Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

This supplement contains the following items:

1. Study Protocol (page 3-67) (2020.07.24)
2. Statistical Analysis Plan (page 68-79) （2020.07.24）

Precision Treatment of Refractory Triple-Negative Breast Cancer Based on Molecular Subtyping

(FUSCC-TNBC- umbrella)

FUTURE Trial

Study Protocol

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ClinicalTrials.gov Identifier: NCT 03805399

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Protocol Abstract

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		mutation B2→without PI3K/AKT mutation B4→without PI3K/AKT mutation	B2: SHR6390 150 mg p.o qd, 3 weeks on, 1 week off. SHR3680 240 mg p.o qd continuously. 4 weeks as a cycle B4: SHR2554 300 mg p.o bid, continuously. SHR3680 240 mg p.o qd continuously. 4 weeks as a cycle
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	D	BLIS subtype→with BRCA1/2 germline mutation	SHR3162 150 mg p.o bid, continuously. Famitinib 20 mg p.o qd continuously. 4 weeks as a cycle
	E	BLIS subtype→without BRCA1/2 germline mutation	E1: Apatinib 500 mg p.o qd continuously. E2: Apatinib 250 mg p.o qd continuously. VP-16 50 mg p.o qd,2 weeks on, 1 week off.

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	F	MES subtype→without PI3K/AKT mutation	Famitinib 20 mg p.o qd continuously. VP-16 50 mg p.o qd,2 weeks on, 1 week off. 3 weeks as a cycle
	G	MES subtype→with PI3K/AKT mutation	Everolimus 10 mg p.o qd continuously. Nab-paclitaxel 100 mg/m^2 i.vgtt d1,8,15, 4 weeks as a cycle
Inclusion criteria	1) Age more than 18 years old. 2) Histologically confirmed invasive TNBC (specific definition: the positive definition of ER <1% of the tumor cells was defined as ER negative, PR <1% tumor cell positive was defined as PR-negative, HER2 0-1 + or HER2 was + + but		

	was detected as negative by FISH or CISH without amplification, defined as HER2-negative). 3) Locally advanced breast cancer or metastatic breast cancer. 4) Refractory triple-negative breast cancer (the existing treatment has failed), specific definition: anthracycline, taxanes, platinum, capecitabine, gemcitabine and vinorelabine, the above commonly used chemotherapeutic drugs failed. 5) There is at least one measurable lesion according to RECIST version 1.1 standard (conventional CT scan ≥ 20 mm, spiral CT scan ≥ 10 mm). 6) The main organ functions are basically normal and meet the following conditions: HB ≥ 90 g/L (no blood transfusion). ANC ≥ 1.5×10^9/L ≥ 75×10^9/L within 14 days), biochemical examination should meet the following criteria: TBIL ≤ 1.5 × ULN (upper limit of normal value). ALT and AST ≤ 3 × ULN, ALT and AST ≤ 5×ULN if there is liver metastasis). Serum Cr ≤ 1×ULN, endophytic creatinine clearance rate > 50 ml/min (Cockcroft-Gault formula). 7) No radiotherapy, endocrine therapy, molecular targeted therapy, and surgery were received within 3 weeks prior to the start of the study, and recovered from the acute toxicity response previously treated. no peripheral neuropathy or I-degree peripheral neurotoxicity. 8) ECOG score ≤ 2 and life expectancy ≥ 3 months. 9) Female subjects with fertility were required to use a medically approved method of birth control during the study treatment and at least three months after the last use of the research drug.

	10) The subjects volunteered to join the study and signed the informed consent form with good compliance and follow-up.
Exclusion criteria	1) Radiotherapy (except for palliative reasons), chemotherapy, immunotherapy, bisphosphonate (except for bone metastases) three weeks before treatment. 2) Uncontrolled central nervous system metastases (symptomatic or requiring the use of glucocorticoids or mannitol to control symptoms). 3) History of clinically important or uncontrolled heart diseases, including congestive heart failure, angina pectoris, myocardial infarction or ventricular arrhythmias in the last six months. Ongoing adverse reactions ≥1 due to previous treatment. The exception to this is hair loss or what researchers believe should not be excluded. Such cases should be clearly documented in the investigator's notes. 4) Pregnant or lactating patients. 5) Malignant tumors in the past five years (except for cured skin basal cell carcinoma and cervical in situ cancer).
Sample size	Participants will enter different treatment arms according to their molecular subtype (IHC staining) and FUSCC 484 gene panel testing results. Seven treatment arms and six regimens were initially set up. 20 patients are planned to be treated per treatment arm.
Research process	Treatment until the tumor progression or an intolerable toxicity.
Safety evaluation	All adverse events during the study period should be recorded in CRF tables, and the researchers should judge the degree of the

	adverse events and their relationship with the tested drugs.
Duration of study	30 months (2018.08-2021.02)
Follow up	12 months after the last case was admitted to the study
Main analysis date	2022.02

Precision Treatment of Refractory Triple-Negative Breast Cancer Based on Molecular Subtyping (FUSCC-TNBC- umbrella) FUTURE Trial

1 Study Background

1.1 Current situation and dilemma of treatment of triple-negative breast cancer

As a special molecular classification of breast cancer, triple-negative breast cancer (TNBC) refers to breast cancer, which lacks the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2), accounting for approximately 15% of the total. It has special molecular expression characteristics, biological behavior and clinicopathological characteristics, showing relatively young age, the risk of early recurrence, high distant metastasis rate, high probability of visceral metastasis and brain metastasis, rapid progression, and limited treatment [1-4]. The concept of triple-negative breast cancer has been proposed for nearly 20 years, and although there are some basic and clinical research results, there has been no breakthrough. A large number of clinical trials have attempted to study the potential therapeutic targets of triple-negative breast cancer. The overall prognosis of triple-negative breast cancer has not improved. Once recurrence and metastasis occur, the overall survival time is only approximately 1 year, and it is still the worst prognosis type in breast cancer.

The reason for the dilemma of TNBC is heterogeneity [5-7]. The naming of TNBC is an exclusive diagnosis, but it is in fact a group of heterogeneous diseases. The research direction is to distinguish the subtypes of TNBCs, to figure out potential therapeutic targets of each subgroup, and to improve the treatment strategy and prognosis of these patients.

1.2 Definition of refractory TNBC in this study

Because of the lack of traditional effective endocrine and anti-HER2 targeted

therapy for triple-negative breast cancer, chemotherapy is the most important systemic treatment for patients with advanced triple-negative breast cancer. The commonly used chemotherapeutic drugs available in China include anthracyclines, taxanes, platinum, capecitabine, gemcitabine and vinorelabine. The overall efficacy of the above conventional chemotherapeutic drugs in the treatment of advanced triple-negative breast cancer is poor. According to the results of several phase 3 clinical trials, the overall survival time of advanced triple-negative breast cancer is approximately 1 year [8-10]. In this study, refractory TNBC was defined as the failure of all the above chemotherapeutic drugs.

1.3 Further classification of TNBC based on multiomics data

Because triple-negative breast cancer has high invasiveness, few treatments and poor prognosis, there have been a series of studies trying to evaluate the efficacy of targeted drugs for triple-negative breast cancer, but they have failed to achieve the desired results. One of the possible reasons for the analysis is that the patients in these studies were generally triple-negative breast cancer, without further accurate classification of triple-negative breast cancer, and lack of more accurate classification optimization treatment. These failed studies suggest that smarter and more precise treatment strategies should be targeted therapies for possible molecular drive events in each subtype.

The difficulties and dilemma in the treatment of TNBC have been mentioned above. As mentioned before, TNBC is a group of heterogeneous diseases. Great effort has been made to further distinguish the subtypes of TNBC according to the characteristics and potential treatment targets of different subtypes to achieve individualized treatment and improve the prognosis of patients. At present, there are three main studies on how to further classify TNBC:

1) The study of Lehmann et al. from the Vanderbilt-Ingram Cancer Center, published in Journal of Clinical Investigation, 2011[11], further divided TNBC into six subtypes: basal-like1 (BL1), basal-like2 (BL2), immune-modulatory (IM), mesenchymal (M), mesenchymal stem cell-like (MSL), and luminal androgen receptor

positive (LAR). The data showed that BL1, IM and MSL had better prognoses. The median total survival time was approximately 20 months. BL-2, M and LAR had poor prognosis, and the median survival was only 6-8 months. Furthermore, GE analysis helps to identify TNBC cell line models representative of these subtypes. Predicted "driver" signaling pathways were pharmacologically targeted in these cell line models as proof of concept that analysis of distinct GE signatures can inform therapy selection. BL1 and BL2 subtypes had higher expression of cell cycle and DNA damage response genes, and representative cell lines preferentially responded to cisplatin. M and MSL subtypes were enriched in GE for epithelial-mesenchymal transition, and growth factor pathways and cell models responded to NVP-BEZ235 (a PI3K/mTOR inhibitor) and dasatinib (an abl/src inhibitor). The LAR subtype includes patients with decreased relapse-free survival and is characterized by androgen receptor (AR) signaling. LAR cell lines were uniquely sensitive to bicalutamide (an AR antagonist). These data may be useful in biomarker selection, drug discovery, and clinical trial design that will enable alignment of TNBC patients to appropriate targeted therapies. The team published a research paper at PloS One in 2016[12] using histopathological quantification and laser-capture microdissection to determine that transcripts in the previously described immunomodulatory (IM) and mesenchymal stem-like (MSL) subtypes, and they found that these transcripts were contributed from infiltrating lymphocytes and tumor-associated stromal cells, respectively. Therefore, they refined TNBC molecular subtypes from six into four tumor-specific subtypes (BL1, BL2, M and LAR) and demonstrated differences in diagnosis age, grade, local and distant disease progression and histopathology. Using five publicly available neoadjuvant chemotherapy breast cancer gene expression data sets, they retrospectively evaluated the chemotherapy response of over 300 TNBC patients from pretreatment biopsies subtyped using either the intrinsic (PAM50) or TNBC-type approaches. Combined analysis of TNBC patients demonstrated that TNBC subtypes significantly differed in response to similar neoadjuvant chemotherapy, with 41% of BL1 patients achieving a pathological complete response compared to 18% for BL2 and 29% for LAR with 95% confidence intervals (CIs; [33, 51], [9, 28], [17, 41], respectively).

2) The study of Bursteinet et al., published in Clin Cancer Res, 2015 [13], suggested that TNBC is a heterogeneous disease. In their study, RNA and DNA profiling analyses were conducted on 198 TNBC tumors and finally classified TNBC tumors into four distinct subtypes: (i) luminal androgen receptor (LAR), (ii) mesenchymal (MES), (iii) basal-like immunosuppressed (BLIS), and (iv) basal-like immune-activated (BLIA). Of these, the prognosis was worst for BLIS tumors and best for BLIA tumors for both DFS (log-rank test: P = 0.042 and 0.041, respectively) and DSS (log-rank test: P = 0.039 and 0.029, respectively). DNA copy number analysis produced two major groups (LAR and MES/BLIS/BLIA) and suggested that gene amplification drives gene expression in some cases [FGFR2 (BLIS)]. Putative subtype-specific targets were identified: (i) LAR: androgen receptor and the cell surface mucin MUC1, (ii) MES: growth factor receptors [platelet-derived growth factor (PDGF) receptor A, c-Kit], (iii) BLIS: an immunosuppressing molecule (VTCN1), and (iv) BLIA: Stat signal transduction molecules and cytokines.

3) **Fudan University Shanghai Cancer Center Four Subtyping** Shao ZM et al.'s study [14-15] comprehensively analyzed the clinical, genomic, and transcriptomic data of a cohort of 465 primary TNBC patients. PIK3CA mutations and copy-number gains of chromosome 22q11 were more frequent in our Chinese cohort than in The Cancer Genome Atlas (TCGA). We classified TNBCs into four transcriptome-based subtypes: (i) luminal androgen receptor (LAR), (ii) immunomodulatory (IM), (iii) basal-like immune-suppressed (BLIS), and (iv) mesenchymal-like (MES). Putative therapeutic targets or biomarkers were identified among each subtype. Importantly, the LAR subtype showed more ERBB2 somatic mutations, infrequent mutational signature 3 and frequent CDKN2A loss. The comprehensive profile of TNBCs provided here will serve as a reference to further advance the understanding and precision treatment of TNBC. According to our previous data, the characteristics of each type and the potential therapeutic targets of the four subtypes are described below:

(i) Luminal androgen receptor subtype (LAR). The prognosis of the LAR type was moderate, accounting for 21.5% of the total. To explore potential therapeutic targets of the four TNBC subtypes, we further investigated the distinct genomic alterations in

each subtype. Memo analysis results implied that both LAR and other subtypes were affected by genomic alterations in receptor tyrosine kinase and the cell cycle pathway, but their activating patterns differed significantly. The LAR subtype featured the highest PIK3CA (37% in LAR vs. 13% in other subtypes, FDR < 0.1) mutations, while other subtypes harbored more copy number amplifications in KRAS and PIK3CA. Interestingly, we found 4 patients (6% in LAR vs 0% in other subtypes, FDR < 0.1) harboring ERBB2 nonsilent SNVs, including activating mutation V777L (in two patients), D769Y (in one patient) and one L755S mutation inferring ERBB2 activation but also resistance to trastuzumab and lapatinib. We further investigated the expression data of these samples. ERBB2 pathway scores defined by Gene Set Variation Analysis (GSVA) demonstrated that patients with ERBB2 mutations also showed activation in the ERBB2 pathway. We also searched the database of our institute and found that within 58 IHC-determined androgen receptor-positive TNBCs, eight had ERBB2 somatic mutations.

Although both the LAR subtype and others showed frequent genomic alterations in cell cycle-related genes, the LAR subtype featured frequent CDKN2A alterations (19% in LAR vs 7% in others) and astonishingly no RB1 loss or mutation. Combined genomic and expression analysis also supported the impact of these two events (figure 4c), which had been linked to the sensitivity of CDK 4/6 inhibitor, on mRNA expression. In general, LAR is characterized by 16% enrichment of HER2 mutation, partial CDKN2A/B deletion and normal RB1, which may be sensitive to anti-HER2 targeted therapy, anti-androgen endocrine therapy or CDK4/6 inhibitor, respectively.

(ii) Immuno-modulatory subtype (IM). The prognosis of the IM type was the best, accounting for 22.8%. Despite the relatively superior outcome of the IM subtype, 10% of patients in this group experienced recurrence and/or metastasis within 5 years after surgery, which prompted us to investigate the potential of additional treatment in this subtype. This subtype was named for its elevated immune cell signaling observed in gene expression data. We first checked the immunogenicity of the IM subtype. HE-stained slides proved that these groups of patients had a higher prevalence of both stromal tumor infiltrating lymphocytes (TILs) and intratumor TILs [16-17]. Although the

mutation load was not significantly higher in the IM subtype, Gene Set Enrichment Analysis (GSEA) between IM TNBCs and other subtypes demonstrated activation in antigen processing- and presentation-related pathways. In addition, combining CIBERSORT and differential expression profiling, we demonstrated that immune-activating cells and immunostimulators were enriched in the IM subtype.

