

Survival Benefits of Statins in Breast Cancer Patients With  
Abnormal Lipid Metabolism (SBSBC)

**Protocol**

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Founder: Wang Xuefei

**Title and Investigators:**

Survival Benefits of Statins in Breast Cancer Patients With Abnormal Lipid Metabolism (SBSBC)

Principle Investigator: Xuefei Wang

Co-investigators: Qiang Sun

**Abstract:**

This is a randomized clinical trial from March 28st 2019 to March 28st 2024. The purpose of this study is to evaluate the survival benefits of statins in breast cancer patients with abnormal lipid metabolism. Consecutive samples will be enrolled based on inclusion and exclusion criteria. They will be grouped randomly into intervention group or control group after informed consent. A third group independent from research team will be in charge of randomization. In this study, 348 patients were randomly divided into two groups according to patients' wishes and written informed consent. The experimental group: control group = 1:1. Patients in both groups will undergo breast cancer treatment. The experimental group used statins, while the control group used dietary intervention instead of statins. The main endpoint was 5 years DFS. The subjects were breast cancer patients. For statistical analysis, t-test will be used between two different groups. Estimated sample size will be calculated using t-test. Log rank test was used with survival curve based on Kaplan Merier method and 95% confidence interval of median survival time. Data and Safety Monitoring Board will periodically review, evaluate and give recommendations to this study in various aspects.

**Research Question:**

Dose statins give survival benefits in breast cancer patients with abnormal lipid metabolism?

**Specific aims:**

To evaluate the survival benefits of statins in breast cancer patients with dyslipidemia (low and medium risk of ASCVD).

**Significance:**

In 2015, there were about 272,000 new cases of female breast cancer and 70,700 deaths in China [1]. The peak incidence of breast cancer among women in East Asia is 45-54 years old. In China, 69.75% of all breast cancer cases are women over 45 years old. Therefore, more than half of breast cancer patients are in perimenopause or menopause at the time of onset[2]. According to the US surveillance, epidemiology and final results database, cardiovascular events in breast cancer patients aged over 66 were the leading cause of death, accounting for 15.9%, and breast cancer-related deaths accounted for 15.1% [3-4]. The estrogen level of postmenopausal women with breast cancer is

significantly reduced by both ovarian dysfunction and drug treatment. Common dyslipidemia and the risk of cardiovascular disease are also increased. Cardiovascular disease-related deaths have jumped to the top of these deaths except for breast cancer. Premenopausal women also suffer from dyslipidemia during adjuvant therapy. However, clinicians often neglect the risk of dyslipidemia and cardiovascular disease.

Adjuvant endocrine therapy is an important part in the treatment of breast cancer. Estrogen in postmenopausal women mainly comes from tissues other than ovaries, such as fat, muscle, skin and so on. It is formed by aromatization of androstenedione and testosterone. Aromatase is an indispensable rate-limiting enzyme in this process. Aromatase inhibitors can block the main source of estrogen in postmenopausal breast cancer patients, so as to control the growth of breast cancer cells and treat tumors [5-8]. The third generation of aromatase inhibitors has become the first choice of adjuvant therapy for estrogen receptor-positive, early postmenopausal breast cancer patients. At present, the recommended time for use is 5 to 10 years [7].

Based on current epidemiological and clinical studies, it is practical and reasonable to set appropriate cholesterol-lowering target values according to patients' overall cardiovascular risk level. For low, medium and high risk patients without ASCVD, the LDL\_C target values recommended by the guidelines for prevention and treatment of adult dyslipidemia in China are < 4.1, 3.4 and 2.6 mmol/L, respectively (corresponding non-HDL\_C target values are LDL\_C + 0.8 mmol/L, cholesterol conversion unit: 1 mmol/L = 1 mg/dl \* 0.0259), beyond which lifestyle interventions and (or) drug therapy should be initiated. These suggestions are based on the epidemiological characteristics of dyslipidemia in Chinese residents and the available clinical evidence, which are the basic criteria for current lipid management. Based on cholesterol theory and many new research results published in recent years, it is possible to further reduce the cardiovascular risk of patients by continuing to reduce LDL\_C or non-HDL\_C levels to a certain extent. At present, the target of blood lipid intervention for breast cancer patients lacks evidence-based medical support. Therefore, the Chinese consensus recommends that cholesterol [9] be controlled more strictly for postmenopausal women, referring to the expert recommendations of the prevention and treatment of dyslipidemia in the 2014 China Cholesterol Education Program. It is suggested that the ideal level of LDL\_C in postmenopausal breast cancer patients without risk factors should be < 3.4 mmol/L.

However, the consensus of Chinese experts on the management of dyslipidemia in early postmenopausal breast cancer published in 2017 has not made clear recommendations on which patients should use lipid-lowering drugs and how much to use. Especially in clinical practice, the control of blood lipid is a grey area for low-risk patients with ASCVD. In recent years, studies have shown that statins can reduce the recurrence and metastasis of breast cancer and improve the overall survival of breast cancer patients [10-13]. Therefore, this study is an active effort to seek a survival benefit program for patients at low and medium risk of ASCVD.

