Chinese Herbal Medicine (Yiqi-Yangyin-Jiedu Decoction) Combined With Osimertinib As First-Line Treatment For Advanced Non-Small-Cell Lung Cancer With EGFR Sensitizing Mutation (CATLA-2): A Study Protocol For A Double-Blind Randomized Controlled Trial

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Research Article

Keywords: Non-small cell lung cancer, Epidermal growth factor receptor, Osimertinib, Yiqi-Yangyin-Jiedu decoction, Chinese medicine

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Title: Chinese herbal medicine (Yiqi-Yangyin-Jiedu decoction) combined with osimertinib as first-line treatment for advanced non-small-cell lung cancer with EGFR sensitizing mutation (CATLA-2): a study protocol for a double-blind randomized controlled trial

Running title: Yiqi-Yangyin-Jiedu decoction plus Osimertinib in advanced NSCLC

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Abstract

Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs) significantly improve the prognosis of non-small cell lung cancer (NSCLC) with EGFR sensitizing mutation. Although third-generation EGFR-TKI osimertinib is demonstrated with superior efficacy compared with first-generation EGFR-TKIs, acquired resistance to EGFR-TKIs remains the bottleneck. The Chinese herbal medicine (CHM) Yiqi-Yangyin-Jiedu decoction (YYJD) has been proved to delay acquired resistance to first-generation EGFR-TKIs in CATLA study, but there is no high-level evidence for its effect when combined with osimertinib. This trial aims to examine the efficacy and safety of YYJD combined with osimertinib as first-line treatment for advanced NSCLC harboring EGFR sensitizing mutation.

Methods: This is a double-blind, multi-center, randomized controlled trial conducted in 8 hospitals in China. A total of 314 participants will be randomly assigned to the osimertinib plus YYJD group (O+YYJD) or the osimertinib plus placebo group (O+placebo). Treatment will last until disease progression or death. Patients diagnosed with stage IV NSCLC harboring EGFR exon 19 del or exon 21 L858R will be enrolled if they are in accordance with deficiency of Qi and Yin pattern, ready to take osimertinib as first-line treatment, aged 18 to 74 years old, and provide signed informed consent. The primary outcome is progression-free survival (PFS). The secondary outcomes include a comparison of overall survival (OS), objective response rate (ORR), disease control rate (DCR), quality of life (QoL). The analysis will be on intention-to-treat and per-protocol subject analysis principles.

Discussion: The goal of this trial is to evaluate the efficacy and safety of YYJD when added to

osimertinib as first-line treatment for advanced NSCLC with EGFR sensitizing mutation.

Trial registration: Chictr.org.cn ChiCTR1900026748. Registered on 20th October 2019.

Keywords: Non-small cell lung cancer, Epidermal growth factor receptor, Osimertinib, Yiqi-Yangyin-Jiedu decoction, Chinese medicine

Background

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death worldwide[1]. First-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib[2] and erlotinib[3], significantly improve the prognosis of advanced NSCLC patients harboring EGFR common sensitizing mutations (mainly exon 19 Del and exon 21L858R), when compared with traditional platinum-based chemotherapy as first-line treatment. Despite initial responses, most patients develop acquired resistance to first-generation EGFR-TKIs, and the disease will progress within 9-11 months[2,3]. Compared with gefitinib, third-generation EGFR-TKI such as osimertinib is reported with advantages in delaying disease progression and prolonging survival time[4,5]. However, acquired resistance to osimertinib develops in a median time of 18.9 months. Thus, optimizing the effect of osimertinib is essential for the long-term survival of NSCLC patients.

Chinese herbal medicine (CHM) has been used for Chinese NSCLC patients receiving EGFR-TKIs for more than 10 years and demonstrates its efficacy in delaying EGFR-TKI resistance and alleviating adverse effects in several clinical trials[6–8]. CHM contains several active compounds that interact with target proteins involved in EGFR-TKI resistance[9]. Our previous multi-center, double-blind, placebo-controlled clinical trial (CATLA study) confirmed that the addition of CHM (Yiqi-Yangyin-Jiedu decoction, YYJD) to EGFR-TKI (gefitinib, erlotinib, or icotinib) significantly prolongs progression-free survival (PFS) and improve quality of life (QoL) in NSCLC patients8. These trials mainly involve first-generation EGFR-TKIs such as gefitinib, erlotinib, and icotinib. However, the application of third-generation EGFR-TKI as first-line treatment for advanced NSCLC with EGFR sensitizing mutations has clinical benefit compared with first-generation EGFR-TKI. The adjuvant value of CHM to third-generation EGFR-TKI has not been explored in clinical trials.