As both clinical and omics features have proven that immune recognition is activated in the IM subtype, the way in which these tumors achieve immune escape is likely to be the recruitment of immune suppressive cells or the activation of immune checkpoint molecules. With the CIBERSORT algorithm, we checked that immune suppressive cell numbers were not elevated in the IM subtype, while expression profiling demonstrated that immunoinhibitors (especially IDO1) were significantly overexpressed in this subtype, providing a rationale for the use of immune checkpoint blockade.

(iii) Basal-like immune suppressed subtype (BLIS). The prognosis of BLIS type was poor, accounting for 36.3%. The HRD (homologous recombination repair defect) score was used to further classify the BLIS subgroup-HRD high score group and HRD low score group to accurately screen those patients who were sensitive to DNA damage, such as platinum drugs. A high HRD score was significantly correlated with mutation of the BRCA gene, and patients might benefit from olaparib [18]. The prognosis of these patients was significantly better than that of patients with low HRD scores. However, the conditions of this study were based on empirical treatment with platinum and failed patients. According to the status of BRCA mutation, patients with BRCA mutation will be treated with PARP inhibitor included therapy. If there was no mutation in the BRCA gene, patients will be treated with apatinib/famitinib, an inhibitor of VEGFR. Apatinib-related efficacy and safety data can be found in the attached researcher's manual.

(iv) Mesenchymal subtype (MES). The prognosis of the MES subtype was poor, accounting for 19.4%. Gene expression profiling revealed that the MES subtype displayed characteristics of breast cancer stem cells (CSCs). We further focused on the JAK/STAT3 signaling pathway, which plays a crucial role in the maintenance of breast CSCs. We observed higher expression of JAK1 and the most important driver of

JAK/STAT3 activation, IL-6, in the MES subtype. Besides, an activated or tyrosine phosphorylated STAT3 (pSTAT3) gene signature score defined by Sonnenblick et al. was also higher in the MES subtype than in other subtypes. These results indicated upregulation of the JAK/STAT3 signaling pathway and the potential of STAT3 inhibitor treatment for this subtype.

Based on the deep mining of multigroup data of TNBC, we designed this study for patients with refractory (existing standard chemotherapy failure) TNBC. Participants will enter different treatment arms according to their molecular subtype (by IHC staining) and FUSCC 500+ gene panel testing results. This kind of exploratory clinical trial is commonly known as an umbrella trial. After multigene detection, it is more beneficial to the individualized treatment and accurate treatment of TNBC by further understanding the nature and characteristics of each subgroup.

2 Study Design

2.1 Systemic design

This study is a prospective, multicenter, open label, umbrella phase II clinical study. It is planned to screen 200 to 300 patients with refractory TNBC who have failed the available treatments (Fig. 1). Based on the different multigene expression profiles and the potential molecular characteristics of different pathways, seven treatment arms were initially set up to eroll 10-20 patients per treatment arm. Therefore, a total of approximately 140 patients were enrolled in this study. Three or more of 20 patients in each arm group who reached CR or PR will be defined to reach the study end point.

This study is an exploratory phase II clinical trial, the main purpose of which is to screen valuable therapeutic arms to develop phase III clinical studies with larger samples.

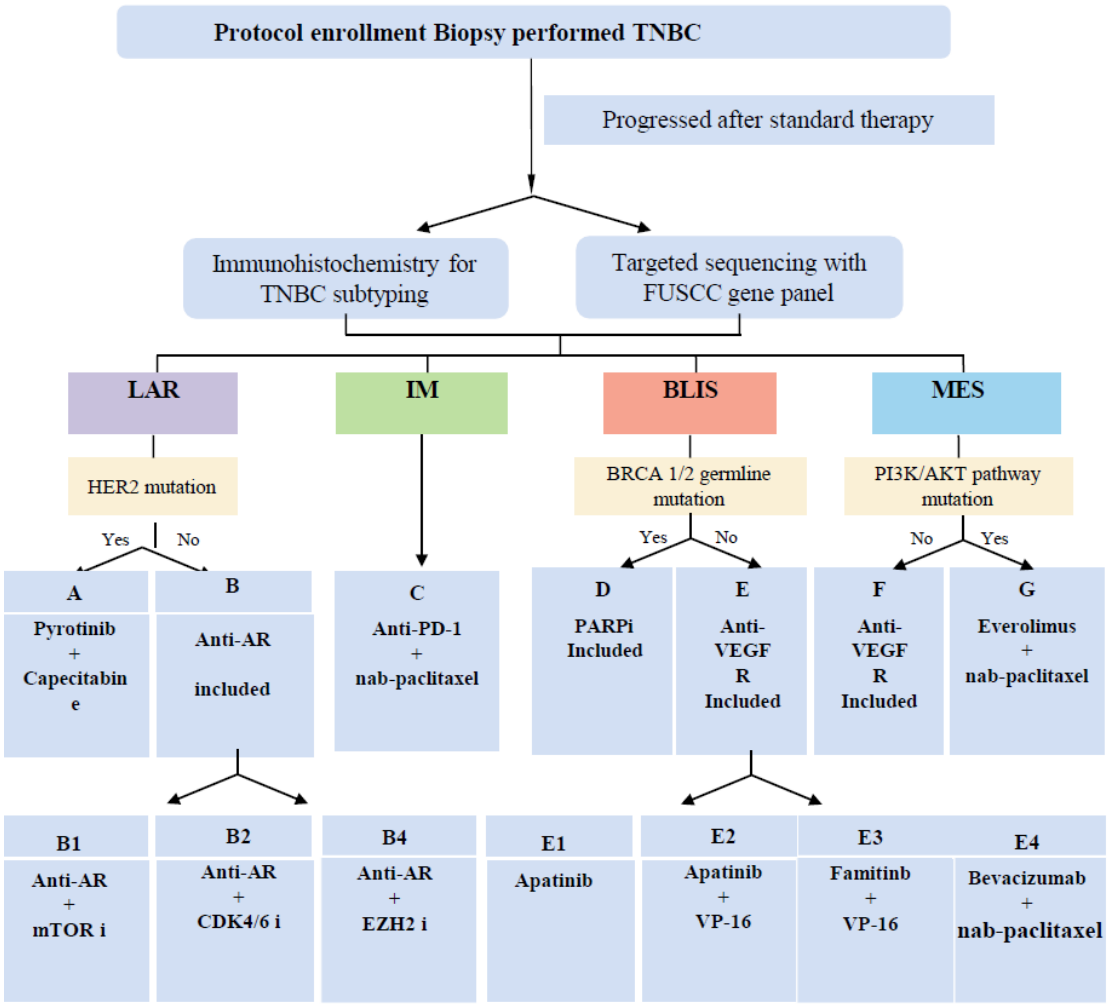


Figure 1. The FUTURE trial schema: integrating TNBC subtyping and genomic targeting

2.2 Sample size estimation

Using Bayesian Predictive Probability to monitor the efficacy of each arm, based on the number of patients who achieved objective remission (CR+PR) observed in real time, based on futility or efficacy considerations, the study can be terminated early for each arm independently. Assume that the reference objective response rate is p0=15%, and the prior probability fits the Beta distribution (0.05, 0.05) as a week prior information. Take the probability threshold of 0.5 for declaring efficacy at the end of the trial in each arm, 0.1 for early termination due to ineffectiveness, and 0.9 for early termination due to effectiveness. Using Bayesian prediction probability, the futility and efficacy boundaries are obtained as shown in Table 1.1, and the simulation results under different true values of ORR are shown in Table 1.2.

Table 1.1 Futility and efficacy Boundaries Based on Bayesian Prediction Probability

Subject number	Futility boundary b1	Efficacy boundary b2
10	0	3
12	1	4
14	1	4
16	2	4
18	2	4
20	3	4

Note:

1. When the observed number of CR+PR cases is less than or equal to the futility boundary value b1, the study can be terminated due to futility;

2. When the observed number of CR+PR cases is greater than or equal to the effective cutoff value b2, the study can be terminated due to effectiveness.

Table 1.2 Simulation results under different true values of ORR

Simulation case	True ORR	Probability of declaring efficacy	Average number of.patients enrolled	Observed ORR
1	10.0%	0.089 [1]	12.52	9.0%
2	15.0%	0.131 [1]	13.14	14.5%
3	20.0%	0.542 [2]	13.09	20.9%
4	30.0%	0.916 [2]	10.24	31.9%

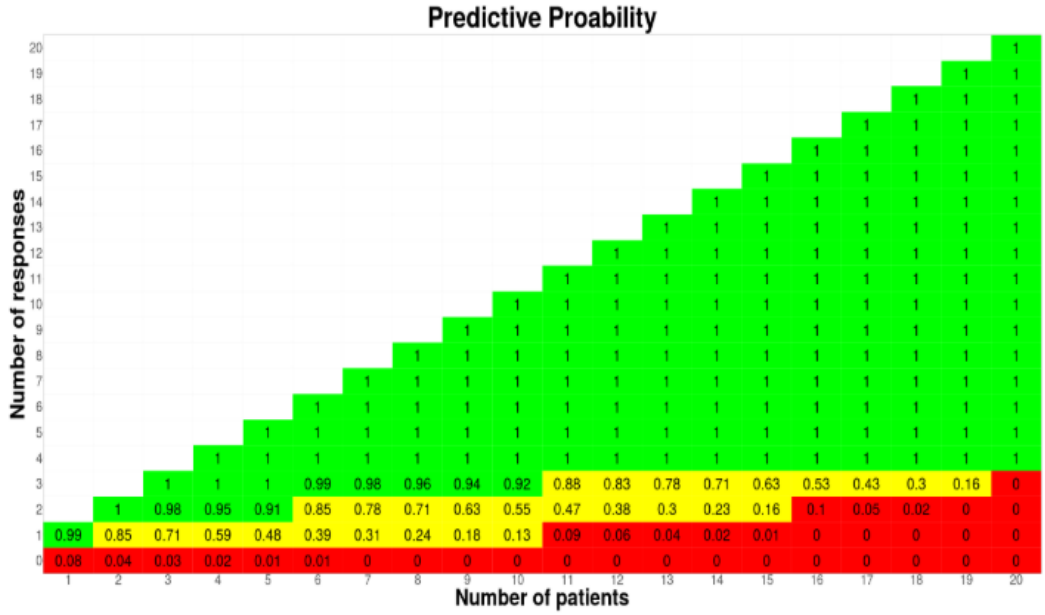
Note:

[1] Cases 1 and 2 give the probability of incorrectly declaring efficacy where the true ORR ≤ p0=15%.

[2] Cases 3 and 4 give the probability of correctly declaring efficacy where the true ORR > p0=15%.

For arm A and arm G, due to the difficulty of enrolling and good efficacy observed, these two arms can be terminated in advance according to Table 2.

Table 2 Decision table based on Bayesian prediction probability



Note:

1. The horizontal axis is the number of patients enrolled, and the vertical axis is the number of patients with CR+PR.

2. Green indicates that the study can be terminated due to effectiveness; red indicates that the study can be terminated due to ineffectiveness; yellow indicates that enrollment needs to be continued.

For the arm C, it can be expanded to a maximum of 41 cases based on the promising efficacy reported in the interim analysis. Assuming an ORR of 30%, at the significant level (alpha one-sided 0.025), the 41 enrolled patients could provide 90% power to make the lower bound of the 95% confidence interval (exact algorithm) of the ORR greater than 10%. After enrolling 20 patients, an interim analysis was conducted to decide whether to expand to 41 patients. The consumption of interim analysis was β=0.02. At the interim analysis, if more than or equal to 4 of the 20 patients achieved CR or PR, another 21 patients will be enrolled. Table 3 presents the 95% confidence interval (exact algorithm) for ORR from 15% to 50% for 20 patients. Considering a dropout rate of 10%, 46 patients were required in this arm.

Table 3 The 95% confidence intervals of ORR in arm C in the first 20 patients (exact algorithm)

ORR（N=20）	The number of CR or PR	95%CI
10%	2	(1.2%, 31.7%)
15%	3	(3.2%, 37.9%)
20%	4	(5.7%, 43.7%)
25%	5	(8.7%, 49.1%)
30%	6	(11.9%, 54.3%)
35%	7	(15.4%, 59.2%)
40%	8	(19.1%, 63.9%)
45%	9	(23.1%, 68.5%)
50%	10	(27.2%, 72.8%)

3 Study Purpose

3.1 Primary purpose

To evaluate the efficacy and safety of precision treatment of refractory TNBC based on molecular subtyping.

3.2 Exploratory purpose

To explore the pharmacokinetics of CDK4/6 inhibitor (SHR6390) in combination with AR inhibitor (SHR3680). A total of 18 blood collection points, each blood collection point to take 2 tubes blood (3 ml each), see 8.3 specific description.

4 Study endpoints

4.1 Primary endpoint

Overall Response Rate, (ORR): CR+ PR

4.2 Secondary endpoints

1) Disease Control Rate, (DCR): CR+PR+SD

2) Progression Free Survival, (PFS)

3) Overall Survival (OS)

4) Safety: CTCAE v5.0

5 Therapeutic Regimen

5.1 The mechanism of drug and supply of drug

Table 4 The drugs used in the FUTURE study

name	target	supply
Pyrotinib	Pan-HER inhibitor	Free
Apatinib	VEGFR inhibitor	Free
SHR3162	PARP inhibitor	Free
SHR6390	CDK4/6 inhibitor	Free
SHR3680	AR inhibitor	Free
SHR1210	Anti PD-1 antibody	Free
SHR2554	EZH2 inhibitor	Free
Everolimus	mTOR inhibitor	Insurance
Capecitabine	Chemo	Insurance
nab-paclitaxel	Chemo	Free
Oral etoposide	Chemo	Insurance
Famitinib	VEGFR inhitior	Free
BP102	Bevacizumab (anti-VEGF)	Free

5.2 Specific regimen

The specific treatment options and dosages of the 7 treatment arms in this study are shown in Table 5. Participants will receive treatment until disease progression or intolerable toxicity. The evaluation will be based on MRI, CT and physical examination according to the novel international standard set by the RECIST committee. Evaluation will be performed every two cycles (A, E and F arms 6 weeks ±3 days and other arms 8 weeks ±3 days). Since the primary endpoint of this study was ORR, patients who

obtained CR or PR required imaging efficacy confirmation after 4 weeks.

In the clinical study process, based on efficacy, safety and existing treatment methods, according to the target and targeted drug availability, a new treatment arm may be added during the treatment process, and then it will be submitted to the Ethics Committee for discussion and approval before implementation.