## **Methods:**

### Overview of design:

A randomized, open, blank controlled, single-center clinical trial was conducted to compare the survival benefits of statins in breast cancer patients with dyslipidemia (low and medium risk of ASCVD). The control group used dietary intervention instead of statins. The main endpoint was 5 years DFS. The subjects were breast cancer patients. In this study, 348 patients were randomly divided into two groups according to patients' wishes and written informed consent. The experimental group: control group = 1:1. Subjects were screened and administered continuously until the disease progressed and the toxicity was intolerable. Informed consent was withdrawn or the researcher decided that the drug must be discontinued.

### Study subjects:

- Target population: Breast cancer patients with dyslipidemia (low and medium risk of ASCVD).
- Accessible population: Breast cancer patients with dyslipidemia (low and medium risk of ASCVD).
- Selection criteria: Well suited to the research question, representative of target populations and available, representative of accessible populations and easy to study. They should be breast cancer patients.
  - 1) Diagnosed as invasive breast cancer, it has been treated surgically, confirmed by histology, cytology or imaging.
  - 2) Female patients (35-75 years old);
  - 3) The low-risk patients with ASCVD;
  - 4) Signed written informed consent approved by IRB or IEC
- Exclusion criteria:
  - 1) The subjects were pregnant or lactating.
  - 2) Pregnancy test positive (urine or serum) in women with potential pregnancy within 7 days before administration.
  - 3) Other invasive tumors (including the second primary breast cancer) may affect the evaluation of outcomes and the compliance of schemes, but subjects who have been cured and survived disease-free for at least five years can be selected.
  - 4) Patients with chronic underlying liver diseases who have abnormal liver function and/or clinical manifestations:  
Serum total bilirubin > 2.5 \*ULN; or INR > 1.5 although there was no increase in bilirubin  
Serum ALT or AST > 3 \*ULN;  
Alkaline phosphatase > 2.5 \*ULN;  
Elevated ALT or AST may gradually recover, but with progressively increased fatigue, nausea and vomiting, fever, right upper abdominal pain or tenderness.
  - 5) Extremely high risk ASCVD patients Including acute coronary syndrome (ACS), stable coronary heart disease, revascularization, ischemic cardiomyopathy, ischemic stroke, transient ischemic attack, peripheral atherosclerosis, etc.

6) High-risk ASCVD patients (in accordance with one of the following circumstances):

LDL-C > 4.9 mmol/L or TC > 7.2 mmol/L Diabetic patients with 1.8 mmol/L < LDL-C < 4.9 mmol/L (or) 3.1 mmol/L < TC < 7.2 mmol/L and age < 40 years

The 10-year risk of ASCVD was moderate and younger than 55 years old. The remaining life risk was assessed. Those with any of the following two or more risk factors are defined as high risk:

Systolic or diastolic blood pressure (> 160 mmHg) or (> 100 mmHg)

a) Non-HDL-C > 5.2 mmol/L (200 mg/dl)

b) HDL-C < 1.0 mmol/L (40 mg/dl)

c) BMI > 28 kg/m<sup>2</sup> Smoking

7) In the abnormal group of simple TG (triglyceride), TG (> 5.7 mmol/L)

8) Other serious diseases, including:

Congestive heart failure (NYHA grade II, III, IV); dyspnea at rest or requiring oxygen therapy; severe infection; uncontrolled diabetes mellitus;

9) If there are serious mental or mental disorders, it is estimated that the subjects' compliance to participate in this study is not strong.

10) Drug allergies to research drugs are known.

11) Participated in other drug clinical trials in the past 30 days.

12) Failure to complete at least one cycle of clinical trials based on this protocol, and failure to evaluate safety and effectiveness.

13) Serious violation of this study program, not in accordance with the prescribed dose, method and course of treatment.

#### Plans for sampling, recruiting and retaining subjects:

- Sample type: Convenience sample
- Sampling procedures: Convenience sampling will be used to enroll a cohort of breast cancer patients with dyslipidemia (low and medium risk of ASCVD), and randomly separate them into two groups. We prepare to use SPSS software to do the randomly separation. Experimental group used statins, the other one used dietary intervention instead of statins.
- Recruitment method: When patients presented our hospital diagnosed of breast cancer with dyslipidemia (low and medium risk of ASCVD), we will review these patients' medical records to find out the potential subjects for this study according to the inclusion and exclusion criteria. The eligible subject who is willing to participate in this study will be enrolled and consented. They will be randomly (using SPSS software) divided into 2 groups. One is statins group, the other one is control group.

#### Measurements:

- Predictor variables:

The predictor variable we are assessing is whether use statins. According to which, we established the intervention group and control group.

- Outcome variables:

The primary outcome: DFS (disease free survival) rate

Secondary outcome: OS (overall survival) rate

- Potential confounders:

Since this protocol is an RCT (randomly clinical trial) on survival benefits between statins group and control group, it will balance the confoundings in it, such as age, slight pathology difference, tumor size difference, lymph node status difference, tumor grade difference, and the different surgeons between the 2 groups.

- Plans for randomization, blinding, run-in period as needed:

#### 1) Randomization

We prepare to use SPSS software to do the randomly separation. According to the inclusions and exclusions, once we find the right patient, we will put the name in computer. The computer will randomly tell which group the patient will be in. After explanations to the patients, and receiving the patient agreements, we will sign the informed consent with them.

#### 2) Blinding

The clinicians and patients will be blinded to the intention of the group divided. Since the patients' and clinicians' subjective motion may affect the outcomes.