The current study (CATLA-2) will determine whether the addition of CHM YYJD to third-generation EGFR-TKI osimertinib (O+YYJD) prolongs PFS compared with osimertinib plus placebo (O+placebo) in advanced NSCLC patients who have an activating EGFR mutation.

Methods/design

Design and setting

This is a multi-center, double-blind, randomized controlled trial, which will be conducted in Yueyang Hospital of Integrated Traditional Chinese and Western Medicine Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai Pulmonary Hospital Affiliated to Tongji University, Shanghai Chest Hospital Affiliated to Shanghai Jiaotong University, Guang'anmen Hospital of China Academy of Chinese Medical Sciences, First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, and Jiangsu Provincial Hospital of Traditional Chinese Medicine. The study aims to enroll 314 advanced lung adenocarcinoma (ADC) patients with EGFR sensitive mutation. Patients will be randomized at a ratio of 1:1 to receive either osimertinib plus YYJD or osimertinib plus placebo. Follow-up will be conducted at baseline, 4 weeks after treatment, and every 8 weeks afterwards until disease progression or death which is evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The study design is based on the SPIRIT 2013 statement[10]. This trial was approved by the Institutional Review Board (IRB) of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine Affiliated to Shanghai University of Traditional Chinese Medicine (No.2020-176). A flow diagram of the trial is shown in Fig. 1. The schedule of enrolment, interventions, and assessments is as shown in Fig. 2.

Participants and recruitment

Participants will be recruited through the outpatient and inpatient ward of the 8 sites. Posters and digital media will be used for recruitment.

Inclusion criteria

1. Pathologically or cytologically diagnosed as NSCLC;

2. Clinically diagnosed as Stage IV;

3. EGFR sensitizing mutations, including exon 19del and exon 21 L858R;

4. Deficiency of qi and yin according to traditional Chinese medicine (TCM) syndrome diagnosis;

5. Aged 18 to 74 years old;

6. No major organ dysfunction: hemoglobin ≥120g/L, absolute neutrophil count (ANC) ≥1.5×109/L, platelets ≥80×109 /L, bilirubin≤1.5ULN, alkaline phosphatase (AP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT)≤2.5×ULN. INR≤1.5, creatinine≤1.5ULN.

Exclusion criteria

1. Those with a history of other malignancies within 5 years;

2. Those with symptomatic brain metastases;

3. Those with congestive heart failure (> class II NYHA heart function), unstable (angina at rest), initial onset (starting within 3 months) angina pectoris, or myocardial infarction occurred within 6 months;

4. Those with active infection (> Grade 2 adverse events according to CTCAE.5.0 version);

5. Those with a history of uncontrollable mental illness.

Western medicine diagnostic criteria

· The diagnosis of ADC is based on *Chinese guidelines for diagnosis and treatment of primary lung cancer (2018 Edition)* issued by the National Health and Family Planning Commission of China.

· The clinical staging is based on *AJCC Cancer Staging Manual (8th edition, published in 2017)*.

· Tissue samples tested by amplification refractory mutation system (ARMS) are preferred for EGFR mutation. If tissues are unavailable or insufficient for testing, free peripheral blood DNA can be alternative.

TCM syndrome diagnostic criteria

The TCM syndrome diagnostic criteria will follow Guiding Principles for Clinical Research of New Chinese Medicines (Trial)[11] and Shanghai Traditional Chinese Medicine Diseases and Syndrome Diagnosis and Treatment Routines[12]. The deficiency of Qi and Yin will be judged by two senior deputy chief physicians during the screening period and should meet two major symptoms and one or more secondary symptoms.

· Main symptoms: Cough, small amount of sputum, fatigue and weakness, dried mouth without polydipsia.

· Secondary symptoms: spontaneous sweat, night sweets, reddish tongue or tongue with teeth imprints, thready and weak pulse.