Table 5 Specific medication options for seven treatment arms

Arms	Conditions	Regimens
A	LAR subtype →HER2 gene mutation/amplification by NGS	Pyrotinib[a] 400 mg qd and capecitabine[b] 1000 mg/m2 bid (d1-d14)
B	LAR subtype→without HER2 gene mutation/amplification by NGS B1→with PI3K/AKT mutation B2→without PI3K/AKT mutation B4→without PI3K/AKT mutation	B1: Everolimus[c] 10 mg p.o qd continuously. SHR3680[d] 240 mg p.o qd continuously. 4 weeks as a cycle B2: SHR6390[e] 150 mg p.o qd, 3 weeks on, 1 week off. SHR3680[d] 240 mg p.o qd continuously. 4 weeks as a cycle B4: SHR2554[f] 300 mg p.o bid, continuously. SHR3680[d] 240 mg p.o qd continuously. 4 weeks as a cycle
C	IM subtype→CD8 high expression	SHR1210[g] 200 mg, i.vgtt, d1,every 2 weeks Nab-paclitaxel[b] 100 mg/m^2 i.vgtt d1,8,15, 4 weeks as a cycle
D	BLIS subtype→with BRCA1/2 germline	SHR3162[h] 150 mg p.o bid, continuously. Famitinib[i] 20 mg p.o qd continuously.

	mutation	4 weeks as a cycle
E	BLIS subtype→without BRCA1/2 germline mutation	E1: Apatinib[j] 500 mg p.o qd continuously. E2: Apatinib[j] 250 mg p.o qd continuously. VP-16[b] 50 mg p.o qd,2 weeks on, 1 week off. 3 weeks as a cycle E3: Famitinib[i] 20 mg p.o qd continuously. VP-16[b] 50 mg p.o qd,2 weeks on, 1 week off. 3 weeks as a cycle E4: BP102[k] 10 mg/kg d1, every 2 weeks. Nab-paclitaxel[b] 100 mg/m^2 i. vgtt d1,8,15, 4 weeks as a cycle
F	MES subtype→without PI3K/AKT mutation	Famitinib[i] 20 mg p.o qd continuously. VP-16[b] 50 mg p.o qd,2 weeks on, 1 week off. 3 weeks as a cycle
G	MES subtype→with PI3K/AKT mutation	Everolimus[c] 10 mg p.o qd continuously. Nab-paclitaxel[b] 100 mg/m^2 i.vgtt d1,8,15, 4 weeks as a cycle

[a] HER1/2/4 inhibtor

[b] chemotherapy

[c] mTOR inhibitor

[d] androgen receptor inhibitor

[e] CDK4/6 inhibitor

[f] EZH2 inhibitor

[g] anti-PD-1 antibody

[h] PARP1 inhibitor

[i] a multitarget inhibitor of c-kit, VEGFR-2 and PDGFRβ

[j] VEGFR2 inhibitor

[k] bevacizumab biosimilar

5.3 Test compound (details of unlisted drugs as described in annex)

5.3.1 Pyrotinib

Pyrotinib (SHR1258) is an orally administered dual irreversible tyrosine kinase inhibitor of epidermal growth factor receptor (HER1) and human epidermal growth factor receptor 2 (HER2), which was developed by Jiangsu Hengrui Pharmaceutical Co., Ltd. The recommended dosage of pyrotinib is 400 mg by oral administration every day.

Pyrotinib has completed phase I and randomized controlled phase II clinical trials in advanced breast cancer in China, and its results have been published in well-known international journals [19-20]. Based on the good tolerance of the phase I study, a phase II domestic multicenter clinical study assigned patients with pyrotinib in combination with capecitabine or lapatinib in combination with capecitabine, which demonstrated that pyrotinib combined with capecitabine showed superior clinical benefit (ORR and PFS) over lapatinib plus capecitabine. PFS is prolonged more than doubled (18.1 months vs. 7.0 months). Due to its excellent efficacy, the drug has entered the CFDA's fast-track designation and will soon be available in China. Two randomized controlled phase III clinical trials of patients with advanced HER2 breast cancer enrollment are almost finished. In addition, there are still many ongoing pyrotinib clinical studies, including the national multicenter randomized controlled double-blind phase III clinical trial of neoadjuvant early HER2 breast cancer led by FUSCC, research on advanced gastric cancer subjects (Research BLTN-Id) and the HER2 mutant non-small cell lung cancer phase II clinical study (HR-BLTN-II-NSCLC study).

Phase II studies have illustrated that pyrotinib combined with capecitabine is well tolerated. Common grade 3-4 toxicities included hand-foot syndrome (24.6%), diarrhea (15.4%), granulocytopeniaoutu (9.2%), and vomiting (4.6%).

5.3.2 SHR6390

Cyclin-dependent kinase (CDK) 4/6 are important therapeutic targets for breast cancer. Targeted endocrine therapy has recently shown impressive effectiveness in hormone receptor-positive and HER2-negative (HR+/HER2-) advanced breast cancer. First-line combination therapy could achieve 24 months of progression-free survival (for endocrine monotherapy it is 14 months), and second-line combination therapy can increase progression-free survival by approximately 6 months. At present, CDK4/6 inhibitors of Pfizer, Novartis and Eli Lilly have all been approved by the FDA for hormone receptor-positive and HER2-negative advanced breast cancer. They have also been recommended by the NCCN as the first-class treatment strategy. Palbociclib, a CDK4/6 inhibitor developed by Pfizer, was approved by the FDA in 2015 and 2016 respectively, in combination with letrozole or fulvestrant for the treatment of HR+/HER2- advanced breast cancer. Novartis' ribociclib was also approved by the FDA in combination with aromatase inhibitors to treat HR+/HER2- advanced or metastatic breast cancer in March 2017. Eli Lilly's abemaciclib was approved for combination with fulvestrant or monotherapy for HR+/HER2- advanced or metastatic breast cancer that progressed after endocrine therapy in September 2017.

SHR6390 is an oral, highly effective and selective small molecule CDK4/6 inhibitor developed by Jiangsu Hengrui Pharmaceutical Co Ltd. In vitro enzymatic tests showed that SHR6390 had CDK4/6 inhibitory activity (IC50 10-12 nM) comparable to that of palbociclib, and its selectivity for CDK4/6 was much higher than that of other CDKs (including CDK1/2/9). In October 2015, SHR6390 successfully obtained clinical trial approval from the China Food and Drug Administration as a new class 1.1 chemical drug. Two phase I studies intended to explore the tolerability and pharmacokinetics of SHR6390 in advanced solid tumors and melanoma are being conducted in China as of December 2017. Phase I clinical trials indicated that the recommended dose for phase II is 150 mg/d, taken orally once a day for 3 consecutive weeks (D1-21) and discontinued at the 4th week (D22-28), and one dose is given every 28 days in the medicine cycle. Fasting is recommended (fasting should be guaranteed at least 1 hour before and 2 hours after taking the drug during the administration period).

In the abovementioned phase I study of advanced solid tumors, among all 20 subjects, most of the drug-related AEs were grades 1-2, grade 3 AEs included neutropenia (7 cases) and leukopenia (5 cases), and no grade 4 AEs were observed. No patients withdrew from the study due to AEs, and no serious adverse events (SAEs) occurred in this study, which was well tolerated.

5.3.3 SHR3680

SHR3680 is a new oral androgen receptor (AR) inhibitor developed by Jiangsu Hengrui Pharmaceutical Co Ltd. SHR3680 is recommended for oral administration at 240 mg once daily.

Preclinical studies have verified that SHR3680 can effectively inhibit AR nuclear translocation, AR transcriptional activity, AR overexpression in prostate cancer cell proliferation and prostate-specific antigen secretion and has no AR partial agonistic effect. SHR3680 is intensively comparable and therefore significantly better than the first generation AR antagonist bicalutamide.

A phase I/II clinical study designed to explore the tolerability, pharmacokinetics, and efficacy of SHR3680 in patients with advanced castration-resistant prostate cancer (CRPC) was launched in China (study number: SHR- 3680-I/II-CRPC-TOL/PK/PD). As of April 25, 2017, the dose climb of the Phase I trial climbed from 40 mg/d to 360 mg/d, accumulating 14 cases, and no dose-limiting toxicity (DLT) was observed. The phase II trial is being expanded in the 80, 160 and 240 mg/d dose groups, and 45 patients were enrolled. SHR3680 is confirmed to be safe, as shown in preliminary results. Common AEs include hot flashes, male mammary gland development and elevated ALT/AST, all of which are mild to moderate. PSA decreases significantly, and bone metastasis can be stabilized. As demonstrated in the blood samples of the 40, 80, 160, and 240 mg/d dose groups, the pharmacokinetics (PK) showed linear characteristics, with good absorption and a plasma half-life of ~ 4 days. In addition, SHR3680 has also undergone a Phase I clinical study of tolerability and pharmacokinetics in patients with advanced CRPC in Australia. As of April 15, 2017, the study had enrolled 3 patients in the 40 mg/d group, and no DLT was reported. AE includes abdominal pain, nausea, runny nose, insomnia, gastroesophageal reflux, and diplopia, mostly mild to moderate.

5.3.4 SHR1210

PD-1 is an immune checkpoint protein involved in the negative regulation of antigen-specific T-cell function. SHR-1210 (also called INCSHR01210), a humanized PD-1 antibody, is an original drug independently developed by Jiangsu Hengrui Pharmaceutical Co Ltd. There is a first human trial (FIH) in Australia in addition to 14 ongoing clinical studies in China.

As of November 2017, the most common AE was hemangioma (occurring in > 30% of subjects receiving SHR-1210, especially cutaneous hemangiomas). Other commonly reported AEs (occurring in > 10% of SHR-1210 subjects) include anemia, fatigue, fever, and elevated transaminase (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]). The most commonly reported (approximately 1% of subjects) serious adverse events (SAEs) in all studies included hemangiomas, lung infections, pneumonia, upper gastrointestinal (GI) bleeding, liver failure, and malignant progressive tumors. Immune-related SAE pneumonia (occurring in 1.1% of subjects) and interstitial lung disease (occurring in 0.5% of subjects) were regarded as SHR-1210-related adverse events. Other immune-related AEs that occurred in ≥5% of SHR-1210 subjects included elevated AST, elevated ALT, rash, diarrhea, and hypothyroidism.

It is recommended that SHR1210 be a fixed dose of 200 mg, intravenous infusion, once every 2 weeks, every 4 weeks as a cycle.

5.3.5 SHR1316

SHR1316 is an original drug independently developed by Jiangsu Hengrui Pharmaceutical Co Ltd. It is a humanized PD-L1 antibody. As of May 15, 2018, phase I clinical studies for SHR1316 have been conducted in Australia and China. The Australian study completed a 20 mg/kg dose group climb. A total of 37 subjects received 4 different dose levels of SHR1316 (1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg), and no DLT or drug-related SAEs occurred. Drug-related AEs include diarrhea, hyperthyroidism, headache, nausea, loss of appetite, fatigue, and infusion-related reactions, all of which are mild or moderate and clinically controllable. A Phase I clinical study (in progress in FUSCC, PI: Professor Hu Xichun) enrolled 6 subjects (3 in the 3 mg/kg dose group and 3 in the 10 mg/kg dose group), and no DLT or drug-

related SAEs occurred. The reported drug-related adverse events, including fatigue, abdominal pain, and increased bilirubin, are mild to moderate and clinically controllable.

5.3.6 SHR3162

The development of PARP inhibitors can be traced back to as early as the 1990s. Initially, attempts were made to enhance the efficacy of chemotherapeutic drugs, but the combination of chemotherapeutic drugs and PARP inhibitors proved to be very toxic, and research was interrupted. In 2005, two Nature articles made breakthrough progress. The use of PARP inhibitors alone can kill DNA repair-defective cancer cells, especially BRCA1/2 mutant cancer cells (BRCA participates in DNA repair). Subsequently, AstraZeneca carried out phase I clinical trials of olaparib (AZD2281), and Sanofi also reported phase II and phase III clinical trials of chemotherapy combined with iniparib for TNBC in 2011. Although it was later confirmed that iniparib is not a true PARP inhibitor, it will produce multiple active fragments in vivo, with a wide range of effects and weak PARP inhibitory effects, but research on PARP inhibitors continues. As of May 2017, a total of 3 PARP inhibitors have been approved by the FDA for the treatment of advanced ovarian cancer: olaparib of AstraZeneca, rucaparib of Clovis, and niraparib of Tesaro.

SHR3162 (Fluzoparib, fluzoparib) is a class of PARP inhibitors developed by Jiangsu Hengrui Pharmaceutical Co Ltd, which belongs to the 1.1 classification of chemical drugs. As of May 2017, fluzoparil capsules have conducted four phase I clinical studies in China, including a phase I clinical study of the tolerability and pharmacokinetics of fluzopalyl in patients with advanced solid tumors (HR-FZPL-I-AST-TOL/PK), an open-dose and dose-climbing phase I study of patinib (FZPL-I-103-GC), an open-dose and dose-climbing phase I study of fluzoparib combined with apatinib (FZPL-I-104 -OC/BC) and a study of food effects and material balance in fluzoparib healthy subjects. The adverse events of fluzoparin include decreases in hemoglobin, leukocytes, granulocytes and platelets, fatigue, anorexia, nausea and vomiting.

After a Phase I clinical study, the recommended dose of SHR3162 is 150 mg orally

twice daily.

5.3.7 Apatinib

Apatinib (Apatinib, trade name: Aitan) is a small molecule VEGFR tyrosine kinase inhibitor. It blocks signal transmission after VEGF binds to its receptor by inhibiting the activity of VEGFR tyrosine kinase and inhibiting tumor angiogenesis.

Apatinib has undergone phase I and phase II trials for advanced gastric cancer in FUSCC, in which as a leader unit, it also conducted a national multicenter phase III clinical trial of advanced gastric cancer (marketed clinical). Apatinib was approved for marketing in October 2014 for the treatment of patients with advanced gastric adenocarcinoma or gastric-esophageal junction adenocarcinoma who have progressed or relapsed after receiving at least two types of systemic chemotherapy. Apatinib monotherapy or combined with SHR-1210 for lung cancer, monotherapy or combined with Fluzaparib for gastric cancer, monotherapy or combination with SHR-1210 for liver cancer, monotherapy for colorectal cancer, and Fluzaparib for ovarian cancer and breast cancer, combined with HS10241 in advanced solid tumor clinical research is ongoing.

FUSCC led two national multicenter phase II clinical trials for recurrent metastatic breast cancer (TNBC and non-TNBC). The dose for patients with recurrent metastatic breast cancer is 500 mg orally once daily. The median progression-free survival for apatinib monotherapy for relapsed and metastatic TNBC after multiple courses of treatment was 3.3 months, and the median overall survival was 10.6 months. The 3/4-degree hematological toxicity of apatinib includes thrombocytopenia (13.6%), leukopenia (6.8%), granulocytopenia (3.4%), and anemia (1.7%). 3/4-degree nonhematological toxicity includes hand and foot syndrome (17%), hypertension (11.9%), proteinuria (13.6%) and increased ALT (11.9%).