#### 3) Run-in design

We would like to recruit patients from the breast surgery department. Clinic doctors in this department will help us to find appropriate patients. Then appraiser will do the diagnostic evaluation. If patients meet the included standard, we will ask them to sign informed consent and the registration form (questionnaire). Meanwhile we will make a calendar for their treatment and supervision.

#### 4) Stratified blocked randomization

In clinical practice, different molecular subtypes do relate to different prognosis and treatment. So we would like to stratify blocked randomization according to molecular subtype. Previous study [12] show that the proportion of luminal A, luminal B, Her-2 positive and triple-negative are 32.73%, 47.01%, 5.71%, 14.55%. And we will do subgroup analysis.

#### **Statistical issues:**

### Primary outcomes:

The research question is whether statins can benefit breast cancer patients with dyslipidemia (low and medium risk of ASCVD). The main endpoint was DFS. A review of the literature suggests that simvastatin reduced the recurrence rate of breast cancer by 10%. The investigator would like to be able to detect a difference of 10% or more in DFS change between the two groups. How many patients are required in each group at  $\alpha$  (two-sided) = 0.05;  $\beta$  = 0.10, power = 0.90.

1. Null Hypothesis: For breast cancer patients with dyslipidemia (low and medium risk of ASCVD) under endocrine therapy, whether statin used is the same in DFS.
2. Alternative Hypothesis (two-sided): For breast cancer patients with dyslipidemia (low and medium risk of ASCVD) under endocrine therapy, whether statin used is different in DFS.
3. Effect size=0.1(10%\*2)
4. Standard deviation of CTC=1
5. Standardized effect size=effect size/standard deviation=0.1/1=0.1
6.  $\alpha$  (two-sided) = 0.05;  $\beta$  = 0.10, power = 0.9
7. Based on Appendix 6A from the text book, the estimated sample size is 157 in each group.
8. Ultimate sample size =  $2*157/0.9= 348$

Looking across from a standardized effect size of 0.10 in the leftmost column in Table 6A and down from  $\alpha$  (two-side) =0.05 and  $\beta$  = 0.10 is the required sample size of 157patients in statins group and control group. With 10% dropout the final sample size is 348[14].

### **Data safety & monitoring:**

The members of DSMB are 3 professors in the breast surgery department, 6 attending doctors and 3 residents. DSMB members will meet:

- 1) before the start of the trial to discuss the study protocol,
- 2) at early stage of about 10-20 patients are enrolled. In order to monitor **enrollment** efficacy, **adverse effects** that might have happened, the efficacy of **blinding** strategy, the current **outcome variables** in control and interventional group (only known to DSMB members), **protocol** compliance and quality control issues.
- 3) Subsequent DSMB meetings will be hold regularly (at least every three months) or anytime when there are safety issues, need to stop the program earlier and so on.

If DSMB find that the statins are causing harm, they could discuss whether to end the study early after balancing between ethical responsibility to the participants and the advance of scientific knowledge.

If DSMB find that the statins are much more effective than anticipated, they could stop the study before the primary endpoint.

## **Ethical considerations:**

In our study, the major ethical issue is the applied population of statins. In order to mitigate this situation, we will:

- 1) Specify the inclusion criteria that specific patients.
- 2) We will monitor patients' liver function and blood lipid levels and adjust the dosage of drugs accordingly.
- 3) Inform the patients with this potential risk comprehensively, have them better understood the potential risk of this study, and write it in the informed consent.
- 4) Use DSMB to monitor any risk related to the intervention.

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Appendix

Statins VS. Dietary Intervention on Breast Cancer Patients

Date: --/-- [dd / mm / yyyy]

Name: \_\_\_\_\_

Address: \_\_\_\_\_

ID No.: \_\_\_\_\_

Medical record No.: \_\_\_\_\_

Sex: Female

Date of birth: --/-- [dd / mm / yyyy]

Pathology: \_\_\_\_\_ molecular type \_\_\_\_\_

T \_\_\_\_\_ N \_\_\_\_\_ M \_\_\_\_\_

ER \_\_\_\_\_ PR \_\_\_\_\_ Her-2 \_\_\_\_\_

Ki-67 \_\_\_\_\_ P53 \_\_\_\_\_

Date of surgery \_\_\_\_\_ surgery type \_\_\_\_\_

Other treatment \_\_\_\_\_

Baseline: date \_\_\_\_\_ statin \_\_\_\_\_

LDL-C \_\_\_\_\_ TC \_\_\_\_\_ TG \_\_\_\_\_ ALT \_\_\_\_\_ CK \_\_\_\_\_ Fatty Liver \_\_\_\_\_

1 month follow-up: date \_\_\_\_\_ statin \_\_\_\_\_

LDL-C \_\_\_\_\_ TC \_\_\_\_\_ TG \_\_\_\_\_ ALT \_\_\_\_\_ CK \_\_\_\_\_ Fatty Liver \_\_\_\_\_

3 month follow-up: date \_\_\_\_\_ statin \_\_\_\_\_

LDL-C \_\_\_\_\_ TC \_\_\_\_\_ TG \_\_\_\_\_ ALT \_\_\_\_\_ CK \_\_\_\_\_ Fatty Liver \_\_\_\_\_

6 month follow-up: date \_\_\_\_\_ statin \_\_\_\_\_

LDL-C \_\_\_\_\_ TC \_\_\_\_\_ TG \_\_\_\_\_ ALT \_\_\_\_\_ CK \_\_\_\_\_ Fatty Liver \_\_\_\_\_