Sample size calculation

The sample size is calculated using SPSS 14.0 software by a biostatistician from the Clinical Evaluation Center of Shanghai University of Traditional Chinese Medicine. In this study, PFS is the primary endpoint, with a two-sided test $\alpha=0.05$, $\beta=0.20$. The median PFS in the control group is expected to be 18 months, median PFS in the experimental group 23 months, recruitment time 18 months and the total study time is 30 months. With the distribution ratio 1:1 of the two groups, the average monthly censorship rate 1%, each group should include 157 cases, and the total sample size is 314 cases.

Randomization and blinding

Eligible patients enrolled at each site will be randomly allocated to either the O+YYJD group or the O+placebo group at a 1:1 ratio through a dynamic random method. When patient gender (male vs. female), age (≥65 years old vs<65 years old), and enrollment center are input as stratified factors, the software will automatically output the results of randomization.

The randomization results and blinding codes will be kept strictly confidential. They will be concealed until interventions are all assigned, and enrollment, follow-up, data collection, data cleaning, and analysis are complete. Participants and researchers, including paramedics, investigators, outcomes assessors, and statisticians, will be unaware of the allocation.

Interventions

Patients in the O+YYJD group will receive osimertinib and YYJD granule. Patients in the O+placebo group will receive osimertinib and placebo.

Yiqi-Yangyin-Jiedu decoction

YYJD is a granular formulation produced by Jiangyin Tianjiang Pharmaceutical Co., Ltd, and composed of *Radix Astragali*, *Radix Codonopsis*, *Poria*, *Rhizoma Atractylodis Macrocephalae* , *Herba Epimedii*, *Common Fenugreek Seed*, *Fructus Psoraleae*, *Radix Adenophorae*, *Radix Glehniae*, *Radix asparagi*, *Radix Ophiopogonis*, *Bulbus Lilii*, *Fructus Ligustri Lucidi*, *Spica Prunellae*, *Rhizoma Arisaematis*, *Devilstongue*, *Pseudobulbus Cremastrae seu Pleiones*, *Herba Selaginellae Doederleinii*, *Chinese Sage Herb*, *Rhizoma Paridis*, *Fructus Jujubae* and *Sun Euphorbia Herb*. YYJD decoction is produced into granules by Jiangyin Tianjiang Pharmaceutical Co Ltd. YYJD is taken with 150-200ml of boiling water twice a day after breakfast and lunch.

Placebo

Placebo is produced by Jiangyin Tianjiang Pharmaceutical Co Ltd with the most similar possible in package, color, smell, and shape to YYJD but without medical ingredients. It is taken with 150-200ml of boiling water, twice a day after breakfast and lunch.

Osimertinib

Osimertinib (TAGRISSO, AstraZeneca, United Kingdom) should be taken 80mg per day. Patients enrolled in this study should continue intervention until disease progression or intolerable adverse effects.

Outcomes

Computed tomography (CT) or magnetic resonance (MR) imaging will be used to assess the tumor at baseline, 4 weeks after treatment, and every 8 weeks afterwards until disease

progression or death. Objective response is evaluated according to RECIST 1.1 established by National Cancer Institute (NCI), divided into the following four situations: Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD).

Primary outcome

· PFS: measured with the date of the videography from a random assignment to the date of objective progression or death by the researcher.

Secondary outcomes

· OS: calculated as the time from randomization to death due to any cause. For subjects who are lost to follow-up before death, the time of the last follow-up is used as the time of no death.

· Objective response rate (ORR): calculated based on the effective rate of CR+PR patients.

· Disease control rate (DCR): calculated based on the effective rate of CR+PR+SD patients.

· Physical condition: assessed following the ECOG PS standard at the same time point of image evaluation.

· QoL: evaluated with Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire[13], Lung Cancer Symptom Scale (LCSS)[14]and TCM syndrome score at the same time point of image evaluation. TCM syndrome score will be evaluated based on the grading scales of lung cancer symptoms required in *the Guiding Principles of Clinical Research of New Chinese Medicine Treating Primary Bronchial Lung Cancer (2002 Edition)* issued by the National Medical Products Administration of China.

· Safety assessments: Participants will be asked and all adverse events (AEs) during treatment will be recorded at each visit, and all AEs reported will be analyzed. Blood, urine, and stool routine, liver function, and kidney function are tested for adverse reactions at the same time point of image evaluation and evaluated according to common terminology criteria for adverse events (CTCAE) version 5.0 (https://ctep.cancer.gov).