5.3.8 Everolimus

Everolimus (trade name: Afinitor) derivatives of rapamycin selectively inhibit mammalian rapamycin target protein (mTOR), especially targeting the mTOR-raptor signaling complex. mTOR is a key serine-threonine kinase in the phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) signaling cascade and is known to be

dysregulated in a variety of human cancers. In January 2013, everolimus was approved for the treatment of advanced RCC in China. In February 2014, everolimus was approved for pNET and TSC-SEGA in China. Everolimus has been approved for oncology indications in more than 105 countries and TSC indications in more than 95 countries.

BOLERO-2, a randomized phase III study, shows the efficacy of combined administration of everolimus and exemestane compared with exemestane monotherapy in HR-positive/HER2-negative recurrent metastatic breast cancer after the failure of nonsteroidal aromatase inhibitors. There were significant improvements in PFS, response rate and clinical benefit rate. The overall response rate (ORR) of the everolimus + exemestane group versus the exemestane + placebo group (12.6% vs. 1.7%, P <0.0001) and CBR (51.3% vs. 26.4%, P < 0.0001), the median PFS of everolimus + exemestane was 11.0 months, compared with 4.1 months with placebo (HR = 0.38, 95% CI: 0.31-0.48, P <0.0001). The results of the main PFS analysis were confirmed. Based on the results of this randomized phase III study, everolimus and exemestane combination therapy has been approved for marketing in the United States (July 2012), the European Union and many other countries. A subgroup analysis of Asian patients in the BOLERO-2 study showed a median PFS of 8.48 months in the everolimus plus exemestane group compared to 4.14 months in the placebo plus exemestane group. In Asian patients, the combined treatment reduced the risk of disease progression by 38% compared to exemestane alone. At present, a national multicenter clinical trial led by FUSCC is ongoing to prepare for its registration in China. The everolimus dose is 10 mg orally once daily.

The safety profile observed by everolimus in BOLERO-2 is consistent with that previously seen in tumor patients, and incidents remain predominantly low-grade (grade 1 or 2). Compared with the control group, an increased risk of noninfectious pneumonia, infection, and stomatitis was observed in the everolimus + exemestane group. The most common AEs reported in patients receiving everolimus plus exemestane (≥10% of patients) were stomatitis, rash, fatigue, diarrhea, decreased appetite, weight loss, cough, taste disorders, dyspnea, headache, arthralgia, peripheral

edema, anemia, nausea, nasal discharge, vomiting, fever, pneumonia, constipation, back pain, itching, insomnia, weakness, elevated AST/ALT/GGT, hyptuof1erglycemia, xerostomia, alopecia, nasopharyngitis, and urinary tract infections. The most common grade 3-4 AEs suspected of being related to treatment with an incidence of ≥2% are stomatitis, fatigue, diarrhea, weight loss, dyspnea, anemia, pneumonia, weakness, hyperglycemia and elevated AST/GGT. For advanced HER2-positive breast cancer, there are two randomized phase III double-blind clinical trials (BOLERO-1 and BOLERO-3) that evaluate the efficacy of chemotherapy plus trastuzumab with or without everolimus as first-line or second-line treatment, respectively. The chemotherapeutics selected for these two clinical trials were paclitaxel and vinorelbine. For TNBC, everolimus cannot be combined with endocrine or anti-HER2 drugs, so it is feasible to choose everolimus combined with paclitaxel, as illustrated in BOLERO-1.

5.3.9 Capecitabine

Capecitabine is a commonly used chemotherapeutic drug for breast cancer and is covered by medical insurance.

5.3.10 Albumin paclitaxel

Albumin paclitaxel is a chemotherapeutic drug approved for breast cancer indications in China and abroad, but its price is relatively high, and it has not been included in the national medical insurance catalog. Patients enrolled in this study required patients who had failed conventional paclitaxel or docetaxel treatment before enrollment. Albumin paclitaxel (domestic or imported) is currently available. To reduce the financial burden of patients, the albumin paclitaxel in this study was temporarily free of charge provided by Hengrui company (it has been marketed in China and has indications for breast cancer). During the course of this study, if the drug entered the national medical insurance catalog, the drug would no longer be free of charge.

5.3.11 VP-16

VP-16 (also known as Etoposide and Etoposide) is an effective component of lignans isolated from Podophyllin. VP-16 is a cell cycle-specific antitumor drug that acts in late S or G2 phase, and its site of action is topoisomerase II, forming a stable

cleavable complex between the three drugs-enzymes-DNA. It interferes with DNA topoisomerase II, which makes the damaged DNA irreparable. Topoisomerase II is inserted into DNA to produce the cleavage response required for general cell functions, and VP-16 appears to stabilize DNA and topoisomerase II double-strand breaks by stabilizing DNA-cleaving complexes. This product activates certain endonucleases in the body or acts on DNA through its metabolites, and its nonglycoside homolog 4-desmethylepipodophyllotoxin can inhibit microtubule assembly.

The current indications for VP-16 include first-line treatment of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). In SCLC, the effective rate is 40%-85%, and the complete remission rate is 14%-34%. For NSCLC, the 2013 NCCN guidelines recommend a combination of platinum as a first-line chemotherapy regimen. For advanced metastatic breast cancer after multiple courses of treatment, oral VP-16 is listed as one of the optional chemotherapy strategies in the previous NCCN treatment guidelines. Its effective rate is 9%-18%, and the median PFS is 3.2 months, but the price is inexpensive, and the oral dosage form is convenient for patients to treat. Adverse reactions include gastrointestinal reactions, allergic reactions, hair loss, etc.

5.3.12 Famitinib

Famitinib (famitinib malate) is a multitarget tyrosine kinase inhibitor. It has a variety of receptor tyrosine kinases, such as VEGFR2, VEGFR3, c-Kit, PDGFRβ, Flt1, Flt3, and Ret. c-Src has good inhibitory activity. Preclinical results show that famitinib has obvious curative effects on a variety of human tumors in nude mouse transplanted tumors, and its antitumor effect is better than that of the similar product sunitinib in vivo and in vitro.

Currently, famitinib is undergoing phase I and phase II clinical trials in multiple centers in China, involving multiple tumors, including advanced intestinal cancer, nasopharyngeal cancer, gastrointestinal stromal tumor, kidney cancer, non-small cell lung cancer, and breast cancer. Phase III clinical trials in advanced colorectal cancer are ongoing, and the drug has not yet been approved for marketing in China. A single-arm phase II clinical result of famitinib in advanced breast cancer that failed multiline treatment showed that of the 27 patients enrolled in the first stage of phase II, 4 patients

had PR, and 2 patients had PR. Confirmed at 4 weeks, the ORR was 7.4%, DCR was 22.2%, and median progression-free survival (mPFS) was 1.9 months, suggesting that famitinib has a certain effect on patients with advanced breast cancer. The second phase of a larger sample is underway. In terms of safety, the common hematological adverse reactions of famitinib were mainly decreased in 24 cases (88.9%) of white blood cell count, decreased in 22 cases (81.5%) of neutrophil count, and decreased in 9 cases (33.3%) of platelet count. Hemoglobin decreased in 2 cases (7.4%). Nonhematological adverse reactions were mainly expressed in 23 cases of proteinuria (48.2%), 21 cases of hand-foot syndrome (77.8%), 14 cases of hypertension (51.8%), 12 cases of fatigue (44.4%), 6 cases of oral ulcers (22.2%), 4 cases of stomatitis (14.8%), 12 cases of elevated TSH (44.4%), 8 cases of AKP (29.6%), 7 cases of transaminase (25.9%), and 4 cases of TBIL (14.8%). In this study, most adverse events were mild-to-moderate (degrees I / II), serious adverse events (degrees III/IV) were relatively rare, and no adverse events of degree IV occurred. Famitinib was well tolerated in all subjects.

5.3.13 BP102 (bevacizumab)

BP102 is an injection of humanized monoclonal antibody of bevacizumab (Avitine ®) developed by Hengrui Pharmaceutical Co., Ltd. All preclinical studies of this product were comprehensively compared with amvittin ®, and pharmaceutical and pharmacological toxicology tests proved that BP102 was similar to the reference drug amvittin ®. Bevacizumab has been widely explored in breast cancer, but only Europe has approved bevacizumab combined with capecitabine or paclitaxel for the treatment of metastatic breast cancer.

The E2100 study enrolled 722 patients with recurrent or metastatic breast cancer, and bevacizumab combined with paclitaxel doubled progression-free survival compared with paclitaxel alone (5.9 months vs. 11.8 months). Accordingly, the US FDA approved bevacizumab in combination with paclitaxel for the first-line treatment of HER2-negative metastatic breast cancer (MBC) in an accelerated approval (fast track) process. The AVADO study enrolled 736 advanced breast cancer patients, and docetaxel combined with bevacizumab significantly prolonged progression-free survival (8.2 months vs. 10.1 months). In the RIBBON-1 study, bevacizumab combined with

capecitabine, taxane, or anthracycline significantly prolonged progression-free survival. In 2011, since bevacizumab did not show overall survival (OS) superiority in a first-line randomized controlled study, the FDA announced the withdrawal of bevacizumab indications for MBC, while the European Medicines Agency (EMA) still retains the indication of combining bevacizumab and paclitaxel for the first-line treatment of MBC. Moreover, the bevacizumab-containing regimen is still one of the standard first-line options for HER2-negative MBC treatment in the US National Comprehensive Cancer Network (NCCN) guidelines. The common moderate adverse effects of bevacizumab are neutropenia, hand and foot syndrome, peripheral neuropathy, leukopenia and hypertension.

Phase I clinical studies have shown that BP102 has biological similarity to Anvitine ® in PK characteristics and tolerable toxicity in patients.

6 Enrollment and Exclusion Criteria

6. 1 Enrollment criteria

Patients must meet all of the following inclusion criteria to be eligible for this study:

1. Females ≥18 years of age.
2. Histologically confirmed invasive TNBC (specific definition: immunohistochemical detection of ER <1% tumor cell positive is defined as ER negative, PR <1% tumor cell positive is defined as PR negative, HER2 0-1 + or HER2 ++ but negative by FISH or CISH, no amplification, defined as HER2 negative).
3. Locally advanced breast cancer (cannot be treated with radical local treatment) or recurrent metastatic breast cancer.
4. Refractory TNBC (existing treatment has failed), specific definition: commonly used chemotherapy drugs available in China include anthracyclines, taxanes, platinum, capecitabine, gemcitabine, and vinorelbine. The abovementioned commonly used chemotherapeutic drugs have failed. The patient's disease was not effectively controlled or in progress before admission.

5. At least one measurable lesion according to RECIST version 1.1 (conventional CT scan ≥20 mm, spiral CT scan ≥10 mm, measurable lesions have not received radiotherapy)
6. The main organ functions are basically normal and meet the following conditions:
7. The standard of routine blood tests should meet the following criteria: HB ≥90 g/L (no blood transfusion within 14 days), ANC ≥1.5 × 109/L, and PLT ≥75 × 109/L.
8. Biochemical examination must meet the following standards: TBIL ≤1.5 × ULN (upper limit of normal value), ALT and AST ≤3 × ULN, if liver metastases, ALT and AST ≤ 5 × ULN, serum Cr ≤1 × ULN, and creatinine clearance rate> 50 ml/min (Cockcroft-Gault formula).
9. Have not received radiotherapy, endocrine therapy, molecular targeted therapy, and surgery within 3 weeks before the start of the study and have recovered from the acute toxicity of previous treatment (if surgery, the wound has completely healed), no peripheral neuropathy or 1 degree peripheral neurotoxicity
10. ECOG score ≤2, and life expectancy ≥3 months.
11. Fertile female subjects need to use a medically approved contraceptive during study treatment and at least 3 months after the last use of the study drug.
12. Subjects volunteered to join the study, signed informed consent, had good compliance, and cooperated with the follow-up.

6.2 Common exclusion criteria

Patients with any of the following were excluded from the study:

1. Radiotherapy (except for palliative reasons), chemotherapy, and immunotherapy 3 weeks before treatment, except bisphosphonates (can be used for bone metastasis).
2. Uncontrolled central nervous system metastasis (referring to symptoms or the use of glucocorticoids or mannitol to control symptoms).
3. A history of clinically important or uncontrolled heart disease, including

congestive heart failure, angina pectoris, myocardial infarction or ventricular arrhythmia in the past 6 months.

4. Adverse reactions with grade ≥1 that are ongoing owing to previous treatment. Exceptions to this are hair loss or the investigator's opinion should not be ruled out. Such cases should be clearly documented in the investigator's notes.
5. Major surgery (except minor outpatient surgery, such as placement of vascular access) within 3 weeks of the first course of trial treatment.
6. Pregnant or lactating patients.
7. Malignant tumors in the past five years (except for cured skin basal cell carcinoma and cervical carcinoma in situ).

6.3 Special exclusion criteria for each arm

6.3.1 Special exclusion criteria for arm A

1. LVEF≥50% (Echocardiography).
2. Have suffered any of the following heart diseases: (1) angina pectoris, (2) arrhythmias requiring medical treatment or clinical significance, (3) myocardial infarction, (4) heart failure, or (5) other heart diseases that were considered unsuitable for this study by the investigator.

6.3.2 Special exclusion criteria for arm B

1. Severe infection within 4 weeks before the first medication (e.g., intravenous drip antibiotics, antifungal or antiviral drugs) or fever of unknown origin> 38.5 °C during screening/before the first dose.
2. A history of epilepsy or a disease that can induce seizures within 12 months before C1D1 (including a history of transient ischemic attack, stroke, brain trauma, and unconsciousness requiring hospitalization).

6.3.3 Special exclusion criteria for arm C

1. Subjects who required systemic treatment with corticosteroids (> 10 mg prednisone equivalent daily) or other immunosuppressants within 2 weeks before the first use of study drugs, except for the use of corticosteroids for the prevention of allergies and nausea and vomiting. In the absence of active autoimmune disease, inhaled or topical use of steroids and adrenal

corticosteroid replacement at doses > 10 mg/day prednisone are allowed.

2. Those who have received antitumor vaccines or have received live vaccines within 4 weeks before the first administration.
3. A history of active autoimmune diseases, such as interstitial pneumonia, colitis, hepatitis, pituitary inflammation, vasculitis, nephritis, hyperthyroidism, and hypothyroidism, including but not limited to these diseases or syndromes. Except for patients with vitiligo or cured childhood asthma/allergies who do not require any intervention in adults, autoimmune-mediated hypothyroidism treated with a stable dose of thyroid replacement hormones, insulin type I diabetes, and asthma patients who need bronchodilators for medical intervention are not included.
4. A history of immunodeficiency, including a positive HIV test, other acquired or congenital immunodeficiency diseases, or a history of organ transplantation and allogeneic bone marrow transplantation.
5. History of interstitial lung disease (except for radiation pneumonia without hormone therapy) and history of noninfectious pneumonia.
6. Subjects had active hepatitis B (HBV DNA ≥ 2000 IU/mL or 104 copies/mL) and hepatitis C (hepatitis C antibody was positive and HCV-RNA was above the lower limit of detection of the analytical method).

