
1428 radiological findings, and/or histological evidence. If the diagnosis
1429 of relapse is based on clinical symptoms without laboratory or
1430 radiological evidence, other supporting evidence should be
1431 collected as much as possible. After a diagnosis of recurrence is
1432 established, the sites and date of relapse should be recorded.

1433 Diagnosis of relapse could also be established if the treatment
1434 strategy is altered based on the hypothesis of relapse, even without
1435 adequate evidence.

1436 Chest wall relapse: Defined as soft tissue recurrence in the area
1437 comprising the sternum as the middle line, the clavicle as the upper
1438 margin, the rib as the lower margin, and the posterior axillary line as
1439 lateral margin.

1440 Regional relapse: Defined as relapse in the area of the
1441 supraclavicular fossa, subclavicular area, ipsilateral internal
1442 mammary area, and/or ipsilateral axillary lymph nodes. Tissue

1443 biopsy should be performed whenever possible.

1444 Distant metastases: Cutaneous or subcutaneous metastasis
1445 should be supported by histological or cytological evidence. Bone
1446 metastasis should be supported by imaging studies (e.g., X-ray or
1447 MR). Metastasis in the lung, liver, or brain should be supported by
1448 CT or MRI.

1449

1450 **7. SAFETY ASSESSMENT**

1451 **7.1 Adverse Events**

1452 **7.1.1 Definition of Adverse Events**

1453 An AE is defined as any untoward medical occurrence during the
1454 period from randomization to the 28th day after the last dose or to
1455 the most recent follow-up, regardless of causal attribution with the
1456 study drug. An AE can be any of the following: A symptom, a sign,
1457 abnormal examination results, or a disease, which may occur at
1458 any time since the initiation of treatment.

1459 An AE should be accurately recorded during the study, including
1460 its time, severity, duration, management, and prognosis.

1461

1462 **7.1.2 Severity of AEs**

1463 Severity of AEs is graded according to NCI CTCAE 4.0 (Appendix

1464 2). Grades of AEs that are not listed in Appendix 2 are as follows:

- 1465 ● Mild: An effect on the daily function of subjects.
- 1466 ● Moderate: A mild effect on the daily function of subjects.
- 1467 ● Severe: A significant effect on the daily function of subjects.

1468

1469 **7.1.3 Association between AEs and Study Treatment**

1470 The relationship between AEs and the study drug should be
1471 assessed by investigators according to the following criteria:

1472 Definitely related: An AE that follows a reasonable temporal
1473 sequence from administration of the study intervention, follows a
1474 known or expected response pattern to the suspected intervention,
1475 and is confirmed by improvement on stopping and reappearance of
1476 the event on repeated exposure

1477 Probably related: An AE that follows a reasonable temporal
1478 sequence from administration of the study intervention, follows a
1479 known or expected response pattern to the suspected intervention,
1480 but that could readily have been produced by the patient's clinical
1481 conditions or other treatments.

1482 Probably unrelated: An AE that does not follow a reasonable
1483 temporal sequence from administration of the study intervention,
1484 does not follow a known or expected response pattern to the

1485 suspected intervention, and could readily have been produced by
1486 the patient's clinical conditions or other treatments.

1487 Unrelated: An AE that does not follow a reasonable temporal
1488 sequence from administration of the study intervention, but follows
1489 a known or expected response pattern to other treatments, and
1490 could readily have been produced by the patient's clinical
1491 conditions or other treatments. The AE can be relieved by
1492 improvement of the clinical conditions or stopping other treatments,
1493 and reappears after repeating other treatments.

1494 Unable to determine: An AE that does not follow a reasonable
1495 temporal sequence from administration of the study intervention,
1496 but follows a known or expected response pattern to the study
1497 intervention, and could readily have been produced by other
1498 treatments.

1499

1500 **7.2 Serious Adverse Events (SAEs)**

1501 **7.2.1 Definition of SAEs**

- 1502 ● Results in death.
- 1503 ● Is life-threatening.
- 1504 ● Requires or prolongs hospitalization.
- 1505 ● Causes persistent or significant disability or incapacity.

1506 ● Results in congenital anomalies or birth defects.

1507

1508 **7.2.2 SAEs Reporting**

1509 Any SAEs occurring during the study or follow-up should be
1510 reported to the PI and ethics committee by telephone within 24
1511 hours regardless of their causal relationship with the study drug.
1512 The PI is responsible of reporting SAEs to the State Food and Drug
1513 Administration (SFDA) (also to the drug manufacturer within 24
1514 hours if the SAE is considered to be related to the study drug).

1515

1516 **8. STATISTICS**

1517 Additional details of the analysis will be provided in the statistical
1518 analysis plan.

1519 **8.1 Statistical Methods**

1520 The primary endpoint is DFS, defined as time from randomization
1521 to the first of breast cancer recurrence or death from any reason.

1522 The secondary endpoints include OS, DDFS, LRFS, and safety.

1523 Efficacy analyses will be based on the FAS population, defined
1524 as all randomized patients excluding those who withdraw informed
1525 consent before protocol treatment, or who had no follow-up data
1526 after randomization. Safety analyses will be based on the safety

1527 analyses set (SAS) population, defined as all randomized patients
1528 who initiated the protocol treatment and who undergo safety
1529 assessment.