Data collection and management

The paper case report forms are filled by the physicians in charge of each center. The filled data is double-checked by administrative staffs who are responsible for data entry and

database maintenance. Researchers in charge of data analysis will be able to access the data only after patient recruitment is completed. The data are monitored by the data management team composed of the project leader of each center. Personal information of potential participants and registered participants will be collected and stored confidentially.

Biological specimens

This trial involves collecting biological specimens for storage. After acquired resistance to osimertinib, a second biopsy and gene test is recommended to discover potential resistance mechanisms. For patients whose tissues cannot be obtained, liquid biopsy with blood ctDNA can be alternative.

Statistical analysis

Data analysis will follow the trial's statistical analysis plan. All data will be processed by statistical analyses with SAS.9.4 software analysis. Two-tailed P values < 0.05 are considered statistically significant. The analysis will follow intention-to-treat, full analysis set, and per-protocol subject principles for the evaluation of primary and secondary outcomes. The safety data set that include all subjects who received at least one treatment after randomization will be used to evaluating safety and tolerance. Missing data will be processed with the multiple imputation method.

The baseline characteristics will be reported according to treatment groups. PFS and OS will be illustrated by the Kaplan–Meier survival curve and compared between groups using the log-rank test. The secondary outcomes will be summarized with frequency, mean, standard deviation, median, and range. At each time point, comparisons between the experimental group and the placebo group will be conducted using the Group t test or Wilcoxon rank-sum test (for measurement data) and rank-sum test and CMH test (for Count data). Fisher's exact test will be used to compare tumor response rates between the arms. For PFS, an adjusted Cox regression model will be used to estimate the adjusted HRs for differences between the treatment arms with the selected prognostic factors, including the center, EGFR mutation type, age, sex, EGFR-TKI drugs, smoking status, and ECOG PS.

Safety will be documented in adverse event forms and presented with descriptive statistics for each group. The frequency difference of adverse events between groups will be assessed by the chi-square test or Fisher's exact test. For different AE severities, a rank-sum test will be performed to analyze the independent ordered multiple category data between the two groups.

Dissemination plans

The results will be published in a paper after the completion of the study.

Discussion

This is a protocol for a multi-center, double-blind, randomized, placebo-controlled trial. This trial will be conducted in outpatient and inpatient settings with experienced investigators from 8 hospitals in different Chinese cities. The goal of this trial is to determine whether the addition of CHM YYJD to third-generation EGFR-TKI osimertinib (O+YYJD) prolongs PFS and QoL in advanced NSCLC patients who have an activating EGFR mutation.

TCM is a symptom-oriented medicine. Syndrome differentiation based on signs and symptoms is the fundamental principle of TCM. Deficiency of Qi and Yin is the most common syndrome differentiation type for NSCLC patients receiving EGFR-TKI[11] whose clinical manifestations include cough without sputum, shortness of breath, fatigue, thirst, red tongue with tooth marks, and weak pulse. CHM with the efficacy of replenishing Qi and/or Yin has been proved beneficial in prolonging PFS by 3-5 months and alleviating adverse effects such as stomatitis, diarrhea, and rashes when combined with first-generation EGFR-TKIs in several clinical trials[6–8]. Its efficacy is related to several active compounds that interact with target proteins involved in EGFR-TKI resistance, such as ADRB2, BCL2, CDKN1A, HTR2C, KCNMA1, PLA2G4A, PRKCA, and LYZ[9]. In our previous multicenter, randomized, double-blind, placebo-controlled CATLA study, YYJD increases median PFS from 10.94 months (95% CI, 8.97–12.45 months) to 13.50 months (95% CI, 11.20–16.46 months) when added to first-generation EGFR-TKIs. When EGFR-TKIs was administered as first-line treatment, PFS was significantly improved by the combination of YYJD (15.97 vs. 10.97 months, P = 0.0447). Accumulated evidence suggested that third-generation EGFR-TKIs such as osimertinib yielded more benefits

to EGFR sensitizing NSCLC patients, compared with first-generation EGFR-TKIs. In the FLAURA study, those who received osimertinib had longer overall survival than those who received gefitinib or erlotinib (hazard ratio for death, 0.80; 95.05% CI, 0.64 to 1.00; P = 0.046)[4]. Thus, osimertinib has been the preferred recommendation for first-line treatment of NSCLC patients with sensitizing EGFR mutations. Preclinical research suggests the potential benefit of CHM Bufalin to reverse acquired resistance to osimertinib through inhibiting Ku70-mediated MCL-1 overexpression[15]. Thus, evidence from a well-designed clinical trial to evaluate the adjuvant benefit of adding CHM to osimertinib is needed.