6.3.4 Special exclusion criteria for arms E and F

1. A history of gastrointestinal bleeding or a clear gastrointestinal bleeding tendency within the past 6 months, such as esophageal varices at risk of bleeding, locally active ulcer lesions, and fecal occult blood ≥ (++) are not eligible for admission. If fecal occult blood (+) is present, gastroscopy is required.
2. Abdominal fistula, gastrointestinal perforation, or abdominal abscess occurred within 28 days before participating in this study.
3. Urine routine shows urinary protein ≥ ++ or confirmed 24-hour urine protein quantification> 1.0 g.
4. Those who had hypertension and could not be reduced to the normal range

with antihypertensive medication (systolic blood pressure> 140 mmHg, diastolic blood pressure> 90 mmHg).

7 Suspension and Exit Criteria

7.1 Suspension criteria

Patients need to stop treatment and continue to be followed up under one of the following conditions:

Patients who cannot tolerate after two dose adjustments.

Patients with a delay of dosing for more than 3 weeks.

Disease progress during treastment (PD).

Intolerable adverse reactions occurred during the test.

Pregnancy.

Patients who are not eligible for further treatment due to violation of the research protocol (at the discretion of the investigator).

Any other conditions that investigators consider it necessary to discontinue treatment.

7.2 Exit criteria

Patients should withdraw from this study under one of the following conditions:

Patient withdraws informed consent.

Complicated diseases that seriously affect clinical evaluation.

Any case where the researcher considers it necessary to withdraw from the study.

Receive other systemic treatments or use of drugs forbidden in this study.

8 Research Process and Specific Projects

8.1 Baseline examination

Tissue specimens of recurrent metastatic TNBC (mainly including breast, axillary lymph nodes, lungs, or liver) were reobtained within 4 weeks before treatment, and the breast cancer tissues were submitted for target sequencing and pathological immunohistochemical detection (ER, PR, HER2, ki67, CK5/6, AR, PD-L1, TIL, CD31) in our hospital. Based on the above results, one of the seven treatment arms was selected according to the protocol of this study.

Baseline assessment of CT or MRI of evaluable lesions of the tumor was

performed within 3 weeks before treatment.

Baseline records of tumor lesions:

According to the RECIST version 1.1 standard, when there is more than one measurable lesion at baseline assessment, all lesions should be recorded and measured. The total number of lesions does not exceed 5 (each organ does not exceed 2). Of the patients, a maximum of 2 or 4 target lesions were selected as baseline measurement lesions. Target lesions must be selected based on size (longest diameter), can represent all involved organs, and measurements must be reproducible. When the largest lesion cannot be measured repeatedly, a new largest lesion that can be repeatedly measured can be selected again.

Measurable lymph nodes must meet the following criteria: CT measurement of short diameter ≥15 mm. The baseline only needs to detect the short diameter. Usually, the short diameter of the nodule is used to determine whether the nodule has tumor metastasis. The nodule size is generally expressed by two-dimensional data of image detection (CT uses the axial plane, MRI uses the axial plane, and one of the sagittal or coronal planes is chosen.) The shortest diameter is the minimum value. For example, a 20 mm x 30 mm abdominal nodule with a short diameter of 20 mm can be considered a malignant, measurable nodule. In this example, 20 mm is the measurement of the nodule. Nodules with a diameter of ≥10 mm but less than 15 mm should not be considered target lesions, and nodules less than 10 mm do not belong to the category of pathological nodules and need not be recorded and further observed.

The sum of the diameters of all target lesions (including the longest diameter of nonnodular lesions and the shortest diameter of nodular lesions) will be reported as the sum of the baseline diameters. If the lymph node diameter is included, as mentioned above, only the short diameter is counted. The sum of the baseline diameters will be used as a reference value for the baseline level of the disease.

All other lesions, including pathological lymph nodes, can be considered nontarget lesions and do not need to be measured but should be recorded at baseline assessment, such as "existing", "missing" or in rare cases "clear progress". Extensive target lesions can be recorded with target organs (e.g. extensive liver metastases).

Basic data were collected within one week before treatment, including medical history, physical examination, general condition score, ECOG score, routine blood tests, routine urine tests, liver and kidney function (total bilirubin, ALT, AST, AKP, LDH, total protein, albumin, urea nitrogen, creatinine, blood glucose), electrocardiogram, hepatitis B (HBV-DNA test if necessary), and tumor markers (CEA, CA-153, CA-125). If necessary, check LVEF.

8.2 During treatment

8.2.1 The blood routine was checked weekly during treatment, and the number of tests was increased if necessary.

8.2.2 Blood pressure was measured 3 times a day for 2 weeks before apatinib treatment. If the blood pressure is abnormal, the blood pressure will be monitored daily. If the blood pressure is normal, the blood pressure will be measured twice a week thereafter. Blood and urine routines are performed once a week, liver and kidney function and electrolyte testing and fasting blood glucose monitoring are performed every 2 weeks, and AE observation and recording are performed at any time. An electrocardiogram is performed every cycle. If symptoms such as pain in the precardiac area and palpitations occur, the myocardial enzyme spectrum (creatine kinase, lactate dehydrogenase) should be detected immediately, the electrocardiogram should be checked at any time, and an echocardiogram should be added. One vital sign, PS score, and physical examination should be performed.

8.2.3 Patients' clinical symptoms (including appetite and pain) and changes in physical signs were observed and recorded. Same as ECOG score.

8.2.4 The occurrence and duration of various adverse reactions during treatment, grade, corresponding treatment, and outcome were recorded, and the relationship with the drug was judged (NCI CTCAE v5.0).

8.2.5 Every two cycles (A arm, E arm, and F arm 6 weeks ± 3 days, other arms 8 weeks ± 3 days) for CT or MRI examination of the relevant lesions, refer to RECIST 1.1 to evaluate the efficacy. Because the primary endpoint of this study was total effectiveness, patients with CR or PR need to be confirmed by imaging at 4 weeks.

8.2.6 The pharmacokinetics evaluations of CDK4/6 inhibitor (SHR6390) and AR

inhibitor (SHR3680) (Arm B) in the first 6-8 patients were before C1D1 administration; 1 hour after C1D1 administration; 2 hours, 4 hours, 6 hours, 8 hours, and 12 hours before C1D2 administration; before C1D15 administration; before C1D20 administration; before C1D21 administration; 1 hour after C1D21 administration; and 2 hours, 4 hours, 6 hours, 8 hours, and 12 hours before C1D22 administration. Blood samples were collected a total of 18 times. At each blood collection point, 2 tubes of 3 ml blood were collected for pharmacokinetic parameter evaluation (Hengrui company was responsible for testing).

8.3 At the end of treatment

At the end of treatment: comprehensive tumor assessment, vital signs, physical examination, ECOG score, blood routine, urine routine, electrocardiogram, liver and kidney function, tumor markers (CEA, CA-153, CA-125), and quality of life score.

8.4 Follow-up

The patient entered the posttreatment follow-up period after the last use of the study drug. For patients who were excluded due to nondisease progression, all subjects were followed up from 21 to 35 days after the last dose. Thereafter, they were followed up every 8 weeks, and imaging tests were performed to observe whether the tumor progressed.

During the follow-up period, the following parameters were recorded: the time of disease progression or death in patients who did not develop disease when taking the study drug, other tumor treatments, SAEs related to the study drug, and follow-up survival status every 3 months (phone follow-up available).

9 Dose Adjustment

9.1 General dosage

When hematological toxicity reaches III or above or nonhematological toxicity reaches II or above, the investigator decides whether to suspend or reduce the dose. In nonhematological toxicity, nausea, vomiting and fever with a certain cause can be controlled (such as infections, tumors, etc.), active symptomatic treatment and treatment can be carried out without dose suspension and dose reduction.

9.2 Provisions for treatment suspension

During treatment, drug administration should be suspended because the drug toxicity has not recovered. The pause time should not exceed 2 times per cycle to ensure the strength of the drug received by the subjects in the trial.

9.3 Dose downregulation

The drug is poorly tolerated, and dose reductions can be performed on the first day of subsequent cycles. Subjects could adjust the dose twice. Once a dose level was lowered, the dose was not allowed to be increased for any reason, but the dose suspension was still allowed. See Table 6 for dose adjustments for each treatment arm.

Table 6 Dose adjustments for each treatment arm

Arm	Drug	Recommended initial dose	First reduction	Second reduction
A	Pyrotinib	400 mg	320 mg	240 mg
	Capecitabine	1000 mg/m2	750 mg/m2	500 mg/m2
B	SHR6390	150 mg	125 mg	100 mg
	SHR3680	240 mg	160 mg	80 mg
	SHR2554	300 mg	250 mg	200 mg
	Everolimus	10 mg	7.5 mg	5 mg
C	SHR1210	200 mg	NA	NA
D	SHR3162	150 mg	100 mg	50 mg
E1	Apatinib	500 mg	375 mg	250 mg
E2	Apatinib	250 mg, tolerable, increased to 375 mg	125 mg	NA
E4	BP102	10 mg/kg	7.5 mg/kg	5 mg/kg
E3、F	Famitinib	20 mg	15 mg	10 mg
E、F	Oral Vp-16	50 mg d1-14	50 mg d1-12	50 mg d1-10

G	Everolimus	10 mg	7.5 mg	5 mg

9.4 Other regulations

To ensure the consistency of dose adjustment throughout the study, a dose pause was first performed during each dose cycle. After taking the dose suspension measure, if the subject is still poorly tolerated, the dose can be adjusted down on the first day of the next dosing cycle. Suspension of treatment).

10 Concomitant Therapy

In patients who do not have a high risk of infection or a risk of bleeding, it is recommended that colony cell stimulating factor, interleukin-11 or thrombopoietin be administered only in the presence of bone marrow suppression of grade III or higher. Researchers have the right to decide whether they need to deal with it accordingly.

Patients can receive the best supportive care. Patients can receive bisphosphonates for bone metastases during treatment. Complicated clinical diseases and various types of AE should be actively treated, such as rash, diarrhea, hypertension, hand and foot syndrome, liver and kidney function impairment, stomatitis, noninfectious pneumonia, and infusion reactions, according to the judgment of the clinician to give symptomatic treatment. All drugs used in combination should be recorded in the case report form (CRF) in strict accordance with GCP regulations.

This plan prohibits the use of SFDA-approved modern Chinese medicine preparations and immunomodulators (such as thymosin, interferon, interleukin-2, and lentinan) for the treatment of breast cancer.

11 Clinical Evaluation

11.1 Main endpoints and observation methods

ORR:

Defined as the proportion of patients whose tumors shrink to a certain amount and remain for a certain period of time, including cases of CR and PR. The solid tumor remission assessment standard (RECIST version 1.1 standard) was used to evaluate objective tumor remission. Subjects must be accompanied by measurable tumor lesions

at baseline. The efficacy evaluation criteria are divided into complete response (CR), partial response (PR), stable (SD), and progress (PD) according to the RECIST version 1.1 standard (see attachment for details 2).

In this study, 20 patients are prepared for each arm. If 3 patients or more achieved CR or PR, this treatment arm would be considered valuable and reached the main endpoint of this study. It is then worth recommending the design of a larger randomized phase III clinical study in the future.

11. 2 Secondary endpoints and observation methods

Disease Control Rate (DCR):

Refers to the percentage of patients who can be evaluated for complete response, partial response, and stable disease for more than 4 weeks.

Progression-Free Survival (PFS):

Refers to the time between the patient's enrollment and any recorded tumor progression or death from any cause, and the analysis of this indicator includes the results of tumor evaluation during study treatment and follow-up. If the patient has several indicators that can be judged as PD, the first indicator to appear when performing PFS analysis, recurrence, new lesions or death are considered to have reached the study endpoint, and the patient uses other systemic or anti-target lesions. Cancer treatment is also considered PD. For patients who did not have PD or died at the end of the study, the time at which the patient did not show PD for the last time was used as the censored data.

Overall survival (OS):

Refers to the time from enrollment to death for any reason.

12 Treatment of Common Adverse Events

12. 1 Treatment of diarrhea

Diarrhea: Investigators should inform subjects of the possibility of diarrhea and its management before starting treatment. Follow-up and observation (≤14 days) is considered first after the onset of diarrhea. Oral montmorillonite powder TID is advised

when subjects experience diarrhea. Those who experience severe diarrhea may be treated with electrolyte solutions. Study Medication is withheld until diarrhea improves to Grade ≤1 or as described in Table 7.

Table 7 Management for diarrhea and guidelines for dose modification for pyrotinib

CTCAEv5.0	Management (After follow-up and symptomatic treatment)	Dose modification
Grade 4	Discontinuation	-
Grade 3	Study medication withheld until toxicity improves to Grade 0 or Grade 1 with no complication	Initial Dose:400 mg First reduction: 320 mg Final reduction: 240 mg
Grade1-2 with complications (including Grade ≥2 nausea or vomiting, fever, hemorrhage or dehydration)		

12.2 Treatment of hand-foot skin reaction

Hand-foot skin reaction (HFSR) is a kind of dermatological adverse event that may occur as a side effect of certain chemotherapy or targeted therapy. Symptoms of HFSR include numbness, tingling, burning, or itching sensation, swelling, redness, tenderness and rash.

Grade:

Grade 1: Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort, which does not disrupt normal activities.

Grade 2: Painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities.

Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living.

Management:

Supportive care is considered, including maintaining skin cleanliness, avoiding pressure and rubbing, using topical steroids and urea cream, and using topical antibiotics when necessary.

Subjects will be withdrawn from this study if they experience HFSR Grade ≥2 3 times and exacerbation.

12.3 Treatment of liver injury

Elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin (TBIL) may indicate possible drug-induced liver injury (DILI), whose diagnostic threshold is associated with the subject's baseline AST/ALT and TBIL levels. Medical review is needed to ascertain whether abnormalities in the liver function test (LFT) are caused by cholestasis, which can be defined as ALP>2×upper limit of normal (ULN) with R<2 in subjects without bone metastasis and hepatic elevation of alkaline phosphatase (ALP) in subjects with bone metastasis. R is calculated as ALT/ALP, using multiples of ULN, and it indicates the cause of elevation of ALT and/or ALP, which includes cholestasis, hepatic cell injury and both.

Study medication of subjects with liver injury and without cholestasis should be withheld immediately, and LFT should be checked again 48 hours after abnormalities are found. Complete evaluation should include laboratory tests, medical history, physical examination, possibility of liver metastasis, new hepatic lesions, obstruction or compression.

Hepatic toxicity should include the following tests: albumin, ALT, AST, TBIL, direct bilirubin (DBIL), indirect bilirubin, ALP, creatine phosphokinase (CPK), prothrombin time (PT) or international normalized ratio (INR), and γ-glutamyl transferase (γ-GT). Subjects with Gilbert syndrome must be monitored for TBIL and DBIL. Monitoring should be more frequent when DBIL abnormalities occur.