1530 For the efficacy analysis, PFS, OS, DDFS, and LRFS will be
1531 analyzed using the Kaplan–Meier method and will be compared
1532 using the log–rank test. The hazard ratio and corresponding 95%
1533 confidence interval will be calculated using stratified Cox
1534 proportional hazard regression.

1535 AEs and SAEs will be summarized by arm. The incidence of
1536 grade 3 HFS will be compared between the two arms using Fisher’s
1537 exact test.

1538 For continuous variables, the distribution, mean, median,
1539 standard deviation, and interquartile rang (IQR) will be calculated
1540 and compared using a *t*–test or non–parametric test. For
1541 categorical variables, the number and percentage will be presented
1542 in contingency table data and compared using the chi–squared test
1543 or Fisher's exact test.

1544 All statistical tests are two–sided with a *P* value of < 0.05 being
1545 considered statistically significant.

1546

1547 **8.2 Sample Size**

1548 The assumptions for sample size calculations as the follows:
1549 5–year DFS is 68% in the control arm [10, 13, 28], and 80% in the
1550 experimental arm. The estimated period of enrollment and
1551 follow–up will be 72 and 36 months, respectively. The design is
1552 based on a 2–sided log–rank test with $\alpha = 0.05$, power = 80%.
1553 The dropout rate is assumed to be 9%. Approximately 424 patients
1554 (212 patients in each arm) will be enrolled.

1555

1556 **9. Ethics**

1557 **9.1 Informed Consent**

1558 Before enrollment, study physicians are responsible for a complete
1559 and comprehensive presentation to patients of the study purpose,
1560 the properties of the drug, its possible side effects and potential
1561 risks. Patients should be informed of their rights, risk, and benefit. It
1562 should be emphasized that they can withdraw from the trial at any
1563 stage of the trial without affecting their subsequent treatment.
1564 Subjects should be promptly informed of any updates of the study,
1565 and a renewed informed consent to continue in the study should be
1566 obtained. Patients should sign the informed consent in duplicate
1567 with their name and date. The two copies are given to the patient
1568 and kept in study archives, respectively.

1569

1570 **9.2 Ethic Policies and Regulations**

1571 The investigator will ensure that this study is conducted in full
1572 conformance with the principles of the “Declaration of Helsinki” as
1573 well as “Guideline for Good Clinical Practice (GCP)” and relevant
1574 laws and regulations of the SFDA, whichever affords the greater
1575 protection to the individual.

1576 The study will be initiated only after the protocol is approved by the
1577 ethics committee of the Sun Yat–sen University Cancer Center. Any
1578 changes to the protocol during the study should be reported to the
1579 ethics committee and filed.

1580

1581 **9.3 Protocol Modifications**

1582 All protocol modifications must be submitted to the Independent
1583 Ethics Committee (IEC). Approval must be awaited before any
1584 changes can be implemented, except for changes necessary to
1585 eliminate an immediate hazard to the trial patients, or when the
1586 change involve only logistical or administrative aspects of the trial.

1587

1588 **10. QUALITY ASSURANCE**

1589 To ensure accordance with study protocols, physicians are asked to

1590 strictly follow the requirements of GCP throughout the trial, to
1591 achieve standard procedures, accurate data, and reliable
1592 conclusions. Specific requirements are as follows:

1593 ✓ Obtain informed consent that is signed by each subject or
1594 their agents.

1595 ✓ Complete the case report form (CRF) as required.

1596 ✓ Follow-up on schedule.

1597 ✓ Keep complete records of laboratory examinations, clinical
1598 records, and the original medical documents of the subjects.

1599

1600 **11. DATA PROCESSING AND STORAGE**

1601 **11.1 Case Report Form (CRF)**

1602 The CRF will be completed by investigators in a timely manner to
1603 ensure the accuracy and timeliness of the content. Generally, the
1604 CRF should not be altered. If there are any errors to be corrected,
1605 the original record should be crossed out with a horizontal line, and
1606 the modified text should be signed and dated. The completed CRFs
1607 are reviewed by the quality control officer for data input. No further
1608 modification of CRFs is allowed once the database is locked.

1609

1610 **11.2 Database Establishment**

1611 Statisticians will have questions in the CRFs checked with
1612 investigators, who should reply and return the CRFs promptly.
1613 Statisticians should establish the database in a timely manner, and
1614 the data will be locked by investigators, statisticians, and research
1615 assistants after the database has been reviewed. To ensure data
1616 security, a non-permitted person cannot modify the data, and the
1617 data must be backed up.

1618

1619 **11.3 Data Storage**

1620 Investigators should keep the data intact. According to the principle
1621 of GCP in China, research data should be stored for at least five
1622 years.