One challenge of this trial is that patient screening and primary outcome evaluation require physicians with TCM and oncology backgrounds, or collaboration between TCM physicians and oncologists. Moreover, this study will be carried out in eight hospitals in different cities of China. Therefore, effective communication is needed for cooperation and support throughout the trial. Thus, we will offer a training workshop before recruitment and hire a clinical research organization to assist with data monitoring and management during the trial.

Another challenge is patient compliance with third-generation EGFR-TKIs, because first-generation EGFR-TKI is still recommended in NSCLC guidelines. We will provide detailed information on the benefit of using osimertinib as first-line treatment compared with first-generation EGFR-TKIs, to make the financial burden caused by osimertinib valuable.

In addition, research assistants will check the data integrity of the QoL scale. Moreover, we will provide a separate space for participants to fill out the QoL forms out of concerns for their privacy.

At the end of this trial, we expect to know YYJD's efficacy in treating advanced NSCLC with sensitizing EGFR mutations and deficiency of Qi and Yin when combined with osimertinib in terms of prolonging PFS and OS. We also want to learn whether it has a positive effect on QoL.

Trial status

Protocol version: v2.0 was finished on 27th July 2020. Participant recruitment started in January 2021 and is expected to end in December 2022.

Abbreviations

ANC: absolute neutrophil count; ADC: advanced lung adenocarcinoma; AP: alkaline phosphatase; ARMS: amplification refractory mutation system; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CHM: Chinese herbal medicine; CT: computed tomography; CTCAE: common terminology criteria for adverse events; DCR: disease control rate; EGFR: epidermal growth factor receptor; EGFR-TKIs: epidermal growth factor receptor tyrosine kinase inhibitors; FACT-L: Functional Assessment of Cancer Therapy-Lung; IRB: Institutional Review Board; LCSS: Lung Cancer Symptom Scale; MR: magnetic resonance; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; QoL: quality of life; RECIST: Response Evaluation Criteria in Solid Tumors; TCM: traditional Chinese medicine; YYJD: Yiqi-Yangyin-Jiedu decoction

Declarations

Acknowledgements

Not applicable.

Authors' contributions

YL and JLY planned the study protocol. YL drafted the manuscript, and JLY revised the manuscript. YBG and LX were responsible for the concept and design of this study. LX was responsible for obtaining ethics approval and the acquisition of funding. YBG, LX, YL, JLY, LJJ, LB, WXY, LZS, and JS recruited and screened eligible patients. YL, JLY, WXY, LZS, JS collected and assembly of data. LJJ and LB were responsible for the data analysis and interpretation. All authors have read and approved the final manuscript.

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201901), The YSN Science Program of the Shanghai University of Traditional Chinese Medicine (No. 2019LK026). The funders played no role in the study design, data collection, analysis, management, and interpretation of data, or writing of the manuscript.

Availability of data and materials

As the research has not yet been completed, the datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine (No. 2020-176). Recruitment of other centers must be approved by the central ethics review before proceeding. Written, informed consent to participate will be obtained from all participants. Besides the investigators, no one can access the final data.

Consent for publication

Not applicable

Competing interests

The authors declare that have no competing interests.