If discontinuation is required because of elevated AST, ALT and/or bilirubin, close observation is recommended, including the following:

i. Liver enzymes and serum bilirubin were reviewed 2 to 3 times a week. If

abnormal results are stabilized or recover to the normal range, the review frequency should be reduced to 1 or fewer times per week.

ii. Obtain a more detailed medical history about current symptoms.

iii. Obtain more detailed medical history and/or history of concomitant diseases, including any preexisting hepatic disease history or risk factors.

iv. Obtain history of concomitant medications (including OTC medicines, Chinese Traditional Medicines and dietary supplements), alcohol, recreational drugs, and special diets.

v. Acute viral hepatitis caused by hepatitis A, B, C, D, and E virus, hepatotropic virus infection (CMV, EBV, or HSV), autoimmune or alcoholic hepatitis, NASH, hypoxic/ischemic hepatic disease, and biliary disease were excluded.

vi. Obtain history of environmental chemical exposure.

vii. Obtain other liver function test results (e.g., INR, DBIL).

viii. Consider a consultation of gastrointestinal or hepatic disease.

12.4 Treatment of hypertension

Angiogenesis inhibitors (e.g., bevacizumab and sorafenib) target the VEGF pathway, leading to new-onset hypertension or worsening of previous hypertension. The main mechanisms may include a decrease in NO/PHI2 secreted by endothelial and platelet cells, abnormality of vessel density (small vessels and capillaries) and disturbance of endothelin. Sunitinib may even lead to a decrease in left ventricular ejection fraction (LVEF).

During the first 6 weeks of using angiogenesis inhibitors, subjects should receive weekly blood pressure monitoring. Those who experience hypertension are considered to control blood pressure with the following standard treatments: angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, diuretics and adrenaline β-receptor blockers, or a combination of listed treatments.

As a reference for the management of hypertension caused by angiogenesis

inhibitors such as apatinib or famitinib, hypertension caused by sorafenib often occurs after 1-2 weeks of treatment and can be commonly controlled with routine anti-hypertension treatment. Patients experiencing resistant hypertension are usually in remission by dose modification or discontinuation.

Preferred treatment for hypertension caused by targeted therapy (not metabolized by liver):

i. Valsartan (Diovan): 80-320 mg qd
ii. Atenolol: 50-100 mg qd
iii. Losartan/Hydrochlorothiazide (Hyzaar): 12.5-100 mg qd
iv. Telmisartan (Micardis): 20-80 mg qd
v. For resistant hypertension, amlodipine (Norvasc) is preferred: 2.5-10 mg qd.

12.5 Treatment of proteinuria

Subjects with urine protein ++ or more should receive a 24-hour urine protein test. Subjects will be withdrawn from the study if they experience nephrotic syndrome.

12.6 Prevention and treatment of stomatitis/oral mucositis/mouth ulcers

To prevent stomatitis, all subjects will be instructed to perform routine “good oral care” each day during the trial. Good oral care will consist of brushing teeth at least twice daily with a soft bristled toothbrush, continuing the current daily flossing routine (if patients are not already flossing daily, they should not be instructed to start flossing, as this could cause oral trauma), and continuing routine dental care/maintenance with their dentist, if they have one. It is recommended that patients use 10 mL of an alcohol-free, 0.5 mg/5 mL dexamethasone steroid mouthwash swishing and spitting the QID, especially during the first 8 weeks of treatment (the majority of stomatitis events occur within the first 8 weeks of treatment). The mouthwash was held in the mouth and swished around the mouth to cover the entire buccal mucosa surface for a minimum of two minutes and then spat out.

Subjects with a clinical history of stomatitis/mucositis/mouth ulcers and those with gastrointestinal morbidity associated with mouth/dental infections, irritation of

esophageal mucosa, e.g., gastroesophageal reflux disease (GERD), and preexisting stomatitis/mucositis must be monitored even more closely. Subjects should be instructed to report the first onset of buccal mucosa irritation/reddening to their investigators immediately.

General guidance and management include patient awareness and early intervention. Stomatitis/oral mucositis/mouth ulcers due to everolimus should be treated using local supportive care. Evaluation for herpes virus or fungal infection should be considered. Subjects should be informed about the possibility of developing mouth ulcers/oral mucositis and instructed to promptly report any signs or symptoms to their investigators. Subjects should be educated about good oral hygiene, instructed to avoid spicy/acidic/salty foods, and should follow the following guidelines:

(i) For mild toxicity (grade 1), use conservative measures such as nonalcoholic mouth wash or normal saline mouth wash several times a day until resolution.

(ii) For more severe toxicity (grade 2, in which case subjects have pain but are able to maintain adequate oral alimentation, or grade 3, in which case subjects cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).

(iii) Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

(iv) Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of everolimus metabolism, therefore leading to higher everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as Acyclovir should be avoided unless a viral infection is diagnosed.

12.7 Treatment of noninfectious pneumontis

Noninfectious pneumonitis is a known side effect of rapamycin analogs. Clinically

significant pneumonitis is typically accompanied by nonspecific symptoms, including dyspnea, nonproductive cough, fatigue, and fever. Diagnosis is generally suspected in individuals receiving mTOR inhibitors who develop these symptoms or in asymptomatic individuals in whom a routine chest CT scan reveals a new ground glass or alveolar infiltrate.

The frequency of symptomatic pulmonary toxicity (all grades) was approximately 13% in a phase III study of everolimus in patients with metastatic renal cell carcinoma. Severe (CTC grade 3) pneumonitis occurred in 4% of patients, and occasional fatality was reported. Lung toxicity was partly or completely reversible in the majority of cases with interventions, including drug interruption, discontinuation and the use of corticosteroids.

Subjects will be routinely questioned as to the presence of new or changed pulmonary symptoms consistent with lung toxicity. CT scans and pulmonary function tests should be performed, as clinically indicated, if there are symptoms that indicate that the patient has developed noninfectious pneumonitis. If noninfectious pneumonitis develops, the guidelines in Table 5 should be followed. Dose modification instructions are also provided in Table 8. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

Table 8 Management of noninfectious pneumonitis and guidelines for dose modification for everolimus

Grade	Required Investigations	Management of Pneumonitis	Dose Modification for Everolimus
Grade 1	CT scans with lung windows. Repeat at least every 8 weeks until return to within normal limits.	No specific therapy is required	Administer 100% of study treatment dose.
Grade 2	CT scan with lung	Symptomatic	Reduce study

	windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every 8 weeks until return to within normal limits. Consider a bronchoscopy with biopsy and/or BAL.	only. Consider corticosteroids if symptoms are troublesome.	treatment dose by 1 dose level until recovery to < Grade 1. Study treatment may also be interrupted if symptoms are troublesome. Patients will discontinue study treatment if they fail to recover to < Grade 1 within 28 days.
Grade 3	CT scan with lung windows pulmonary function testing includes: spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to< Grade1. May restart study treatment within 28 days at a reduced dose (by one level) if evidence of clinical benefit.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible,	Consider corticosteroids if infective origin is ruled out. Taper	Discontinuation.

	includes: spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and/or BAL is recommended if possible.	as medically indicated.	

12.8 Management of hyperlipidemia and hyperglycemia

Management of hyperlipidemia should consider previous lifestyle and serum lipid levels. Subjects who experience hypercholesterolemia grade ≥2 (>300 mg/dL or 7.75 mmol/L) or hypertriglyceridemia grade ≥2 (>2.5×ULN) should consider receiving 3-hydroxy-3-methyl glutaryl (HMG) - coenzyme A reductase (e.g., atorvastatin, pravastatin or fluvastatin) or other appropriate lipid-lowering medication apart from diet control.

Note: Combined treatment with HMG-CoA reductase and Fenofibrate may lead to rare but severe musculoskeletal toxicity, whose symptoms and signs include rhabdomyolysis, significant elevation of CPK, myoglobinuria, acute kidney injury or even death. Thus, the risk/benefit ratio for each subject should be calculated before treatment of hyperlipidemia.

There have been reports of hyperglycemia in patients receiving everolimus. It is suggested to monitor fasting plasma glucose before and after subjects receive everolimus and monitor more frequently if subjects receive everolimus with other medications that could lead to hyperglycemia. Optimal glycemic control is suggested before subjects receive everolimus.

Table 9 Management of Hyperlipidemia and Hyperglycemia and Guidelines for Dose Modification for Everolimus

Grade	Dose Modification
Grade 1	Continue treatment at investigator discretion and apply symptomatic treatment
Grade 2	Continue treatment at investigator discretion and apply symptomatic treatment
Grade 3	Interrupt until resolved to grade 0-1 and decrease one dose level when resuming treatment
Grade 4	Discontinuation and treatment as appropriate

12.9 Guidelines for supportive care of immune checkpoint inhibitors SHR-1210 or SHR-1316

Subjects will receive appropriate supportive care investigators consider necessary. Supportive care dealing with potential immune-related adverse effects (irAEs) will be listed below, including oral or intravenous corticosteroids and other anti-inflammatory agents when symptoms are resistant to corticosteroids. Tapering corticosteroids may take several periods because of possible recurring symptoms. We rule out other possible reasons that may need supportive care, e.g., metastatic diseases or bacterial or viral infection. Supportive treatment will be conducted when investigators ascertain that AE is associated with SHR-1210 or SHR-1316 and will not be conducted when AE is not associated with SHR-1210 or SHR-1316.

If capillary endothelial proliferation occurs, biopsy and pathological examination should be conducted if possible. Subjects experiencing severe and enduring capillary endothelial proliferation are suggested to undergo endoscopy and MRI scans to ascertain if there is visceral or mucous involvement.

Symptoms and signs of enterocolitis (e.g., diarrhea, abdominal pain, hematochezia or mucous stool, with or without fever) and intestinal perforation (e.g., peritoneal irritation signs and intestinal obstruction) should be monitored closely. All subjects experiencing diarrhea/colitis will be suggested to take enough liquid. Intravenous infusion of liquid and electrolyte is recommended if oral intake is inadequate. GI consultation and endoscopy are considered to diagnose or rule out colitis for diarrhea

grade ≥2. Oral corticosteroids are considered for grade 2 diarrhea/colitis. Intravenous corticosteroids followed by oral large doses of corticosteroids are considered for diarrhea/colitis grade ≥3. After the grade of symptoms decreases to 1 or less, steroid reduction should be initiated, of which the duration should not be less than 4 weeks.

For grade 2 liver function injuries, intravenous or oral corticosteroids should be used, and liver function should be monitored more frequently until recovery to baseline level (liver function test repeats every week are considered). For grade 3-4 adverse events, intravenous corticosteroids should be used for 24-48 hours. After the grade of symptoms decreases to 1 or less, steroid reduction should be initiated, of which the duration should not be less than 4 weeks.

Thyroid disease can occur at any time during treatment, so monitoring subjects for changes in thyroid function (at the beginning of treatment and at regular intervals during treatment) and clinical signs and symptoms of thyroid disease is necessary. Nonselective adrenaline β-receptor blockers (e.g., propranolol) are recommended as the initial treatment for grade 2 hyperthyroidism. Intravenous corticosteroids followed by oral corticosteroids are recommended for grade 3-4 hyperthyroidism. After the grade of symptoms decreases to 1 or less, steroid reduction should be initiated, of which the duration should not be less than 4 weeks. Proper hormone replacement therapy may be needed during tapering. Thyroid hormone replacement therapy (e.g., levothyroxine) is considered for grade 2-4 hypothyroidism.

Intravenous corticosteroid is recommended for Grade 2 pneumonitis. After the grade of symptoms decreases to 1 or less, steroid reduction should be initiated, of which the duration should not be less than 4 weeks. Prophylactic antibiotics should be used in cases of long-term use of corticosteroids.

Corticosteroids are recommended for grade 2 hypophysitis. After the grade of symptoms decreases to 1 or less, steroid reduction should be initiated, of which the duration should not be less than 4 weeks. Proper hormone replacement therapy may be needed during tapering. Intravenous corticosteroids followed by oral corticosteroids are recommended for grade 3-4 hypophysitis. After the grade of symptoms decreases to 1

or less, steroid reduction should be initiated, of which the duration should not be less than 4 weeks. Proper hormone replacement therapy may be needed during tapering.

Corticosteroids are recommended for grade 2 nephritis. Intravenous corticosteroid is recommended for grade 3-4 nephritis or renal failure. After the grade of symptoms decreases to 1 or less, steroid reduction should be initiated, of which the duration should not be less than 4 weeks.

12.10 Management of infusion-related reactions

The infusion reaction may be triggered by infusion of the immune checkpoint inhibitor SHR1210 or SHR1316, and it should be graded and managed according to Table 10.

Table 10 Grade and management of infusion reaction

Grade	Symptoms	Treatment	Dose Delay/Modification of SHR1210/SHR1316
Grade 1	Mild transient reaction.	Bedside observation, close monitoring till recovery. Prophylactic medicine shall be given before infusion: Diphenhydramine 50 mg, or equivalent and/or Acetaminophen 325-1000 mg, administered at least 30 mins before the infusion of study medication.	Maintain dose level

Grade 2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids). Prophylactic medications indicated for <=24 hours)	Intravenous infusion of normal saline, Diphenhydramine 50 mg IV or equivalent and/or Acetaminophen 325 1000 mg. Bedside observation, close monitoring until the recovery. Corticosteroids could be considered. Record the infusion volume of study drug in CRF. Prophylactic medicine shall be given before infusion: Diphenhydramine 50 mg, or equivalent and/or Acetaminophen 325 1000 mg, administered at least 30 mins before the infusion of study medication. Glucocorticoid (equal to Hydrocortisone 25 mg) if necessary.	Interruption. Readministration after symptoms disappear at 50% of the initial infusion rate. If there is no complication within 30 minutes, increase to the original 100% infusion rate. Closely monitor. If symptoms recur, discontinue the drug.

Grade ≥3	Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion). Recurrence of symptoms following initial improvement. Hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences. Urgent intervention indicated.	The infusion of study medication shall be immediately discontinued. Recommend bronchodilator, subcutaneous Epinephrine 0.2-1 mg 1: 1000 solution, or 0.1-0.25 mg 1: 10000 solution slow iv injection, if necessary, and/or intravenous injection equivalent to Diphenhydramine 50 mg + 100 mg Methylprednisolone. Comply with guidelines for allergic reactions of the study site. Bedside observation, close monitoring till recovery.	Discontinuation

13 Management of Complimentary Trial Compounds

13.1 Dispensation of compounds

This research was conducted in the Department of Breast Surgery, Fudan University Shanghai Cancer Center. Enrolled subjects may acquire compounds from Hengrui Medicine according to Table 1, which are under unified management of the hospital, and obtain medication number and corresponding study medication will be distributed. Designated personnel of the hospital are put in charge of keeping compounds, filling in records of receiving and using compounds and retrieving the remaining compounds and empty bottles promptly during the test. The usage and records of compounds should be checked at regular intervals, and retrieved medication should be administered at any time.