RT (recurrence time)\_\_\_\_\_

Other event\_\_\_\_\_

1 year follow-up: date\_\_\_\_\_statin\_\_\_\_\_

LDL-C\_\_\_\_\_TC\_\_\_\_\_TG\_\_\_\_\_ALT\_\_\_\_\_CK\_\_\_\_\_Fatty Liver\_\_\_\_\_

RT (recurrence time)\_\_\_\_\_

Other event\_\_\_\_\_

1.5 year follow-up: date\_\_\_\_\_statin\_\_\_\_\_

LDL-C\_\_\_\_\_TC\_\_\_\_\_TG\_\_\_\_\_ALT\_\_\_\_\_CK\_\_\_\_\_Fatty Liver\_\_\_\_\_

RT (recurrence time)\_\_\_\_\_

Other event\_\_\_\_\_

2 year follow-up: date\_\_\_\_\_statin\_\_\_\_\_

LDL-C\_\_\_\_\_TC\_\_\_\_\_TG\_\_\_\_\_ALT\_\_\_\_\_CK\_\_\_\_\_Fatty Liver\_\_\_\_\_

RT (recurrence time)\_\_\_\_\_

Other event\_\_\_\_\_

2.5 year follow-up: date\_\_\_\_\_statin\_\_\_\_\_

LDL-C\_\_\_\_\_TC\_\_\_\_\_TG\_\_\_\_\_ALT\_\_\_\_\_CK\_\_\_\_\_Fatty Liver\_\_\_\_\_

3 year follow-up: date\_\_\_\_\_statin\_\_\_\_\_

LDL-C\_\_\_\_\_TC\_\_\_\_\_TG\_\_\_\_\_ALT\_\_\_\_\_CK\_\_\_\_\_Fatty Liver\_\_\_\_\_

RT (recurrence time)\_\_\_\_\_

Other event\_\_\_\_\_

3.5 year follow-up: date\_\_\_\_\_statin\_\_\_\_\_

LDL-C\_\_\_\_\_TC\_\_\_\_\_TG\_\_\_\_\_ALT\_\_\_\_\_CK\_\_\_\_\_Fatty Liver\_\_\_\_\_

4 year follow-up: date\_\_\_\_\_statin\_\_\_\_\_

LDL-C\_\_\_\_\_TC\_\_\_\_\_TG\_\_\_\_\_ALT\_\_\_\_\_CK\_\_\_\_\_Fatty Liver\_\_\_\_\_

RT (recurrence time)\_\_\_\_\_

Other event\_\_\_\_\_

4.5 year follow-up: date\_\_\_\_\_statin\_\_\_\_\_

LDL-C\_\_\_\_\_TC\_\_\_\_\_TG\_\_\_\_\_ALT\_\_\_\_\_CK\_\_\_\_\_Fatty Liver\_\_\_\_\_

5 year follow-up: date\_\_\_\_\_statin\_\_\_\_\_

LDL-C\_\_\_\_\_TC\_\_\_\_\_TG\_\_\_\_\_ALT\_\_\_\_\_CK\_\_\_\_\_Fatty Liver\_\_\_\_\_

RT (recurrence time)\_\_\_\_\_

Other event\_\_\_\_\_

Appendix

Survival Benefits of Statins in Breast Cancer Patients With  
Abnormal Lipid Metabolism (SBSBC)

**Informed Consent**

NCT number: 03971019

Informed Consent Version: V5

Informed Consent Version Date: 1 August 2019

Founder: Wang Xuefei

# Subject Informed Consent

## **Respected patients:**

We invite you to participate in a clinical trial. Before you decide whether to participate in the study, it is important to understand the purpose of the study and its impact on you. Please read the following information carefully. You can discuss your participation in this research with your relatives, friends and family doctors. Once all the questions are answered, you are satisfied with the explanation of the study, and you decide to participate, you will be invited to sign this informed consent.

## **Name of research project:**

Survival Benefits of Statins in Breast Cancer Patients with Abnormal Lipid Metabolism.

**Research leader:** Wang Xuefei

**Contact number:** 13001289600

**SETTING:** Peking Union Medical College Hospital, Chinese Academy of Medical Sciences

## **1. Research background and purpose:**

### **Background:**

You were invited to participate in a study on the survival benefits of statins for breast cancer patients with dyslipidemia (low and medium risk of ASCVD). This study is a single-center, randomized controlled clinical trial, which will be conducted under the guidance of professional doctors and relevant research teams. In addition, this study has been approved by relevant ethics committees to ensure that your rights and interests are protected.