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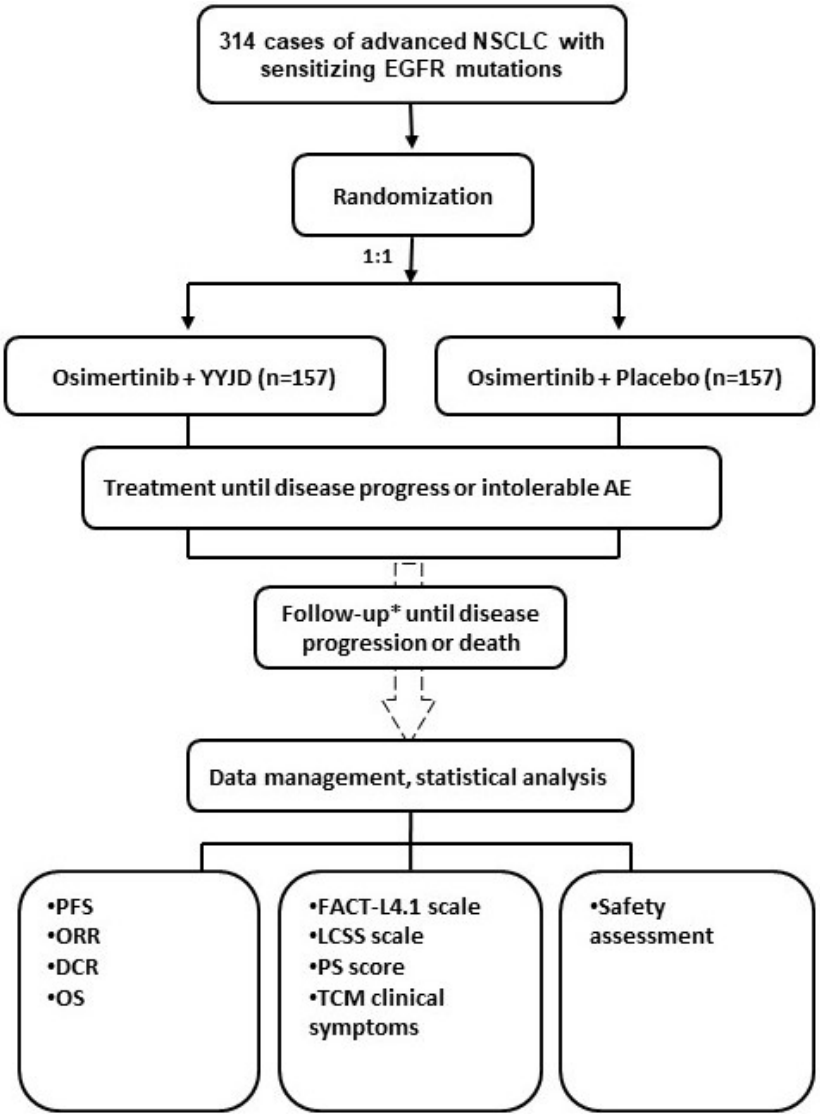
Fig. 1 Study flow



* Follow-up will be conducted at baseline, 4 weeks after treatment, and every 8 weeks afterwards until the death of the patients.

Fig. 2 Schedule of treatment and assessment

	STUDY PERIOD				
	Enrolment	**Baseline**	**Treatment period**		**Follow-up**
TIMEPOINT	Before treatment	0	4 weeks after treatment	Every 8 weeks afterwards until disease progression or death	Until death
ENROLLMENT					
Eligibility screen	×				
Informed consent	×				
Allocation		×			
INTERVENTION					
O+YYJD			←	→	
O+placebo			←	→	
ASSESSMENTS					
Demographics	×				
Medical history	×				
CT or MR imaging	×		×	×	
PFS				×	
ORR				×	
DCR				×	
OS					×
ECOG PS		×	×	×	
FACT-L4.1 scale		×	×	×	
LCSS scale		×	×	×	
TCM symptoms		×	×	×	
Blood routine		×	×	×	
Urine routine		×	×	×	
Stool routine		×	×	×	
Liver function		×	×	×	
Kidney function		×	×	×	
Adverse events			×	×	