13.2 Storage and Management of Compounds

According to Good Clinical Practice (GCP), study medication is uniformly stored, distributed and recycled by the study site. Compounds are stored sealed, protected from light at room temperature, with a tentative expiration date of 2 years.

13.3 Disposal of Remaining Compounds

Investigators should record the date and dosage of each subject's medication. The total amount of study medication was 120% of the predesigned dosage. The remaining compounds should be returned to Hengrui Medicine at the end of the trial.

14 Adverse Events

14.1 Definition

An adverse event (AE) is any undesirable medical event experienced by clinical trial subjects after administration of certain compounds; however, AEs do not always reflect a causal relationship with intervention.

14.2 Adverse event reporting period

The reporting period starts from enrollment and lasts until the final follow-up. Any adverse event that occurs during this period should be filled in the case report form.

14.3 Serious adverse event (SAE)

An adverse event is defined as a SAE if it agrees with one or more of the following criteria:

i. Death.
ii. Life-threatening.
iii. Hospitalization (initial or prolonged).
iv. Disability or permanent damage.
v. Congenital Anomaly/Birth Defect, important Medical Events.

14.4 Report of severe adverse events

For all serious adverse events, the trial should be suspended immediately, and corresponding measures to protect subjects should be practiced. Serious adverse events will be recorded in a table and reported to the director of the unit and the sponsor within 24 hours by phone or fax. The investigator shall fill in the severe adverse event report form and fax it to the State Food and Drug Administration. Investigators should follow patients with severe adverse events until resolution. Relevant medical documents should be included within the original material, including report sheets of laboratory tests (e.g. X-ray examination, electrocardiogram, etc.).

14.5 Record and report

The investigator should explain to the patient in detail and ask the patient to truthfully reflect the change in the condition after the administration. Physicians should avoid induced questions. While observing the curative effect, physicians pay close attention to observing adverse events, analyzing the causes, making judgments, and following up observations and records to count the incidence of adverse reactions.

For adverse events that occurred during the trial, the time of onset, symptoms, severity, duration, treatment and prognosis should be recorded in the case report to evaluate their significance with the test compound. The detailed record should be provided, signed and dated by investigators. The adverse events will be graded based on NCI-CTC 3.0. For each symptom, the highest grade experienced since the last follow-up should be reported.

Determination of the relationship between adverse events and clinical trial: Attribute to one of the five categories: definitely related, probably related, probably unrelated, unrelated and not appreciable. The first two categories are considered adverse events, and the proportions of adverse events will be calculated.

i. Definitely related: The chronological order of adverse events after trial onset is reasonable, and the reaction is consistent with the known type of reaction. The situation improves after dis-administration, and the reaction reappears after readministration

ii. Probably related: The chronological order of adverse events after trial onset is reasonable, and the reaction is consistent with the known type of reaction. The clinical condition or alternative intervention may also cause such a reaction.

iii. Probably unrelated: The chronological order of adverse events after trial onset is less reasonable, and the reaction is less consistent with the known type of reaction. The clinical condition or alternative intervention may also cause such a reaction.

iv. Unrelated: The chronological order of adverse events after trial onset is unreasonable, and the reaction is inconsistent with the known type of reaction. The clinical condition or alternative intervention may also cause such a reaction. Improvement of disease status or stopping intervention other than test compounds leads to elimination of such reaction, which will relapse with the restart of alternative intervention.

v. Not appreciable: The onset of reaction and trial lack clear chronological order, and the reaction is similar to the known reaction type. Concurrent use of other medications may cause the same reaction.

15 Data Processing

15.1 Requirements of data filled by investigators

For all the subjects who have filled in the informed consent and were selected to enter the trial, every item in the case report form should be recorded carefully and in detail, and no blank or missing item is allowed (the blank space without record should be crossed).

i. All data in the case report form should be checked with the subject's medical record data to ensure accuracy.

ii. As the original data, the case report form is only allowed to be crossed with any

correction made, and the corrected data should be annotated with the signature of the investigator and the date.

iii. The copy of the laboratory test reports should be placed after the case report form.

iv. Data that are significantly higher or beyond the clinical acceptance range should be verified, and necessary explanations should be made to subjects by the investigator.

v. Please refer to the case report form for instructions.

15.2 Data traceability and completion of CRF

The original record is the study medical record for proper preservation. The case report form from the research medical record is filled in by the researcher. Each included case must complete the case report form.

16 Data Set for Statistical Analysis

After the completion of the trial scheme and case report form, the analysis plan shall be formulated, and necessary modifications shall be made during the trial process. The plan will be completed before data locking, and the statistical analysis report will be provided after data analysis.

16.1 Analysis data set

i. Full Analysis Set (FAS): Full analysis set refers to the collection of qualified cases and shedding cases, with the exception of the cases excluded.

ii. Per-Protocol population (PP) Data Set: The PP data set is defined as restricted to all cases that meet the inclusion criteria and complete the treatment plan, with good compliance, no banned compounds and fulfilled required contents in the case report form, as well as the observation record documents from subjects whose compliance satisfies the study protocol requirement.

iii. Safety Data Set: Safety Data Set refers to the data with safety records after receiving at least one treatment, with the exception of the cases excluded.

16.2 Method of statistics

i. Whether subject to normal distribution: if not, modify statistical methods or perform data transformation.

ii. Whether there is outlier: make statistical and professional analysis, and decide whether to include or not.

iii. Whether there is missing value: when a primary therapeutic index of individual subject fails to be measured, the last observation data should be transferred.

iv. The percentage of dropouts should not exceed 20%; otherwise, it requires analysis and explanation.

v. Descriptive statistical analysis: e.g., mean, standard deviation, maximum, minimum, confidence interval, rate, etc.

16.3 Method of analysis

i. Measurement data: t test, paired t test, rank sum test, paired rank sum test, etc.

ii. Enumeration data: Fisher's exact test was used, and the rank sum test was adopted to rank the data.

iii. Analysis of efficacy indicators: The CMH test, chi-square test or logistic regression will be used for enumeration data. Analysis of variance or rank sum test will be used for measurement data according to the feature of the data. The Kaplan–Meier method or Cox regression will be used for survival data.

iv. FAS analysis and PP analysis: PP analysis and FAS analysis will be conducted simultaneously for the main efficacy indicators.

16.4 Statistic expressions

i. The report is mainly represented by tables with the title, annotation and number of cases, which are self-evident.

ii. Two-sided P values will be calculated for all statistical tests. A value of $P < 0.05$ is considered significant.

16.5 Analysis software

All statistical analyses will be performed using R version 3.6.1 (Foundation for Statistical Computing, Vienna, Austria).

16.6 Interim Analysis

An interim analysis will be conducted when 20 subjects are enrolled in at least one arm and at least one subject is enrolled in each arm to preliminarily evaluate the efficacy and safety of the drug combination in each arm. With the estimated enrollment speed, approximately 50% of subjects would have been enrolled by the interim analysis time

point.

17 Quality Control and Quality Assurance

Regular supervision and inspection will be performed during the trial to ensure the implementation of the study protocol. The raw data will be reviewed to ensure consistency with data in the case report form.

18 Ethical Principle

The study procedure must strictly conform to the requirements of Good Clinical Practice of SFDA and the Declaration of Helsinki.

Institutional Ethics Committee (IEC)

This protocol and written informed consent as well as material directly related to subjects should be submitted to the ethics committee. The trial can only be initiated after the achievement of written approval of the ethics committee.

Informed consent form (ICF)

Prior to enrollment, the investigators are responsible for oral and written consent about information including objective, procedure and potential risks of the study to every subject. The subject should be informed about the right to decide whether to participate in the trial and that the subject is free to withdraw from trial any time willingly. Subjects or their legal representatives will read and understand the informed consent form, sign it, and keep the copy of the signature page.

19 Trials Progress and Data Retention.

19.1 Trial progress

Duration of inclusion: 30 months (from October 2018 to February 2021).

Duration of follow-up after treatment: 12 months after inclusion of the last subject.

Date of primary analysis: February 2021.

19.2 Data retention

The case report forms will be confirmed with signatures by investigators. After completion of the trial, all case report forms, detailed materials about classic cases and

clinical trial record forms will be conserved. Investigators will keep original materials relevant to subjects of CR or PR, laboratory results, signed informed consent originals and copies of case report forms.

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Precision Treatment of Refractory Triple-Negative Breast Cancer Based on Molecular Subtyping

(FUSCC-TNBC- umbrella)

FUTURE Trial

Statistical Analysis Plan (SAP)

Study institute: Fudan University Shanghai Cancer Center

Major study investigator: Zhi-Ming Shao, MD. PhD.

ClinicalTrials.gov Identifier: NCT 03805399

Contents

1. Introduction

The FUTURE trial is a phase II biopsy-mandated, subtyping-based and genomic biomarker-guided umbrella trial to evaluate if targeting the subtypes therapeutically might improve patient outcomes.

1.1 Study Design

This is a Phase II, open-label, umbrella study.

1.2 Sample Size

Based on the different multigene expression profiles and the potential molecular characteristics of different pathways, seven treatment arms and six treatment groups were initially set up to eroll 10-20 patients per treatment arm. Therefore, a total of approximately 140 patients should be enrolled in this study. Three or more than 3 of 20 patients in each arm group who reached CR or PR will be defined to reach the study end point.

2. Study Endpoints

2.1 Efficacy Endpoints

2.1.1 Objective response rate, ORR

The primary endpoint will be the objective response rate (ORR) [PR+CR], with responders requiring a confirmatory response assessment no sooner than 4 weeks after the first response assessment. Assessment of tumor response is based upon on-site readings by local radiologists using RECIST1.1.

2.1.2 Disease Control Rate, DCR

One of the secondary endpoints will be the disease control rate (DCR) [CR+PR+SD].

2.1.3 Progression-Free Survival, PFS

One of the secondary endpoints will be progression free survival (PFS). Progression-free survival is defined as the interval from the first dose start date to the date of disease progression defined as documented PD or death from any cause, whichever occurs first.

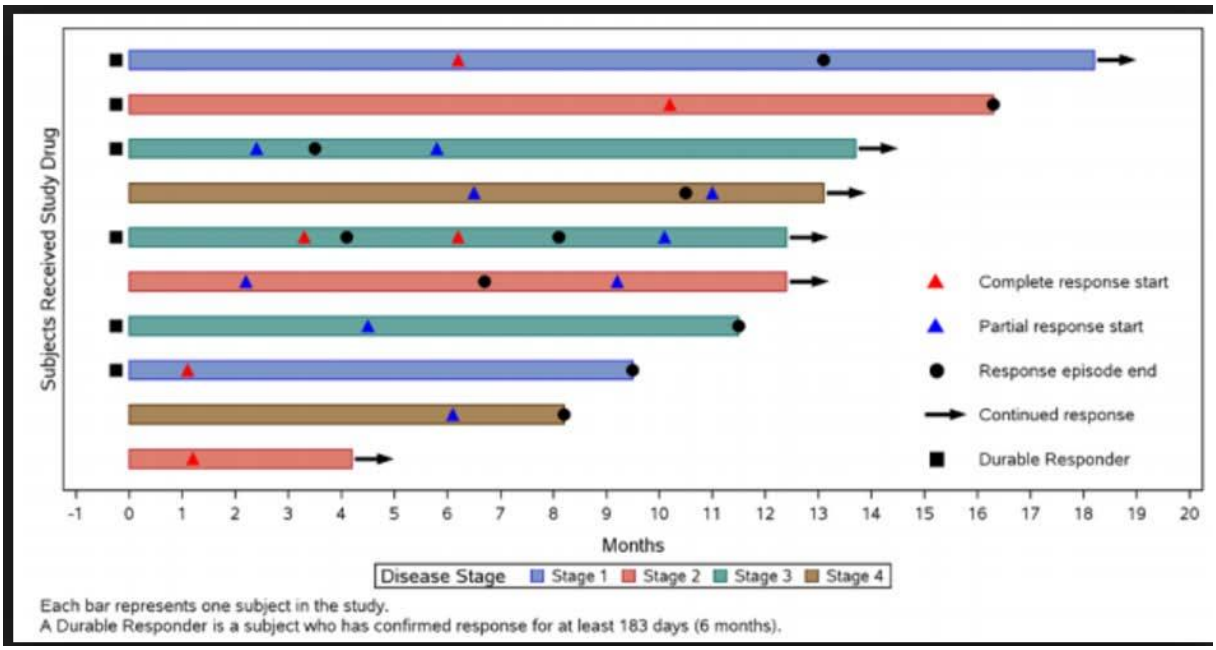
2.1.4 Overall Survival, OS

Overall survival is defined as the time fromthe date of the first dose start date to the date of death due to any cause. Patients without documentation of death at the time of the data cut off for analysis will be censored at the date the patient was last known to be alive or the data cut off date,whichever is earlier. The last known alive date is the last record in the study database. This date may be the maximum of the last visit date or last contact date, including telephone follow-up where the patientis known to be alive.

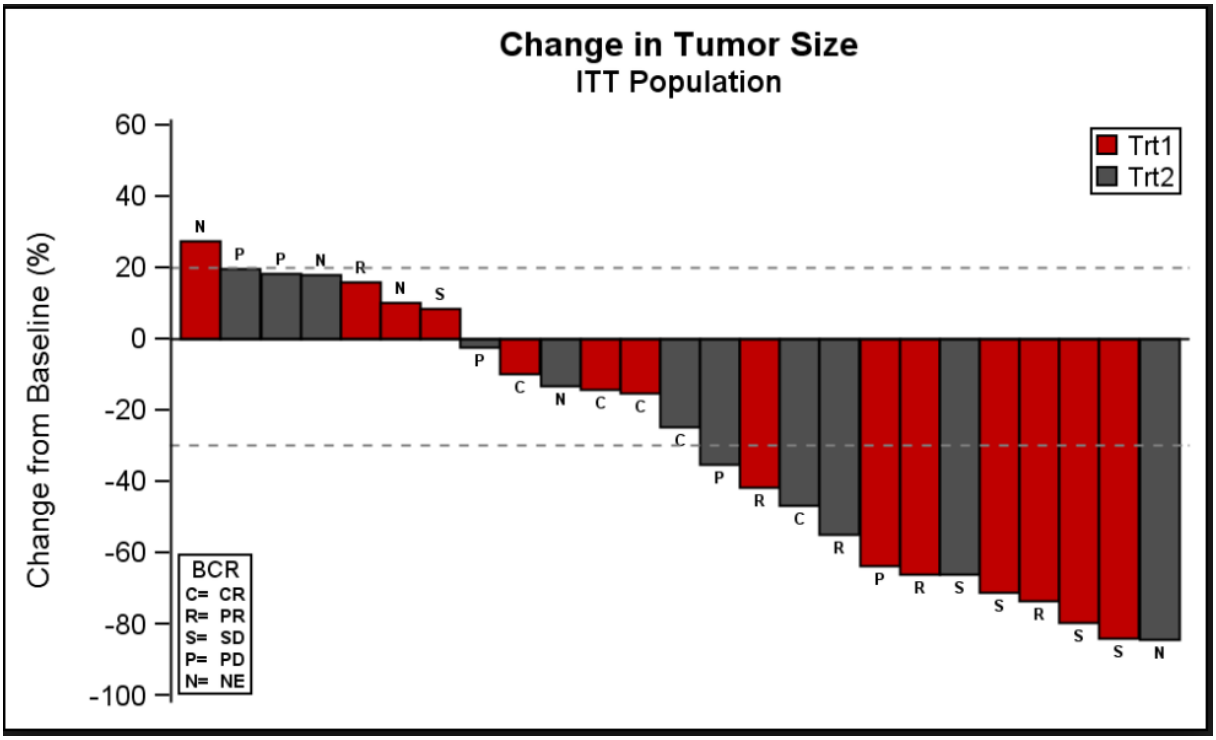
2.1.5 Other Analyses Related to Efficacy

Swimmer plots of treatment duration showing the date of progression or death, whichever is earlier, will be presented. Treatment ongoing status will be marked at the end of the plot. Waterfall plots of the percent change from baseline in target lesion measurement will be presented.