You are currently diagnosed with breast cancer and abnormal lipid metabolism occurred. The estrogen level of postmenopausal women with breast cancer is significantly reduced by both ovarian dysfunction and drug treatment. Common dyslipidemia and the risk of cardiovascular disease are also increased. Cardiovascular disease-related deaths have jumped to the top of these deaths except for breast cancer. However, clinicians often neglect the risk of dyslipidemia and cardiovascular disease. Based on current epidemiological and clinical studies, it is practical and reasonable to set appropriate cholesterol-lowering target values according to patients' overall cardiovascular risk level. For low, medium and high risk patients without ASCVD, the LDL\_C target values recommended by the guidelines for prevention and treatment of adult dyslipidemia in China are < 4.1, 3.4 and 2.6 mmol/L, respectively (corresponding non-HDL\_C target values are LDL C + 0.8 mmol/L, cholesterol conversion unit: 1 mmol/L = 1 mg/dl \* 0.025 9), beyond which lifestyle intervention and/or drug therapy should be initiated. These suggestions are based on the epidemiological characteristics of dyslipidemia in Chinese residents and the available clinical evidence, which are the basic criteria for current lipid management. Based on cholesterol theory and many new research results published in recent years, it is possible to further reduce the cardiovascular risk of patients by continuing to reduce LDL\_C or non-HDL\_C levels to a certain extent.

The goal of blood lipid intervention for postmenopausal breast cancer patients lacks evidence-based medical support. Therefore, it is recommended that cholesterol should be controlled more strictly for postmenopausal women, referring to the expert recommendations of the prevention and treatment of dyslipidemia in the 2014 China Cholesterol Education Program. It is suggested that the ideal level of LDL\_C in postmenopausal breast cancer patients without risk factors should be  $< 3.4$  mmol/L. Recent studies have shown that statins can reduce the recurrence and metastasis of breast cancer and significantly improve the overall survival of breast cancer patients. However, the consensus of Chinese experts on lipid abnormality management in early postmenopausal breast cancer published in 2017 has not made clear recommendations on which patients should use lipid-lowering drugs and how much to use. Especially in clinical practice, the control of blood lipid is a grey area for low-risk patients with ASCVD. Therefore, this study is an active effort to find a more suitable survival benefit program for low-risk patients with ASCVD.

### **Research purposes:**

To further evaluate the survival benefit of statins for breast cancer patients with abnormal lipid metabolism (low and moderate risk of ASCVD). Because some retrospective studies have proved that statins can reduce the recurrence and metastasis of breast cancer, at the same time, they can also prevent cardiovascular and cerebrovascular diseases in breast cancer patients with abnormal lipid metabolism. This study is intended to provide a convenient and effective intervention program for breast cancer patients with abnormal lipid metabolism (low and medium risk of ASCVD).

### **2. Research contents, methods and procedures:**

This study is a randomized, open, single-center clinical study, which will be conducted in a single center of Peking Union Medical College Hospital. It is expected that 348 subjects will participate in the study.

According to the results of pathological examination and laboratory examination after operation, if you fully meet the criteria of inclusion and exclusion, all patients with breast cancer who have abnormal lipid metabolism after operation will be assessed by the researcher (clinician). Firstly, the patients were randomly divided into statin group and dietary intervention group, but the distribution of patients in the two groups was uniform and did not change with the subjective will of clinicians or patients and their families. Complete their respective treatment cycles. The annual follow-up was continued after the completion of the study.

### **Selection criteria:**

All the following conditions should be met before they can be enrolled in the group:

1. Diagnosed as invasive breast cancer, it has been treated surgically, confirmed by histology, cytology or imaging.
2. Female patients (35-75 years old);
3. Low-risk patients with ASCVD;

#### 4. Signed written informed consent approved by IRB or IEC

If you participate in the research, you will need to do the following work:

(1) First of all, you need to understand the whole process of the research and participate voluntarily, and sign the informed consent.

(2) You have undergone surgical treatment (including those who have obtained histological or cytological histological examinations) and have definite pathological and immunohistochemical results after surgery. Before you are selected for the study, you will undergo the following examinations to determine whether you can participate in the study:

The doctor will inquire about and record your medical history, and conduct physical examination/signs/physical fitness score/tumor assessment for you.

You need to take blood for routine blood test, blood biochemistry (blood cell count, biochemistry, etc.), pregnancy test (if you are a woman of childbearing age).

Based on the results, the research doctor will assess whether you meet the inclusion criteria and do not meet the exclusion criteria.

(3) If you pass the above tests, the following steps will be taken to conduct the research:

According to your condition, the clinician decides to assign it to the statin group (simvastatin 20mg/d qn Po (adjustable dosage according to the monthly blood lipid level), atorvastatin 10mg/d qn po (patients who can not tolerate the side effects of simvastatin can consider replacing this drug) and the control group (dietary intervention group, guiding patients to control diet, improving lifestyle, etc.). You will be followed up every 3-6 months for the next 3 years and receive necessary adjuvant treatment.

During the treatment period, you need to be closely followed up, and will undergo clinical examinations, hematological examinations and so on. Other examinations (such as imaging examinations) will be performed according to your course of disease. During the last follow-up in the treatment period, you will be given a comprehensive examination (hematological examination, clinical examination and imaging examination). Antineoplastic therapy after disease progression is determined by the researchers and recommended for follow-up and recording. These may cause trouble or inconvenience to you.

(4) Other matters requiring your cooperation:

You must come to the hospital according to the doctor's appointed follow-up time. Your follow-up is very important because the doctor will judge the effect of your treatment.

(5) Drug information:

The eligible patients will be randomly assigned to the following treatment groups according to the ratio of 1:1:

1. Statin regimen group (experimental group):

on the basis of dietary intervention

Simvastatin 20mg/d qn po (dosage can be adjusted according to monthly blood lipid level review)



Atorvastatin 10mg/d qn po (patients who cannot tolerate the side effects of simvastatin may consider replacing this drug)

## 2. Dietary intervention group (control group)

Guiding patients to control diet, improve lifestyle, etc.