1623

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13. APPENDIX 1

1807

Schedule of the study

	Baseline (within 7 days before enrollment)	Treatment	End of treatment	Follow-up (d)	
Informed consent	√				
Screening form	√				
Blood samples	√	√	√	as clinically indicated	
Medical records and examinations					
Observations	Medical history(a)	√			
	Physical examination	√	√	√	
	Vital signs	√	√	√	
	ECOG score	√	√	√	
	Complete blood count	√	√	√	as clinically indicated
	Blood chemistry test(b)	√	√	√	as clinically indicated
	Coagulation function (4 items)	√	√	√	as clinically indicated
	CEA/CA153	√	√	√	as clinically indicated
	Electrocardiogram	√	√	√	as clinically indicated

	Echocardiogram	√		√	as clinically indicated
	Imaging examination(c)	√		√	as clinically indicated
	Adverse events		√	√	√
	Concomitant medication		√	√	√
	Assessment of recurrence and metastasis		√	√	√

1808

1809 **NOTES:**

1810 a) Medical history: Risk factors of heart disease and history of nervous system
1811 disease should be recorded;

1812 b) Blood chemistry tests: Hepatic function (AST, ALT, T-Bil, D-Bil, TP, and
1813 ALB), renal function (BUN and Cr), serum electrolytes (K⁺ and Ca²⁺), serum
1814 LDH and AKP, and serum glucose.

1815 c) Imaging examination: Including chest X-ray and abdominal ultrasonography.
1816 Bone ECT scan is recommended for patients with disease of stage ≥ IIB,
1817 unexplained bone pain, or elevated serum ALP; Mammography is repeated
1818 annually;

1819 d) Follow-up is repeated every 3 months (± 28 days) during the first 2 years
1820 after randomization, every 6 months (± 28 days) during the 3rd to 5th year
1821 after randomization, and then annually thereafter.

1822

1823

1824 **APPENDIX 2 Common Terminology Criteria for Adverse Events v4.0**

1825 ✓ The CTCAE v4.0 manual can be found at the following URL:

1826 <http://ctep.cancer.gov/forms/CTCAEv4.pdf>.

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SYSUCC–001 Study Protocol Amendment List

1831

page	item	Before amendment (Protocol Ver.2.0 November 30, 2012)	After amendment (Protocol Ver.3.0 January 9, 2017)	Reasons
cover		Ver.2.0 approved date: November 30, 2012	Ver.3.0 approved date: January 9, 2017	–
P76	8.2 Sample size	An interim analysis when the last one patient has completed 18 months of follow–up.	(None)	The number of DFS events was much lower than expected after the last one patient has completed 12 months of follow–up

1832

1833

page	item	Before amendment (Protocol Ver.1.0 April 5, 2010)	After amendment (Protocol Ver.2.0 October 20, 2012)	Reasons
Cover	Cover	Ver.1.0 approved date: April 5, 2010	Ver.2.0 approved date: October 20, 2012	–
P5	1.1 Study Design	684 subjects will be randomized in a 1:1 fashion (342 in each arm)	424 subjects will be randomized in a 1:1 fashion (212 in each arm)	Considering the influence of duration of enrollment and follow-up on sample size, also too high drop-out rate
P6	1.3 Main Inclusion/Exclusion Criteria□	1) Female, aged ≥ 18 years old and ≤ 75 years.	1) Female, aged ≥ 18 years old and ≤ 70 years.	Fewer patients and poorer compliance
P6	1.3 Main Inclusion/Exclusion Criteria	3) Pathologic stage $T_{1c-3}N_{0-2}M_0$	3) Pathologic stage $T_{1b-3}N_{0-3}M_0$	Findings from retrospective studies showed the number of positive lymph nodes could not be used for predicting the survival rate. Adjuvant chemotherapy was recommended to

				patients with T _{1b} disease by NCCN guideline
P6	1.3 Main Inclusion/ Exclusion Criteria	1) Patients with T4, including inflammatory carcinomas.	1) Patients with bilateral breast cancer, inflammatory carcinomas.	according to the American Joint Committee on Cancer 2010 staging system
P7	1.3 Main Inclusion/ Exclusion Criteria	2) Patients with N3.	2) Patients with positive supraclavicular or internal mammary lymph node.	Treatment for positive supraclavicular or internal mammary lymph node remains controversial
P14	4.1 Summary of Design	Approximately 684 subjects with TNBC will be randomized in a 1:1 fashion (342 in each arm) to receive treatment	Approximately 424 subjects with TNBC will be randomized in a 1:1 fashion (212 in each arm) to receive treatment	Considering the influence of duration of enrollment and follow-up on sample size, also too high drop-out rate
P14	4.1 Summary of Design	This study will be completed in approximately 84 months including 48 months for accrual and approximately 36 months follow-up	This study will be completed in approximately 96 months including 60 months for accrual and approximately 36 months follow-up survival for the last subject	Slower enrollment than expected