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Figures

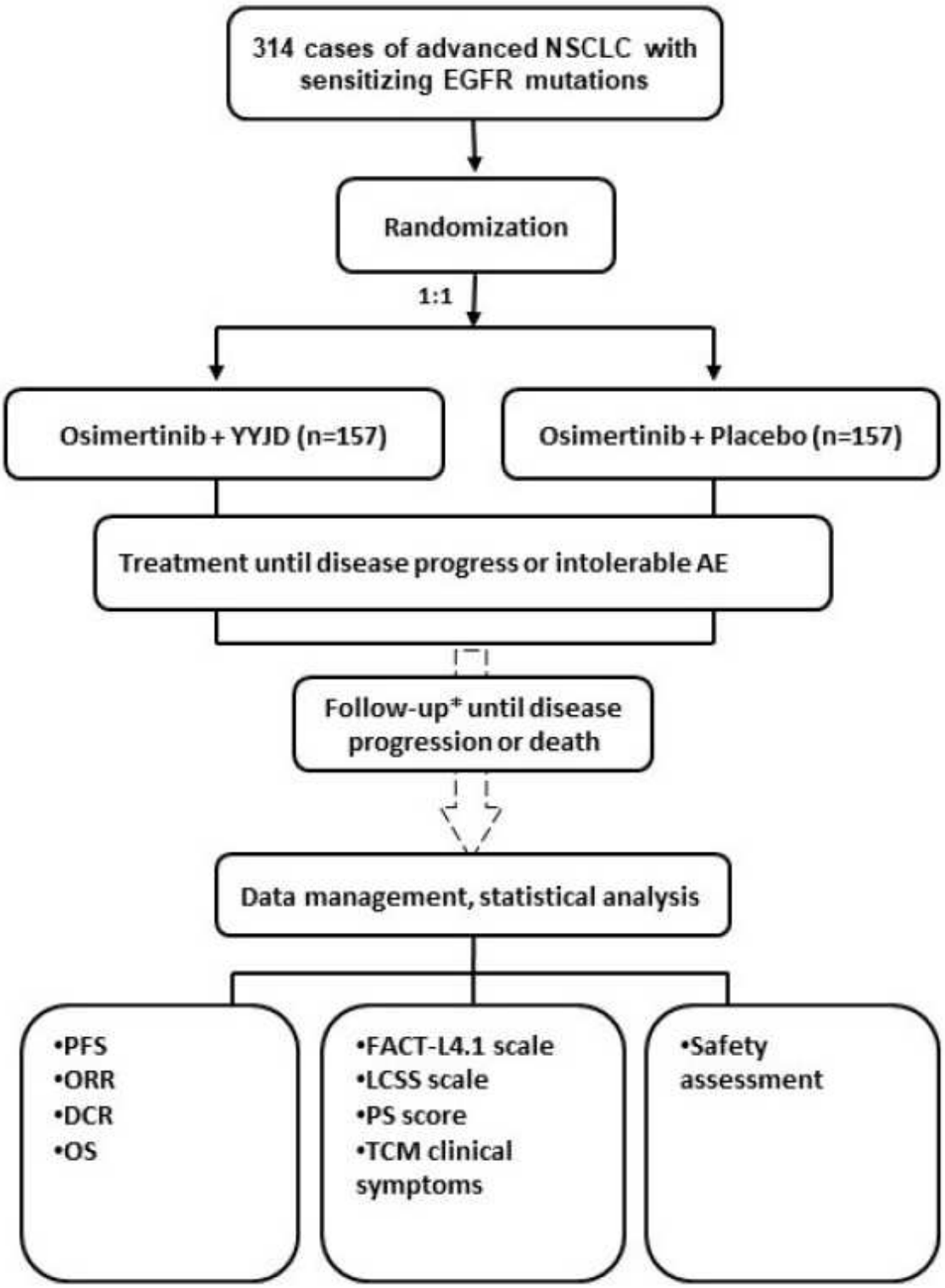

Figure 1

Study flow * Follow-up will be conducted at baseline, 4 weeks after treatment, and every 8 weeks afterwards until the death of the patients.

	STUDY PERIOD				
	Enrolment	Baseline	Treatment period		Follow-up
TIMEPOINT	Before treatment	0	4 weeks after treatment	Every 8 weeks afterwards until disease progression or death	Until death
ENROLLMENT					
Eligibility screen	×				
Informed consent	×				
Allocation		×			
INTERVENTION					
O+YYJD			←	→	
O+placebo			←	→	
ASSESSMENTS					
Demographics	×				
Medical history	×				
CT or MR imaging	×		×	×	
PFS				×	
ORR				×	
DCR				×	
OS					×
ECOG PS		×	×	×	
FACT-L4.1 scale		×	×	×	
LCSS scale		×	×	×	
TCM symptoms		×	×	×	
Blood routine		×	×	×	
Urine routine		×	×	×	
Stool routine		×	×	×	
Liver function		×	×	×	
Kidney function		×	×	×	
Adverse events			×	×	

Figure 2

Schedule of treatment and assessment

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRIT2013Checklist.pdf