The dosage of the above drugs can be adjusted according to the adverse reactions of the subjects. Subjects continued to use drugs until the disease progressed and the toxicity was intolerable. The informed consent was withdrawn or the researcher decided that the drug must be discontinued. Several suspensions of medication due to adverse events are allowed throughout the course. In case of drug missed, the time and cause of drug missed should be recorded in detail, and then continue to take medicine according to the plan cycle without supplement or periodic adjustment. Please tell your doctor in charge before you take any other drugs.

You are not allowed to use any other anticancer drugs during the study period. If you need any other treatment, please contact your doctor beforehand.

Please keep medicines out of reach of children.

## **3. Possible risks (or discomfort, inconvenience) and benefits (benefits to individuals or social groups) of participating in the study:**

### **(1) Risk:**

During the study period, there may be pain or cyanosis, which can cause temporary pain at the puncture site.

All therapeutic drugs may have side effects:

- Adverse events of Simvastatin

Simvastatin is generally well tolerated and most of its side effects are mild and transient. In clinical controlled trials, only less than 2% of patients stopped taking simvastatin because of its side effects. In the clinical trials of the existing control group, the incidence of adverse reactions (divided into possible, suspicious or affirmative) related to drugs was greater than or equal to 1% with abdominal pain, constipation, gastrointestinal flatulence, and the incidence of adverse reactions was between 0.5% and 0.9% with fatigue and headache. Reports of myopathy are rare. The following adverse reactions have been reported in clinical trials without control group or in post-marketing applications:

Pruritus and anemia;

Rhabdomyolysis and hepatitis are rarely reported.

Jaundice.

Significant allergic syndrome including one or more of the following characteristics has rarely been reported: neurovascular edema, lupus-like syndrome, rheumatic polymyalgia, vasculitis, thrombocytopenia, eosinophilia, arthritis, arthralgia, urticaria, fever, flushing, dyspnea, and discomfort.

Laboratory tests revealed that significant and persistent elevations of serum transaminases were rarely reported. Liver function abnormalities were mild or transient. Increased serum creatine kinase (CK) levels from skeletal muscle have been reported.

- Adverse events of atorvastatin

There are occasional reports of acute renal failure secondary to myoglobinuria caused by rhabdomyolysis in skeletal muscle lipitor and other statins. Renal damage may be a risk factor for rhabdomyolysis, and patients with this disorder need to closely monitor the effects of drugs on skeletal muscle. Like other statins, atorvastatin occasionally causes myopathy (defined as muscle pain or muscle weakness, accompanied by creatine phosphokinase CPK (more than 10 times the normal upper limit). Combination of high-dose atorvastatin with specific drugs such as cyclosporine or CYP3A4 inhibitors (such as clarithromycin, itraconazole and HIV protease inhibitors) increases the risk of myopathy or rhabdomyolysis. Patients with diffuse myalgia, muscle tenderness or weakness, and/or significant creatine phosphokinase elevation should be considered as myopathy. Patients should be advised to immediately report unexplained muscle pain, muscle tenderness or muscle weakness, especially when accompanied by discomfort or fever. Lipitor should be discontinued if significant elevation of creatine phosphokinase levels or confirmed/suspected myopathy occurs. Cyclosporin A and fibric acid derivatives (beta drugs) should be used concurrently during the treatment of these drugs. Erythromycin, Clarithromycin, Ritonavir, Quinavir in Gaza or Lopinavir and Ritonavir in combination. Nicotinic acid or imidazole antifungal agents increase the risk of myopathy. Doctors should carefully weigh the potential benefits and risks when considering the combination of atorvastatin and fibric acid derivatives (beta drugs), erythromycin, clarithromycin, ritonavir, quinavir or lominavir plus ritonavir, immunosuppressive agents, imidazole antifungal agents or lipid-lowering doses of niacin, and carefully monitor any muscle pain or muscle risk in patients. Signs and symptoms of tenderness or muscle weakness, especially during the first few months of treatment and during an increase in the dosage of any drug. When atorvastatin is used in conjunction with the previously mentioned drugs (see Drug Interaction), consideration should be given to reducing the initial and maintenance doses of atorvastatin. In this case, regular determination of creatine phosphokinase should be considered, but such monitoring cannot ensure that serious myopathy can be prevented. The recommended prescription dosage and the summary of the drug interactions are shown in Table 2 (for details, [usage dosage], [drug interactions], [pharmacology and toxicology]). Any patient who has acute or severe conditions that indicate myopathy or risk factors (such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, uncontrolled seizures) is liable to induce renal failure secondary to rhabdomyolysis should suspend or discontinue lipitor therapy. 2. Liver dysfunction, like other lipid-lowering treatments, can be caused by statins. Clinical trials showed that 0.7% of patients treated with Lipitor had persistent elevation of serum aminotransferase (2 or more times higher than the upper limit of normal value 3 times). The incidence of transaminase abnormalities in shore patients with dosage of 10, 20, 40 and 80 mg was 0.2%, 0.2%, 0.6% and 2.3%, respectively. The following results were observed in patients taking Lipitor in clinical trials. One patient developed jaundice, and the elevation of liver function test (LFT) in other patients was not related to jaundice and other clinical signs or symptoms. After lowering the dosage, discontinuing or discontinuing the use of drugs, the transaminase level