		survival for the last subject enrolled.	enrolled.	
P21	5.2 Inclusion Criteria	1) Female, aged ≥ 18 years old and ≤ 75 years.	1) Female, aged ≥ 18 years old and ≤ 70 years.	See above
P21	5.2 Inclusion Criteria	3) Pathologic stage $T_{1c-3}N_{0-2}M_0$	3) Pathologic stage $T_{1b-3}N_{0-3}M_0$	See above
P22	5.3 Exclusion Criteria	1) Patients with T4, including inflammatory carcinomas.	1) Patients with bilateral breast cancer, inflammatory carcinomas.	See above
P22	5.3 Exclusion Criteria	2) Patients with N3.	2) Patients with positive supraclavicular or internal mammary lymph node.	See above
P32	8.2 Sample Size	The estimated period of enrollment and follow-up will be 48 and 36 months, respectively. The design is based on 2-sided log-rank test with $\alpha=0.05$, power=90%, and an	The estimated period of enrollment and follow-up will be 60 and 36 months, respectively. The design is based on 2-sided log-rank test with $\alpha=0.05$, power=80%, and an interim	See above

		interim analysis when the last one patient has completed 12 months of follow-up. The dropout rate is assumed to be 20%. Approximately 684 patients (342 patients in each arm) will be enrolled.	analysis when the last one patient has completed 18 months of follow-up. The dropout rate is assumed to be 9%. Approximately 424 patients (212 patients in each arm) will be enrolled.	
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STATISTICAL ANALYSIS PLAN

1837

TITLE: A MULTICENTER, PHASE III
RANDOMIZED STUDY OF
METRONOMIC CAPECITABINE
MAINTENANCE AFTER
STANDARD TREATMENT IN
PATIENTS WITH OPERABLE
TRIPLE-NEGATIVE BREAST
CANCER

PROTOCOL NUMBER: SYSUCC-EBC-CHEMO-001

STUDY DRUG: Capecitabine

PLAN PREPARED BY: Ying Guo and Ji-Bin Li

PLAN VERSION: 1.0

APPROVAL DATE: April 5, 2010

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1861 **1. BACKGROUND**

1862 The SYSUCC–001 trial is a multicenter, phase III, randomized
1863 controlled study to compare the efficacy and safety of metronomic
1864 capecitabine maintenance for one year with observation after
1865 standard local and systemic treatment in patients with operable
1866 triple negative breast cancer (TNBC).

1867 The primary objective of this study is to evaluate whether the
1868 addition of metronomic capecitabine maintenance to standard
1869 alone treatment improves disease–free survival (DFS), compared
1870 with standard treatment. Secondary objectives include determining
1871 whether the addition of metronomic capecitabine maintenance to
1872 standard treatment could improve overall survival (OS), distant
1873 disease–free survival (DDFS), locoregional recurrence–free
1874 survival (LRFS) and safety.

1875 The purpose of this Statistical Analysis Plan (SAP) is to provide the
1876 details of the proposed analyses of the data collected during this
1877 trial.

1878

1879 **2. STUDY DESIGN**

1880 The SYSUCC–001 trial is a multicenter, phase III, randomized
1881 controlled study. A total of 684 patients will be enrolled from

1882 approximately 18 sites in China. Eligible patients will be
1883 randomized between the two study arms in a 1:1 ratio.

1884

1885 The sample size of the study is primarily driven by the analysis of
1886 DFS. To detect a hazard ratio (HR) of 0.58 in DFS (an estimated
1887 improvement of 12% in the 5-year DFS from 68% in the control
1888 arm to 80% in the capecitabine maintenance arm), approximately
1889 148 DFS events will be required to achieve a statistical power of 90%
1890 at a 2-sided significance level of 5%. The estimated periods of
1891 enrollment and follow-up will be 48 and 36 months, respectively.
1892 After considering a dropout rate of 20%, approximately 684 patients
1893 (342 patients in each group) will be enrolled in the study [1-5].

1894

1895 **Interim Analyses:** One interim analysis of DFS is planned on the
1896 basis of the results of the regular follow-up at 12 months after the
1897 completion of enrolment. This interim analysis consists of a
1898 comparison of the primary endpoint, the DFS, between groups; if
1899 significant differences are found, a secondary endpoint, OS, will be
1900 likewise compared between the groups. To maintain the primary
1901 errors in the whole study at a level of 5% (with two sided), the
1902 multiplicity in the primary endpoint analysis was adjusted using the

1903 Lan–DeMets alpha spending function with an O’Brien–Fleming
1904 boundary method. The p–value will be 0.003 for the interim DFS
1905 analyses, and 0.047 for final DFS analysis [1-5].

1906

1907 **3. RANDOMIZATION**

1908 After verification of the inclusion and exclusion criteria, eligible
1909 patients will be randomized using the method of stratified permuted
1910 blocks to receive metronomic capecitabine maintenance treatment
1911 or observation. Patients will be stratified according to lymph node
1912 status (negative vs. positive). A computerized number generator
1913 using Software SAS (version 8.01) generated a randomization table,
1914 the results of which were placed in sequentially numbered opaque
1915 envelopes and remained concealed until after enrollment.