Example of swimmer plot:



Example of waterfall plot:



2.2 Safety Endpoints

Safety will be assessed for the overall safety population. Data will be presented in terms of AEs, laboratory data, and vital signs.

- Adverse Events
- Clinical laboratory evaluations
- Vital Signs

3. Statistical Analysis

Using Bayesian Predictive Probability to monitor the efficacy of each arm, based on the number of patients who achieved objective remission (CR+PR) observed in real time, based on futility or efficacy considerations, the study can be terminated early for each arm independently. Assume that the reference objective response rate is p0=15%, and the prior probability fits the Beta distribution (0.05, 0.05). Take the final threshold value of 0.5 for the arm to achieve effectiveness, 0.1 for early termination due to ineffectiveness, and 0.9 for early termination due to effectiveness. Using Bayesian prediction probability, the futility and efficacy boundaries are obtained as shown in Table S1.

Table S1 Futility and Efficacy Boundaries Based on Bayesian Prediction Probability

Subject number	Futility boundary b1	Efficacy boundary b2
10	0	3
12	1	4
14	1	4
16	2	4
18	2	4
20	3	4

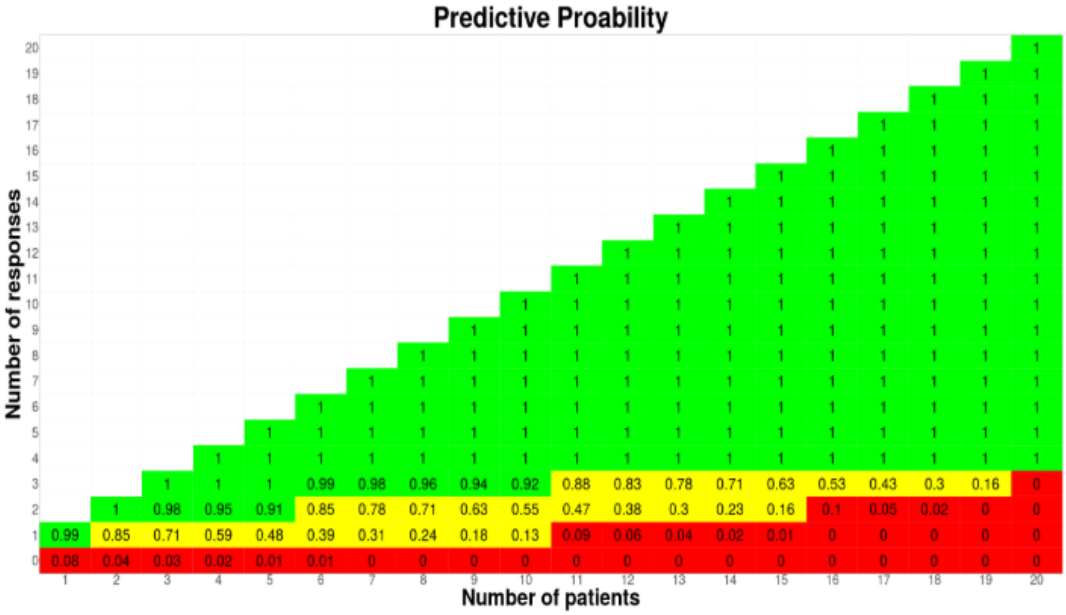
Note:

1. When the observed number of CR+PR cases is less than or equal to the futility boundary value b1, the study can be terminated due to futility;

2. When the observed number of CR+PR cases is greater than or equal to the effective cutoff value b2, the study can be terminated due to effectiveness.

For arm A and arm G, due to the difficulty of enrolling and good efficacy observed, according to the above parameters and the thresholds in Table S1, the study of each arm can be terminated in advance according to Table S2.

Table S2 Decision table based on Bayesian prediction probability



Note:

1. The horizontal axis is the number of patients enrolled, and the vertical axis is the number of patients with CR+PR.

2. Green indicates that the study can be terminated due to effectiveness; red indicates that the study can be terminated due to ineffectiveness; yellow indicates that enrollment needs to be continued.

For the arm C, it can be expanded to a maximum of 41 cases based on the promising efficacy reported in the interim analysis. Assuming an ORR of 30%, at the significant level (alpha one-sided 0.025), the 41 enrolled patients could provide 90% power to make the lower bound of the 95% confidence interval (exact algorithm) of the ORR greater than 10%. After enrolling 20 patients, an interim analysis was conducted to decide whether to expand to 41 patients. The consumption of interim analysis was β=0.02. At the interim analysis, if more than or equal to 4 of the 20 patients achieved CR or PR, another 21 patients will be enrolled. Table S3 presents the 95% confidence interval (exact algorithm) for ORR from 15% to 50% for 20 patients. Considering a dropout rate of 10%, 46 patients were required in this arm.

Table S3 The 95% confidence intervals of ORR in arm C in the first 20 patients (exact algorithm)

ORR（N=20）	The number of CR or PR	95%CI
10%	2	(1.2%, 31.7%)
15%	3	(3.2%, 37.9%)
20%	4	(5.7%, 43.7%)
25%	5	(8.7%, 49.1%)
30%	6	(11.9%, 54.3%)
35%	7	(15.4%, 59.2%)
40%	8	(19.1%, 63.9%)
45%	9	(23.1%, 68.5%)
50%	10	(27.2%, 72.8%)

3.1 General Considerations

3.1.1 Analysis Sets

Per-Protocl (PP) set: The PP data set is defined as restricted to all the cases that meet the inclusion criteria and complete the treatment plan, with good compliance, no banned compounds and fulfilled required contents in the case report form, as well as the observation record documents from subjects whose compliance satisfies the study protocol requirement.

Intention to Treat (ITT) Set: The ITT population includes all patients who have signed informed consent, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol.

Safety Set: This will include all patients who received at least 1 dose of medication, irrespective of dose.

3.1.2 Methods for Handling Missing Data

Missing or partial dates will not be imputed except for AE and concomitant medication data. In this case, the listings will show these dates as missing, but the following approach will be used to define whether an AE is treatment-emergent or a therapy is considered a prior medication.

Missing Data Imputation for Adverse Event/Concomitant Medication Start Dates

If the stop date is nonmissing and the imputed start date is after the stop date, the stop date will be used as the start date.

(1) Missing day only

- If the month and year of the AE/the concomitant medication are the same as the month and year of the first dose date, the first dose date will be used.

- If the month and year are before the month and year of the first dose date, the last day of the month will be assigned to the missing day.

- If the month and year are after the month and year of the first dose date, the first day of the month will be assigned to the missing day.

(2) Missing day and month

- If the year is the same as the year of the first dose date, the first dose date will be used.

- If the year is prior to the year of the first dose date, December 31st will be assigned to the missing fields.

- If the year is after the year of the first dose date, January 1st will be assigned to the missing fields.

(3) Missing day, month, and year

- The first dose date will be used.

Missing Data Imputation for Missing Adverse Event/Concomitant Medication Stop Date

If the start date is nonmissing and the imputed stop date is before the start date, the start date will be used. If the death date is available and the imputed stop date is after the death date, the death date will be used.

(1) Missing day only

- The last day of the month will be assigned as the missing day.

(2) Missing day and month

- December 31st will be assigned to missing fields.

(3) Missing day, month and year

- The event will be regarded as ongoing.

Missing/Partial Dates during Screening Visit

The following rules apply to dates recorded during the screening visits (e.g., prior therapies/medications, medical history):

(1) Missing day only

- The first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the 15th will be used.

(2) Missing day and month

- If the year is the same as the year of the first dose of study drug, the 15th of January will be used unless it is later than the first dose, in which case the date of the first of January will be used.

- If the year is not the same as the year of the first dose of study drug, the 15th of June will be used, unless other data indicate that the date is earlier.

(3) Missing day, month, and year

- No imputation will be applied.

Missing Last Dosing Date

Missing/incomplete last dose date from the treatment discontinuation page will be imputed as follows:

(1) Missing day only

- If the treatment discontinuation reason is death, the death date will be used.

- If the last available dosing date from dosing data matches the partial last dose date from the treatment discontinuation page, the last available dosing date will be used.

- Otherwise, the first day of the month will be used.

(2) Missing day and month

- If the treatment discontinuation reason is death, the death date will be used.
- If the last available dosing date from dosing data matches the partial last dose date from the treatment discontinuation page, the last available dosing date will be used.
- Else January 1 will be used.

(3) Missing day, month and year

- If the treatment discontinuation reason is death, the death date will be used.
- Otherwise, the last available dosing date will be used.

The imputed last dose date will be compared to the available study discontinuation date and the data cutoff date. Then, the earliest date will be used.

3.2 Study Subjects

3.2.1 Subject Disposition

Disposition in terms of the number of patients screened/entered into the study, treated, permanently discontinued treatment, and reasons for treatment discontinuation will be summarized for the ITT population and the safety population. The number of patients included in each population will be summarized by a flow chart. A by-patient listing for disposition will be provided, including whether the patient is included in each of the analysis sets, treatment status, date of stopping treatment, date of stopping study participation, reason for treatment discontinuation, study completion status, and survival follow-up status.

A separate listing will be provided for patients who were registered into the study but did not receive the study drug and the reason for not receiving the study drug. Screen failures and entered-butnot-dosed patients will be excluded from all analyses.

3.2.2 Demographics

Baseline characteristics will include age, Eastern Cooperative Oncology Group (ECOG) performance status, numbers of metastatic organs and metastatic sites at initial diagnosis and at screening.

3.2.3 Medical History

Prior systemic anticancer therapy will be summarized. The number of prior anticancer therapies for metastatic disease (<3 prior lines vs 3-6 prior lines vs >6 prior lines) and types of prior chemotherapies for metastatic disease will also be summarized categorically.

3.2.4 Major Protocol Deviations

A bypatient listing with major study protocol violations and deviations will be provided for patients.

Protocol violations to be programmed

- Inclusion/Exclusion Criteria

- <2 weeks between previous treatment, immune therapy, chemotherapy, or investigational therapy for metastatic disease and start of treatment.

- Informed Consent

- Patient's written informed consent not available.

- Patient's written informed consent too late (after start of study-specific procedures)

- Prohibited Medication

- Anticancer therapy during treatment.

- Radiation during treatment.

- Prophylactic medication of hematopoietic growth factors or blood transfusions before Cycle 1.

3.3 Efficacy Analysis

Formal statistical hypothesis testing will not be performed. Descriptive statistics, data summaries and graphical methods will be used to assess the efficacy. The primary endpoint will be the objective response rate (ORR) [PR+CR], with responders requiring a confirmatory response assessment no sooner than 4 weeks after the first response assessment. Assessment of tumor response is based upon on-site readings by local radiologists using RECIST 1.1. The earliest imaging date of the associated imaging

methods was used as the response assessment date. Secondary efficacy endpoints will include disease control rate (DCR, CR+PR+SD), progression-free survival (PFS), and overall survival (OS). PFS and OS data will be analyzed via the Kaplan–Meier method and 95% CI from the Clopper-Pearson method with log-log transformation.

3.4 Safety Analysis

Safety will be assessed for the safety population. Data will be presented in terms of AEs, laboratory data, and vital signs.

3.4.1 Extent of Exposure

The extent of exposure mainly summarizes the drug exposure time, the cumulative dosage and the drug intensity.

3.4.2 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AEs that begin or worsen on or after the start of the study drug through 30 days after the last dose of the study drug. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 unless otherwise specified. The severity will be graded based on the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. All AEs will be listed. Only TEAEs are summarized and will be referred to as AEs hereafter. The timing of AEs and concomitant medications will take into account the date and the time of the AE or concomitant medication. The frequency and severity of AEs will be tabulated by MedDRA SOC and PT. For this purpose, an AE that occurs more than once within each patient will be counted only once (at the worst CTCAE grade and relationship category). Additional bypatient listings will be provided for AEs leading to on-treatment death, serious AEs (SAEs), and AEs leading to discontinuation of treatment (excluding AEs leading to death).

3.4.3 Laboratory Evaluations

Clinical laboratory data results will be reported in standard international units and Chinese conventional units. Baseline is defined as the last observation occurring prior to the first treatment administration of medication. Observations occurring on the same day as the first treatment administration may be the baseline assessment only if the time of assessment occurs prior to the time of treatment. If this cannot be determined, the

observation will be assumed to have occurred after dosing. If a lab value is reported using a nonnumeric qualifier (e.g., less than [<] a certain value or greater than [>] a certain value), the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier. Hematology and serum chemistry data will be listed by patient and summarized by study visit. Actual values by visit and change from baseline will be summarized by mean, median, standard deviation, minimum, maximum and number of patients. Shift tables from baseline to worst CTCAE grade on treatment and from worst to last CTCAE grade on treatment will be presented where CTCAE grade is available. Shift tables will be presented based on CTCAE v5.0 criteria, using grades 1 through 4 as well as a grade 0 indicating no abnormality. These shift tables will report the shift from baseline CTCAE grade to worst grade on treatment and from worst to last on-treatment visit.

3.4.4 Vital Signs

The actual value and change from baseline (most recent evaluation within 28 days prior to beginning study therapy) to each on-study evaluation, including baseline and end of treatment, will be summarized for vital signs. Vital sign measurements will be presented for each patient in a bypatient data listing.

4. Interim Analysis

An interim analysis will be conducted when 20 subjects are enrolled in at least one arm and at least one subject is enrolled in each arm to preliminarily evaluate the efficacy and safety of the drug combination in each arm. With the estimated enrollment speed, approximately 50% of subjects would have been enrolled by the interim analysis time point.