returned to or approached the level before treatment without sequelae. Eighteen of 30 patients whose liver function test index was continuously elevated continued to be treated under the condition of reducing the dosage of Lipitor. Liver function should be checked before treatment, 12 weeks after treatment and 12 weeks after dosage increase, and regular check-ups (e.g. half a year) should be conducted thereafter. Usually, abnormal liver enzymes occur within 3 months before Lipitor treatment, and the elevation of transaminase in patients should be monitored until they return to normal. If ALT or AST continues to rise more than three times the normal limit, it is recommended to reduce the dosage of this drug or stop using it. Lipitor should be used with caution in patients with excessive drinking and/or a history of liver disease. It is forbidden to use this product for active liver disease or continuous elevation of aminotransferase of unknown origin (see taboo for details).

Other adverse reactions reported in placebo-controlled studies included:

Whole body: Physical discomfort, fever:

Digestive system: abdominal discomfort, belching, gastrointestinal distention, hepatitis, cholestasis;

Musculoskeletal system: skeletal muscle pain, muscle fatigue, neck pain, joint swelling:

Nutrition and metabolic system: elevated transaminase, abnormal liver function, elevated blood alkaline phosphatase, elevated creatine phosphokinase and hyperglycemia;

Nervous system: nightmare;

Respiratory system: epistaxis;

Skin and appendages: urticaria

Special sensation: blurred vision, tinnitus;

Genitourinary system: urinary leukocyte positive.

## **(2) Attention:**

You must discuss with your doctor the various side effects that may occur so that you can better distinguish between the occurrence of some risks in treatment, some of which are extremely rare and some of which are very common. If any unusual reaction or discomfort occurs at any time during the study, or new changes occur in the condition, or any unexpected situation, whether or not it is related to drugs, please inform your doctor in time.

We will closely monitor the adverse events that happen to you. If a serious adverse event occurs, your treatment may be terminated. At this time, we will propose alternative treatment. Similarly, if your doctor considers it in your best interest, he or she may terminate your treatment. Any new information that may affect your decision to continue to participate in this study will be notified to you once it is recognized. At the same time, we will also notify you of the relevant information if new findings occur during the study. If you suffer damage due to the direct cause of the study, the applicant will be liable for any serious adverse reactions that the researchers believe are directly related to the research drug, the treatment costs and the corresponding financial compensation according to the law.

Pregnancy is taboo during your treatment and during the next year. Pregnant or lactating women are not allowed to participate in this study. Effective contraceptive measures must be taken for women of childbearing age during the study period and within 12 months after completion of treatment. If you are pregnant during this study, you must inform your doctor immediately.

In this study, some patients may have poor response to treatment, and can not obtain direct benefits from treatment.

During the study period, you need to visit the hospital on time and do some blood tests. These are all for your health.

If you decide to withdraw from the study or if your disease progresses or your health does not meet the requirements of the study, your doctor may ask you to stop taking the drug immediately. After withdrawal, the doctor will give you a physical examination and corresponding physical and chemical examination to ensure that you are not affected by any adverse events in the study.

### **(3) Benefit:**

Your condition may be improved by treatment with statins, which may reduce recurrence and prolong survival.

This clinical study will provide important information for medical research, including whether statins can reduce recurrence and prolong survival in breast cancer patients. This information may help other breast cancer patients benefit in the future, and because statins are oral medicines (no need for in-patient infusion), once a day is convenient to take orally, and dosage adjustment is convenient, it may provide convenience for patients entering the clinical study group.

If the treatment is randomly assigned to a statin regimen, you can get the support of the researchers.

Due to individual differences, any treatment may be ineffective, and this study does not fully guarantee that you will benefit from the treatment. This is the treatment risk that every patient will face, even if they do not participate in this clinical study, the treatment risk will exist. Of course, the results of the study can also help other patients with treatment in the future.

### **(4) Alternative therapy:**

Participation in this study is entirely voluntary. If you choose not to participate, or withdraw at any stage of the study, you will receive alternative treatment. You should discuss alternative therapies with your doctor before deciding whether to join the study.

### **(5) Personal information preservation:**

Your medical records (case reports, examination reports, etc.) will be kept intact in the hospital. The doctor will record the results of laboratory tests on your outpatient or inpatient medical records. Researchers, representatives of bidders, ethics committees and drug regulatory authorities will be allowed to access your medical records. Any public report on the results of this study will not disclose your personal identity.

#### **4. Consultation on relevant contents:**

You have the right to consult on the content of the research, and you have the right to consult on your rights or related risks, and the right to consult on the telephone (Ethics Review Committee telephone): 010-69154494.

#### **5. The right to withdraw from research:**

Your participation in this study is entirely voluntary. For no reason whatsoever, your unwillingness to participate in or continue to participate in this study will not have any impact on your rights and interests. In addition, you have the right to withdraw from this study at any time. If you do not follow the doctor's instructions, or if the doctor considers your health and benefits, the doctor or researcher may ask you to withdraw.

Whether you participate in the research depends entirely on your willingness. You may refuse to participate in the study or withdraw from the study at any time during the course of the study. This will not affect your relationship with the doctor, nor will it affect the loss of your medical treatment or other benefits.

If you withdraw from the study for any reason, you may be asked about your use of the test drug. If the doctor thinks it is necessary, you may also be required to have a laboratory examination and a physical examination.