1916

1917 **4. STATISTICAL METHODS**

1918 **4.1 Analysis populations**

1919 **4.1.1 Full Analysis Set (FAS) Population**

1920 The Full Analysis Set (FAS) is defined as all randomized patients
1921 excluding those who withdraw informed consent before protocol
1922 treatment, or who had no follow–up data after randomization. The
1923 primary analysis population for all efficacy endpoints will be the

1924 FAS population.

1925

1926 **4.1.2 Per–Protocol Set (PPS) Population**

1927 The Per Protocol Set (PPS) is defined as all randomized patients
1928 who have completed the study without major protocol violations,
1929 such as patients who discontinue the study across the protocol
1930 treatment for reasons determined to be unrelated to breast cancer
1931 treatment, and patients who refuse any follow–up or visit, not
1932 including breast cancer recurrence or death.

1933

1934 **4.1.3 Safety Population**

1935 The Safety Analyses Set (SAS) is defined as all randomized
1936 patients who initiate the protocol treatment.

1937

1938 **4.2 Efficacy Analysis**

1939 The following sections outline the planned analysis of the primary
1940 and secondary efficacy endpoints of this study. All efficacy analysis
1941 will be performed based on the FAS population.

1942

1943 **4.2.1 Analysis of the Primary Endpoint**

1944 The primary endpoint is DFS, defined as the time from

- 1945 randomization to the first occurrence of the following events:
- 1946 1) Relapse of breast cancer in the ipsilateral chest wall and
1947 regional lymph nodes
 - 1948 2) Distant metastases (histologically confirmed or clinically
1949 diagnosed)
 - 1950 3) Breast cancer related, non–breast cancer–related or unknown
1951 deaths
 - 1952 4) Contralateral breast cancer

1953 Patients who have not had an event at the time of data analysis will
1954 be censored at the last date they were known to be alive and
1955 event–free.

1956 The null hypothesis for the primary endpoint is that the survival
1957 distributions of DFS in the two treatment groups are the same. The
1958 alternative hypothesis is that the survival distributions of DFS in the
1959 treatment and the control arm are different:

1960 $H_0: S_{\text{capecitabine}} = S_{\text{observation}}$ vs. $H_1: S_{\text{capecitabine}} \neq S_{\text{observation}}$

1961 We will estimate survival curves in each treatment arm using the
1962 Kaplan–Meier estimator and the hazard ratio with 95%CI between
1963 treatment arms based on the proportional hazards model, with
1964 assumptions of proportional hazards confirmed based on the
1965 Schoenfeld residuals for the final dataset. We will use a two–sided

1966 log-rank test at the final analysis (at a significance level of 0.047).

1967 Stratified analyses of the lymph node status will also be conducted.

1968

1969 **4.2.2 Analysis of the Secondary Endpoints**

1970 The Secondary Endpoints are defined as follows:

1971 Overall Survival (OS) is defined as the time from randomization to
1972 death caused by any reason. Patients who are alive (including lost
1973 to follow-up) at the time of the analysis will be censored at the date
1974 when they were last known to be alive.

1975 Distant disease-free survival (DDFS) is defined as the time from
1976 randomization to the first occurrence of any of the following events:
1977 Distant metastases, death caused by any reason, and contralateral
1978 invasive breast cancer. Patients who have not had a distant
1979 recurrence event at the time of data analysis will be censored at the
1980 date when they were last known to be alive.

1981 Locoregional recurrence-free survival (LRFS) is defined as the
1982 time from randomization to the first occurrence of any of the
1983 following events: ipsilateral breast or chest wall, regional lymph
1984 node, and death caused by any reason.

1985 The primary analyses for all secondary endpoints will be performed
1986 at the time of the primary analysis of the primary endpoint DFS. The

1987 estimated Kaplan–Meier curves and the hazard ratio with 95% CI
1988 will be calculated based on the proportional hazards model and the
1989 endpoints will be compared using a two–sided log–rank test (at a
1990 significance level of 0.05).

1991

1992 **4.2.3 Subgroup Analysis**

1993 At the time of the primary analysis, exploratory analyses will be
1994 performed for DFS to determine whether the magnitude of the
1995 effectiveness of the addition of capecitabine maintenance might
1996 differ according to patient sub–populations.

1997 Variables to be considered for defining subgroups of interest
1998 include the node status as well as other disease– or patient–related
1999 prognostic or predictive factors. We will conduct the subgroup
2000 analysis by estimating the hazard ratio with 95% CI and the test
2001 interaction, if applicable, among subgroups with two–sided
2002 p–values) for the following items:

2003 ✓ Age (≤ 40 / > 40 and median and range)

2004 ✓ Tumor size at diagnosis (T1 / T2 / T3)

2005 ✓ Histological grade (I / II / III)

2006 ✓ Nodal stage (N0 / N+)

2007 ✓ Stage (I / II / III)

- 2008 ✓ KI-67 ($\leq 14\%$ / $> 14\%$)
- 2009 ✓ Lymphovascular invasion (positive / negative)
- 2010 ✓ Neo-/adjuvant regimens (anthracycline-based/
2011 taxane-based/ anthracycline- and taxane-based)
- 2012 The above background variables will be compared using statistical
2013 test (at a two-sided significance level of 0.05).