If you do not participate in this study, or withdraw from the study halfway, it will not affect the doctor to give you other appropriate treatment.

If you choose to participate in this research, we hope that you can insist on completing the whole research process.

It's up to you to decide whether to participate in this research or not. You can discuss it with your family or friends before making a decision. Before you make a decision to participate in the study, ask your doctor as many questions as possible until you fully understand the study.

#### **6. Compensation for research:**

If you have any side effects or damage, please inform your research doctor immediately. The clinician will give you active treatment and corresponding treatment measures, and ensure that you can receive appropriate treatment in time. Doctors and researchers will do their best to prevent and treat the possible harm caused by this study. If adverse events occur in clinical trials, the Committee of medical experts will identify whether they are related to clinical drugs. In the event of serious adverse events related to research drugs or this study, the applicant will provide financial compensation for severe damage related to clinical trials in accordance with relevant Chinese regulations and the principle of patient supplementation for clinical observation, and the patients will receive relevant compensation and free treatment. At the same time, if there are more than three levels of adverse events (especially serious adverse events), they will be reported to Peking Union Medical College Hospital within 24 hours according to the regulations.

Follow-up investigations will be conducted by the breast surgery department of Peking Union Medical College Hospital and further treatment will be carried out.

### **7. Confidentiality system:**

The medical information you receive from participating in this research institute will be kept confidential. The results of the study, published in academic journals, do not reveal any information that identifies you personally. The Peking Union Medical College Hospital will keep all the records of your research and the relevant hospital and office records. No one is authorized to obtain such information.

You have the right to privacy, and the information obtained during this study will be strictly confidential. According to the quality management criteria for clinical trials of drugs, bidders, third-party companies authorized by bidders, government and health regulators, the State Food and Drug Administration of China (CFDA) or the Independent Ethics Committee may review the information related to your participation in this study and your own medical records in order to confirm the authenticity of clinical research procedures and/or data. And it's done without violating your privacy. In addition, during this study, bidders will take the necessary confidentiality measures to identify your records through your initials, your birthday, your gender and your research number, rather than through your full name or any detailed address. We will protect your privacy and your personal data as required. Research data may be published or submitted to Chinese regulators or health insurance companies in order to obtain regulatory approval or to study drug claims.

Under no circumstances will your personal identity be disclosed. We will make every effort to protect the privacy of your personal medical data within the limits permitted by law.

### **8. This informed consent is in duplicate, one for each subject and one for each researcher, and is valid upon signature by both parties.**

#### **Subjects' informed consent:**

I have read the above in detail and fully understood it. I have carefully considered the above contents, especially the rights, risks and benefits of my participation in this study.

I volunteered to participate in this research and would like to cooperate with researchers. At the same time, I declare that I can withdraw from this study for any reason at any time without losing any legitimate rights. And I confirm that there is ample time to consider this, and I understand that:

I voluntarily signed this informed consent, volunteered to participate in this study, and agreed to follow the program recommended by the research doctor for treatment, and notified the researchers of various related events that occurred during the study. I have understood that adverse events may occur with the use of the drug. I agree to visit the research doctor in charge and take my blood samples for examination on time during the research.

If I need to take any other medication because of the change of my condition, I will consult the research doctor in advance or tell the doctor truthfully afterwards.

I can always consult my research doctor for more information. I am free to withdraw my informed consent at any time without explaining the appropriateness of my decision or affecting my subsequent medical treatment or my relationship with my doctor.

I know that if I drop out of the study, especially because of the drug, I will tell the doctor about the change of the condition and complete the corresponding physical and chemical examinations, which will be very beneficial to me and the whole research.

I agree that representatives of drug regulatory authorities, ethics committees or bidders should consult my research materials.

I know that the research doctor will keep my data strictly confidential, and I have the right to access my data through the research doctor at any time. I agree that these data will be used by research doctors for evaluation and publication of research results.

Note: According to the requirement of the Human Genetic Resources Management Office, when submitting an informed consent for a research project involving human genetic resources management, if it involves sending out information such as samples or data or testing by a third-party domestic institution, the subject should be clearly informed in the informed consent. Please add this item to the list. It does not involve deleting this item.

Subject name: \_\_\_\_\_ date: \_\_\_\_year, \_\_\_\_month, \_\_\_\_day

Researcher's Name: \_\_\_\_\_ Date: \_\_\_\_Year, \_\_\_\_Month, \_\_\_\_Day

Statements and signatures of legal representatives (if applicable)

I confirm that the researcher has explained to the participants and me the details of the study, including its powers, possible benefits and risks, and will provide us with a signed copy of the informed consent. I agree to participate in the study on behalf of the participants.

Official letters of legal representatives: \_\_\_\_\_

Signature by legal representative: \_\_\_\_\_

Relations with subjects: \_\_\_\_\_

Date: \_\_\_\_\_

Statements and signatures of witnesses (if applicable)

Subjects have shown that he or she is unable to read. One or more researchers have read and explained this informed consent, including its power and possible benefits and risks, discussed with the subjects, given them the opportunity to ask questions and fully explained it, and will provide a signed copy of the informed consent for the subjects. I have witnessed the process of informed consent.

Witnesses in block letters: \_\_\_\_\_

Witness's signature: \_\_\_\_\_

Date: \_\_\_\_\_