2014

2015 **4.2.4 Exploratory Analysis**

2016 In the capecitabine arm, a tabulation of those patients who have
2017 completed the protocol as planned against those who did not
2018 complete the protocol as planned will be performed. Completion/
2019 reduction/stop numbers and proportion of capecitabine are
2020 calculated at every 3-month visit, to show relative dose intensity
2021 (RDI) of capecitabine, which is defined as the actual cumulative
2022 dose compared to planned total dose.

2023 To determine the relationship between the RDI of capecitabine and
2024 DFS, estimated Kaplan-Meier curves and the hazard ratio with 95%
2025 CI will be calculated based on the proportional hazards model and
2026 the comparison will be tested using a two-sided log-rank test (at a
2027 significance level of 0.05).

2028

2029 **4.3 Safety Analyses**

2030 Safety data will be summarized based on the Safety Population.

2031 Verbatim descriptions of treatment–emergent adverse events (AEs)
2032 will be mapped to MedDRA thesaurus terms and graded according
2033 to NCI–CTCAE version 4.0. All AEs, including serious adverse
2034 events (SAEs), will be summarized by treatment arm and
2035 NCI–CTCAE grade. Comparisons between treatment groups will
2036 use the chi squared test (grade0–2/grade3–4) with a two–sided
2037 p–value (at a significance level of 0.05). The variables to be tested
2038 are:

- 2039 ✓ White blood cell count
- 2040 ✓ Neutrophil count
- 2041 ✓ Platelet count
- 2042 ✓ Hemoglobin
- 2043 ✓ AST
- 2044 ✓ ALT
- 2045 ✓ Total Bilirubin
- 2046 ✓ Creatinine
- 2047 ✓ Appetite loss
- 2048 ✓ Abdominal pain / Diarrhea
- 2049 ✓ Nausea

- 2050 ✓ Vomiting
- 2051 ✓ Stomatitis
- 2052 ✓ Fatigue
- 2053 ✓ Hand-foot syndrome (HFS)

2054

2055 **5. REFERENCES**

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2063 analysis of clinical trials.' *Biometrika*, 64, pages 191-199.
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2066 Lan-DeMets Method.' Technical Report 60, Department of
2067 Biostatistics, University of Wisconsin-Madison.

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STATISTICAL ANALYSIS PLAN

2071

TITLE: A MULTICENTER, PHASE III
RANDOMIZED STUDY OF
METRONOMIC CAPECITABINE
MAINTENANCE AFTER
STANDARD TREATMENT IN
PATIENTS WITH OPERABLE
TRIPLE-NEGATIVE BREAST
CANCER

PROTOCOL NUMBER: SYSUCC-EBC-CHEMO-001

STUDY DRUG: Capecitabine

PLAN PREPARED BY: Ying Guo and Ji-Bin Li

PLAN VERSION: 3.0

APPROVAL DATE: January 19, 2017

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2096 **1. BACKGROUND**

2097 The SYSUCC–001 trial is a multicenter, phase III, randomized
2098 controlled study to compare the efficacy and safety of metronomic
2099 capecitabine maintenance for one year with observation after
2100 standard local and systemic treatment in patients with operable
2101 triple negative breast cancer (TNBC).

2102 The primary objective of this study is to evaluate whether the
2103 addition of metronomic capecitabine maintenance to standard
2104 treatment improves disease–free survival (DFS), compared with
2105 standard treatment alone. Secondary objectives include
2106 determining whether the addition of metronomic capecitabine
2107 maintenance to standard treatment could improve overall survival
2108 (OS), distant disease–free survival (DDFS), locoregional
2109 recurrence–free survival (LRFS) and safety.

2110 The purpose of this Statistical Analysis Plan (SAP) is to provide the
2111 details of the proposed analyses of the data collected during this
2112 trial.

2113

2114 **2. STUDY DESIGN**

2115 The SYSUCC–001 trial is a multicenter, phase III, randomized
2116 controlled study. A total of 424 patients will be enrolled from

2117 approximately 13 sites in China. Eligible patients will be
2118 randomized between the two study arms in a 1:1 ratio.

2119

2120 The sample size of the study is primarily driven by the analysis of
2121 DFS. To detect a hazard ratio (HR) of 0.58 in DFS (an estimated
2122 improvement of 12% in the 5-year DFS from 68.0% in the control
2123 arm to 80.0% in the capecitabine maintenance arm), approximately
2124 109 DFS events will be required to achieve a statistical power of 80%
2125 at a 2-sided significance level of 5%. The estimated periods of
2126 enrollment and follow-up will be 60 and 36 months, respectively.
2127 After considering a dropout rate of 9%, approximately 424 patients
2128 (212 patients in each group) will be enrolled in the study [1, 2].

2129 **Interim Analyses:** One interim analysis of DFS is planned on the
2130 basis of the results of the regular follow-up at 18 months after the
2131 completion of enrolment. So far, however, the number of events is
2132 too much lower than expected. This interim analysis is cancelled
2133 and approved by SYSUCC Ethics Committee. The p-value for final
2134 DFS analysis will be 0.047 yet.

2135

2136 **3. RANDOMIZATION**

2137 After verification of the inclusion and exclusion criteria, eligible

2138 patients will be randomized using the method of stratified permuted
2139 blocks to receive metronomic capecitabine maintenance treatment
2140 or observation. Patients will be stratified according to lymph node
2141 status (negative vs. positive). A computerized number generator
2142 using Software SAS (version 8.01) generated a randomization table,
2143 the result of which were placed in sequentially numbered opaque
2144 envelopes and remained concealed until after enrollment.

2145

2146 **4. STATISTICAL METHODS**

2147 **4.1 Analysis populations**

2148 **4.1.1 Full Analysis Set (FAS) Population**

2149 The Full Analysis Set (FAS) is defined as all randomized patients
2150 excluding those who withdraw informed consent before protocol
2151 treatment, or who had no follow-up data after randomization. The
2152 primary analysis population for all efficacy endpoints will be the
2153 FAS population.

2154

2155 **4.1.2 Per-Protocol Set (PPS) Population**

2156 The Per Protocol Set (PPS) is defined as all randomized patients
2157 who have completed the study without major protocol violations,
2158 such as patients who discontinue the study across the protocol

2159 treatment for reasons determined to be unrelated to breast cancer
2160 treatment, and patients who refuse any follow-up or visit, not
2161 including breast cancer recurrence or death.

2162

2163 **4.1.3 Safety Population**

2164 The Safety Analyses Set (SAS) is defined as all randomized
2165 patients who initiate the protocol treatment.

2166

2167 **4.2 Efficacy Analysis**

2168 The following sections outline the planned analysis of the primary
2169 and secondary efficacy endpoints of this study. All efficacy analysis
2170 will be performed based on the FAS population.

2171

2172 **4.2.1 Analysis of the Primary Endpoint**

2173 The primary endpoint is DFS, defined as the time from
2174 randomization to the first occurrence of the following events:

2175 5) Relapse of breast cancer in the ipsilateral chest wall and
2176 regional lymph nodes

2177 6) Distant metastases (histologically confirmed or clinically
2178 diagnosed)

2179 7) Breast cancer related, non-breast cancer related or unknown

2180 deaths

2181 8) Contralateral breast cancer

2182

2183 Patients who have not had an event at the time of data analysis will
2184 be censored at the last date they were known to be alive and
2185 event-free.

2186 The null hypothesis for the primary endpoint is that the survival
2187 distributions of DFS in the two treatment groups are the same. The
2188 alternative hypothesis is that the survival distributions of DFS in the
2189 treatment and the control arm are different:

2190 $H_0: S_{\text{capecitabine}} = S_{\text{observation}}$ vs. $H_1: S_{\text{capecitabine}} \neq S_{\text{observation}}$

2191 We will estimate survival curves in each treatment arm using
2192 Kaplan–Meier estimator and the hazard ratio with 95%CI between
2193 treatment arms based on the proportional hazards model, with
2194 assumptions of proportional hazards confirmed based on the
2195 Schoenfeld residuals in the final dataset. We will use a two-sided
2196 log-rank test for the final analysis (at a significance level of 0.047).
2197 Stratified analyses of the lymph node status will also be conducted.

2198

2199 **4.2.2 Analysis of the Secondary Endpoints**

2200 The Secondary Endpoints are defined as follows:

2201 Overall Survival (OS) is defined as the time from randomization to
2202 death caused by any reason. Patients who are alive (including lost
2203 to follow-up) at the time of the analysis will be censored at the date
2204 when they were last known to be alive.

2205 Distant disease-free survival (DDFS) is defined as the time from
2206 randomization to the first occurrence of any of the following events:
2207 distant metastases, death caused by any reason, and contralateral
2208 invasive breast cancer. Patients who have not had a distant
2209 recurrence event at the time of data analysis will be censored at the
2210 date when they were last known to be alive.

2211 Locoregional recurrence-free survival (LRFS) is defined as the
2212 time from randomization to the first occurrence of any of the
2213 following events: ipsilateral breast or chest wall, regional lymph
2214 node, and death caused by any reason.

2215 The primary analyses for all secondary endpoints will be performed
2216 at the time of the primary analysis of the primary endpoint (DFS).

2217 The estimated Kaplan-Meier curves, and the hazard ratio with 95%
2218 CI, will be calculated based on the proportional hazards model, and
2219 the endpoints will be compared using a two-sided log-rank test (at
2220 a significance level of 0.05).

2221

2222 **4.2.3 Subgroup Analysis**

2223 At the time of the primary analysis, exploratory analyses will be
2224 performed for DFS to determine whether the magnitude of the
2225 effectiveness of the addition of capecitabine maintenance might
2226 differ according to patient sub-populations.

2227 Variables to be considered for defining subgroups of interest
2228 include the node status as well as other disease- or patient-related
2229 prognostic or predictive factors. We will conduct the subgroup
2230 analysis by estimating the hazard ratio with 95%CI and test the
2231 interaction, if applicable, among subgroups with two-sided p-value
2232 for the following items:

- 2233 ✓ Age (≤ 40 / > 40 and median and range)
- 2234 ✓ Tumor size at diagnosis (T1 / $\geq T2$)
- 2235 ✓ Histological grade (I+II/III)
- 2236 ✓ Nodal stage (N0 / N+)
- 2237 ✓ Stage (I / II / III)
- 2238 ✓ Ki-67 ($< 30\%$ / $\geq 30\%$)
- 2239 ✓ Lymphovascular invasion (positive / negative)
- 2240 ✓ Neo-/adjuvant regimens (anthracycline- or taxane-based/
2241 anthracycline- and taxane-based)

2242 The above background variables will be compared using statistical

2243 test (two-sided significance level is 0.05).

2244

2245 **4.2.4 Exploratory Analysis**

2246 In the capecitabine arm, a tabulation of those patients who have

2247 completed the protocol as planned against those who did not

2248 complete the protocol as planned will be perform. Completion /

2249 reduction / stop numbers and proportion of capecitabine are

2250 calculated at every 3-months visit to show the relative dose

2251 intensity (RDI) of capecitabine, which is defined as the actual

2252 cumulative dose compared to planned total dose.

2253 To determine the relationship between the RDI of capecitabine and

2254 DFS, estimated Kaplan–Meier curves and the hazard ratio with 95%

2255 CI will be calculated based on the proportional hazards model and

2256 the comparison will be tested using a two-sided log–rank test (at a

2257 significance level of 0.05).

2258

2259 **4.3 Safety Analyses**

2260 Safety data will be summarized based on the Safety Population.

2261 Verbatim descriptions of treatment–emergent adverse events (AEs)

2262 will be mapped to MedDRA thesaurus terms and graded according

2263 to NCI–CTCAE version 4.0. All AEs, including serious adverse

2264 events (SAEs), will be summarized by treatment arm and
2265 NCI-CTCAE grade. Comparisons between treatment groups will
2266 use the chi squared test (grade0-2/grade3-5(4)) with a two-sided
2267 p-value (at a significance level of 0.05). The variables to be tested
2268 are:

- 2269 ✓ White blood cell count
- 2270 ✓ Neutrophil count
- 2271 ✓ Platelet count
- 2272 ✓ Hemoglobin
- 2273 ✓ AST
- 2274 ✓ ALT
- 2275 ✓ Total Bilirubin
- 2276 ✓ Creatinine
- 2277 ✓ Appetite loss
- 2278 ✓ Abdominal pain / Diarrhea
- 2279 ✓ Nausea
- 2280 ✓ Vomiting
- 2281 ✓ Stomatitis
- 2282 ✓ Fatigue
- 2283 ✓ Hand-foot syndrome (HFS)

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2285

2286 **5. REFERENCES**

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2288 Statistic in Complex Clinical Trials', Biometrics, Volume 44,
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2291 Survival Trials', Statistics in Medicine, Volume 21, pages
2292 1969-1989.

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SYSUCC–001 Statistical Analysis Plan Amendment List

2296

page	item	before amendment (ver. 2.0)	after amendment (ver.3.0)
Cover	Cover	Version 2.0 approved date: November 30, 2012	Version 3.0 approved date: January 19, 2017
Page 107	2. STUDY DESIGN	(None)	So far, however, the number of events is too much lower than expected. This interim analysis is cancelled and approved by SYSUCC Ethics Committee. The p–value for final DFS analysis will be 0.047 yet.
Page 112	4.2.3 Subgroup Analysis	Tumor size at diagnosis (T1 /T2/T3)	Tumor size at diagnosis (T1 / >=T2)
Page 112	4.2.3 Subgroup Analysis	Histological grade (I /II/III)	Histological grade (I + II/III)
Page 112	4.2.3 Subgroup Analysis	KI–67 (≤14% / >14%)	KI–67 (<30% / ≥30%)
Page 112	4.2.3 Subgroup Analysis	Neo-/adjuvant regimens (anthracycline–based/ taxane–based/ anthracycline– and taxane–based)	Neo-/adjuvant regimens (anthracycline– or taxane–based/ anthracycline– and taxane–based)

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page	item	before amendment (ver. 1.0)	after amendment (ver.2.0)
Cover	Cover	Version 1.0 approved date: April 5, 2010	Version 2.0 approved date: November 30, 2012
Page 96	2. STUDY DESIGN	A total of 684 patients will be enrolled from approximately 18 sites in China.	A total of 424 patients will be enrolled from approximately 13 sites in China.
Page 96	2. STUDY DESIGN	Approximately 148 DFS events will be required to achieve 90% power at a 2–sided significance level of 5%. The estimated period of enrollment and follow–up will be 48 and 36 months, respectively. After considering 20% dropout rate	Approximately 109 DFS events will be required to achieve 80% power at a 2–sided significance level of 5%. The estimated period of enrollment and follow–up will be 60 and 36 months, respectively. After considering 9% dropout rate
Page 96	2. STUDY DESIGN	One interim analysis of DFS is planned on the basis of the results of the regular follow–up study 12 months after the completion of enrolment.	One interim analysis of DFS is planned on the basis of the results of the regular follow–up study 18 months after the completion of enrolment.

2299

2300